doi: 10.7499/j.issn.1008-8830.2020.03.002

Consideration of the respiratory support strategy of severe acute respiratory failure caused by SARS-CoV-2 infection in children

Giuseppe A Marraro[1,2] Claudio Spada[1,2]

(1. Healthcare Accountability Lab, University of Milan, Milan, Italy; 2. Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian 362000, China)

Abstract: The recent ongoing outbreak of severe pneumonia associated with a novel coronavirus (SARS-CoV-2), currently of unknown origin, creates a world emergency that has put global public health institutions on high alert. At present there is limited clinical information of the SARS-CoV-2 and there is no specific treatment recommended, although technical guidances and suggestions have been developed and will continue to be updated as additional information becomes available. Preventive treatment has an important role to control and avoid the spread of severe respiratory disease, but often is difficult to obtain and sometimes cannot be effective to reduce the risk of deterioration of the underlining lung pathology. In order to define an effective and safe treatment for SARS-CoV-2-associated disease, we provide considerations on the actual treatments, on how to avoid complications and the undesirable side effects related to them and to select and apply earlier the most appropriate treatment. Approaching to treat severe respiratory disease in infants and children, the risks related to the development of atelectasis starting invasive or non-invasive ventilation support and the risk of oxygen toxicity must be taken into serious consideration. For an appropriate and effective approach to treat severe pediatric respiratory diseases, two main different strategies can be proposed according to the stage and severity of the patient conditions: patient in the initial phase and with non-severe lung pathology and patient with severe initial respiratory impairment and/or with delay in arrival to observation. The final outcome is strictly connected with the ability to apply an appropriate treatment early and to reduce all the complications that can arise during the intensive care admission. **[Chin J Contemp Pediatr, 2020, 22(3): 183-194]**

Key words: SARS-CoV-2; Severe acute respiratory failure; Pediatric acute respiratiry distress syndrome; Pneumonia; Ventilation; Child

The recent ongoing outbreak of severe pneumonia associated with a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), currently of unknown origin, creates a world emergency that has put global public health institutions on high alert.

In the past two decades other pathogens have been responsible for severe respiratory disease outbreaks (in 2002 - 2003 the severe acute respiratory syndrome coronavirus - SARS-CoV, and in 2012 the Middle East respiratory syndrome coronavirus - MERS-CoV), but SARS-CoV-2, although similar to some beta-corona-viruses, appears to have different characteristics from SARS-CoV and MERS-CoV[1-3].

The current SARS-CoV-2 infection, that causes coronavirus disease 2019 (COVID-19), seems to affect older people, especially if they suffer from other comorbidities, and involving also children, according to preliminary data so far available. The infection is characterized by severe and sometimes fatal respiratory failure, similar to acute respiratory distress syndrome (ARDS), rapidly evolving after initial fever

[Received] February 2, 2020; [Accepted] February 14, 2020
[Author Biography] Prof. Giuseppe A Marraro is a specialist in anesthesia and intensive care, neonatology, and pediatrics. Email: gmarraro@picu.it.

and cough. In most cases the syndrome resolves with common symptomatic treatments, but the most severe cases can require hospitalization in intensive and sub-intensive care units[4-6].

At present there is limited clinical information of the SARS-CoV-2 infection about the age of the most affected patients, animal source of the virus, incubation period, epidemic curve, viral kinetics, transmission route, pathogenesis, autopsy findings, response to existing antiviral drugs, specific treatment for the respiratory failure and severe pneumonia. Although currently there is no specific treatment recommended for SARS-CoV-2 infections, because many characteristics of the SARS-CoV-2 are unknown, uncertain or incomplete, important elements for the treatment of this severe respiratory syndrome are becoming clearer. Technical guidances and suggestions have been developed and will continue to be updated as additional information becomes available, essentially on how to prevent and control the spread of the epidemic[7-10].

Drawing on experience and evidence reported from the previous epidemics of SARS-CoV and MERS-CoV, it appears that the real efficacy of the applied treatment compared to the side effects connected with it has not been adequately investigated and reported so far.

Recent experiences and evidence on the treatment of severe lung diseases and pediatric acute respiratory distress syndrome (pARDS) in particular, provide some considerations on the actual treatments and how to avoid complications and the side effects related to them. This in order to define an effective treatment that could be helpful for a large number of patients, unfortunately in increasing numbers, affected by SARS-CoV-2[11-14].

1 Treatment outlines for severe pediatric respiratory disease

First of all two main considerations have to be point out.

(1) Avoid delay and apply earlier the most appropriate treatment.

(2) Minimize and control the side effects related to the treatments applied, particularly for the patients that apparently are at lower risk.

The delay in activating appropriate treatment (e.g. airway protection and artificial ventilation support) on the one hand clearly exposes to the risk of applying therapy too late, and on the other creates the need to employ more invasive methodologies and therapy for the treatment of complicated patients. Intensive treatments of patients with severe and well-established pathologies will be more invasive and therefore can negatively affect the outcome.

Approaching to treat severe respiratory disease in infants and children, the risks related to the development of atelectasis starting invasive or non-invasive ventilation (NIV) and the risk of oxygen toxicity must be taken into serious consideration.

The first lesson of atelectasis development comes from the induction of general anesthesia. Only few minutes after the induction of general anesthesia (after sedation and paralysis) atelectasis develops in dependent lung areas related to the positive pressure applied to introduce the gases into the lung (the dynamics of gas introduction completely changes in the lung compared to spontaneous breathing) and to the need for high O_2 concentration (FiO_2) to prevent hypoxemia during the intubation.

The desaturation that appears during surgery, without correlation with high FiO_2, is an undisputed sign that less ventilated areas develops in the dependent lung regions due to mechanical ventilation. These desaturations resolves with adequate manual recruitment maneuvers and with the application of post-recruitment suitable positive end-expiratory pressure (PEEP) level[15-17].

