



# Management of the Normal and Difficult Pediatric Airway: Unique Challenges in the Time of COVID-19

Edgar Kiss<sup>1,2</sup> · Annery Garcia-Marcinkiewicz<sup>3,4</sup> · John Zhong<sup>1,2</sup> · Matthew Roberts<sup>1</sup> · Neethu Chandran<sup>1,2</sup> · Rhae Battles<sup>1,2</sup> · Rita Saynalath<sup>1,2,5</sup> · Iamze Agdgomelashvili<sup>6,7</sup> · Patrick Olomu<sup>1,2</sup>

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## Abstract

**Purpose of Review** This review focuses on the challenges faced by acute care healthcare workers in the management of the normal and difficult pediatric airway during the COVID-19 pandemic and how these protocols and practices evolved during the pandemic. The current state of knowledge on timing of surgery and anesthesia is also discussed.

**Recent Findings** In the early days of the pandemic, information about the SARS-CoV-2 virus and disease process was scarce. Governmental, healthcare, and professional organizations created several guidelines to protect invaluable healthcare workers from the contagious virus while also delivering appropriate care to children with COVID-19. With the emergence of new studies and the deployment of new life-saving COVID-19 vaccines and other therapies, these guidelines evolved. The use of aerosol containment devices such as aerosol boxes and flexible barrier techniques was found to be ineffective in reliably containing virus particles while posing potential harm to both healthcare workers and patients. Also, the definition of aerosol-generating and dispersing medical procedures was vastly broadened. To date, use of appropriate personal protection equipment and COVID-19 vaccination are the most effective ways to protect healthcare workers and safely manage children infected with SARS-CoV-2 who require airway intervention.

**Summary** Evidence-based public health measures and appropriate personal protective equipment remain the best way to protect both healthcare workers and patients. As the virus and population evolve and COVID-19 vaccines become more widely available, clinicians must be willing to adapt to the emerging evidence of their impact on how safe pediatric perioperative care is delivered.

**Keywords** COVID-19 · SARS-CoV-2 · Airway management · Pediatrics · Aerosol generating procedures · COVID-19 vaccines

✉ Patrick Olomu  
Patrick.Olomu@UTSouthwestern.edu

<sup>1</sup> Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

<sup>2</sup> Division of Pediatric Anesthesiology, Children's Health System of Texas, Dallas, TX, USA

<sup>3</sup> Department of Anesthesiology and Critical Care Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>4</sup> The Children's Hospital of Philadelphia, Philadelphia, PA, USA

<sup>5</sup> Outcomes Research Consortium, Cleveland, OH, USA

<sup>6</sup> Tbilisi State Medical University, Tbilisi, Georgia

<sup>7</sup> Ingorokva High Medical Technology University Clinic, Tbilisi, Georgia

## Introduction

In late December 2019, reports of several cases of an unusual pneumonia started emerging from the city of Wuhan in China [1–6]. The causative agent was soon determined to be a novel coronavirus subsequently named the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease it caused was named Coronavirus Disease 2019 (COVID-19). Infections in children comprised only a small fraction of the total cases, accounting for less than 2% of total cases in China, Italy, and the USA [6, 7]. Even though infections were usually mild, a small subset of at-risk children developed severe disease requiring hospitalization, mechanical ventilation, and occasionally Extra-Corporeal Membrane Oxygenation (ECMO) [8]. The first US data on SARS-CoV-2 deaths in pediatric patients were reported by

the Centers for Disease Control and Prevention (CDC) in September 2020 [9]. From February 12 to July 31, 2020, there were 121 deaths reported in children. Of note, a majority (78%) was from historically minoritized groups.

As the virus continued its deadly march across the globe, healthcare organizations began deploying trusted public health measures, local resources, and available capabilities to combat the disease. Concurrently, the World Health Organization (WHO) and other regional and local healthcare and professional organizations began developing protocols to contain the disease and protect healthcare workers (HCWs) from contracting the virus while providing life-saving care for infected patients. This review focuses on the unique challenges faced by acute care HCWs in the management of the normal and difficult pediatric airway during the COVID-19 pandemic and the innovative ways in which the global healthcare community worked in a collaborative fashion to battle this highly contagious once-in-a-lifetime global pandemic. The current state of knowledge on timing of surgery and anesthesia after SARS-CoV-2 infection is also discussed.

