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Review

COVID-19 Treatment at a Glance

Hüseyin Arıkan[1], Dilek Karadoğan[2], Fatma Tokgöz Akyıl[3], Aycan Yüksel[4], Zehra Nur Töreyin[5], Canan Gündüz Gürkan[6], Feride Marim[7], Tuğba Şişmanlar Eyüboğlu[8], Nagehan Emiralioğlu[9], Tuğba Ramaslı Gürsoy[8], İrem Şerifoğlu[10], Abdulsamet Sandal[11], Aslı Öncel[12], Berrin Er[13], Neslihan Köse[14], Dorina Esendağlı[15], Mina Hızal[16], Aslıhan Banu Er[17], Fatma Esra Günaydın[18], İlknur Kaya[19], Hilal Özakıncı[20], Ümran Özden Sertçelik[12], Hatice Çelik Tuğlu[21], Nilüfer Aylin Acet Özürk[18], Özlem Ataoğlu[22], Ahu Cerit Çakır[23], Hüseyin Toptay[24], Merve Erçelik[22], Elif Develi[25], Selman Çelik[26], Fatma Gülsüm Karakaş[27], Halime Yıldırım[28], Damla Karadeniz Güven[12], Nazlı Çetin[29], Sümeyye Nur Aslan Küçükyurt[30], Mehmet Fatih Elverişli[32], Pinar Yıldız Gülhan[33], Metin Akgün[34]

[1]Department of Internal Medicine, Intensive Care Unit, Yüzüncü Yıl University, Dursun Odabaş Medical Center, Van, Turkey
[2]Department of Chest Diseases, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey
[3]Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
[4]Department of Chest Diseases, Ufuk University School of Medicine, Ankara, Turkey
[5]Department of Occupational Health and Diseases, Adana City Research and Training Hospital, Adana, Turkey
[6]Department of Chest Diseases, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
[7]Department of Chest Diseases, Kütahya University of Health Sciences School of Medicine, Kütahya, Turkey
[8]Department of Pediatric Pulmonology, Gazi University School of Medicine, Ankara, Turkey
[9]Department of Pediatric Pulmonology, Hacettepe University School of Medicine, Ankara, Turkey
[10]Clinic of Chest Diseases, Kırıkhan State Hospital, Hatay, Turkey
[11]Department of Occupational Health and Diseases, Ankara Occupational and Environmental Diseases Hospital, Ankara, Turkey
[12]Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey
[13]Department of Internal Medicine, Hacettepe University School of Medicine, Unit of Intensive Care, Ankara, Turkey
[14]Clinic of Chest Diseases, Bilecik State Hospital, Bilecik, Turkey
[15]Department of Chest Diseases, Başkent University School of Medicine, Ankara, Turkey
[16]Department of Pediatric Pulmonology, Ankara Training and Research Hospital, Ankara, Turkey
[17]Department of Chest Diseases, Denizli State Hospital, Denizli, Turkey
[18]Department of Chest Diseases, Allergy and Immunology, Uludağ University School of Medicine, Bursa, Turkey
[19]Clinic of Chest Diseases, Ardahan State Hospital Ardahan, Turkey
[20]Department of Pathology, Ankara University, School of Medicine, Ankara, Turkey
[21]Department of Chest Diseases, Kahramanmaraş Afşin State Hospital, Kahramanmaraş, Turkey
[22]Department of Chest Diseases, Düzce University, School of Medicine, Düzce, Turkey
[23]Clinic of Chest Diseases, Siirt State Hospital, Siirt, Turkey
[24]Department of Intensive Care Unit, Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, İzmir, Turkey
[25]Department of Physiotherapy and Rehabilitation, Yeditepe University, School of Health Sciences, İstanbul, Turkey
[26]Department of Nursing, Yeditepe University, School of Health Sciences, İstanbul, Turkey
[27]Department of Chest Diseases, İstanbul Cerrahpasa University, Cerrahpaşa School of Medicine, İstanbul, Turkey
[28]Department of Medical Biology, University of Health Sciences, School of Medicine, İstanbul, Turkey
[29]Department of Chest Diseases, Pamukkale University School of Medicine, Denizli, Turkey
[30]Department of Chest Diseases, Osmangazi University School of Medicine, Eskişehir, Turkey
[32]Clinic of Chest Diseases, Ünye State Hospital, Ordu, Turkey
[33]Department of Chest Diseases, Düzce University School of Medicine, Düzce, Turkey
[34]Department of Chest Diseases, Atatürk University School of Medicine, Erzurum, Turkey

