

Management of Severe Acute Respiratory Distress Syndrome in COVID-19: A Literature Review

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ABSTRACT

Serious complication may occurred in COVID-19 patients, including Acute Respiratory Distress Syndrome (ARDS) that causes death. Currently, ARDS from COVID-19 is still an ongoing challenge. Adequate treatment in ARDS management might significantly decreases morbidity and mortality.

Keywords: ARDS; Coronavirus; COVID-19; Management

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INTRODUCTION

COVID-19 is a disease that is caused by SARS-CoV2 infection. Its first case was found in Wuhan, Hubei province, China (Bogoch II, *et al.*, 2020). World Health Organization (WHO) determined that SARS-CoV2 outbreak is a global emergency which required international cooperation to suppress morbidity and mortality rate because of its rapid spread. COVID-19-related diseases might be fatal, for example pneumonia, Acute Respiratory Distress Syndrome (ARDS), septic shock, and even causes deaths. COVID-19 causes variable symptoms, from asymptomatic form to serious complications including hypoxia from ARDS (WHO, 2020). A study in Wuhan reported that the onset of ARDS started 9 days after infection, and might progressively worsen that might lead to death. High risk population such as elderly and patient who had comorbid diseases are at risk developing a more severe form of ARDS, whereas children are less susceptible to develop severe ARDS (WHO, 2020).

ARDS and Multi Organ Dysfunction (MODS) are induced by massive inflammatory response or cytokine storm. When infection occurs in elderly patients, massive inflammatory response might follow and leads to ARDS. Microbial products or cell damage related to endogen molecule bind Toll-like receptor in lung epithelial, therefore activating innate immune system that is induced by alveoli macrophage. Innate immune system mechanism might bring beneficial effect by capturing pathogens, but also increases damage in alveoli (Pierrakos C, *et al.*, 2012, Galani V, *et al.*, 2010).

Besides inflammation, another important pathological process related to ARDS is disruption of lung microvascular barrier that is caused by increased epithelial and endothelial permeability. During lung lesion, increase of thrombin, Tumor Necrosis Factor- α (TNF- α), vascular endothelial growth factor, and leukocyte destabilize VEcadherin bond, an important component in endothelial stabilization, therefore causing further increase of endothelial permeability and alveoli fluid accumulation. Damage of lung endothelial is induced by inflammation and increases capillary permeability, leading to lung edema (Huppert LA, *et al.*, 2019).

Chinese CDC classified ARDS into several stages according to its clinical symptoms:

- Mild disease: Absent of pneumonia or mild pneumonia

- Severe disease: dyspneu, respiratory rate ≥ 30 , oxygen saturation (SpO_2) $\leq 93\%$, PaO_2/FiO_2 ratio or P/F (ratio between oxygen pressure (oxygen partial pressure, PaO_2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2)) < 300 , and/or lung infiltrate $> 50\%$ in 24-48 hours;

- Critical disease: respiratory failure, septic shock, and/or MOD or MOF

According to epidemiology data, mild symptoms occurred in 81%, severe stage 14%, and critical stage 5% (Wu Z, McGoogan JM, 2020).

ARDS diagnosis is based on clinical data and ventilation criteria. Its classification is based on hypoxia grade.

- Mild ARDS: $200 \text{ mmHg} < PaO_2/FiO_2 \leq 300 \text{ mmHg}$. Patient does not need assisted ventilation or Non-Invasive Ventilation (NIV) with Positive End-Expiratory Pressure (PEEP) or continuous positive airway pressure (CPAP) $\geq 5 \text{ cmH}_2\text{O}$.

- Moderate ARDS: $100 \text{ mmHg} < PaO_2/FiO_2 \leq 200 \text{ mmHg}$.

- Severe ARDS: $PaO_2/FiO_2 \leq 100 \text{ mmHg}$ (WHO, 2014).

Worsening symptoms in COVID-19 patients requires comprehensive management. In this article, we reviewed ARDS-19 management in COVID-19 patients.

MATERIALS AND METHODS

We selected relevant articles published between January 2010 to September 2020 by searching through PubMed and Google Scholar. We used keywords 'COVID-19', 'SARS-CoV-2', 'ARDS', 'critical care' and 'management' to search relevant articles. This search generated 167 results. All abstracts were screened and we retained the full paper for relevant articles for further analysis.

The inclusion criteria for articles are COVID-19 with ARDS, adult ARDS patient age 18-60, study design for Randomized Control Studies (RCT), cohort studies, case report, case series, cross-sectional studies, and previous literature reviews. We also included previous guidelines from different societies regarding ARDS and COVID-19. The exclusion criteria are COVID-19 without ARDS, COVID-19 with any other disease than ARDS, COVID-19 in children, duplicate articles, articles from conferences or scientific letter. In total, 117 studies comprising case reports, case series, and case-control studies (reporting a total of 185.672 COVID-19 patients with ARDS)

were included.