Transferring this knowledge to patients artificially ventilated in intensive care, often deeply sedated and sometimes unfortunately paralyzed, immediate treatments useful to prevent this complication (dependent atelectasis) must be considered. The question that must be posed is: “are

the appearance of a deterioration of the underlying lung disease after 24 hours of artificial ventilation linked to the worsening of the disease or are induced by inappropriate treatment?" This involves doctors, nurses and all healthcare professionals who participate in patient care and cure.

Special consideration should be paid to the appropriate use of O_2 not strictly controlled, as more and more evidences are reporting not only on its sure benefit but also the side effects that may arise from not controlled use. Oxygen, like any other drugs, should only be administered when specifically indicated, and at the appropriate concentration as its unmonitored and unrestricted use can be potentially harmful.

Definite treatment guidelines have been laid down and updated by the British Thoracic Society (BTS), which recommends the use of O_2 as a drug in that it had to be specifically prescribed and continuously monitored. According to these guidelines, supplemental oxygen is indicated if oxygen saturation is <94%, or <88% in chronic lung diseases[18]. The literature to date recommends caution in oxygen supplementation because high oxygen levels might lead to production of oxygen free radicals, and exposes to cytotoxic and functional risks all body organs. The harmful effects of excessive oxygen therapy have been clearly described in chronic obstructive pulmonary disease, obesity hyperventilation syndrome and myocardial infarction[19-21].

Severe hypoxemia should be treated promptly with high FiO_2 but the oxygen concentration must be decreased as soon as possible to avoid the risk of hyperoxia. It appears reasonable to aim peripheral oxygen saturation of 94% to 98%, particularly as soon as clinical condition of the patient is improved. Despite this knowledge, there has been unrestricted use of O_2 therapy over the last few years, and it is still controversial[22].

In most hospitals, and particularly in the Emergency Department, specific guidelines for the therapeutic use of O_2 are not followed. In these context, the lack of strict adherence to the guidelines is probably due to an over cautious approach to prevent hypoxia.

Among the complications of inappropriate use of oxygen, the damage to the lung surfactant generally is under evaluated. The surfactant deficiency causes an instability of the alveolar surface and favors the atelectasis. Atelectasis and pneumonia are consequential and well described in the literature from long time[23-25].

Other concerns derive about the use of dry and cold oxygen and its complications: development of consolidated secretions that are difficult to eliminate with cough; dry secretions that occlude the terminal bronchioles and favor atelectasis; cold and dry gases that damage the mucous membrane of the airways, accentuating the sensation of dryness not only of the upper airways but also of the trachea and bronchi (sensation of retrosternal pain).

High FiO_2 produces free oxygen radicals which causes direct damage to the lung and favors the release of inflammation mediators which can lead to multi-organ failure[26].

The exact level of risk limit of oxygen toxicity is unknown because it is impossible to carry out studies on healthy humans for ethical reasons, but the evidences are clear with respect to the harmfulness of high oxygen concentrations which play a decisive role in the appearance of retinopathy of prematurity, respiratory distress syndrome and bronchopulmonary dysplasia (BPD) of the premature infant. The existing literature suggests an appropriate use to improve saturation by accepting SpO_2 limits of 92%-94% to reduce the risks connected to the concentration of O_2. Unfortunately, everything is left to the personal interpretation of existing data and to the good sense of the operator who sometimes "navigates a sea of uncertainty", leaning towards the use of higher concentrations for safety reasons, underestimating the risk to which exposes the patient.

The ventilator supports to be applied, including the increasing doses of O_2, must be implemented in logic and consequent progression by carefully evaluating the real need of the patient (improvement of oxygenation? improvement of ventilation?) and the

pros and cons of the treatment to be applied.

Essentially, the approach must assess whether the child needs additional oxygen, or if her/his work of breathing (WOB) has become excessive and unsustainable. In this case the patient has clear signs of fatigue (activation of the accessory respiratory muscles, high respiratory rate, irregularity of the respiratory rhythm, etc.). At this point ventilatory support must be applied instead of increasing the FiO_2. A positive example is provided by the application of nasal continuous positive airway pressure (nCPAP) in the newborn. Its application not only normalizes breathing and reduces the need for intubation, but also significantly reduces the need for high doses of oxygen to obtain a normal level of oxygenation[27-30].

2 Clinical approach to severe pediatric respiratory disease

2.1 NIV

The NIV support has precise indications for its use, often not carefully evaluated and followed, and appropriate starting time for its application. These indications define the pulmonary pathologies that can be treated: mild respiratory failure (PaO_2/FiO_2 200-300) and in some cases initial conditions of moderate respiratory failure (PaO_2/FiO_2 150-200) in patients who have not high WOB. The device used as patient-ventilator interface (face-masks must be adequate and comfortable) and the ventilator setting play an important role in its effectiveness. The effective use of NIV must be assessed as avoidance of intubation and intensive care unit (ICU) survival at least within 24 hours. Close monitoring after 1 hour of NIV, heart rate, PaO_2/FiO_2 and bicarbonate, is required since are independently predictive of NIV failure[31-32].

The initial failure is well defined by the various protocols and no hesitation or delay must be posed to move on more invasive approach[33-37].

Earlier treatment is fundamental because the ventilatory support can be less invasive and the lung pathology is not consolidated and/or complicated, therefore easier to treat.

The patient's collaboration (which in the early pediatric age may not be easy to obtain especially if the patient is hypoxic and/or hypercapnic) and the role of nursing play a fundamental role in the NIV success. The patient in non-invasive ventilation needs careful monitoring and continuous human assistance more than the intubated and ventilated patient.

In summary, NIV treatment requires:

(1) Appropriateness and timeliness of the start of treatment;

(2) Adequate interface (e.g. facial or nasal mask, nasal prongs, etc.);

(3) Adequate ventilation setting;

(4) Careful and alert nursing.

