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Therapeutic Options and Critical Care Strategies in COVID-19 Patients; Where Do We Stand in This Battle?

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ABSTRACT

A pandemic of COVID-19 made an appearance in Wuhan, China, in late December 2019 and rapidly became a serious concern worldwide, with killing more than 238000 people until 3rd May 2020. Given the fact that a vaccine against the virus probably won't be available anytime in the near future, the therapeutic strategies have become more prominent. Many supposedly effective drugs are under evaluation which may hinder the replication of SARS-CoV-2, and subsequently the infection. Lately on 1th may 2020, FDA authorized the use of experimental drug, Remdesivir for "emergency purpose" in COVID-19 cases. Chloroquine and hydroxychloroquine, among the very first under-trial drugs, have been revealed to have promising impacts in treatment of SARS-CoV2. Broad-spectrum antivirals as well as HIV protease-inhibitors are still subject to assessment. Particularly angiotensin-converting enzyme 2 (ACE2) inhibitors are increasingly taken into consideration because of ACE2 being recognized as a host-cell receptor for COVID-19. Immune-Enhancement therapy by Interferons and Intravenous immunoglobulin (IVIG) has been shown to be effective in some cases. Moreover, Convalescent Plasma Therapy and auxiliary blood purification were considered as the treatment of SARS-CoV2 infection. Among the critically ill patients, Oxygen-therapy, timely usage of inflammatory inhibitors, and controlling viral shedding by antivirals may reduce the mortality and morbidity of COVID-19.

INTRODUCTION

On December 31st, 2019, the existence of a large group of patients with a mysterious pneumonia of viral cause was brought to light in Wuhan, Hubei Province of China. The Chinese authorities notified the world that a virus was spreading inside their communities. Then, on February 11th, 2020, the international officials, called this new coronavirus family member which was responsible for the disease, the "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2). World Health Organization (WHO) identified the related illness as "Coronavirus Disease 2019" (COVID-19) [1]. Subsequently, on March 11th, 2020, WHO decided to declare the current global dilemma, as a pandemic [2]. Based on the report of WHO on May 3rd, 2020, a total of more than 3.3 million patients globally have definite diagnosis of COVID-19, and the world death toll from the disease has currently surpassed 238000 which has resulted in a mortality rate of approximate 7.1 percent [3]. Figure 1 indicates the most current distribution of COVID-19 cases in the world. As it's been announced and also, as it is shown in Chart 1, the situation in certain regions of the world is quite similar to an almost crisis. Europe has been tremendously affected by the virus in terms of both mortality and morbidity. Spain, Italy, along with United Kingdom are the three main countries having the greatest amounts of cases and deaths in European pacific region. In western pacific region, China accompanying with Singapore are considered as the two territories having the most significant amount of cases and deaths. Among middle east region countries, Iran has the greatest number of confirmed

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cases and fatality rate [3]. Clinically, fever, dry cough, dyspnea and fatigue are the most common manifestations of the disease, while the manifestations related to the upper airways are not noticeable. Gastrointestinal manifestations also have been seen in some cases. Septic shock is among the main concerning complications in COVID-19 patients, as well as acute respiratory distress syndrome (ARDS) [4]. Various types of radiologic findings commonly show multiple ground glass and infiltrative views in pulmonary tissue on both sides. Chest CT scan is utilized for the diagnosis of the disease as a salient addition to the RT-PCR test [5]. The treatment modalities are still remained as the big missing piece of the novel coronavirus puzzle. While the effectiveness of different variety of drugs are still under evaluation, optimized supportive care is the centerpiece of treatment. according to the efficacy which was shown on other family members of SARS-CoV2 like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), some drugs have been under investigation [6]. Moreover, as the hyper-inflammatory state and cytokine storming is considered as the concerning complication of COVID-19, particular interests in the field of evaluating cytokine release inhibitors have been increased [7]. All that has been briefly stated, indeed is pointing to this fact that how great of a crisis COVID-19 situation is, and how much more troublesome it could get, if proper measures will not be taken. It has never been more obvious that one of the most effective measures in these circumstances is developing an up-to-date therapeutic strategy and treatment plan. By conducting this narrative review, we've aimed to evaluate different medications, along with their drawbacks and benefits, as well as the proper critical care for seriously ill patients.