## Initial Response and Recommendations

At the onset of the COVID-19 pandemic, little information was available to provide evidence-based guidelines for safe airway management practices. To fill this void, publications of protocols used to manage prior respiratory viruses, direct first-hand experience narratives from the hot zones, and consensus statements from the WHO, professional organizations, and other experts started emerging to provide HCWs with a roadmap to guide their practices [1, 2, 3, 4, 5, 6, 10, 11, 12]. Many of these initial publications emphasized known public health measures, such as use of appropriate personal protective equipment (PPE), proper PPE donning and doffing techniques, use of face shield, avoidance of self-contamination, practice of appropriate hand hygiene, and use of appropriate fit-tested N95 respirators.

Public health officials also leaned on reports from China and experiences from prior respiratory outbreaks, such as the Coronavirus outbreak in Toronto in 2003 and the Middle Eastern Respiratory syndrome (MERS) outbreak in 2012. The first temporary COVID hospital was built in Wuhan within 33 h from initial planning to full operational status and patient acceptance [13]. Designed like a United States-style military hospital, it had a capacity of 1000 beds. The purpose was to prevent overflowing of designated hospitals with COVID-19 patients. These public health procedures and practices provided the initial road map for many countries on how to manage the evolving public health crisis. However, these measures could not be easily replicated in other countries. In the USA, a naval hospital ship was

deployed to the coast of New York and a New York City convention center was converted into a field hospital for COVID-19 patients.

Additionally, specific steps for the process of endotracheal intubation and extubation were developed and a synopsis of common recommendations is shown in Table 1. The most common indications for intubation in a COVID-19 patient are for emergent/urgent surgical procedures and mechanical ventilation for COVID-19-associated respiratory insufficiency. The main goals of airway management therefore was to limit aerosol generation and propagation. Factors associated with infectivity include viral load (disease burden), proximity to the viral source, and forced air (speed of aerosolization).

## Specific Recommendations for Pediatric Patients Requiring Airway Management

Even though infection in children comprised only a small fraction of total infections, asymptomatic transmission from children to HCWs was found to be a significant problem [10]. Furthermore, evidence-based guidance to support safe practice of pediatric anesthesia and airway management was sparse. In fact, some pediatric hospitals created “COVID-19 intubation teams” primarily staffed by anesthesiologists to perform intubations hospital wide in an attempt to minimize HCW exposure [6].

To address this knowledge gap and promote safe practice of pediatric anesthesia during the pandemic, the Pediatric Difficult Intubation Collaborative (PeDI-C; [pediregistry.org](http://pediregistry.org)), an international special interest group of the Society for Pediatric Anesthesia, convened a webinar to generate consensus guidelines about airway management during aerosol-generating procedures (AGP) [10]. A summary of these guidelines is shown in Tables 2 and 3 and a flowchart of steps in airway management is shown in Fig. 1.

## Management of the Difficult Airway in the Pediatric Patient with COVID-19

According to the American Society of Anesthesiologists, a patient is defined as having a difficult airway when difficulty or failure is experienced by a physician trained in anesthesia care, including but not limited to difficulty with face mask ventilation, supraglottic airway (SGA) placement, tracheal intubation, extubation, and surgical airway [14]

An observational prospective study of pediatric difficult airway patients in an international registry found a difficult airway incidence of 2–5 per 1000 children. Direct laryngoscopy was found to be the most commonly used technique

**Table 1** Common recommendations for managing patients with COVID-19

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Postponement or cancelation of non-emergent or non-urgent surgery

Utilization of negative pressure operating rooms

Use of a dedicated anesthesia machine

Application of a viral filter between the endotracheal tube connector and the distal end of the anesthetic breathing system

General anesthesia is the preferred technique to assure a controlled environment with no coughing and bucking with aerosolization

Rapid sequence or modified rapid sequence induction is recommended to prevent coughing and aerosolization

Ensure tight mask seal during preoxygenation

Utilization of a barrier technique (flexible barrier, intubation box, or other modification to limit aerosol dispersion and risking HCW infection)

Oral intubation with a video laryngoscope is recommended. High viral loads have been observed in the nasal passages and may pose increased risk to the clinician ‡

The most experienced clinician should perform the intubation. Inexperience trainees should not be allowed to intubate these patients

A cuffed endotracheal tube should be used to minimize aerosolization

Use of a closed airway suction system if available

Extubate the patient in the operating room if criteria are met. A barrier technique should be used to limit aerosol dispersion