2.2 Invasive ventilatory support

To apply invasive ventilatory support, two basic critical considerations must be pointed:

(1) Timing of the application. It is advisable to avoid any delay because the pathology can be easily worsening;

(2) Choice of the most appropriate and effective ventilatory strategy for the specific patient.

Significant heterogeneity exists between individual intensive care units on the ventilation model to be applied. In the investigation carried out by Jabaley et al[38], assist/control ventilation was the most commonly recorded mode (51%), followed by adaptive support ventilation (23.1%). Volume-controlled modes were about twice as common as pressure-controlled modes (64.4% vs 35.6%). Very few units heightened utilization of high frequency oscillatory ventilation (HFOV) and synchronized intermittent mandatory ventilation (SIMV).

The 2017 Cochrane review reported that infants ventilated using volume-targeted ventilation (VTV) had reduced rates of death, BPD, pneumothorax, hypocarbia, severe cranial pathologies and duration of ventilation. Probably VTV modes also improve neurodevelopmental outcomes[39].

The main advantage of the volume-controlled ventilation (VCV) is the delivery of stable tidal

volume. To avoid the high peak inspiratory pressure (PIP) low tidal volume strategy is needed. VCV favors the redistribution of gases in the lung during the pause at the end of inspiration in steady flow condition. Prolonging the end inspiratory pause, the redistribution of lung gases can be promoted in areas that need more time to be reopened.

The disadvantages of pressure-controlled ventilation (PCV) are due to the variability and instability of the tidal volume when lung resistance and compliance change - i.e. before and after aspiration of secretions; asthma attack. Its stable pressure curve between the end of inspiration and the beginning of expiration preferentially can favor the diffusion of gases in the better ventilated areas, without any benefit for the consolidated areas.

SIMV often used in the initial acute phase of treatment can result in a greater risk of BPD, duration of ventilation and mortality[40].

SIMV should preferably be used for weaning from ventilator, because it can allow the transition from totally controlled ventilation to progressive increase of spontaneous breathing. Spontaneous breaths can be supported by adequate pressure support delivered by ventilator so that the overall result of spontaneous and controlled breaths are similar to those of the patient in normal conditions. The increase in respiratory rate during mixed (controlled and spontaneous breathing) ventilation increases the WOB, oxygen consumption, and predisposes to respiratory fatigue.

The other ventilation methods, some of which are not yet clearly evidence-base, should be considered only if properly applied conventional ventilation models fail[13].

Based on current evidence and updated specific knowledge, HFOV and extra corporeal membrane oxygenation (ECMO), proposed for the treatment of severe ARDS not improved with conventional ventilation methods, have the following limitations.

Elective HFOV compared with conventional mechanical ventilation results in a small reduction in risk of chronic lung disease, but evidence is weak, and this benefit could be counteracted by an increased risk of acute air leak (pneumothorax). Adverse effects on short-term neurological outcomes have been observed in some studies[41].

There are no data from randomized controlled trials supporting the use of rescue HFOV in term or near term infants with severe pulmonary dysfunction[42].

Initial success of ECMO in neonates has led to application in patients of all ages with respiratory and/or cardiac failure. Over time the population of neonates and infants requiring ECMO has changed significantly, leading to longer run times, higher mortality rates, and more long-term sequelae in survivors[43]. The use of inhaled nitric oxide in pulmonary hypertension, surfactant replacement, and high frequency ventilation decreased the need for the highly invasive therapy of ECMO. ECMO still remains a rescue therapy for pulmonary hypertension and congenital diaphragmatic hernia in all pediatric ages[44-45].

3 Respiratory support strategy for SARS-CoV-2-associated respiratory diseases

3.1 Patient in the initial phase and without severe lung pathology

In the patients in the initial phase and with non-severe lung pathology it is fundamental to carefully evaluate if the respiratory failure is related to oxygenation or ventilation. In many cases both conditions are affected. Appropriate evaluation of WOB can help to evaluate if the improvement of gas exchange can be obtained increasing only FiO_2 or if is necessary to apply a ventilation support. In case that increase of FiO_2 is appropriate it is necessary to remember:

(1) Oxygen must be supplemented with extreme caution, taking into account both advantages and disadvantages of its use. O_2 must be administered adequately humidified and heated, especially at

concentrations above 3-4 L/min, using effective humidifiers / heaters.

(2) Most of the high flow systems have the disadvantage of using high oxygen concentration exposing to the risk of O_2 toxicity, and insufficient humidification and warming of the ventilated gases. High gas flow passing through the humidifiers does not receive sufficient humidification and heating. The connecting circuit from the humidifier to the patient is generally too long and favors a further loss of heat and humidification before gases reach the lung. The resulting complications have been clearly illustrated above.

(3) Minimize the invasiveness of central vascular accesses and bladder catheterization, reserving them only for cases where they are really useful and necessary.

(4) Promote active and passive respiratory physiotherapy, avoiding the supine decubitus in an obligatory position in the bed.

An adequate and correct control of hydration plays an important role in fluid balance in critically ill children. It has been demonstrated that the over-infusion of the patient with sepsis is at the origin of the development of ARDS. The same can be assumed in infants and children with respiratory failure[46].

3.2 Patient with severe respiratory failure

It is necessary to evaluate immediately if there are the clinical conditions to apply non-invasive ventilation. NIV must be applied only if there are clear indications. The attempt to apply NIV in cases not frankly indicated wastes precious time in the application of more appropriate treatment. The delay, on the one hand favors the worsening of the underlying lung pathology, on the other determines the need to apply more invasive methods more prone to complications and side effects that can compromise the final outcome.

Critically ill infants and children must be managed considering the following critical implications:

(1) Define a priori the correct indications for the early intubation and mechanical ventilation. Invasive ventilation can fail because it is applied too late when respiratory pathology is no longer treatable[29].

(2) Safe, rapid and non traumatic intubation must be performed by skilled operator, and ventilation model to use must be suitable for the specific patient and the stage of the lung disease to be treated.