RESULTS AND DISCUSSION

ARDS management in COVID-19

Mechanical ventilation: When ARDS occurs, patients might continue to experience increase work of breathing or hypoxemia despite they have already been given supplementary oxygen via a face mask with reservoir bag (flow rates of 10-15 L/min). Hypoxemic respiratory failure in ARDS usually derived from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation. Fan et al (Fan E, *et al.*, 2017) stated that despite researches that had been conducted in the past decades, mechanical ventilation is still the cornerstone of ARDS management (Rhodes A, *et al.*, 2016). A group of experts from France recommended mechanical ventilation for patients who are predicted to fail other oxygenation/ventilation strategies with the symptomatic challenges of ARDS (Bouadma L, *et al.*, 2020). Whittle et al also proposed an algorithm where patients with severe respiratory failure, multi-organ failure, hemodynamic shock, or those with comorbid to be given mechanical ventilation (Whittle JS, *et al.*, 2020).

American Thoracic Society/European Society of Intensive recommended to use mechanical ventilation that uses lower tidal volumes (4-8 ml/kg predicted body weight) and lower inspiratory pressures (plateau pressure, 30 cm H₂O) for ARDS patients (Fan E, *et al.*, 2017). Surviving Sepsis Campaign Guideline in 2016 recommended using a target tidal volume of 6 mL/kg Predicted Body Weight (PBW) compared with 12 mL/kg in adult patients with sepsis-induced ARDS (Rhodes A, *et al.*, 2016).

During COVID-19 pandemic, Wu et al stated that approximately 5% to 10% of patients require Intensive Care Unit (ICU) admission and mechanical ventilation (Wu Z, McGoogan JM, 2020). Bhatraju et al also stated that in their case series in Seattle region that the most common reasons for admission to the ICU were hypoxemic respiratory failure leading to mechanical ventilation, hypotension requiring vasopressor treatment, or both (Bhatraju PK, *et al.*, 2020). There are certain concerns regarding the use of mechanical ventilation for ARDS because endotracheal intubation produces high amount of Aerosol Generating Procedures (AGPs), contributing to the risks associated with mechanical ventilation (Whittle JS, *et al.*, 2020). Therefore, health care workers are advised to take extra measures such as using appropriate PPE that include gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). If possible, adequate ventilated single rooms should be used, meaning negative pressure rooms with a minimum of 12 air changes per hour or at least 160 L/second/patient in facilities with natural ventilation. No unnecessary individuals should be present in the room. Care for the patient in the same type of room after mechanical ventilation begins (WHO, 2020).

Mechanical ventilation for ARDS-related COVID-19 patients were used often, especially in severe ARDS. Ferrando et al conducted a multicenter, prospective, observational study in consecutive, mechanically ventilated patients with ARDS (as defined by the Berlin criteria) affected with COVID-19 with 742 patients that were admitted to ICU at a network of Spanish and Andorran hospitals. They concluded that patients' compliance with lung-protective ventilation was high, and the risk of 28-day mortality increased with the severity of ARDS (Ferrando C, *et al.*, 2020).

A different result was reported by Zangrillo *et al.* They conducted a case series of 73 patients at multiple hospitals in Milan with ARDS that were mechanically ventilated. Twenty patients previously received non-invasive ventilation previously. They concluded that although multiple

advanced critical care interventions were implemented, COVID-19 ARDS was associated with prolonged ventilation and high short-term mortality, where 6 patients (8.2%) had died at the first 7 days, and at the 19th day of follow up, 17 patients (23.3%) had died. Older age and pre-admission hypertension were key mortality risk factors (Zangrillo A, *et al.*, 2020).

ECMO: ExtraCorporeal Membrane Oxygenation (ECMO) is a term to describe an extracorporeal circuit that directly oxygenates blood and clears carbon dioxide from blood. In ARDS, a cannula (27-32 Fr) is inserted to central vein. Blood will be extracted from vein and enters an extracorporeal circuit in a mechanical pump before entering oxygenator. In oxygenator, blood passes one side of membrane that provides a blood-gas interface for gas diffusion. Oxygenated blood will be warmed up and cooled down and enters the central vein again. This technique is named "VenoVenous" (VV) ECMO. If the blood is from and goes back to artery, usually femoral or subclavian artery (closed chest) or aorta (open chest), it is called VenoArterial (VA) ECMO (Brodie D, Bacchetta M, 2011, Combes A, *et al.*, 2017, Combes A, *et al.*, 2014, Papazian L, *et al.*, 2019, Makdisi G, Wang IW, 2015, Park PK, *et al.*, 2011, Dirnberger D, *et al.*, 2015, Ferguson ND, *et al.*, 2012, Gattinoni L, 2010, Shekar K, *et al.*, 2012, Raghavendran K, Napolitano LM, 2011, Combes A, *et al.*, 2018, Beiderlinden M, *et al.*, 2006).