Transfer the patient directly to the floor, bypassing the recovery room. A surgical mask or an N95 respirator should be applied to the patients face during transport

For transport of an intubated patient to the intensive care, manual ventilation is recommended. A transport ventilator is not recommended

Proper disposal and disinfection of all equipment must be performed

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‡Wang et al., [38]

**Table 2** Synopsis of guidelines created by the pediatric difficult intubation collaborative

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Premedication

- Effective Premedication
- Facilitates IV placement
- Calms the child
- Nasal administration of premedication is undesirable
- No parental presence at induction
- Minimize HCW exposure
- Conserves PPE

Induction of anesthesia

- Intravenous induction is preferred
- Assess child's disposition—screaming/crying child may result in higher respiratory droplets
- Rapid sequence induction/Modified Rapid Sequence Induction
- Deep muscle relaxation
- Gentle positive pressure ventilation with tight mask fit

Mask induction

- Reduced flow rates
- Tight mask seal
- Use transparent plastic barrier
- Two-hand mask ventilation

Airway Device Placement

- Cuffed tracheal tube
- Video laryngoscope—to maintain “social distance” from patient's airway and the “hot zone.”
- Use transparent barrier
- Most experienced laryngoscopist should attempt tracheal intubation
- In-line closed suction system is preferred
- ICU should intubate in negative pressure room prior to transport
- LMA with a good seal is acceptable in some cases

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**Table 3** Synopsis of guidelines created by the pediatric difficult intubation collaborative (continued from Table 2)

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Checking for Leak
Avoid auscultation of hot zone
Avoid listening for a leak
Use hand-held or in-line manometers
Inspiratory/Expiration VT
Use flow-volume loops on anesthesia machine if available
Use Point of Care Ultrasound (POCUS)
Wireless Stethoscope
Maintenance of Anesthesia
Use full PPE during entire case
Risk of ventilator disconnection
Accidental extubation
Procedural aerosolization procedures—endoscopy, dental drills
Keep barrier if possible or wet towels/gauze
Limit aerosol dispersion
Emergence & Extubation
Use in-line suction for tracheal suctioning
Consider deep extubation
Decreased coughing
Decreased bucking
IV propofol/ dexmedetomidine
Use protective barrier
Place suction under drape to create ‘negative’ pressure
Institutional protocols and workflows
Patient Transport
ETCO <sub>2</sub> line should be placed after viral filters
Provide deep sedation and muscle relaxation
Prevent coughing in route
Potential accidental extubation
Least desirable techniques
High-Flow Nasal Cannula (HFNC)
Bag Mask Ventilation (BMV)
Operating Room Infrastructure
Use negative pressure Operating Room for AGPs
Ensure adequate air exchange and filtration time of Operating Room
If negative pressure Operating Room is not available, use High Efficiency Particulate Air (HEPA) filters
Avoid rooms with connected ventilation systems

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in children with a known difficult airway despite a first pass success rate of only 3% (16/461) [15●●]. Complications occurred in 20% of cases and were associated with multiple intubation attempts (>2), weight less than 10 kg, a short thyromental distance, and direct laryngoscopy persistence (>3 attempts prior to switching to an indirect technique or a different modality). Table 4 shows the recommended difficult airway management guidelines for children with COVID-19 by Matava, et al. [10●].

As the pandemic evolved and more information emerged, it was recognized that certain initial recommendations on the management of the difficult pediatric airway needed to be modified. A modified Delphi process was therefore initiated to address the specific airway challenges relating to pediatric airway management and provide updated recommendations [16]. A summary of these modifications is listed below.

