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Commentary

Management of Critically Ill-Adult Patients with Severe COVID-19 in Intensive Care Unit

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COVID-19 (coronavirus disease-2019), a respiratory tract infection caused by a newly emergent coronavirus, called "severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2)" that was first identified in Wuhan city, China, late December 2019. It is a betacoronavirus closely linked to the SARS virus. Approximately 14% to 20% of COVID-19-infected cases develop severe COVID-19 requiring hospital admission and oxygen support and around 5% to 10% of infected cases require admission to the intensive care unit (ICU). A recent multivariable analytic study demonstrated that d-dimer > 1 µg/L, higher Sequential Organ Failure Assessment (SOFA) score (ranges from 0 to 24 points related to six organ systems: 1) respiratory (hypoxemia defined by low partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2)); 2) coagulation (low platelets); 3) liver (high bilirubin); 4) cardiovascular (hypotension); 5) central nervous system (low level of consciousness defined by Glasgow Coma Scale) and 6) renal (low urine output or high creatinine) and older age on hospital or ICU admission were related to higher mortality. This study also revealed the longest duration of viral shedding in COVID-19 survivors of 37 days and a median duration of viral ribonucleic acid (RNA) detection of 20.0 days (Interquartile range (IQR): 17.0 - 24.0) in survivors. COVID-19 virus was detectable until death in non-survivors. Currently, there is no known difference the clinical manifestations of COVID-19 pregnant and non-pregnant women or adults of reproductive age. Pregnant and recently pregnant women with suspected or confirmed COVID-19 should be treated with supportive therapies related to immunologic and physiologic adaptations during and after pregnancy.

The frequency of repeated specimen collection (upper respiratory tract: nasopharyngeal and oropharyngeal; lower respiratory tract: expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage in ventilated patients) for COVID-19 testing by reverse transcriptase polymerase chain reaction (RT-PCR) in hospitalized patients will depend on local epidemic characteristics and resources (a positive rapid diagnostic test for dengue does not exclude the COVID-19 testing). Two negative RT-PCR tests at least 24 hours apart in a clinically recovered patients is recommended for hospital discharge. Patients with severe acute respiratory infection (SARI) and respiratory distress, hypoxemia or shock that indicates severe COVID-19 is managed by supplemental oxygen therapy targeting SpO_2 > 94%. Patients with severe COVID-19 should be closely monitored for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis. Timely, effective, and safe supportive therapies is the cornerstone for patients with severe COVID-19. Empiric antimicrobials, based on the basis of microbiology results, the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia or sepsis), local epidemiology and susceptibility data, and national treatment guidelines are given to treat all possible pathogens causing SARI and sepsis as soon as possible within one hour of initial assessment for severe COVID-19 patients with sepsis. A COVID-19 patient with respiratory distress who is failing to respond to standard oxygen therapy is indicated severe hypoxemic respiratory failure in acute respiratory distress syndrome (ARDS) requiring advanced oxygen or ventilatory support (minimum flow rates of 10 - 15 L/min is required to maintain bag inflation at FiO_2 = 0.06 - 0.95).

Endotracheal intubation with airborne precaution should be performed by a trained and experienced health provider. Patients with ARDS should be pre-oxygenated with 100% FiO_2 for 5 minutes via a face mask with reservoir bag, bag-valve mask, high-flow nasal oxygen (HFNO) or non-invasive ventilator (NIV) due to rapidly oxygen desaturation during intubation. After an airway assessment that reveals no signs of difficult intubation, rapid-sequence intubation is appropriate. Adult ARDS patients should be strongly implemented with mechan-

ical ventilation using lower tidal volumes (4 - 8 ml/kg predicted body weight (PBW)) and lower inspiratory pressures (plateau pressure < 30 cmH_2O). This recommendation is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria by using the initial tidal volume of 6 ml/kg PBW. If undesirable side effects (e.g. blood pH < 7.15, dyssynchrony) occur, the tidal volume up to 8 ml/kg PBW is allowed. Permissive hypercapnia is also permitted. For controlling respiratory drive and achieving tidal volume targets, the use of deep sedation may be required. For pregnant women, being placed in the lateral decubitus position may benefit, whereas there is little evidence on prone position in pregnant women. Higher positive end-expiratory pressure (PEEP) (avoiding disconnecting the patient from the ventilator, that results in loss of PEEP and atelectasis) instead of lower PEEP and recruitment manoeuvres (RM) is advised in COVID-19 patients with moderate or severe ARDS. PEEP titration requires consideration of benefits to reduce atelectrauma and improve alveolar recruitment. Monitoring of patient with moderate or severe ARDS to identify those who respond to initial application of a different RM protocol or higher PEEP are advised to stop these interventions in non-responders. A previous randomized controlled trial (RCT) demonstrated that high PEEP and prolonged high pressure RMs demonstrated harm. Neuromuscular blockage by continuous infusion, including systemic corticosteroids should not be routinely used in COVID-19 patients with moderate-severe ARDS (PaO_2/FiO_2 < 150). Nevertheless, continuous neuromuscular blockage may still be considered in ARDS patients with dyssynchrony despite sedation or refractory hypoxemia or hypercapnia (rare finding).