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Abstract

As coronavirus disease 2019 (COVID-19) spreads across the world, the ongoing clinical trials are leading to a big race worldwide to develop a treatment that will help control the pandemic. Unfortunately, COVID-19 does not have any known effective treatment with reliable study results yet. In this pandemic, there is not a lot of time to develop a new specific agent because of the rapid spread of the disease. The process of developing a vaccine is long and requires hard work. Although the pathophysiology of the disease is not fully understood, some of the proposed treatment alternatives are based on old evidence and some have been used with the idea that they might work owing to their mechanism of action. The efficacy, reliability, and safety of the currently available treatment alternatives are therefore a matter of debate. Currently, the main therapies used in the treatment of COVID-19 are antiviral drugs and chloroquine/hydroxychloroquine. Other proposed options include tocilizumab, convalescent plasma, and steroids, but the mainstay of the treatment in intensive care units remains supportive therapies.

KEYWORDS: Coronavirus disease 2019, treatment, hydroxychloroquine, tocilizumab, convalescent plasma

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INTRODUCTION

"…fires had been put out by volunteers using brickmason's ladders and buckets of water carried in from wherever it could be found, and methods so disorderly that they sometimes caused more damage than the fires."

Love in the Time of Cholera – Gabriel Garcia Marquez

Address for Correspondence: Dilek Karadoğan, Department of Chest Diseases, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey
E-mail: cakmakcidilek@yahoo.com

With early data indicating that one of five patients with coronavirus (CoV) disease 2019 (COVID-19) develop acute respiratory distress syndrome (ARDS), an understandably alarming situation has emerged in the absence of definitive treatments [1]. However, some pharmacotherapies have been recommended for critically ill COVID-19 patients: systemic corticosteroids, antivirals such as oseltamivir, ganciclovir, lopinavir/ritonavir and remdesivir, chloroquine/hydroxychloroquine, angiotensin receptor blockers (ARB) and even soluble angiotensin converting enzyme 2 (ACE2), convalescent plasma and tocilizumab. These are in addition to standard, supportive therapies such as oxygenation, ventilation and rational fluid management in the intensive care unit (ICU). While this short summary is inarguably incomplete and should not replace clinical judgement regarding individual patient management, it is intended to remind clinicians therapeutic recommendations based on relatively sparse evidence.

Chloroquine/Hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HQ) have the same mechanism of action against CoVs, but in vitro data suggest that HQ may be more potent. The mechanisms of action of these drugs are diverse and include inhibition of viral cell binding, endosomal membrane fusion, and post-translational modification of viral proteins. Also, CQ is a well-known modulator of the immune system. For example, CQ inhibits interleukin-1 beta, interleukin-6 (IL-6), tumor necrosis factor-alpha, interferon-alpha, among others [2]. The first clinical data for CQ and HQ were encouraging, and HQ is reported to be better tolerated [3, 4]. In early phase of pandemic, observational data have also been reported showing that in a small number of patients the addition of azithromycin supports the antiviral effects of CQ [5]. In fact, after this study, the President of the United States (USA) Donald Trump reported this on social media as one of the most important developments in the history of medicine and attracted the attention of the world. However, the Surviving Sepsis Campaign (SSC) COVID-19 guidelines stated that there is insufficient evidence to publish a recommendation on the use of CQ or HQ in critically ill adults with COVID-19 [6]. Infectious Diseases Society of America (IDSA) guidelines recommended the use of CQ/HQ treatment as a part of a clinical trial since the benefits and risks of treatment in hospitalized COVID-19 patients are not yet known [7]. In the following days, observational and randomized controlled studies of HQ have been published. A randomized-controlled study from China had demonstrated no clinical and virologic benefit of HQ in 150 patients with mild to moderate disease. Moreover, an increased side effects were stated compared to control group [8]. Clinical benefit has not been demonstrated in two major observational studies published after the approval of the use of hydroxychloroquine in COVID-19 treatment in the USA [9, 10]. In addition, in a multinational registry study the use of CQ/HQ has been reported to be associated with a decrease in in-hospital survival. But this report resulted in a controversy and authors failed to provide database. As a result, it has been retracted [11]. In the randomized, controlled, open label trial of RECOVERY, mortality and time until discharge with either HQ (1,561 patients) or standard care (3,155 patients) were compared. Incidence of death at 28 days was 27% in HQ arm and 25% in standard care arm (Rate ratio:1.09, CI: 0.97-1.23). Hospital stay was longer in HQ group (16 days, vs. 13 days, respectively). The trial was terminated due to lack of efficacy with HQ [12]. These findings resulted in revoking of emergency use authorization (EUA) of CQ/HQ by USA Food and Drug Administration (FDA) on 15 June 2020 [13]. However, while revoked this EUA provided patients access to a probable therapy and resulted in a robust clinical data on effectiveness. In March 2020, World Health Organization (WHO) had initiated a large, randomized adaptive trial which started originally with four arms (remdesivir, HQ, lopinavir and interferon beta-1a). Being as an adaptive trial, some treatment arms were dropped, new treatment options were added as time passed. On 19 June 2020, WHO announced that trial's HQ arm was discontinued as interim analysis showed little or no effect [14]. Interim results published on December 2 showed that mortality was 11% in HQ group and 9.2% in control group (rate ratio, 1.19; 95% CI, 0.89 to 1.59; p=0.23). Hospital stay, ventilatory support requirement and mortality were not reduced with HQ in hospitalized patients [15]. In conclusion, clinical studies have not demonstrated any clinical benefit on the use of CQ and HQ in COVID-19.