1. Clinicians should consider other induction techniques, including inhalational induction with spontaneous breathing. Whether an apneic technique with muscle relaxation is superior to spontaneous breathing remains unresolved. Also, pediatric anesthesiologists are very comfortable with inhalational induction and maintenance of a tight mask fit in most instances.
2. The use of supplemental oxygen remains unchanged. Furthermore, the most effective method of oxygenation in the specific clinical situation should be used with less emphasis on aerosolization risk if team members use appropriate PPE and are fully vaccinated.
3. The recommendation to limit the number of people in the operating room is no longer supported because of the proven effectiveness of PPE and vaccination.
4. The recommendation for the use of videolaryngoscopy remains unchanged and the use of direct laryngoscopy in the setting of difficult airway management is not recommended. Videolaryngoscopy increases the “social distance” between the laryngoscopist and the patient’s airway, has a high first pass success rate, and is very effective in difficult airway situations. No consensus was reached on the type of videolaryngoscope blade to use. In addition, direct laryngoscopy has an abysmal first attempt success rate in the setting of pediatric difficult airway, and multiple direct laryngoscopy attempts are associated with increased complications risks [15●●]. A recent study comparing Miller-type video blades and straight blade direct laryngoscopy in infants showed a 5.5% absolute risk difference in favor of videolaryngoscopy and a 12% improvement in first attempt success rate in infants under 6.5 kg in the videolaryngoscope group [17●●]. Other reported advantages of videolaryngoscopy include an increased ‘mouth-to-mouth’ distance compared to direct laryngoscopy [18●]. In this study involving 25 participants, mounted cameras were used to measure the ‘mouth-to-mouth’ distance during simulated manikin intubations using videolaryngoscopy and direct laryngoscopy. The authors found a doubling of the ‘mouth-to-mouth’ distance when videolaryngoscopy was used (16.4 cm for direct laryngoscopy versus 35.6 cm for videolaryngoscopy ( $p < 0.0001$ )). The time to intubation was similar in both groups. Zeidan et al. have also described a stylet-free channeled videolaryngoscope with closed-circuit ventilation as a technique to