(3) Set PEEP level to reduce FiO_2 and keep alveoli and terminal bronchioles continuously open. The role of PEEP is fundamental during the first 3 years of life for the anatomical characteristics of the airways. PEEP in this age group keeps the terminal bronchioles continuously open, avoids the high closing volume and reduces the pressures necessary to introduce the gas into the alveoli.

A higher level of PEEP must be applied after lung recruitment to keep the recruited lung areas open. In case of consolidated lung pathology PEEP setting became more challenging and the efficacy is limited. Hemodynamic involvement can occur if high PEEP level is applied to not severely compromised lung and in hypovolemic patients[13,47].

(4) Sedation has to be minimized to reduce the discomfort related to the invasive maneuvers - i.e. bronchial suctioning and painful maneuvers- and muscles paralysis must be avoided, bearing in mind the appearance of immediate complications (atelectasis) described in patients undergoing general anesthesia.

(5) Low tidal volume strategy allowed to improve survival in ARDS and is largely suggested in pARDS and in severe respiratory failure. This strategy in pediatric age poses two problems that can create difficulty in its application: use of uncuffed tubes and acceptable level of tidal volume to avoid the risk of ventilating only the dead space.

Using uncuffed tubes the exhaled tidal volume is more useful instead of the inspiratory tidal volume to evaluate the quantity of gas that reaches the alveoli. The exhaled tidal volume expresses the real quantity of air that reaches the lungs and comes out.

Moderate tidal volume (7-8 mL/kg) can be

useful to compensate for the large dead space created if excessively long endotracheal tube and ventilator circuit are used[48]. An appropriate evaluation of the acceptable level of tidal volume must be done by placing the patient in SIMV and evaluating the minute volume that she/he ventilates. The minute volume obtained divided by the prefixed tidal volume gives the optimal respiratory rate for the specific patient.

(6) Prone position of short duration, no more than 1-2 hours three or four times a day, can be applied from starting invasive ventilation. Prone position allows the recruitment of the dependent lung areas that immediately lead to atelectasis[49]. This position can reduce the risk of barotrauma related to the need to apply manual recruitment maneuvers or increase tidal volume to improve ventilation.

While the 12-hour duration of the prone-position is suggested for the consolidated dependent lung areas of the patient treated for several days with artificial ventilation, the duration of 1 or 2 hours maximum allows to recruit lung areas recently atelectasis by all types of applied ventilation mode, as clearly demonstrated and discussed above[15-17]. When the dependent lung areas have been consolidated, the short duration of the prone position is insufficient to recruit the closed lung areas. In this case the effectiveness of the prone-position is enhanced if, immediately after placing the patient in prone-position, manual recruitment maneuvers are performed or the tidal volume is periodically increased as in "sigh ventilation" mode[50-51]. This distinction between already consolidated and recently atelectasis lung dependent areas, as criteria to define the duration of prone-position, is old-time acquired knowledge that should be considered by those who mechanically ventilate patients[52-53].

The chest X-ray is insufficient to highlight the presence of depending lung atelectasis since the chest image shows the non-dependent part of the lung which is over-distended and better ventilated. Only the CT scan highlights the real condition of the lung and the efficacy of the treatment applied. Unfortunately CT scan cannot be easily done both for the complexity to mobilize the patient and for logistical problems.

(7) Extubation should be anticipated as soon as the patient is stable and the lung pathology improves without unnecessary delay. Ventilated patient is exposed to the risk of ventilation associated pneumonia (VAP), which generally occurs 3-4 days after the start of the ventilation support, of barotrauma and to the negative effects of inappropriate bronchosuction. The weaning must be continued without accelerating the disconnection from the respiratory support. The earlier suspension of respiratory support exposes to the risk of a reintubation, which may not be easy to perform, and to deterioration of the respiratory pathology[54-56].

(8) Nursing plays an important role for these patients. Careful control of the infusion pathways and the quantity and quality of administered fluids are an integral part of the support and can make the difference for the success of the treatment applied and final outcome[48].

(9) The management of the cuff and the bronchosuctioning play a fundamental role in reducing the complications and improve the outcome. The over-distended cuff of the endotracheal tube causes ischemia of the tracheal mucosa that can develop to granuloma resulting in necrosis and tracheal stenosis. The presence of secretions between the vocal cords and the cuff and below the cuff up to the tip of the tube, are difficult to remove with normal suction and are involved in the development of the VAP. The deflation of the cuff three times per day while the patient is connected to the ventilator, favors the elimination of the secretion towards the pharynx from where can be easily suctioned.

To perform a safe, accurate and atraumatic removal of the secretions it is necessary to keep them fluid with appropriate humidification and heating of the ventilated gases, and mobilized by means of physiotherapy towards the trachea from where they must be removed.

(10) Invasive bronchoscopic maneuvers must be reduced to the minimum because they are traumatic

to the trachea and bronchi. They must be carried out if strictly indicated and useful to clarify the diagnosis that is not possible to obtain with alternative non-invasive methods, and to evaluate additional possible treatments (i.e. surfactant supplementation, local application of drugs). Bronchoscopy can exposes not only to the risk of airway trauma, but also favors alveolar collapse due to negative aspiration pressure, the spread of localized pathology to the entire lung areas, and the mechanical removal of the pulmonary surfactant.

4 In summary

Preventive treatment has an important role to control and avoid the spread of severe respiratory disease in pediatrics. Prevention can be not easy to obtain and sometimes cannot be effective to reduce the risk of deterioration of the underlining lung pathology, because preventive measures can fail for reasons difficult to identify.

The appropriate clinical treatment must carefully considers from the initial approach to the patient, both the benefits that may follow appropriate therapy to maximized it, and the risks related to the side effects that the applied treatment can cause aiming to minimize them.

The final outcome is strictly connected with the ability to apply earlier appropriate treatment and to reduce the complications that can arise during the intensive care treatment.

The authors have no competing interests to disclose.

[References]

[1] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019[J]. N Engl J Med, 2020, 382(8): 727-733.