Either HFNO or NIV should be used only in selected COVID-19 patients with hypoxemic respiratory failure from ARDS (dominant finding and most common reasons for ICU admission leading to mechanical ventilation and/or hypotension requiring vasopressor treatment with high mortality rate) and should be closely monitored for clinical deterioration. Adult HFNO systems can deliver 60 L/min of O_2 flow and FiO_2 up to 1.0. HFNO, NIV, and bubble CPAP with monitoring should be used with airborne precautions due to uncertainty around the potential for aerosolization until further completion of evaluation of safety. HFNO decreases the need for intubation. Nevertheless, HFNO is not recommended in COVID-19 patients with some comorbidities, such as abnormal mental status, multiorgan failure, hemodynamic instability, cardiogenic pulmonary edema, or exacerbation of chronic obstructive pulmonary disease (COPD), although some data indicate that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia. Referral of COVID-19 patients with refractory hypoxemia despite pulmonary protective ventilation is required extracorporeal membrane oxygenation (ECMO).

Common complications of COVID-19-related ARDS include acute kidney injury (AKI, approximately 29%), elevated hepatic enzymes (approximately 29%) and cardiac injury (cardiomyopathy, pericarditis, pericardial effusion, arrhythmia, and sudden cardiac death, approximately 23%, 33% in a United States cohort). Encephalitis is rare. Prevention of complications in COVID-19 patients with critical illness anticipates several outcomes, such as reduction of days of invasive mechanical ventilation by using weaning protocols and minimizing continuous or intermittent sedation; reduction of incidence of ventilator-associated pneumonia by using oral intubation, semi-recumbent position of the patients, closed suctioning system, a new ventilator circuit for each patient and changing heat moisture exchanger; and reduction of incidence of pressure sores-stress ulcers and gastrointestinal (GI) bleeding by patient turning every 2 hours, giving early enteral nutrition (within 24 - 48 hours of hospital admission), administering proton-pump inhibitors or histamine-2 receptor blockers; reduction of incidence of catheter-related bloodstream infection by using checklist with completion verified by a real-time observer as a daily reminder to remove catheter if no longer needed; reduction of venous thromboembolism by using low molecular-weight heparin (preferable if available) or heparin 5,000 units subcutaneously twice daily, or by using intermittent pneumatic compression devices, and reduction of incidence of ICU-related weakness by actively mobilizing the patients early in the course of illness when it is safe to do.

Vasopressors are needed in COVID-19 patients with septic shock to maintain mean arterial pressure (MAP) at least 65 mmHg and serum lactate level at least 2 mmol/L in absence of hypovolemia. Fluid resuscitation with 250 - 500 ml of crystalloid fluid, including normal saline and Ringer's lactate solutions as rapid bolus in first 15 - 30 minutes and reassess for signs of fluid overload after each bolus. Determining need for additional fluid boluses (250 - 500 ml) based on clinical response and improvement of perfusion target (MAP > 65 mmHg, urine output > 0.5 mL/kg/hour, improvement of skin mottling and extremity perfusion, capillary refill, level of consciousness,

serum lactate level, and heart rate. Dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local experience and local resource should include intrathoracic pressure during mechanical ventilation, stroke volume, inferior vena cava size, pulse pressure, variations in systolic pressure or fluid challenges with serial stroke volume measurements, and passive leg raises. Vasopressors, such as norepinephrine (first-line treatment, dopamine is not recommended if norepinephrine is not available), epinephrine, vasopressin, and dobutamine (low risk of tachyarrhymia) can be administered via a peripheral intravenous route if central venous catheters are not available.

Currently, there are limited evidences on clinical manifestations and perinatal outcomes after COVID-19 during pregnancy or puerperium. Nevertheless, all recently pregnant women with COVID-19, including pregnant women with covering from COVID-19 should be provided with information and counselling on safe infant feeding and appropriate infection prevention and control (IPC) for preventing COVID-19 virus transmission. Infants born to mothers with suspected, probable, or confirmed COVID-19 should be breastfed according to standard infant feeding guidelines.

In conclusion, currently, there is no specific anti-COVID-19 therapy. There are several ongoing clinical trials on various potential antivirals both in China, United States, and many other countries.

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