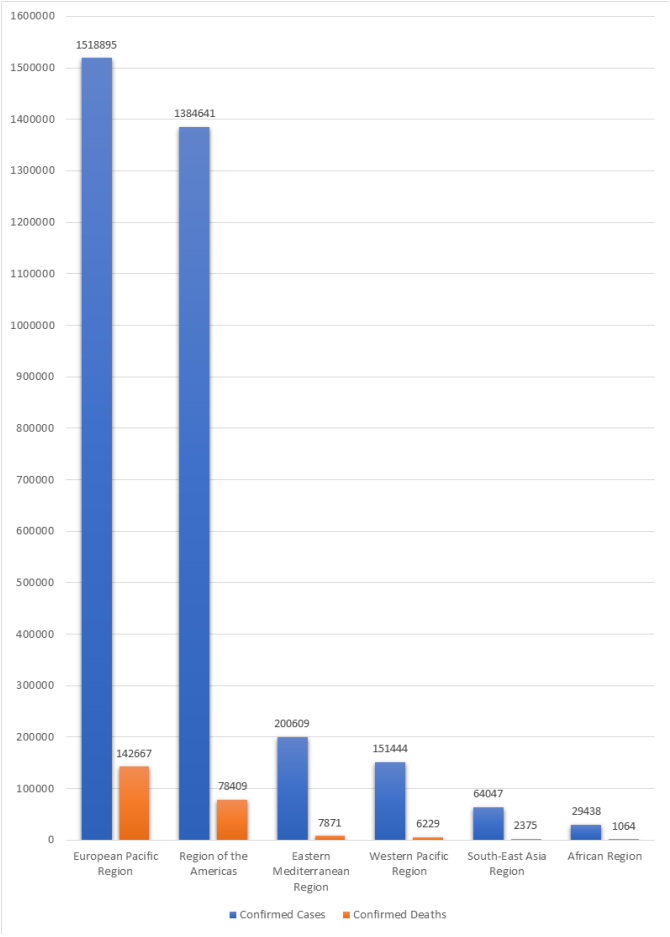

Chart 1: Comparison of confirmed cases and deaths of COVID-19 outbreak in 6 regions of the world in the May 3rd, 2020

DIFFERENT GROUPS OF MEDICATION

1. Anti-Viral Drugs

1.1 Lopinavir/Ritonavir (Kaletra): Lopinavir, classified in the drug group of protease inhibitors, is utilized for the treatment of patients affected prolongedly with HIV-1 [8]. its mechanism of action is blocking the main protease of SARS-CoV-1, resulting in inhibition of viral replication [9]. Real-world information supporting the treatment of COVID-19 with Lopinavir/Ritonavir keeps coming out. Chu et al. have discovered that Lopinavir/Ritonavir has an anti-SARS-CoV effect within both in-vitro settings and clinical studies [10]. Published evaluations from Korea and China show reduced viral load, and clinical improvement of COVID-19 patients after onset of Lopinavir/Ritonavir treatment [11-13]. However, Cao and colleagues illustrated the results of comparing twice a day use of Lopinavir/Ritonavir 400/100 mg to standard care, for treating the pneumonia caused by SARS-CoV-2. This study upshot, demonstrated no benefit regarding a Lopinavir/Ritonavir treatment beyond standard card [14]. Considering the currently available data, it is yet to be determined whether Lopinavir/Ritonavir could significantly affect the status of COVID-19 patients, either as monotherapy or in combination-therapy. Moreover, close monitoring is needed during the administration of this drug, because particularly elevated levels of AST or ALT suggesting the gastrointestinal complications and hepatoxicity may exclude patients with COVID-19 from clinical trials [15].

1.2 Darunavir: Darunavir is a 2nd generation drug in HIV-1 protease inhibitor family. On February 4th, 2020, researchers in China declared that Darunavir can desirably control the SARS-CoV-2 in laboratory-based setup [16]. Cell-based experimental studies established that Darunavir within in-vitro situation remarkably hindered replication of virus, when having 300 ?M concentration. It was also determined that its inhibition efficiency was 280-fold compared to what was observed in the untreated group [16]. The combination of Darunavir and Ritonavir has poor in-vitro efficacy against SARS-CoV-2. Taking into consideration the similar mechanism od actions of Lopinavir and Darunavir, it is improbable that Darunavir would render any benefit if Lopinavir does not [17].