[2] World Health Organization. Coronavirus disease (COVID-19) technical guidance[EB/OL]. [February 14, 2020]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance.

[3] World Health Organization. Coronavirus disease (COVID-2019) situation reports[EB/OL]. [February 14, 2020]. www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.

[4] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China[J]. Lancet, 2020, 395(10223): 497-506.

[5] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study[J]. Lancet, 2020, 395 (10223): 507-513.

[6] Cai JH, Wang XS, Ge YL, et al. Shanghai's first child with a new coronavirus infection[J]. Chin J Pediatr (中华儿科杂志), 2020, 58(2): 86-87.

[7] Horton R. Offline: 2019-nCoV outbreak - early lessons[J]. Lancet, 2020, 395(10221): 322.

[8] McIntosh K. Coronaviruses[EB/OL]. [February 14, 2020]. www.uptodate.com/contents/coronaviruses.

[9] Working Group for the Prevention and Control of Neonatal 2019-nCoV Infection in the Perinatal Period of the Editorial Committee of Chinese Journal of Contemporary Pediatrics. Perinatal and neonatal management plan for prevention and control of 2019 novel coronavirus infection (1st Edition)[J]. Chin J Contemp Pediatr (中国当代儿科杂志), 2020, 22(2): 87-90.

[10] Pediatric Branch of Hubei Medical Association, Pediatric Branch of Wuhan Medical Association, Pediatric Medical Quality Control Center of Hubei. Recommendation for the diagnosis and treatment of novel coronavirus infection in children in Hubei (Trial version 1)[J]. Chin J Contemp Pediatr (中国当代儿科杂志), 2020, 22(2): 96-99.

[11] Marraro GA, Chen C, Piga MA, et al. Acute respiratory distress syndrome in the pediatric age: an update on advanced treatment[J]. Chin J Contemp Pediatr (中国当代儿科杂志), 2014, 16(5): 437-447.

[12] Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference[J]. Pediatr Crit Care Med, 2015, 16(5): 428-439.

[13] Kneyber MCJ, de Luca D, Calderini E, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC)[J]. Intensive Care Med, 2017, 43(12): 1764-1780.

[14] Marraro G. Ventilation support of infants and children in special clinical contexts[M]//Marraro G. Ventilation Support in Neonates, Infants and Children. Mumbai, India: The National Book Depot, 2019: 312-340.

[15] Hedenstierna G. Atelectasis and its prevention during anaesthesia[J] . Eur J Anaesthesiol, 1998, 15(4): 387-390.

[16] Serafini G, Cornara G, Cavalloro F, et al. Pulmonary atelectasis during paediatric anaesthesia: CT scan evaluation and effect of positive endexpiratory pressure (PEEP)[J]. Paediatr Anaesth, 1999, 9(3): 225-228.

[17] Hedenstierna G. Alveolar collapse and closure of airways: regular effects of anaesthesia[J]. Clin Physiol Funct Imaging, 2003, 23(3): 123-129.

[18] O'Driscoll BR, Howard LS, Earis J, et al. British Thoracic

Society Guideline for oxygen use in adults in healthcare and emergency settings[J]. BMJ Open Respir Res, 2017, 4(1): e000170.

[19] dos Santos CC, Slutsky AS. The contribution of biophysical lung injury to the development of biotrauma[J]. Annu Rev Physiol, 2006, 68: 585-618.

[20] Cornet AD, Kooter AJ, Peters MJ, et al. The potential harm of oxygen therapy in medical emergencies[J]. Crit Care, 2013, 1817(2): 313.

[21] Pierson DJ. Oxygen in respiratory care: a personal perspective from 40 years in the field[J]. Respir Care, 2013, 58(1): 196-204.

[22] Sieber R, Osterwalder J. Treatment algorithm reduces oxygen use in the Emergency Department[J]. Eur J Emerg Med, 2016, 23(2): 114-118.

[23] Warner DO. Preventing postoperative pulmonary complications: the role of the anesthesiologist[J]. Anesthesiology, 2000, 92(5): 1467-1472.

[24] Nakos G, Tsangaris H, Liokatis S, et al. Ventilator-associated pneumonia and atelectasis: evaluation through bronchoalveolar lavage fluid analysis[J]. Intensive Care Med, 2003, 29(4): 555-563.

[25] Tsangaris H, Lekka M, Nakos G. Should we start considering surfactant for atelectasis?[J]. Am J Respir Crit Care Med, 2005, 172(1): 141-142.

[26] Plötz FB, Slutsky AS, van Vught AJ, et al. Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses[J]. Intensive Care Med, 2004, 30(10): 1865-1872.

[27] Narendran V, Donovan EF, Hoath SB, et al. Early bubble CPAP and outcomes in ELBW preterm infants[J]. J Perinatol, 2003, 23(3): 195-199.

[28] Buckmaster AG, Arnolda G, Wright IM, et al. Continuous positive airway pressure therapy for infants with respiratory distress in non tertiary care centers: a randomized, controlled trial[J]. Pediatrics, 2007, 120(3): 509-518.

[29] Marraro GA, Yu R, Liang Y, et al. Best clinical practice and evidence-based assessment in pediatric ventilation support[J]. Pediatr Crit Care Med, 2016, 17(11): 1097-1099.

[30] Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome - 2016 update[J]. Neonatology, 2017, 111(2): 107-125.

[31] Carrillo A, Gonzalez-Diaz G, Ferrer M, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure[J]. Intensive Care Med, 2012, 38(3): 458-466.

[32] Nicolini A, Tonveronachi E, Navalesi P, et al. Effectiveness and predictors of success of noninvasive ventilation during H1N1 pandemics: a multicenter study[J]. Minerva Anestesiol, 2012, 78(12): 1333-1340.

[33] Bernet V, Hug MI, Frey B. Predictive factors for the success of noninvasive mask ventilation in infants and children with acute respiratory failure[J]. Pediatr Crit Care Med, 2005, 6(6): 660-664.