It is still a debate when to start ECMO. ELSO organization suggested that ECMO can be started PaO₂/FIO₂ ratio lower than 150 with 70 < FIO₂ < 100 and 10 < PEEP < 20 cm H₂O. Furthermore, inclusion criteria in a study from EOLIA underlined PaO₂/FIO₂ ratio below 100 as an indication for ECMO. The newest Berlin Definition for ARDS suggested PaO₂/FIO₂ ratio below 70 is an indication to start ECMO (Combes A, *et al.*, 2017, Combes A, *et al.*, 2014, Papazian L, *et al.*, 2019, Raghavendran K, Napolitano LM, 2011, Combes A, *et al.*, 2018, Beiderlinden M, *et al.*, 2006).

There are several adverse effects that are expected in ECMO usage. Adverse effects might be related to underlying pathological condition, or to the procedure itself. VV ECMO had lesser complication compared to VA ECMO, and children were less susceptible to complication compared to adults, except for neurological complications. The most common complication for ECMO is bleeding, occurring in 10%-30% cases. Infection might occur in ECMO circuit because it is basically a large intravascular foreign body, and manipulation might increase infection risk (Papazian L, *et al.*, 2019, Makdisi G, Wang IW, 2015, Ferguson ND, *et al.*, 2012).

Currently, ECMO is one of treatment alternatives for diseases that causes ARDS, such as H1N1 infection, MERS (Middle East Respiratory Syndrome) and all types of pneumonia (Combes A, *et al.*, 2018, Beiderlinden M, *et al.*, 2006, Pappalardo F, *et al.*, 2013, Grasso S, *et al.*, 2012, Alshahrani MS, *et al.*, 2018). In COVID-19, WHO interim guideline for suspected COVID-19 cases included VV ECMO for ARDS patients that are treated in centers that provided adequate facilities. However, its efficacy is influenced by clinician's expertise and whether available health care system is ready to provide such facility. Taniguchi et al in their case report reported a 72 years old woman with COVID-19-related ARDS that was treated successfully with ECMO, where they suggested observation of lung plasticity and interstitial biomarker in ECMO usage for COVID-19 case (Taniguchi H, *et al.*, 2020). Zhan et al also reported a 52 years old man with fever as his chief complaint for 13 days and had worsening symptoms 3 days before he was admitted to hospital. Patient was treated with rescue ECMO on 11th day of treatment and was given pressure-controlled ventilation, where patient had improved saturation (Zhan WQ, *et al.*, 2020). A multicenter study by Jacobs et al included 32 patients in nine hospitals. In 24 days, 17 pa-

tients remained in ECMO, 10 patients were deceased before or right after decannulation, five patients survived and were extubated from ECMO. They concluded that ECMO played a role in stabilization and survival of critical COVID-19 patients (Jacobs JP, *et al.*, 2020).

However, unsatisfactory outcomes were also reported in another studies. Yang et al reported that 52 patients were treated in ICU with COVID-19, where six of them (11.5%) were treated with ECMO. From 52 patients, only 20 survived, and only one of them was treated with ECMO (Yang X, *et al.*, 2020). Zhou et al reported 191 patients with COVID-19, where only 3 patients were treated with ECMO and none of them survived (Zhou F, *et al.*, 2020).

Prone positioning: Prone positioning has already been used for decades in ARDS management. Improved oxygenation following prone positioning is caused by decrease of intrapulmonary shunt (Qs/Qt) and improved lung ventilation (VA) and lung perfusion distribution (Q) and also improved matching (VA/Q). Prone positioning also decreases pleural pressure gradient from nondependent region to dependent region, partially because of gravitational effect and lung conformational shape that matches thorax cavity. Therefore, aeration distribution and pulmonary tension will be more homogenous. A previous study revealed that prone positioning can be conducted if PaO₂/FiO₂ was lower than 100 mmHg after 24-48 hours (Guerin C, *et al.*, 2014, Scholten EL, *et al.*, 2017, Gattinoni L, *et al.*, 2010).

Generally, even though minor complications might occur, severe complications rarely occur and might be evaded most of the time. However, current available data was produced from clinicians that were familiar with this technique, therefore severe complication risk might be larger than what had been previously reported. The most common complication is pressure sore that is caused by skin compression and facial edema, that is oftenly seen by the patients' family. Another complication is episodes of transient hypoxemia that is caused by desynchronization with respiratory device, arterial hypotension and arrhythmia, accidental chest tube extubation and venous access removal (Scholten EL, *et al.*, 2017, Gattinoni L, *et al.*, 2010, Ding L, *et al.*, 2020).

Several studies already assessed prone positioning efficacy for ARDS. Cornejo et al reported that patients who were performed prone positioning had significantly lower un-aerated tissue (501 ± 201 vs 322 ± 132 gr, p<0,001) compared to patients with supine position (Cornejo RA, *et al.*, 2013). Guérin et al reported that prone positioned patients had significantly lower 28-days and 90-days mortality rate compared to supined patients (Guérin C, *et al.*, 2013). Meta-analysis studies from Sud et al and Park et al also reported a significant reduced in mortality (Sud S, *et al.*, 2014, Park SY, *et al.*, 2015).