Antivirals

Lopinavir/ritonavir (LPV/r) is an antiviral most commonly used in treatment of human immune-deficiency virus (HIV) infection. Lopinavir is a protease inhibitor that also plays a role in the CoV life cycle, while ritonavir acts as a lopinavir enhancer by inhibiting lopinavir's CYP3A-mediated metabolism. There is older evidence to support the use of LPV/r in the first severe acute respiratory syndrome CoV (SARS-CoV) epidemic, and these were the basis for research in SARS-CoV-2 [16, 17]. However, a recent randomized controlled trial (RCT) failed to show positive effects for LPV/r as monotherapy in severe COVID-19. In addition, those treated with lopinavir/ritonavir had more adverse effects [18]. IDSA guideline recommended using LPV/r for clinical study purposes only. Recently published interim results of WHO Solidarity Trial showed no mortality difference between LPV/r and its control group (10,6% vs 10,5% rate ratio, 1.00; 95% CI, 0.79 to 1.25; p=0.97). Also, LPV/r did not result in prevention of mechanical ventilation requirement or reduction in duration of hospitalization [15].

Remdesivir is a nucleotide analog inhibitor of RNA-dependent RNA polymerases that have activity against RNA viruses (eg Ebola, SARS-CoV and Middle East respiratory syndrome-Cov [MERS-CoV]). More specifically, remdesivir is an adenosine analog that gets incorporated in the viral RNA chains and results in premature termination [19]. In the first COVID-19 case reported in the USA, intravenous remdesivir was used

MAIN POINTS

- Treatment of COVID-19 is a challenging process.
- Evidence regarding therapy options are ever changing.
- In the intensive care settings mainstay of treatment is still best supportive care until a definitive treatment or a protective vaccine.

without reporting any adverse events [20]. Afterwards, a series of 53 cases were published and became the focus of great media attention. Although no viral data were given, 68% of patients reported to have clinical improvement and mortality rate was reported to be 13% [21]. However, no clinical benefit was shown in the first RCT published. This was attributed to the inability to reach targeted patient numbers by the authors [22]. Immediately after the publication of this study, the initial results of a US-based randomized controlled clinical trial were shared at a press conference by Anthony Fauci, director of the National Institute for Allergy and Infectious Diseases. According to the first results, remdesivir has been reported to shorten the time to recovery compared to placebo. Final report showed that median recovery time was significantly shorter in patients receiving remdesivir (10 days vs. 15 days, rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; p<0.001) [23]. In August 2020 results of industry sponsored GS-US-540-5774 trial were published. According to a 7-point scale clinical status of patients were evaluated at day 11. The probability of improvement on 7-point scale was higher in 5-day remdesivir group compared to standard care group (odds ratio, 1.65; 95% CI, 1.09 to 2.48; p=0.02) [24]. Following these promising results US FDA approved remdesivir for treatment of COVID-19 requiring hospitalization on October 22 [25]. However, recently published interim results of WHO Solidarity Trial showed no difference in mortality between remdesivir and its control group (rate ratio, 0.95; 95% CI, 0.81 to 1.11; p=0.50). Additionally, remdesivir was not demonstrated to reduce mechanical ventilation reqirement and to decrease the duration of hospitalization [15]. Uncertainty still remains regarding remdesivir.