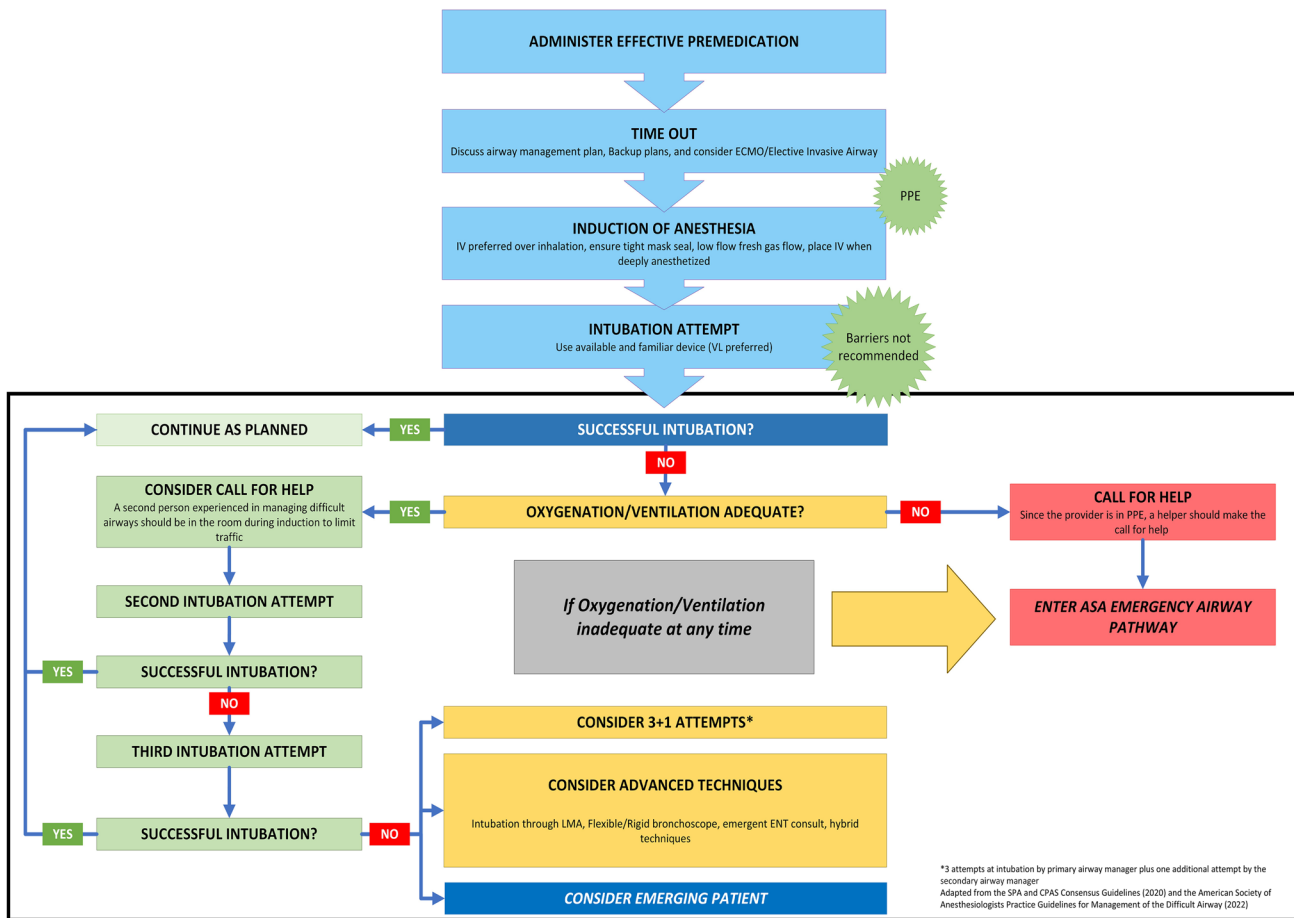


Fig. 1 COVID-19 Airway Management FlowChart Infographic

**Table 4** Difficult airway management in children with COVID-19

Assemble a team
Huddle and perform Just-in-Time training
Most experienced laryngoscopist should intubate
Decreased time
Decreased number of attempts
Decreased exposure
Preferred Techniques for Difficult Airway
Videolaryngoscopy should be primary technique
FOB thru SGA
Combined Video/FOB
Freehand FOB
Oral FOB is preferred
Two-hand mask ventilation
Give Muscle Relaxant (Rocuronium) if safe
Have Sugammadex immediately available
Prepare for emergency front of neck access (e-FONA)

minimize aerosolization [19]. Furthermore, fewer severe complications and esophageal intubations occurred in the videolaryngoscope group. These and other positive reports have raised the question of whether videolaryngoscopy should be used universally for all intubations [20]. However, the high cost of durable high-quality video laryngoscopy platforms makes it less likely for this goal to be achieved, especially in resource-poor countries.

- Junior trainees may now be allowed to participate in difficult airway managements provided that all clinicians involved wear appropriate PPE and are fully vaccinated.
- The operating room is the preferred location to manage the pediatric difficult airway patient with COVID-19. Moving away from the operating room purely for induction in a negative pressure room is no longer recommended.
- The use of barrier methods is no longer supported. In fact, the WHO, regulatory organizations (such as the Food and Drug Administration), and professional societies have withdrawn their support for their use. Also,

there is emerging evidence that their use may actually increase the risk of clinician exposure and further complicate airway management.

8. Awake extubation should be performed in the operating room as long as extubation criteria are met.

## Role of Aerosol Containment Devices for Airway Management During the COVID-19 Pandemic

Even before the onset of the COVID-19 pandemic, aerosol-generating procedures (AGPs) were a known source of potential infection to HCWs. Early in the pandemic, infection in HCWs accounted for about 4% of total cases, including severe and fatal cases [21–23]. Anesthesiologists, intensivists, and first responders are at particular risk for developing COVID-19 disease presumably from droplet exposure, aerosol transmission, and proximity to the viral source.

Droplets are heavy and usually spread within a maximum of six feet radius from the source. Aerosols, by contrast, are small particles with a wider dispersal radius and can remain suspended in the air for prolonged periods of time. They can penetrate or even go around standard surgical masks [24●●]. It is however important to note that the comparison between droplets and aerosols may just be an academic exercise as particles of various sizes between droplets and aerosols are released and all of them can transmit the virus [25].

Because of the severe contagiousness of SARS-CoV-2, public health and professional organizations moved to expand the list of AGPs beyond the “traditional” list of tracheal intubation, bronchoscopy, and tracheostomy. This broader definition included non-invasive ventilation (NIV), high-flow nasal oxygen (HFNO), nebulization, nasogastric tube placement, thoracentesis, upper and lower endoscopy, cardiac catheterization, exercise tolerance tests, pulmonary function tests, percutaneous gastrostomy tube placement, laparoscopy, facial surgery especially requiring drilling, second stage of labor, and others [24●●]. For clarity, some of these procedures are better described as “aerosol dispersing” procedures.

With global PPE shortages, reports began emerging about the potential role of barrier techniques for HCWs protection. Furthermore, after experiments on simulated aerosol spread showed only a small degree of protection with PPE alone, flexible enclosures and intubating boxes started appearing in the literature (Fig. 2). Dr. Hsien Yung Lai developed the first prototype “aerosol box” [26]. Variations of this initial prototype soon began appearing in different countries as the fight to control the virus intensified [27]. Despite a lack of scientific evidence on their safety and effectiveness, their use spread globally.