Prone positioning technique were performed in COVID-19 cases. A study in Italy suggested that ventilation in prone position should be maintained >12 hours per day (Cascella M, *et al.*, 2021). A study from Yang et al in 52 COVID-19 patients with ARDS reported six (11.5%) of them were treated with prone positioning, where two patients (10%) managed to survive from a total of 20 survived patients (Yang X, *et al.*, 2020). Bhatraju et al in their case report revealed that 5 from 18 COVID-19 patients with ARDS used prone positioning technique, but they did not report mortality rate in those patients (Bhatraju PK, *et al.*, 2020).

Corticosteroids: Inflammatory dysregulation, both in endothelial and epithelial spaces, are key roles for ARDS pathogenesis. Recent studies revealed that overproduction of proinflammatory cytokines (tumor necrosis factor, interleukin (IL)-1, IL-6, IL-8) and neutrophil recruitment in lungs mediated ARDS process. Furthermore, duration of inflammatory cytokine production revealed to be connected with poorer

outcome in ARDS patients (Lamontagne F, *et al.*, 2010, Thompson BT, 2010, Khilnani GC, Hadda V, 2011). Glucocorticoid's mechanism of action is through its binding with its receptors on cytoplasm. These receptors modulate transcription rate in many elements, including nuclear factor-κB and activated protein-C. These responses further modulate proinflammatory cytokine production such as TNF-α, IL-1α, IL-1β, interferon-γ, IL-2, IL-3, IL-5, IL-6, IL-8, IL-12, and granulocyte-macrophage colony-stimulating factor (Lamontagne F, *et al.*, 2010, Hough CL, 2014, Meduri GU, *et al.*, 2007). Glucocorticoid also modulates several anti-inflammatory cytokines (ie., IL-4, IL-10, dan IL-13). Moreover, glucocorticoid also suppress phospholipase A2, cyclo-oxygenase, and inducible nitric oxide synthase synthesis. Glucocorticoid also inhibits fibroblast proliferation and collagen deposit; stimulating T cells, eosinophil, and monocytes apoptosis; while also inhibits neutrophil activation (Thompson BT, 2010, Meduri GU, *et al.*, 2007, Annane D, *et al.*, 2006).

There are many adverse effects of corticosteroids, including hyperglycemia, fluid retention, electrolyte imbalance, pancreatitis, increase of infection rate, neuromuscular weakness, gastrointestinal bleeding, and many more. In ARDS, corticosteroids are relatively safe to be use with strict follow-up, therefore adverse effects might be treated immediately. Adverse effects are reported variably in previous studies (Annane D, *et al.*, 2006, Hough CL, *et al.*, 2009).

Corticosteroid usage in ARDS gave variable results in various studies. Ruan et al reported that corticosteroid was beneficial for persistent ARDS if its onset was less than 14 days and did not recommend its usage for late onset ARDS (>14 days) (Ruan SY, *et al.*, 2014). An observational study from Prabhu et al reported that early glucocorticoid significantly decreased mean ventilator usage time (4.61 ± 2.81 vs 6.44 ± 4.47) and mortality (30.9% vs 80%, p<0.001) (Prabhu VA, *et al.*, 2017). Consensus of American College of Critical Care Medicine suggested that moderate dose of glucocorticoid must be considered in early onset severe ARDS (PaO₂/FiO₂<200 mm Hg) and before 14 days in persistent ARDS (Marik PE, *et al.*, 2008).

In COVID-19 pandemic, corticosteroid has already been used as one of the strategies to treat ARDS with variable results. Wang et al studied 26 patients who received intravenous methylprednisolone with 1-2 mg/kg/day dosage for 5-7 days. Patients who received methylprednisolone significantly had shorter days of using supplementary oxygen therapy compared to patients who did not received it (8.2 days (IQR 7.0-10.3) vs. 13.5 days (IQR 10.3-16); P<0.001) (Wang Y, *et al.*, 2020). Yang et al studied 30 patients (58%) who received glucocorticoid from a total of 52 patients. Fourteen patients (70%) managed to survive, whereas 16 patients (50%) did not (Yang X, *et al.*, 2020). Zhou et al also studied 57 patients (30%) from a total of 191 patients, where 31 (23%) of them managed to survive while 26 (48%) of them did not (p=0.0005) (Zhou F, *et al.*, 2020). Zha et al studied 11 patients who received corticosteroid and did not find any correlation between corticosteroid therapy and viral clearance (hazard ratio (HR), 1.26; 95% CI, 0.58–2.74), hospital admission time (HR, 0.77; 95% CI, 0.33-1.78), nor duration of symptoms (HR, 0.86; 95% CI, 0.40–1.83) (Zha L, *et al.*, 2020).

High Flow Nasal Cannula: High Flow Nasal Cannula (HFNC) therapy is given through air/oxygen blender, active heated humidifier, single heated circuit, and nasal cannula. Air/oxygen blender is set at FiO₂ 0.21-1.0 and flow rate up to 60 L/minute. Given gas is warmed and humidified by an active humidifier through a warmed circuit. Warm and humidified gas has beneficial physiologic effects (Roca O, *et al.*, 2016).