1.3 Favipiravir: Favipiravir, a novel example of RNA-dependent type RNA polymerase inhibitor, can selectively impede the RNA polymerase in a wide diversity of viruses, including influenza virus, to an extent that even influenza viral particles, which are refractory to other antiviral agents can be efficaciously contained by Favipiravir. As well as its anti-influenza activity, Favipiravir can actually block the replication of a wide diversity of viral particles including RNA viruses [18]. Favipiravir is firstly transformed into an active phosphoribosyl structure within cells, then RNA polymerase of virus identifies it as

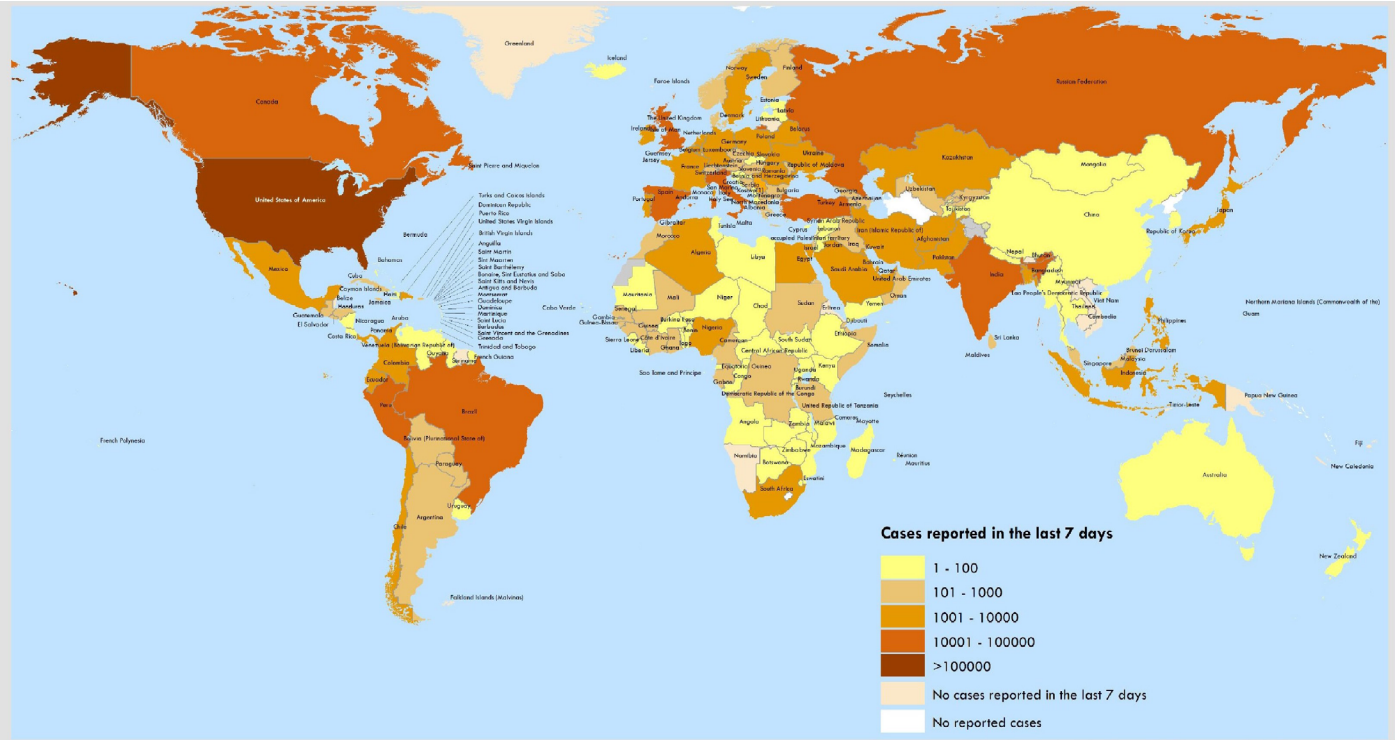

Figure 1. Distribution of COVID-19 patients throughout the world in May 3rd 2020.(source: World Healt Organization fact sheet 104)

a substrate, which in turn hampers RNA polymerase activity effectively [19]. Ergo, Favipiravir might provide potential antiviral features against SARS-CoV-2, being a RNA virus itself. A study about Favipiravir was conducted which aimed at treating COVID-19. This trial depicted that Favipiravir showed more influential antiviral activity compared to Lopinavir/Ritonavir [20]. Although, it is crucial to understand that this agent is still being evaluated by some clinical studies, and therefore far it has been proven appropriately helpful against SARS-CoV-2.