In a far-reaching scoping review utilizing a Delphi method and a modified nominal group technique to evaluate the supporting evidence for the use and potential risks of aerosol containment devices, Sorbello et al. [28●●] reviewed 52 publications and 6 websites. Many of these publications were expert opinions, small case series, and small sample simulation studies. The major findings from their review were as follows:

- Use of barriers adds to the complexity of airway management.
- Evidence for barriers increasing HCWs protection was lacking.
- Barriers can compromise/damage PPE integrity which increases contamination risk.



**Fig. 2** **A** Flexible enclosure created with a PVC frame and large plastic bag. Due to poor visibility through the plastic, video-assisted intubation was recommended. **B** Plexiglass shield with a plastic bag taped to the sides of the shield. The operator has a clearer view of the patient. **C** Intubation box made of plexiglass with holes for hands. The box is designed to lay over the patient’s head creating a barrier between the operator and patient to limit viral dispersion. (Used with permission, Dr. Edgar Kiss and Dr. Patrick Olomu, University of Texas Southwestern Medical Center/Children’s Health System of Texas, Dallas, Texas)

- Response to an airway emergency can be delayed by barriers and access for an assistant can be limited.
- Secondary aerosolization can occur during and after barrier removal following airway management.
- Barrier use provides no usable access for advanced airway devices such as a fiberoptic bronchoscope/flexible intubating scope—a crucial device in difficult airway management.
- A lack of cleaning standards for reusable barrier devices may cause both patient and HCWs contamination.

The authors therefore concluded that concrete evidence to support the protective effect of barrier techniques was lacking and that their use may actually lead to patient harm and HCWs contamination. They cautioned that barrier devices were not a substitute for proper PPE and their use cannot be recommended until well-conducted studies are published.

### What are the Risks to HCWs Following Tracheal Intubation in COVID-19 Patients?

In an international prospective study of HCWs involved in AGPs such as tracheal intubation in suspected or confirmed COVID-19 patients, El-Boghdady, et al. [29●●] studied 5148 tracheal intubation episodes by 1718 HCWs in 503 hospitals across 17 countries. Using Cox regression analysis, they studied the association between the incidence of laboratory-confirmed COVID-19 diagnosis or new symptoms requiring self-isolation or hospitalization after a tracheal intubation episode. The authors found a 10.7% overall incidence at a median of 32 days with an increasing cumulative incidence over 21 days. The authors expressed concern about the workforce capability and care delivery implications of such a high incidence. A limitation to this important study is the possibility that some HCWs might have been infected with SARS-CoV-2 from the community and not during an AGP.

### Airway Management and Pulmonary Complications in SARS-CoV-2 Patients

In a retrospective cohort analysis of 99 COVID-19-negative and 51 COVID-19-positive patients at a single tertiary institution between April 28 and September 30, 2020, Saynhath, et al. found a higher incidence of perianesthetic respiratory complications in COVID-19-positive patients [30●]. The only significant confounding factor was being a member of the Black race. There was no difference in the incidence of non-respiratory complications. Additionally, no children suffered severe complications, such as post-operative pneumonia, acute respiratory distress syndrome, or death.

The PAWS-COVID (Pediatric AirWay complicationS during COVID-19) study was an international observational registry designed to collect data on airway management outcomes in children with COVID-19 undergoing general anesthesia [31●●]. The authors hypothesized that children with suspected or confirmed COVID-19 would experience more hypoxemia and complications than those without. Data were collected in 78 international centers from April 3 to November 1, 2020. In phase I of the study, outcomes data were collected on all children under the age of 18 undergoing general anesthesia over a consecutive two-week period. In phase II, outcomes data were collected on children with test-confirmed or suspected COVID-19 infection. Patients who were already intubated were excluded. The authors found a higher incidence of mild hypoxemia and respiratory complications in children with COVID-19 compared to those without. The hypoxemia was usually mild and occurred mostly during airway device removal. Use of barriers was found to be associated with a greater incidence of hypoxemia, especially when used during emergence and extubation.