In ARDS, mean flow rate is increased. Peak inspiration flow rate surpasses flow rate that is produced by conventional oxygenation devices, therefore creating gas dilution and decreases amount of oxygen that

reaches alveoli. In HFNC, gas dilution decreases. Moreover, HFNC decreases dead space in upper airway because continuous high flow gas might remove Carbon dioxide (CO₂), therefore preventing re-inhalation of previous exhaled gas. Another advantage of HFNC is it induces certain level of positive airway pressure and increases End-Expiratory Lung Volume (EELV) because of its resistance that is caused by continuous high flow gas (Messika J, *et al.*, 2015, Nishimura M, *et al.*, 2016, Möller W, *et al.*, 2015, Möller W, *et al.*, 2017, Sztrymf B, *et al.*, 2011).

HFNC is often used in hypercapnic respiratory failure in patients who do not tolerate Non-Invasive Ventilator (NIV) well. HFNC can also be used as a first line treatment for mild to moderate hypoxemic ARDS, but is not recommended for severe hypoxemic ARDS (Kang BJ, *et al.*, 2015, Moretti M, *et al.*, 2000, Carrillo A, *et al.*, 2012). A study reported that HFNC can be used in de novo respiratory failure when patients needed >9 L/minute oxygen with conventional oxygen mask to maintain SpO₂ >92%, where PaO₂ and PaO₂/FiO₂ significantly increased after 1 hour usage of HFNC compared to baseline value (141 ± 106 vs. 95 ± 40 mmHg, p=0.009 and 169 ± 108 vs. 102 ± 23, p=0.036, respectively) (Messika J, *et al.*, 2015).

A study from Kang *et al* reported that HFNC for less than 48 hours is correlated with higher ICU mortality and lower extubation success and ventilator weaning, and also lower ventilator-free days (Kang BJ, *et al.*, 2015). Another study also reminded the risk of non-invasive respiratory support, including HFNC and NIV, which might exacerbate Chronic Obstructive Pulmonary Disease (COPD) and poorer treatment outcome. Improper intubation starting time might be caused by patients who feel more comfortable using HFNC and might tolerate it in a long period of time (Carrillo A, *et al.*, 2012).

In COVID-19 cases, Phua *et al* (Phua J, *et al.*, 2020) suggested that HFNC and NIV can be given in mild ARDS patients with strict monitoring, airborne precaution, and more suggested to be performed in single rooms (Nishimura M, *et al.*, 2016). Literature review from Whittle *et al* (Whittle JS, *et al.*, 2020) concluded that all ARDS guidelines for COVID-19 cases suggested HFNC as a form of treatment (Bhatraju PK, *et al.*, 2020). Newest publications regarding the latest HFNC system found that with better interface, HFNC would not cause dispersion of exhaled gas and therefore had low airborne risk (Phua J, *et al.*, 2020).

HFNC treatment outcomes are variable in COVID-19-related ARDS. A study from Geng *et al* observed 8 patients who were given HFNC in mild-moderate ARDS. The outcome was satisfactory in mild-moderate ARDS, but could not be used as a substitute for severe ARDS. They also suggested strict monitoring to prevent delayed intubation (Li J, *et al.*, 2020, Geng S, *et al.*, 2020). Zhou *et al* in their study that include 191 patients gave HFNC for 41 patients (21%). From 54 patients who died, 33 (61%) of them were given HFNC and from 137 patients who survived, 8 (6%) of them used HFNC (p<0,0001) (Zhou F, *et al.*, 2020). Yang *et al* gave HFNC therapy in 33 (63,5%) patients out of 52 patients. From 32 patients who died, 16 (50%) of them were given HFNC and from 20 patients who survived, 17 (85%) of them were given HFNC (Yang X, *et al.*, 2020).

Antiviral agents: Remdesivir is a prodrug of nucleoside adenosin analog and shows a wide spectrum of antiviral activity against several RNA viruses such as filoviruses and coronaviruses. Based on several data that are collected from in vitro cell line and mice model, remdesivir might disrupt NSP12 polymerase and even in a setting where intact activity of ExoN proofreading was found (Guo YR, *et al.*, 2020, Grein J, *et al.*, 2020, Agostini ML, *et al.*, 2018). In a previous study, Jordan *et al* mea-

sured polymerase activity of MERS-CoV in vitro by producing viral nsp8 and nsp12 in a purified complex through nsp5 protease-nsp7-nsp8-nsp12 coexpression strategy incorporating expression system of baculovirus. Remdesivir was proven to terminate elongation of RNA in MERS-CoV polymerase complexes. The authors also suggested a delayed mechanism of chain termination because it occurred when three nucleotides were further incorporated into newly formed RNA (Jordan PC, *et al.*, 2018).