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor. The first experience of its use in the treatment of COVID-19 was shared at a press conference by an official of the Ministry of Science and Technology of China. It has been stated to be used in 340 patients and shortened fever duration, decreased viral load and improved radiological findings were reported [26]. The initial results of a total of 80 patients (including the study group and the control group) showed that favipiravir had a stronger antiviral effect than LPV/r. There was no significant adverse reaction in the favipiravir treatment group and significantly fewer side effects than the LPV/r group [27]. In the randomized controlled study published without peer-review comparing favipiravir and umifenovirin, no significant difference was found between the two drugs when the recovery rate was evaluated on the seventh day. But with favipiravir, fever and cough have been reported to have a shorter recovery time [28]. An observational study from Japan including 2,158 cases from 407 centers has shown higher rates of clinical improvement at day 7 and 14 with favipiravir. But this report did not undergo a peer-review process and published online on the Japanese Association for Infectious Diseases web site [29]. Unfortunately, better structured randomized controlled trials for favipiravir have not yet been published and evidence is scarce. Also, there is emerging evidence regarding ineffective plasma concentrations in critically ill patients with usual dosing. Despite this uncertainties, favipiravir is being used in several countries with emergency approvals by medical authorities.

Considering the reports showing the epidemiological and clinical features of the patients, although it isseen that patients are using oseltamivir or ganciclovir, the literature supporting the use of these agents is small and in vitro data show that these drugs have at least no role against SARS-CoV [30-32].

Tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody that targets IL-6 receptors. It is used in the treatment of rheumatoid arthritis (RA) and has a good safety profile. During the course of COVID-19, a fatal clinical situation named as 'cytokine storm' could develop, characterized by excessive cytokine release and multiple organ failure. This is also called secondary hemophagocytic lymphohistiocytosis (sHLH). Classically, sHLH is roughly manifested by cytopenia, high levels of serum ferritin, persistent fever, and ARDS [33]. A potential way to screen for severe COVID-19 patients where anti-inflammation is required is to calculate HScore. A 170 or higher HScore has very good sensitivity and specificity for the diagnosis of sHLH [34]. TCZ was shown to be associated with decreased incidence of mechanical ventilation in hospitalized patients with COVID-19 [35]. In contrast, several RCTs reported non-significant difference in in-hospital mortality with TCZ [36, 37]. On the other hand, earlier use of TCZ before clinical progression, may be more efficacious. A multi-center study had compared outcomes of severe COVID-19 patients who received TCZ within the first two days or not. In-hospital mortality was found to be lower in patients receiving TCZ early [38]. In a series of 43 severe COVID-19 patients, a reduced mortality and shorter duration of hospital stay were shown in patients whom TCZ was administered before ICU admission [39]. No serious adverse effects were reported in any of these studies.

Anakinra

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist which inhibits the proinflammatory cytokines IL-1α and IL-1β and is approved for RA and cryopyrin-associated periodic syndromes. Lately there is a tendency among clinicians in using anakinra in COVID-19 patients with cytokine-storm. However, there is no completed RCT nor clinical trial against or in favor of anakinra. Decreased rates of need for intubation and mortality were reported in severe COVID-19 patients treated with anakinra in a small retrospective cohort study [40]. In another cohort including three groups of moderate-severe COVID-19 patients who received high-dose (5 mg/kg twice a day intravenously) anakinra, low-dose (100 mg twice a day subcutaneously) anakinra, and standard treatment; significantly higher survival was found in high-dose anakinra group than standard treatment group [41]. A few case series have reported that all COVID-19 patients receiving anakinra survived, respiratory failure was improved, and no secondary bacterial infection was encountered [42, 43]. Mortality rate was significantly lower in COVID-19 patients with hyperinflammation and respiratory failure treated with anakinra plus methylprednisolone compared to control group (adjusted HR 0.18 (95%CI 0.07-0.50), p=0.001) [44]. There is no compelling evidence for anakinra in severe COVID-19, still there are ongoing clinical trials evaluating its efficacy.