1.4 Remdesivir: Remdesivir is known as a nucleoside analogue as well as a wide-spectrum antiviral agent with particular protective properties against Ebola virus in humans and other coronaviruses in non-human primates. Remdesivir selectively affect viral polymerases, so it is quite anticipated to have a low tendency to cause toxicity in humans [21]. The therapeutic value of Remdesivir was first explained in an animal experiment against Ebola [22]. In the mentioned study, infected rhesus monkeys that underwent Remdesivir treatment with once-a-day dosing showed promising signs of suppression of viral replication in addition to protection from the fatal disease. Other animal experimental models underlined that Remdesivir could efficaciously decrease the amount of viral particles in the pulmonary cells of the mice afflicted with MERSCoV, diminishing pathological damage to the tissue, which can prevent lung hemorrhage [23]. In the suggested approach to the outbreak of COVID-19, Wang and others disclosed that Remdesivir forcefully stops SARS-CoV-2 in low micromolar amounts, while being highly selective [24]. In the United States, Holshue and colleagues disclosed the first spectacularly treated patient, whose life had been saved by using Remdesivir [25]. Some studies have come up with this idea that the significance of early initiation of therapy to reduce virus replication and improve tissue repairing is undeniable; and that is mainly because Remdesivir is less clinically beneficial with high-titer virus inoculum. Impressively, the authors also heeded that prophylactic use of Remdesivir decreased MERS-CoV replication, which was quite similar to what was found in a murine model with SARS-CoV-1 [23, 26], and also in an in-vitro setting with SARS-CoV-2 and other coronaviruses [24, 26]. In March 2020, the company of Gilead sciences initiated randomized, open-label, multicenter Phase 3 clinical research to assess how efficacious and safe Remdesivir is in 1000 adults with COVID-19 diagnosis. On May 1st ,2020, Food and Drug Administration (FDA) allowed the emergency use of Remdesivir for critically ill COVID-19 patients [27].

1.5 Chloroquine and Hydroxychloroquine: Chloroquine has been a broadly-utilized anti-malaria agent ,which has been proved to be a powerful wide-spectrum antiviral in 2006 [28]. Moreover, Chloroquine has the characteristics of anti-inflammatory and immuno-modulatory by inhibiting the production of Tumor necrosis factor ? (TNF-?) along with Interleukin type 6 (IL-6) [29]. In the first half of February, Wang et al. illustrated puissant inhibition of SARS-CoV-2 by Chloroquine when taking two 500-mg tablets PO daily [24] similar to some clinical studies in China through this outbreak [30]. According to the works of Per Gao et al., it was indicated that chloroquine phosphate actually outdoes the control treatment in inhibiting the exacerbation of pneumonia, improving lungs radiographic findings, and curtailing the course of the disease [30]. X. Yao et al. evaluated the possible doses of Chloroquine and Hydroxychloroquine to find the optimized dose in treatment of COVID-19. They revealed that within in-vitro settings Hydroxychloroquine is more potent than chloroquine. As a conclusion, they suggested a 800 mg daily dose of hydroxychloroquine, followed by an overall maintenance dose of 400 mg per day divided in two separate doses, which was three-fold more potent compared to the 500 mg twice daily administration of chloroquine in 5 days [31]. Currently the

evidence is quite inconclusive about the effectiveness or comparative effectiveness of either Hydroxychloroquine or Chloroquine. Moreover, Chloroquine has recently become scarce and even unavailable for ordering due to a huge demand for it, all because of a significant interest gained as a potential medicinal alternative for the management of COVID-19.

1.6 Umifenovir (Arbidol): Umifenovir is a component derived from indole, which has showed positive efficacy in inhibition of virus-to-host cell attachment in different groups of influenza, and type C hepatitis virus [32]. Study of Khamitov et al. in 2008 also corroborated the anti-viral effect of Arbidol on SARS-CoV in the cell cultures [33]. The works of L. Deng and other colleagues revealed that COVID-19 patients under the treatment of Arbidol combined with Lopinavir/Ritonavir had a significant clinical improvement in comparison with patients administrated with Lopinavir/Ritonavir alone [34]. A randomized clinical trial has illustrated that COVID-19 infected cases who were treated by Arbidol, had an impressive reduction in fatality rate along with a better efficacy of treatment, in comparison with those administrated with Kaletra [35]. Nevertheless, it is still needed to do further research on the effectivity of Arbidol specifically in much larger populations, so there can be a more solid conclusion ensured.

