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

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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.

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

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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 disease syndrome (ARDS), rapidly evolving after initial fever 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, appears that the real efficacy of the applied treatment compared to the side effects connected with them have 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 Non-invasive ventilation

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, 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 fails because 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 consider 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.