Time of remdesivir administration to exert its antiviral effect varied between studies. A study in rhesus macaque model of MERS-CoV infection reported that remdesivir as prophylactic treatment that was given 24 hours prior to inoculation induced decrease of lung lesions through inhibition of MERS-CoV replication in airway tissue. When used as therapeutic treatment, remdesivir that was given 12 hours post-inoculation showed beneficial effects through clinical signs improvement, decrease of viral replication and severity of lung lesions (de Wit E, *et al.*, 2020). Another study in African green monkeys model of Nipah virus infection reported that monkeys who were given remdesivir 24 hours after inoculation only showed mild respiratory signs compared to control group which developed severe respiratory signs (Lo MK, *et al.*, 2019).

A literature review who examined previous studies regarding remdesivir safety profile found that it had acceptable safety profile (Ko WC, *et al.*, 2020). However a randomised, double-blind, placebo-controlled, multicenter trial by Wang *et al* revealed that out of 155 patients who received remdesivir, 102 (66%) experienced its adverse effects such as constipation, thrombocytopenia, anemia, hypokalemia, hypoalbuminaemia, and increased level of total bilirubin. Furthermore, 18 patients immediately discontinued its use and 28 patients experienced serious adverse effects. Remdesivir administration should be monitored strictly because of its possible serious adverse effects (Wang Y, *et al.*, 2020).

In the current COVID-19 pandemic, remdesivir has been used with variable outcomes. A cohort study by Grein *et al* observed 53 patients who received remdesivir at least in one dose. Clinical improvement was found in 36 (68%) out of 53 patients (Grein J, *et al.*, 2020). A case report by Hillaker also reported a satisfactory outcome in a previously healthy 40 years old man with COVID-19-related ARDS despite late initiation of remdesivir (Hillaker E, *et al.*, 2020). A double-blind, randomized, placebo-controlled trial by Beigel *et al* also revealed that in 538 patients who were given remdesivir and 521 patients who received placebo, remdesivir significantly reduced length of hospital stay (11 days; 95% confidence interval (CI), 9-12), compared to length of hospital in patients who received placebo (15 days; 95% CI, 13-19) (Beigel JH, *et al.*, 2020).

US. Food and Drug Administration (FDA) previously had approved lopinavir (LPV) and ritonavir (RTV) as therapies for SARS and MERS-CoV, both were caused by coronavirus. Lopinavir itself is a Human Immunodeficiency Virus 1 (HIV-1) protease inhibitor that is often combined with ritonavir to increase its half-life by inhibiting cytochrome P4507. Its antiviral property against MERS-CoV has been shown in vero cells (concentration in which 50% reduction in replication (EC50) is reached = 8 μM) (Cao B, *et al.*, 2020, Sheahan TP, *et al.*, 2020).

Adverse events might occur by the administration of lopinavir-ritonavir, both mild and serious. Lopinavir-ritonavir significantly increased oral oxycodone plasma concentration in patients who experienced severe pain (Nieminen TH, *et al.*, 2010). Renal lithiasis was also reported in HIV patients who received lopinavir/ritonavir tablet

formulation (Tosini W, *et al.*, 2010). A study by Cao et al revealed that patients who were administered with those combined drugs revealed adverse events (48.4% from total of patients) from mild adverse events to serious adverse events, which occurred in 19 patients (ie., ARDS, acute kidney injury, secondary infection, shock, severe anemia, acute gastritis, hemorrhage of lower digestive tract) (Cao B, *et al.*, 2020).

Lopinavir-ritonavir treatment in COVID-19 patients, like other previous treatment, showcased variable results. In a case report by Lim et al, a 54 years old patient was treated with the drug combination and revealed a significant decrease and no or little titers of coronavirus (Lim J, *et al.*, 2020). However, a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection by Cao et al revealed that lopinavir-ritonavir was not superior compared to standard care (Cao B, *et al.*, 2020). A multicentre, prospective, open-label, randomised, phase 2 trial in COVID-19 adult patients in six hospitals in Hong Kong revealed that triple combination consisted of ribavirin, lopinavir, ritonavir and interferon beta-1b gave better outcome compared to patients who received lopinavir-ritonavir only (Hung IF, *et al.*, 2020).

Immunomodulators: As previously mentioned, massive inflammatory response or cytokine storm might induce ARDS and MODS. Antiviral agents revealed variable outcomes, therefore another therapy is needed to combat COVID-19 (Zhao M, *et al.*, 2020). One of the proposed therapy is immunomodulatory therapy. This therapy is expected to down-regulate cytokine storm, therefore its used combined with antiviral agent is thought to be beneficial for physicians because it will give more time for physicians to provide supportive treatment for COVID-19 patients (Alijotas-Reig J, *et al.*, 2020).

Chloroquine and its derivative hydroxychloroquine were initially used as anti-malarial drugs, and because of its immunomodulator properties, they are both used for autoimmune and rheumatic diseases, including rheumatoid arthritis and SLE, and also showed to have potential antiviral effects against SARS and avian influenza H5N1. They have anti-aggregate, anti-inflammatory, and immune-regulatory properties because of their ability to stabilize lysosomal membranes, inhibit phospholipase activity, block several pro-inflammatory cytokines production, and impair reactions of complement-dependent antigen-antibody. Their antiviral effects come from their ability to alter cell membrane pH that is vital for viral fusion and might interfere glycosylation process in viral proteins (Zhao M, *et al.*, 2020, Wozniacka A, *et al.*, 2006).