1.7 Ribavirin: Ribavirin is known to be a nucleoside analogue with a wide variety of antiviral features. Different combinations of Ribavirin, Interferon, with other antiviral agents are currently being studied in multiple clinical trials. Wang et al. assessed how efficacious in-vitro Ribavirin was versus SARS-CoV-2, which in fact appeared to be over 100-fold less effective than Remdesivir [24]. Furthermore, in a comparison research, the fatality rate and complications caused by ARDS was notably decreased within SARS-CoV-1 infected individuals, when undergoing the combination-therapy of both Ribavirin and Ritonavir [10]. The possibility of hematologic toxicity at high dosages probably exceed potential clinical benefit, and for that reason, Ribavirin was not viewed as a feasible candidate for further evaluation by the WHO research and development plan for SARS-CoV-2. A lack of in-vitro efficacy and toxicity profile along with poor outcomes are in fact among the main reasons for such matter.

1.8 Oseltamivir: Provided its antiviral powers against influenza, substantial attention has been attracted to Oseltamivir, as a strong treatment option for COVID-19. This got more intense because of the preliminary report from Huang and colleagues in Wuhan where managed COVID-19 patients received Oseltamivir as well as wide-spectrum antimicrobials [36]. The only data evaluating Oseltamivir activity against Coronaviruses pointed it out to be ineffective in SARS-CoV-1 inhibition at a concentration of 10,000 ?M/L [37]. That is because Coronaviruses do not deploy neuraminidase in the first place, so there is no enzyme to be blocked from use by Oseltamivir. This fact would also hold true for Zanamivir, Peramivir, or any other neuraminidase inhibitor drugs. Consequently, considering the crucial need for these medications in the management of influenza and rising concern for drug scarcity with Oseltamivir, these drugs should be avoided in patients with COVID-19 specifically when influenza has been excluded from the diagnosis.

1.9 Nitazoxanide: Nitazoxanide has demonstrated positive efficacy against different varieties of viruses such as influenza, parainfluenza, and SARS-COV-1 in some of in-vitro trials [38]. It is suggested that the main antiviral property of Nitazoxanide is concerned with inhibiting the host-regulated cycles which are related to replication rather than the viral pathways themselves [38]. Even though the in-vitro activity of Nitazoxanide had hopeful results as a treatment of SARS-CoV-2, in recent clinical trial studies [24, 38], it did not show an effective role in decreasing the hospitalization period or improving clinical manifestations in COVID-19 patients [39]. Notwithstanding, more clinical evaluations are required, so we could start a proper discussion surrounding the effectiveness of Nitazoxanide against SARS-CoV-2.

2. Immune-Enhancing Drugs

2.1 Interferons: It has been depicted in various clinical studies that Interferon-? had been helpful in treatment of individuals who were affected by SARS-CoV-1 [40]. In a study, it was delineated that Interferons can be an efficacious inhibiting factor of the replication in different virus genomes, for instance MERS virus, which in fact is considered a member of Coronavirus family [41]. Those findings in addition to interferon's innate anti-viral ability, propounded that it can be utilized in the therapeutic procedure of COVID-19. Generally, both interferon-? and interferon-? have been proven to suppress the viral replication of SARS-CoV in-vitro [42]. But on a more specific note, research conducted within laboratory-based settings firmly indicated that interferon-? in concentrations greater than1000 U/ml, could slightly hinder SARS-CoV replication [43]. In a retrospective study conducted on patients afflicted with MERS who had undergone combination therapy within 1-3 days of ICU admission, the mixture of drugs was not connected with improved mortality or increased viral clearance [44]. Of note, it is critical to know that its downsides include severe cytopenia, hepatoxicity, and risk of developing fatal or life-threatening ischemia or infection, specifically when combined with Ribavirin.

2.2 Intravenous immunoglobulin (IVIG) and Thymosin alpha-1: Intravenous immunoglobulin is deemed as the most harmless immune regulator in abiding use for every age group. It might also be of help in inhibiting the release of pro-inflammatory factors, and in turn enhance the making of anti-inflammatory factors [45]. as a further matter, Thymosin alpha-1 can increase immunity in fighting against SARS, ably containing the distribution of virus [46]. Accordingly, IVIG therapy and Thymosin alpha-1 has been considered as treatments for SARS-CoV-2. Although, the supporting information on the matter are considerably poor and clinical studies are still in process.