### Timing of Surgery Following SARS-CoV-2 Infection and the Role of COVID-19 Vaccination

Recommendations regarding the optimal timing of surgery following COVID-19 infection have been variable. Adding further complexity to the issue is the multitude of factors that may impact when an operation can be performed safely [32●●]. These include the severity or symptomatology of the infection, vaccination status, baseline comorbidity burden, and the extent of surgery (e.g., major vs. minor surgery), among others. For example, an initial study of 122 adult patients undergoing curative cancer surgery from the COVIDSurg Collaborative found that the risk of pulmonary complications and death did not decrease until after four weeks from a positive COVID test [33]. However, a larger, more recent study by the COVIDSurg and GlobalSurg Collaboratives found evidence of a stepwise decline in perioperative mortality and postoperative pulmonary complications up to seven weeks from an initial positive COVID test [34●●]. In this study of 3,127 patients, 30-day mortality decreased as time between positive COVID testing and surgery increased (OR 4.1, 3.9, 3.6, 1.5 for 0–2 weeks, 2–4 weeks, 5–6 weeks, and  $\geq 7$  weeks, respectively). Strengths of the study included its large size, international cohort, and inclusion of numerous covariates highlighted by prior studies in calculation of its adjusted odds ratios for primary outcomes and sensitivity analyses.

Given the rapid development and dissemination of COVID-19 vaccines, vaccination status represents an additional factor that must be considered prior to the development of stronger recommendations on the appropriate timing of surgery after

COVID-19 infection. Le et al. performed a retrospective cohort study of 229,913 patients investigating this question [35]. They found no difference in perioperative complication rates between fully vaccinated and COVID-negative patients at any timepoint (RR 0.66, 0.74, 1.00 for patients having surgery 0–4 weeks, 4–8 weeks,  $\geq 8$  weeks after infection, respectively). It therefore appears that COVID-19 vaccination status may be an important predictor of perioperative outcomes.

An informal survey of both USA and international Children's hospitals performed in an online pediatric airway experts' forum and the Wake Up Safe Organization showed that the timing of elective surgeries varies depending on severity of illness and resolution of symptoms. Seven out of 12 institutions (58%) use a wait period of 2 weeks or less before rescheduling children who are asymptomatic or had mild upper respiratory symptoms (rhinorrhea and nasal congestion). The guidelines for waiting after moderate/severe symptoms for these institutions was uniformly greater than 4 weeks. Some institutions require a wait period of 4–6 weeks and a negative COVID-19 test for immunocompromised patients.

At our tertiary care pediatric hospital (first and senior authors), a 6-week wait period is recommended for elective cases. Urgent procedures are performed after a 10-day quarantine period and typically admit them postoperatively due to a higher risk of airway complications. Except for immunocompromised patients and patients with respiratory comorbidities (asthma, bronchopulmonary dysplasia), no other distinction is made between symptomatic or asymptomatic patients.

In total, these studies demonstrate that while the appropriate timing of surgery after COVID-19 infection likely lies between four and seven weeks, this represents a dynamic situation that may change as newer therapies become available. Going forward, investigations into the mechanisms of poor perioperative outcomes following SARS-CoV-2 infection and the validation of risk stratification tools such as exercise testing, pulmonary function tests, and potential biomarkers must be conducted [36].

## Conclusion

The worldwide COVID-19 pandemic stressed the healthcare system of almost every country. Armed with limited information on airway management for children with COVID-19 requiring airway intervention, pediatric anesthesiologists around the world, and other caregivers rallied to provide guidelines for the safe management of both the normal and difficult pediatric airway while maximizing protection of invaluable healthcare workers. These guidelines evolved over the course of the pandemic as more information about this highly contagious virus emerged. Many novel devices

such as the aerosol box and other barrier methods gained worldwide usage in a desperate attempt to control the virus. Many of these devices were later found to not only be ineffective but also potentially harmful to both HCWs and patients. The most effective way to protect HCWs performing AGPs such as airway management is the use of appropriate PPE, use of proper PPE donning and doffing techniques [37], and vaccination against COVID-19. As the pandemic winds down, the focus now should be on leveraging lessons learned in this pandemic and conducting evidence-based research to guide our preparedness for the next pandemic.

**Author Contributions** EK co-wrote the manuscript and prepared tables and figures PO wrote the manuscript AGM summarized assigned articles for the manuscript. JZ summarized assigned articles for the manuscript. MR summarized assigned articles for the manuscript. NC summarized assigned articles for the manuscript. RS provided articles for the manuscript and edited the manuscript. RB summarized assigned articles for the manuscript. IA edited the manuscript. All authors reviewed the manuscript.

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## Declarations

**Competing Interests** The authors have no financial or personal competing interests.

**Ethical Approval** Not applicable.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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