Azithromycin is antibiotic belonged to neomacrolide group that has a 15-membered macrolactam ring structure, also named as "azalide," which was obtained through macrocyclic lactone ring chemical modification from erythromycin; another macrolide that is isolated from *Streptomyces* species (Retsema J, Fu W, 2001). Besides antibacterial activity, azithromycin also showcases pleiotropic, anti-inflammatory, and immunomodulatory effects on innate immune response and are not limited by microbes presence in the airways (Vos R, *et al.*, 2012). In the setting of transplantation, immunomodulatory effects a murine model of isolated lung ischemia-reperfusion injury, pretreatment of azithromycin reduced leukocyte, lymphocyte, and neutrophil numbers, as well as 8-isoprostane, IL-1 β and, although to a lesser extent, IL-6, and GRO/KC levels after ischemia and reperfusion (Geudens N, *et al.*, 2008).

Several adverse events have been reported for chloroquine and hydroxychloroquine administration. Common adverse events for their usage are nausea, headache, and pruritus. Life threatening adverse event such as arrhythmias was also reported, and the risk is enhanced with the use of azithromycin. Other adverse events that are uncommon

include neuropsychiatric effects, hypoglycemia, drug-drug interactions, and idiosyncratic hypersensitivity reactions (Juurlink DN, 2020).

Interleukin-6 is one of inflammatory indicator that can be found in the blood. Its elevated level might predic fatal outcome in COVID-19 patients (Ruan Q, *et al.*, 2020). IL-6 is capable to bind transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and its resulting complex might combine with gp130, a signal transducing component, and induces inflammatory response. Tocilizumab is a specific monoclonal antibody which blocks IL-6 by its bond with sIL-6R and mIL-6R, therefore blocking signal transduction (Ruan Q, *et al.*, 2020, Tanaka T, *et al.*, 2016).

A systematic review regarding tocilizumab treatment for rheumatoid arthritis revealed that adverse events that might occur are nasopharyngitis, respiratory tract disorder, skin and soft tissue pathology (e.g. rash) and gastrointestinal side effects (e.g. nausea) (Campbell L, *et al.*, 2011). A randomized trial of tocilizumab in Systemic Juvenile Idiopathic Arthritis revealed that in double-blind phase, 159 adverse events, including 60 patients who developed infections, 19 patients developed neutropenia (17 patients with grade 3 and 2 patients with grade 4), and 21 had aminotransferase levels above 2.5 times the normal upper limit (De Benedetti F, *et al.*, 2012).

Chloroquine and its derivative hydroxychloroquine alongside macrolide (azithromycin) were recently used for COVID-19 treatment. Cortegiani et al in their systemic review that included six articles (one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents) and 23 ongoing clinical trials in China reported that there is a rationale, available evidence of their effectiveness and evidence of safety (Cortegiani A, *et al.*, 2020). Another review from Sahraei et al reported although both chloroquine and hydroxychloroquine had similar antiviral activity, hydroxychloroquine should be preferred over chloroquine because of its lower risk of ocular toxicity (Sahraei Z, *et al.*, 2020). On a contrary, a multinational registry analysis by Mehra et al for the use of hydroxychloroquine or chloroquine with or without a macrolide in COVID-19 treatment that included data from 671 hospitals in six continents suggested that the authors were unable to confirm hydroxychloroquine or chloroquine benefit, whether both of them were used alone or in combination with a macrolide. In fact, each of the drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias (Mehra MR, *et al.*, 2019).

A study by Xu et al in severe COVID-19 patients treated with tocilizumab in Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) and Anhui Fuyang Second People's Hospital reported that tocilizumab might improve clinical outcome rapidly in severe and critical COVID-19 patients, therefore reducing mortality rate (Xu X, *et al.*, 2020). Another study from Luo et al also reported similar results, where tocilizumab appeared to be an effective option for patients in the risk of cytokine storm. They also suggested repeated dose of tocilizumab to reach a satisfactory outcome (Luo P, *et al.*, 2020). A case report by Michot et al reported a 42-year-old male recently diagnosed with metastatic sarcomatoid clear cell renal cell carcinoma and also confirmed to have SARS-CoV-2 infection, which led to severe lung disease. They reported that severe COVID-19-related lung disease was successfully treated with tocilizumab as an anti-interleukin 6 receptor treatment (Michot JM, *et al.*, 2020).