3. Anti-Inflammatory Agents

3.1 Tocilizumab (Actemra): IL-6 is one of the key factors responsible for immunologic response and symptoms in patients presenting with cytokine storming syndrome [47]. Hyper-inflammatory responses due to elevated IL-6, has been observed in severe cases of COVID-19 and were related with risen mortality [48]. Tocilizumab, a humanized antibody inhibiting IL-6

receptors, has been the first FDA-approved therapeutic agent for treating different types of arthritis including rheumatoid arthritis [49]. Immunotherapy with Tocilizumab is mentioned as a therapeutic option for severe or critical cases of COVID-19 with increased levels of IL-6 in some of the major COVID-19 guidelines published in different countries [50]. The optimal timing of administrating Tocilizumab during the disease course is yet to be described. Besides, a known IL-6 threshold has still not been introduced for progression to severe disease. It is essential to continue to follow the long-term results in these patients for fully evaluating the risk versus benefit of Tocilizumab, mainly because Tocilizumab might render a patient more prone to bacterial infection, and has been connected with neutropenia and thrombocytopenia [51].

3.2 Corticosteroids: There has been a huge amount of interest and controversy surrounding the impact of corticosteroids in subduing critical pneumonia caused by coronaviruses. The potential advantage of these drugs to dull the inflammatory cascade observed in severe disease is required to be carefully assessed, while considering the apprehensions for secondary infections, adverse reactions, and other complications of corticosteroid treatment. Several examinations demonstrated no influence on results [52], one report showed diminished mortality in critically ill patients [53], and others have proved worse results for patients receiving steroids, including enhanced time of viral clearance [54], or a rise in the composite endpoint of ICU admission or death [55]. Some proofs regarding SARS-CoV-2 underlined a lessened fatality in individuals with ARDS [56]. Because glucocorticoid could subdue immunity and could detain clearance of SARS-CoV-2 [57], physicians need to meticulously analyze the risks and benefits of corticosteroids on an individual basis. This need for pros and cons evaluation in individual patients and attentive contemplation of dose, is fully explained in COVID-19 guidelines published by China's officials. In fact, within this very document the authors stated "Based on respiratory distress and chest imaging, may consider glucocorticoid that is equivalent to methylprednisolone one to two mg per kg per day for three to five days or less [58]."

4. Miscellaneous Therapeutic Measures

4.1 Convalescent Plasma Therapy: Since no vaccine has been discovered for SARS-CoV-2, passive immunotherapy by convalescent plasma may be a helpful choice for controlling the infection of COVID-19 [59]. The role of convalescent Plasma in treatment of viral infections including influenza and hepatitis has been shown in clinical researches [60, 61]. Patients who are relieved from a viral infection, have high levels of antibodies against the virus in their blood. The use of these immune factors, may prevent the excess replication and decrease the load of virus, as well as preventing the individual form being infected for another time. Since the maximum level of viral load happens mostly in the first seven days of the infections caused by viruses, it could be expected that convalescent plasma therapy in primary stages of the disease produce better results [59, 62]. To evaluate the efficacy of Convalescent Plasma treatment, Shen C. et al. treated 5 immensely ill COVID-19 cases who were suffering from the complication of ARDS with convalescent Plasma. As a result, 4 patients were relieved from ARDS in the second week after transfusion and the viral load had been noticeably reduced [63]. Notwithstanding, the small statistical population of the study makes it difficult to precisely discuss about the efficacy of convalescent Plasma in treatment of SARS-CoV-2 infection.

4.2 Auxiliary Blood Purification Treatment: Angiotensin-converting enzyme 2 (ACE2) receptors are vastly observed in kidneys, which are one hundred folds greater than their distribution in the respiratory system [64, 65]. Based on the recent findings, ACE2 receptors are considered to be the cell entering receptors for the causative virus of COVID-19 [66]. Therefore, it could be expected that kidneys, may also be targeted by this virus. In SARS-CoV-2 infected patients, the excess and uncontrolled immune system response leads to great number of inflammatory factors production and release which may cause multi organ damage [67]. Timely initiation and persistent therapy of blood purification in affected patients may improve renal function. Moreover, removing the cytokines from the blood plasma by blood purification therapy could prevent the patient from cytokine storming syndrome and subsequent organ dysfunction. Furthermore, as the COVID-19 patients may have electrolyte disturbance induced by SARS-CoV-2 attachment to ACE2 receptors and associated hypokalemia [68], blood purification could reduce the risk of water-electrolyte disorder and its complications.