[34] Nava S, Navalesi P, Conti G. Time of non-invasive ventilation[J]. Intensive Care Med, 2006, 32(3): 361-370.

[35] Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome[J]. Crit Care Med, 2007, 35(1): 18-25.

[36] Yoshida Y, Takeda S, Akada S, et al. Factors predicting successful noninvasive ventilation in acute lung injury[J]. J Anesth, 2008, 22(3): 201-206.

[37] Abadesso C, Nunes P, Silvestre C, et al. Non-invasive ventilation in acute respiratory failure in children[J]. Pediatr Rep, 2012, 4(2): e16.

[38] Jabaley CS, Groff RF, Sharifpour M, et al. Modes of mechanical ventilation vary between hospitals and intensive care units within a university healthcare system: a retrospective observational study[J]. BMC Res Notes, 2018, 11(1): 425.

[39] Klingenberg C, Wheeler KI, McCallion et al. Volume-targeted versus pressure-limited ventilation in neonates[J]. Cochrane Database Syst Rev, 2017, 10(10): CD003666.

[40] Greenough A, Rossor TE, Sundaresan A, et al. Synchronized mechanical ventilation for respiratory support in newborn infants[J]. Cochrane Database Syst Rev, 2016, 9(9): CD000456.

[41] Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants[J]. Cochrane Database Syst Rev, 2015(3): CD000104.

[42] Henderson-Smart DJ, De Paoli AG, Clark RH, et al. High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term[J]. Cochrane Database Syst Rev, 2009(3): CD002974.

[43] Fletcher K, Chapman R, Keene S. An overview of medical ECMO for neonates[J]. Semin Perinatol, 2018, 42(2): 68-79.

[44] Maslach-Hubbard A, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: history, development and current status[J]. World J Crit Care Med, 2013, 2(4): 29-39.

[45] Prine KB, Goracke K, Rubarth LB. Extracorporeal membrane oxygenation in the NICU[J]. Neonatal Netw, 2015, 34(3): 183-188.

[46] Marraro GA, Genovese U, Spada C, et al. Can the treatment approach of sepsis with balanced crystalloid fluids translate into therapy for acute respiratory distress syndrome if considered as "lung-limited sepsis"?[J]. Crit Care Med, 2017, 45(7): 1246-1248.

[47] Koopman AA, Kneyber MCJ. Setting positive end-expiratory pressure in pediatric acute respiratory distress syndrome: cookbook or individualized titration?[J]. Am J Respir Crit Care Med, 2018, 198(6): 822-823.

[48] Marraro G. Mechanical ventilation support[M]//Marraro G. Ventilation Support in Neonates, Infants and Children. Mumbai, India: The National Book Depot, 2019: 83-88.

[49] Curley MA, Thompson JE, Arnold JH. The effects of early and repeated prone positioning in pediatric patients with acute lung injury[J]. Chest, 2000, 118(1): 156-163.

[50] Marraro GA. Protective lung strategies during artificial ventilation in children[J]. Paediatr Anaesth, 2005, 15(8): 630-637.

[51] Moraes L, Santos CL, Santos RS, et al. Effects of sigh during pressure control and pressure support ventilation in pulmonary and extrapulmonary mild acute lung injury[J]. Crit Care, 2014, 18(4): 474.

[52] Douglas WW, Rehder K, Beynen FM, et al. Improved

oxygenation in patients with acute respiratory failure: the prone position[J]. Am Rev Respir Dis, 1977, 115(4): 559-566.
[53] Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury[J]. Am J Respir Crit Care Med, 1998, 157(2): 387-393.
[54] Mayordomo-Colunga J, Medina A, Rey C, et al. Non invasive ventilation after extubation in paediatric patients: a preliminary study[J]. BMC Pediatr, 2010, 10: 29.
[55] Gupta P, Kuperstock JE, Hashmi S, et al. Efficacy and predictors of success of noninvasive ventilation for prevention of extubation failure in critically ill children with heart disease[J]. Pediatr Cardiol, 2013, 34(4): 964-977.
[56] Fedor KL. Noninvasive respiratory support in infants and children[J]. Respir Care, 2017, 62(6): 699-717.

The following is the Chinese translation of this paper, translated by associated professor WANG Xia, PICU of Xiangya Hospital, CSU.

以下是本文的中文摘译。

新型冠状病毒肺炎儿童重症急性呼吸衰竭的呼吸支持策略建议

最近，一种新型冠状病毒（命名为 SARS-CoV-2）引起的重症肺炎在中国暴发流行，造成了一场全球公共卫生机构高度戒备的紧急状态。SARS-CoV-2 感染的特点是在最初的发热和咳嗽后迅速演变成严重甚至致命的呼吸衰竭，类似于急性呼吸窘迫综合征（ARDS）。在大多数情况下，可以通过常规的对症治疗痊愈，但严重者要入住重症监护病房（ICU），这类患者病死率很高 [4-6]。

目前关于 SARS-CoV-2 感染的临床资料有限。对于 SARS-CoV-2 病毒肺炎儿童急性呼吸衰竭的呼吸支持策略，我们根据以往 SARS 冠状病毒（SARS-CoV）和中东呼吸系统综合征冠状病毒（MERS-CoV）的经验，特别是近年来在重症肺部疾病和儿童 ARDS 治疗方面的经验和证据，提出以下建议。

1 儿科重症呼吸系统疾病的治疗原则

儿科重症呼吸系统疾病治疗的两个原则包括：（1）避免延误，及早采用最适当的呼吸支持方法；（2）使呼吸支持的副作用（肺不张及氧毒性）降到最低。

在治疗婴幼儿重症呼吸系统疾病时，需要考虑有创或无创通气支持引起肺不张及氧中毒的风险。使用镇静和肌松药会导致肺不张的发生，需考虑“机械通气 24 h 后，肺部病变恶化是与疾病本身恶化有关，还是由不适当的治疗引起”。