Convalescent Plasma therapy

Convalescent Plasma was used in previous outbreaks (SARS-CoV, H5N1 avian influenza, H1N1 influenza, Ebola virus in 2014, and MERS-CoV in 2015). Convalescent Blood Products (CBP) are derived

from whole blood or plasma of previously infected patients who survived and developed humoral immunity against previous pathogen that infected the patients. Convalescent Plasma (CP) is based on passive immunization strategy and is obtained through apheresis. During apheresis, besides neutralizing antibodies (NAbs), other proteins such as clotting factors, natural antibodies, pentraxins, defensins, and other undefined proteins are obtained from donors (Burnouf T, Seghatchian J, 2014, Rojas M, *et al.*, 2020).

There is no standard dose for CP transfusion. Previous studies on CP therapy for coronavirus infections reported CP transfusion dose between 200 and 500 mL in single or double scheme dosages (Rojas M, *et al.*, 2020). The current recommendation for CP transfusion is 3 mL/kg per dose in two days. CP generally showed a great safety profile in previous studies (Bloch EM, *et al.*, 2020). But a study by Van Griensven *et al* regarding CP for Ebola treatment in Guinea, 2016 revealed there were several minor adverse events that occurred, such as nausea, skin erythema, and fever. There was no major adverse event that was reported (Van Griensven J, *et al.*, 2016).

A case series by Shen *et al* observed 5 critically ill COVID-19-related ARDS patients who were given convalescent plasma, antiviral agents, and methylprednisolone and were receiving mechanical. ARDS in four patients improved 12 days after transfusion, and 3 patients were weaned from mechanical ventilation after 2 weeks of treatment (Shen C, *et al.*, 2020). Another study from Duan *et al* observed 10 patients who were severely ill and were given one dose of 200 mL of Convalescent Plasma (CP) from recently recovered donors with the neutralizing antibody titers above 1:640 alongside antiviral agents and supportive care. Clinical symptoms were subsequently improved within 3 days after CP administration and no adverse event was observed (Duan K, *et al.*, 2020).

Zhang *et al* in their case reports observed four critically ill COVID-19 patients who received convalescent plasma therapy and supportive care. All four patients (including a pregnant woman) recovered (Zhang B, *et al.*, 2020). Another case report by Anderson *et al* also reported an obstetric patient with severe COVID-19 who received convalescent plasma and remdesivir, where the patient subsequently improved and extubated 5 days after remdesivir administration, and was discharged from hospital (Anderson J, *et al.*, 2020).

Antithrombotics: Disseminated Intravascular Coagulation (DIC) is an acquired syndrome that is characterized by activation of widespread intravascular coagulation that might be caused by insults. Its main mechanism is through activation of tissue factor-dependent coagulation that is induced by cytokines, anticoagulant pathways control that is insufficient, and fibrinolysis suppression that is mediated by plasminogen activator inhibitor 1 (Gando S, *et al.*, 2016). These abnormalities cause dysfunction of endothelial and thrombosis of microvascular, which might cause organ dysfunction and poor outcome for patients (Jose RJ, Manuel A, 2020).

COVID-19–Associated Coagulopathy (CAC) is a term to describe coagulation changes in COVID-19 patients. Currently, there is still little knowledge whether SARS-CoV-2 virus might have procoagulant effect itself (Jose RJ, *et al.*, 2020). Activation of coagulation pathways during immune response to infection causes proinflammatory cytokines overproduction. Thrombin might also exert multiple cellular effects and further increases inflammation through Proteinase-Activated Receptors (PARs), mainly PAR-1. Its generation is strictly controlled by negative feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system. Defect in procoagulant–anticoagulant balance induces micro-

thrombosis, disseminated intravascular coagulation, and multiorgan failure—found in severe COVID-19 pneumonia with increased level of d-dimer concentrations being a poor prognostic marker (Tang N, *et al.*, 2020). Furthermore, a long term bed rest might also increase the risk of Venous Thromboembolism (VTE) in severe COVID-19 (Connors JM, Levy JH, 2020).

Management of DIC is to first identify the underlying condition. In addition to preventing VTE, LMWH prophylaxis might decrease thrombin generation and altered DIC course (Tang N, *et al.*, 2020). For VTE, therapeutic anticoagulation is the main choice for treatment. Agents selection must consider concomitant comorbidities such as hepatic or renal dysfunction, gastrointestinal disease, and thrombocytopenia. In many treated patients with VTE, parenteral anticoagulation (e.g., UFH) is selected because it has not shown any interactions with other investigational COVID-19 therapies (Connors JM, Levy JH, 2020).

A study from Llitjos *et al* who observed 26 patients with severe COVID-19 who were screened for VTE. They suggested considering both systematic screening of VTE and early therapeutic anticoagulation in severe COVID-19 patients (Llitjos JF, *et al.*, 2020). Klok *et al* also suggested to apply thrombosis prophylaxis in all COVID-19 patients because of a remarkably high number of patients (31%) with thrombotic complications (Klok FA, *et al.*, 2020). Paranjpe *et al* in their study of 2,773 COVID-19 patients, 786 (28%) received systemic treatment-dose anticoagulant during their hospital course and suggested that systemic treatment-dose anticoagulant might be associated with improved outcomes (Paranjpe I, *et al.*, 2020).

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