4.3 Angiotensin II receptor blocker (ARBs)/ Angiotensin converting enzyme (ACE) Inhibitors: Renin-angiotensin system (RAS) is reported to have a crucial part in regulating acute viral lung injury and hypertension resulted from viral infections such as influenza virus and SARS-CoV [69, 70]. The pathogenesis of inflammatory lung disease and hypertension is associated with alterations in RAS functioning. Earmarking RAS for a therapy target is an efficacious clinical technique for antihypertension treatment. ARBs and ACE Inhibitors, by blocking ACE/Angiotensin II/Angiotensin 1 Receptor, have been widely used as medicines for cases with hypertension. New research shows that COVID-19 cases with hypertension have been prone to experience severe conditions [71]. Researches also indicated that cases with COVID-19 have elevated levels of Angiotensin II in comparison with healthy individuals [72]. The unusual rise in the levels of Angiotensin II was correlated with pulmonary insufficiency and hypertension. Furthermore, it has been demonstrated that RAS inhibitors are related to diminished mortality in sepsis patients [73]. Angiotensin II increases the production of inflammatory cytokines [74]. Inordinately elevated amounts of inflammatory cytokines are in fact damaging COVID-19 cases' outcomes. A new research by Meng J. and others found that cases undergoing therapy with ARBs or ACE Inhibitor had a lower serious disease prevalence and a lower peripheral blood IL-6 level [75]. Although, no more verified clinical proof has been published to date.

CRITICAL CARE STRATEGIES

Hospitalization might not be primarily required for cases with a mild clinical presentation, although in the second week of illness it is quite expected that clinical manifestations aggravate with the disease developing to lower respiratory tract ,which is why

all patients must be watched strictly [76]. Probable elements of danger for developing the critical form of disease can be as follows: being aged, chronic ailments such as cancer, diabetes, renal disorders, liver disorders, cerebrovascular disorders, heart failure, and of course pulmonary disorders as well as pregnancy and autoimmune conditions [48]. However, the possible risk factors are not just limited to what was mentioned. Whether a patient has to be put in the inpatient or outpatient department must be decided based on an individual patient-by-patient rationale. The admitted patients should stay in bed rested, being monitored for vital signs, and also as a strong recommendation, they should be provided with caring treatment to make sure that adequate intake of energy and balance for pH levels, electrolytes and water along with other inner environment factors are all maintained. The patient has to be watched for blood routine test, CRP, PCT, arterial blood gas analysis, organ function tests as well as chest imaging. The laboratory findings has showed to be predictable for the prognosis of COVID1-9 [77]. In highly ill patients, controlling the severity of the condition and enhancing the quality of respiratory status is based on three key principles:

1. Oxygen Therapy

An efficacious oxygen therapy should be provided for the patient, being constituted of nasal cannula, non-invasive ventilation (NIV), high flow nasal oxygen (HFNO) therapy, and invasive mechanical ventilation considering patient respiratory status [76, 78]. Oxygen therapy has always been the first option introduced to cases afflicted with shock, hypoxemia, respiratory distress and severe respiratory infections. There are certain measures concerned with oxygenation that can impressively help patients get better [79].

HFNO has always been among the effective measures. HFNO can bestow a Fraction of inspired oxygen (FiO2) of up to 1.0, and 60 Liter per minute of gas flow [80]. HNFO as against standard oxygen therapy, can effectually decrease the necessity of tracheal intubation. There are particular contraindications such as patients afflicted with abnormal mental status, hypercapnia, multi-organ failure and hemodynamic instability must not be provided with HFNO [76]. However, HFNO might be harmless to utilize in individuals with non-aggravating hypercapnia of mild to moderate degree. With all that being mentioned, it's important to note that if the respiratory distress doesn't get better or even gets worse immensely while receiving HFNO (gas flow of more than 50 L/min, FiO2 of more than 70%, for one hour), the method of breathing support has to be altered [76, 80].

NIV, as the second strategy for respiratory support, renders a definite positive-pressure ventilation provided by the sealed mask. For increasing oxygenation, HFNO might be of use accompanying fitful short-term NIV (1 to 2 hours) [76, 81]. But in the event of pandemic viral diseases resulting in hypoxemic respiratory failure, NIV guidelines do recommend to utilize respiratory support treatment. A few evidence have demonstrated that NIV has an increased rate of failure in MERS cases [76, 82].