严格控制氧气的使用。英国胸科协会（BTS）建议将氧气作为药物使用，氧饱和度 <94% 或慢性肺部疾病者 <88% 时需要补充氧气 [18]。高氧可能导致氧自由基的产生，过度氧疗对慢性阻塞性肺疾病、肥胖换气过度综合征和心肌梗死等疾病有不良的影响 [19-21]。严重的低氧血症应及时用高 FiO_2 处理，但必须尽快降低氧浓度，当患者病情稳定时，以 94%~98% 的外周血氧饱和度（SpO_2）为目标是合理的。不适当使用氧气可导致肺表面活性物质缺乏而致肺泡塌陷和肺不张 [23-25]。干冷的氧气还会导致干性分泌物形成，阻塞细支气管导致肺不张，还会损害呼吸道黏膜，造成上呼吸道、气管和支气管的干燥感（胸骨后疼痛感）。

高浓度氧疗产生的氧自由基会对肺造成直接损伤，促进炎症介质的释放，从而导致多器官功能衰竭 [26]。有证据表明高浓度氧气在早产儿视网膜病变、呼吸窘迫综合征和早产儿支气管肺发育不良（BPD）的发生中起决定性作用。现有的文献建议限制 SpO_2 在 92%~94% 以降低与高浓度氧相关的风险。

必须仔细评估患儿的实际需要，是需要改善氧合还是改善通气，以及呼吸支持治疗的利弊。如果患儿的呼吸功过度增加，如明显的呼吸肌疲劳迹象（辅助呼吸肌运动、呼吸频率高、呼吸节律不规律等），此时需要应用通气支持而不是增加 FiO_2。经鼻持续正压通气在新生儿中的应用就是一个很好的例子。它的应用不仅使患儿呼吸正常，减少了气管插管的需要，而且显著减少了为获得正常氧合水平而使用高浓度氧的几率 [27-30]。

2 儿科重症呼吸系统疾病的呼吸支持方法

2.1 无创辅助通气

无创辅助通气的适应证：用于轻度呼吸衰竭（PaO_2/FiO_2 200~300）和呼吸功没有增加的中度呼吸衰竭（PaO_2/FiO_2 150~200）的初始治疗。

患儿 – 呼吸机接口的设备（口罩须合适、舒适）和呼吸机参数的设置对治疗效果起重要作用。

无创辅助通气治疗的原则是尽早使用，因为疾病早期侵入性更小，肺部病变还处于可逆阶段。若无

创辅助通气实施后 24 h 内避免了气管插管，并在 ICU 内存活说明治疗有效。此外，需在给予无创辅助通气后 1 h 密切监测心率、PaO_2/FiO_2 和碳酸氢盐的变化（这些指标能独立预测无创辅助通气治疗是否失败）以评估治疗是否有效 [31-32]。如无效，应及时改为有创辅助通气支持 [33-37]。

无创辅助通气治疗需注意以下几点：（1）及时、合理地启动该治疗；（2）选用合适的面罩或鼻塞；（3）参数设置要充分有效；（4）敏锐的观察、细致的护理是治疗成功的基础。

2.2 有创通气支持

有创通气支持的两个关键因素：（1）避免延误，因为肺部病变很容易恶化；（2）为特定患者选择最合适和有效的通气策略。

在所应用的通气模式上，各 ICU 之间存在差异。Jabaley 等 [38] 进行的调查研究显示，辅助 / 控制通气是所调查 ICU 中最常使用的模式（51%），其次是适应性支持通气模式（23.1%）；容量控制模式大约是压力控制模式的两倍（64.4% vs 35.6%）；较少 ICU 使用高频振荡通气和同步间歇指令通气模式。

2017 年 Cochrane 综述报告显示，容量目标通气可降低婴儿的病死率、机械通气时间及 BPD、气胸、低碳酸血症、严重颅脑病变的发生率，而且这种通气模式也许能改善神经发育结局 [39]。

容量控制通气的主要优点是提供稳定的潮气量，但高吸气峰压需要使用小潮气量低通气，该通气模式有利于吸气末停顿时肺内气体的再分布。延长吸气末停顿时间，可以促进肺复张。

压力控制通气的缺点主要是当肺阻力和顺应性改变时，潮气量会发生变化，如气管内吸痰以及哮喘发作时。其吸气结束与呼气开始之间的压力曲线稳定，有利于气体在通气较好的区域内扩散。

同步间歇指令通气常用于急性期初始治疗，可导致发生 BPD 的风险增加、通气时间延长和病死率的增加 [40]。

同步间歇指令通气这种模式最好在准备脱离呼吸机时使用。通过呼吸机提供足够的压力支持，可以支持自主呼吸，使自主呼吸和控制呼吸的总体效果接近特定儿童的正常呼吸频率。混合通气（控制呼吸和自主呼吸）时呼吸频率的增加会导致呼吸功和耗氧量增加，从而导致呼吸肌疲劳。

其他通气模式只有在常规通气失败的情况下才考虑 [13]。基于现有的证据和最新的知识，高频振荡通气和体外膜氧合（ECMO）常被用于治疗传统通气方法不能改善的重症 ARDS，其局限性如下。

选择性高频振荡通气与常规机械通气相比，可使慢性肺疾病的风险降低，但目前证据不足。选择性高频振荡通气发生气胸的风险可能增加，会抵消这一益处。在一些研究中观察到对短期神经结局的不良影响 [41]。没有随机对照试验的数据支持在有严重肺功能障碍的足月或近足月婴儿中使用高频振荡通气进行抢救性治疗 [42]。

ECMO 在新生儿应用中的初步成功导致了其在所有年龄患者呼吸和 / 或心脏衰竭中的应用。随着时间的推移，需要 ECMO 的新生儿和婴儿的数量发生了显著的变化，导致了更长的运行时间、更高的病死率和更多的幸存者的远期后遗症 [43]。

吸入性一氧化氮在肺动脉高压中的应用、表面活性剂替代治疗和高频通气的应用降低了对 ECMO 这种高侵入性治疗的需要。目前 ECMO 仍然是所有年龄阶段儿童肺动脉高压和先天性膈疝的一种挽救性治疗 [44-45]。

3 SARS-CoV-2 相关的呼吸道疾病的呼吸治疗策略建议

3.1 疾病初期和肺部病变不严重的患儿

对于疾病初期和肺部病变不严重的患儿，首先需仔细评估呼吸衰竭是与氧合有关还是与通气有关。在多数情况下，与二者都相关。需要正确评估呼吸功的增加，有助于明确是否仅通过提高 FiO_2 或需要采用通气支持才能改善气体交换。需要注意以下几点：

（1）氧疗需非常谨慎，需要权衡使用氧气的利弊。氧气必须使用有效的加湿器 / 加热器充分加湿和加热，尤其是氧流量在 3~4 L/min 以上时。

（2）目前使用的多数高流量吸氧的缺点是：①高浓度氧的氧毒性；②气体的加湿和升温不足。

（3）尽量减少中心血管置管和膀胱置管。

（4）提倡主动和被动呼吸理疗，避免长期卧床。

（5）危重症儿童需适当控制液体摄入。脓毒症患者的过度输液是 ARDS 发生的根源 [46]。

3.2 重症呼吸衰竭的患儿

对于重症呼吸衰竭的患儿，应用无创通气时必须及时评估患儿的临床情况。只有当患儿有绝对的无

创通气指征时，才可以使用。在没有明确指征的情况下尝试无创通气是在浪费宝贵的抢救时机。这种延迟，一方面促进肺部病变恶化，另一方面也决定了需要采用更高级别侵入性的治疗，更容易出现并发症和副作用，危及最终转归。需要注意以下几点：

（1）预先确定早期插管和机械通气的适应证。当肺部病变无法治疗时，太迟使用有创通气可能导致治疗失败[29]。

（2）气管插管需要安全、快速、非创伤性，必须由熟练的操作人员进行，通气模式的选择必须根据患者的具体情况和肺部的病变情况来决定。

（3）设置与 FiO_2 配套的呼气末正压（PEEP），保持肺泡和终末支气管持续开放。对于 <3 岁的患儿，必须设置 PEEP，以使终末支气管持续开放，避免肺泡塌陷。肺复张后必须应用正确的 PEEP，以保持复张的肺区域开放。值得注意的是，在合并肺部病变的情况下，PEEP 设置变得更具挑战性，且疗效有限。在肺损害不严重和低血容量患儿使用高 PEEP 可能出现血流动力学不稳定[13,47]。

（4）镇静必须减少到最低限度，避免使用肌松药，以减少肺不张的发生。

（5）低潮气量策略可提高 ARDS 的存活率，在儿童 ARDS 和重症呼吸衰竭的患儿中也有广泛的应用。但这一策略在儿童患者中的应用存在两个问题，可能造成应用困难：使用无气囊的气管插管和选用的潮气量需避免死腔通气。使用无气囊的气管插管时根据呼气潮气量评估到达肺泡的实际气体量是更有效的。呼出的潮气量表示到达肺部并呼出的实际空气量。

如果使用过长的呼吸机回路，中等潮气量（7~8 mL/kg）可以有效地补偿气管内插管导致大的死腔通气[48]。评估可接受的潮气量水平时，需在患儿使用同步间歇指令通气模式时评估其分钟通气量来进行适当的计算，获得的分钟通气量必须除以预先设定的潮气量。

（6）在有创通气开始，就可应用短时间的俯卧位，每次不超过 1~2 h，每天可数次。俯卧体位有利于肺复张[49]。当采用人工通气或增加潮气量时，这个体位可降低气压伤的风险。而对于呼吸机辅助通气数天后出现肺不张的患儿，则建议使用 12 h 的俯卧位[15-17]。此时，短时间的俯卧位不能有效促进肺复张，需要在刚刚俯卧过来时给予人工通气或定期给予叹气通气模式来增加潮气量促进肺复张[50-51]。机械通气过程中依赖性肺不张出现时间的长短是决定使用俯卧位时间长短的依据[52-53]。

（7）胸部 X 线片不足以明显显示依赖性肺不张的存在，因为胸片一般对肺过度膨胀和通气良好的非依赖性部分显示更好。只有 CT 扫描可显示肺的真实情况和治疗效果。但由于危重病人转运风险大，CT 扫描不容易进行。

（8）一旦病情稳定，肺部病变改善，则应尽早拔管，以避免呼吸机相关性肺炎（通常发生在机械通气后 3~4 d）和气压伤的风险，不适当的气管内吸痰也会对病情不利。撤机过程不要太急，过早地暂停呼吸支持会有再插管的风险，还可使正在改善的肺部病变再次恶化[54-56]。

护理很重要。正确采用液体输注途径，控制输注液体的量和质量是支持治疗的一个组成部分，影响治疗的成功和最终转归[48]。

气管导管上的气囊和支气管抽吸的处理对减少并发症和改善预后有重要作用。气囊过度充盈会导致气管黏膜缺血，进而发展为肉芽肿，导致坏死和气管狭窄。支气管镜检查不仅存在气道损伤的风险，而且由于负压误吸、局部病变扩散至整个肺区、机械清除肺表面活性物质等，容易导致肺泡塌陷，应最大限度地减少侵入性支气管镜操作，仅在有严格的指征时应用。

4　总结

正确的呼吸支持策略需要对患儿的病情进行仔细评估，既要考虑到呼吸支持手段可能带来的最大益处，也要考虑其副作用，从而将其最小化。患儿最终转归与早期正确的呼吸支持和减少在 ICU 住院期间可能出现的并发症的策略密切相关。

（翻译：王霞，中南大学湘雅医院儿科 PICU）

（本文编辑：邓芳明）