Invasive mechanical ventilation as the third supportive means for respiration, should be carried out immediately if ARDS keeps getting worse under the support of HFNO or NIV [83]. In fact, if the demand for FiO2 and gas flow is more than 70% and 50 L/min, respectively, endotracheal intubation is indicated [76]. Endotracheal intubation should be implemented by experienced professionals who have the expertise, while considering all airborne precautions. That's mainly because endotracheal intubation is a procedure that might create abundant amounts of transmissible aerosols.

Extracorporeal Life Support (ECLS) as the final strategy for respiratory support, is thought of as a strong recommendation in the cases that have refractory type of hypoxemia which is hard to be treated using protective lung ventilation [84]. Whilst the steps of invasive mechanical ventilation are going on, if the individual keeps staying in hypoxia condition, accompanied with risen carbon dioxide partial pressure, particularly after prone ventilation and muscle relaxation, it is crucial to carry out ECLS [76], Although, it is strongly indicated that ECLS treatment should only be implemented in the presence of adequate expertise [84, 85]. Presently, the ECLS in ICU offers two settings of Extracorporeal Membrane Oxygenation (ECMO): The VV-ECMO (in which the blood gets oxygenized by membrane oxygenator before returning to right atrium through internal jugular vein), and VA-ECMO (in which the blood gets oxygenized by membrane oxygenator straight before getting into aortic system through femoral artery). As a matter of fact, in some severe ARDS cases only if the lung injury score exceeds 3 or the pH becomes less than 7.2, ECMO might be of use but not for all ARDS patients [76, 85].

2. Utilizing Antiviral Agents

The administration of powerful antiviral agents for limiting the replication of virus could be of help in improving the condition of patient. Indeed, it is quite implausible to be released from intensive respiratory ventilation and to improve oxygen saturation without the proper use of antivirals [86]. In recent case-control study of Q. Cai and others, cases treated by Favipiravir plus aerosol inhalation of Interferon-? demonstrated a considerable viral clearance time compared to control arm group who underwent the combination-therapy of Lopinavir/Ritonavir and Interferon-?. Additionally, chest x-ray of patients under the treatment of Favipiravir showed remarkable improvement in this study [87]. In other recent studies, Remdesivir is deemed as another useful drug in managing the viral load, and ameliorating patients admitted to intensive critical care units [86].

3. Inhibiting Cytokine Release

The S component of the SARS-COV-2 attaches to the ACE2 receptor of host-cell and releases RNA after the fusion with cell membrane. Pattern recognition receptor (PRRs) of host-cell which are mainly considered as Toll like receptors (TLR) will recognize the viral RNA [88]. These complicated signaling procedures will lead to production of Interferons and a series of inflammatory cytokines [89]. Based on the mentioned molecular findings, it could be expected that drug administration of interferons which are thought as the downstream cascade molecules of immune response to SARS-CoV-2, may enhance the immunity against COVID-19. On the other hand, triggering of series immune response and cytokine storming may lead the patient into life-threatening condition, in which some pro-inflammatory and inflammatory factors have been showed to increase in

COVID-19 patient's plasma considering Interferon gamma, TNF- ?, Interleukin types of 1, 2, 4, 6, 7, and 10 [36, 90]. Timely Inhibition of cytokine release expectedly could help prevent the threatening complications in patients. The appropriate onset of administrating and dosing range of anti-inflammatory drugs including Tocilizumab; both required to be more evaluated; are vital to be considered. Furthermore, there are plenty of challenges to be faced for using such drugs which could have negative impact in treatment of COVID-19. Some of the most troublesome of which includes the high expense, black market intervention and their unavailability [76].

CONCLUSION

Despite the fact that several months have passed from the onset of COVID-19 pandemic, a solid comprehensive treatment strategy which is adequately reliable, has not been fully established. However, the recent studies have shown more promising effects of particularly Remdesivir on SARS-CoV-2 among anti-viral drugs as well. Oxygenation is the first mainstay of treatment in COVID-19 ill patients in which the type of support differs according to their condition, including HFNO, NIV, intubation and ECMO. Interferons, intravenous Immunoglobulins, and Thymosin ?-1 may increase immunity in fighting against COVID-19. Inhibition of inflammatory factors and cytokine storming could have a critical role in the progress of the disease. An important key is the time of initiation and dosage of these drugs. Treatment with convalescent plasma and Auxiliary Blood Purification may be life-giving in some cases.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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(https://www.who.int › situation-reports › 20200503-covid-19-sitrep-104)

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