Table 1. Completed randomized controlled trials regarding systemic corticosteroids in patients with COVID-19

Clinical trial	Country	Drug	Dose and duration	Primary outcome
RECOVERY[48]	UK	Dexamethasone	6 mg po/IV	Lower incidence of death within 28 days (RR=0.83; [95%CI], 0.75 to 0.93; P<0.001)
GLUCOVID[49]	Spain	Methylprednisolone	40 mg IV, twice a day, for 3 days and 20 mg IV, twice a day, for 3 days	Reduced risk of the composite endpoint of admission to ICU, NIV or death (RR=0.55 [95% CI 0.33-0.91]; p=0.024)
CoDEX[50]	Brazil	Dexamethasone	20 mg IV for 3 days and 10 mg IV for 3 days	Increased ventilator-free days (difference, 2.26; 95% CI, 0.2-4.38; P=0.04)
CAPE-COVID[51]	France	Hydrocortisone	200 mg for 4-7 days 100 mg for 2-4 days 50 mg for 2-3 days	Decreased treatment failure defined as death or need for mechanical ventilation or high-flow oxygen on day 21 (difference of proportions, –8.6% [95% CI, –24.9% to 7.7%]; P=0.29)
REMAPCAP[52]	Multinational	Hydrocortisone	200 mg for 7 days	Improved organ support–free days (days alive and free of respiratory or cardiac support in ICU)
MetCOVID[53]	Brazil	Methylprednisolone	0,5 mg/kg IV, twice a day, for 5 days	No difference in mortality at 28 days

ICU: intensive care unit, NIV: non-invasive ventilation

Systemic Corticosteroids

This is undoubtedly a subject of intense debate, and an entire article alone can be devoted to this topic. WHO strongly recommends systemic corticosteroids in patients with severe and critical COVID-19; however, for non-severe patients WHO suggests not to use systemic corticosteroids weakly and conditionally [45]. National Institutes of Health (NIH) recommends use of dexamethasone at dose of 6 mg/day for up to ten days or until hospital discharge in hospitalized COVID-19 patients who require supplemental/high flow oxygen or noninvasive/invasive mechanical ventilation or ECMO [46]. WHO and NIH recommendations also resonates with a meta-analysis by Cano et al. in which corticosteroids are shown to reduce mortality in severely ill COVID-19 patients (OR, 0.65; 95% CI, 0.51-0.83; p=0.0006) [47]. The RECOVERY trial revealed that in patients requiring supplemental oxygen or invasive mechanical ventilation administration of dexamethasone (6 mg/daily, for ten days) resulted in lower mortality rates compared to usual care [48]. Other RCTs also provide a clear benefit for corticosteroid use in terms of short-term mortality and need for mechanical ventilation (Table 1) [49-53]. Severe hospitalized COVID-19 patients with arterial oxygen saturation between 75% and 89% were randomized into two groups as, methylprednisolone pulse (250mg/day for 3 days) group and standard care alone group in a single-blind study. Pulse methylprednisolone was associated with significantly higher rate of improvement compared to the standard care group (94.1% vs. 57.1%; p<0.001) [54]. It may be concluded that systemic corticosteroids are beneficial in treatment of severe and critically ill COVID-19 patients at equivalent doses of 6 mg/daily dexamethasone for 7-10 days without any unfavorable serious adverse effects. Advantages of systemic corticosteroids like being easily accessible worldwide with a low cost and simply administration, enhance the importance of these agents in the treatment of this pandemic. Figure 1 shows the current recommendations for anti-inflammatory treatments for hospitalized patients with hypoxemia [45, 46].

Angiotensin

There are conflicting hypotheses around the angiotensin system in the setting of the SARS-CoV-2 infection. Firstly, there are two ACEs you should know: ACE that converts angiotensin I into vasoconstrictor angiotensin II, and ACE2 that converts angiotensin II to vasodilator angiotensin 1-7. ACE2 acts as binding protein for SARS-CoV and SARS-CoV-2 [55]. Previous research has shown that long-term therapy with ARB increases ACE2, which has caused some to fear ARBs during the pandemic [56]. However, others also argued that upregulation of ACE2 by ARBs may be somewhat paradoxically useful during SARS-CoV-2 infection. This is because angiotensin receptors stimulated by angiotensin II cause increased pulmonary vascular permeability. Accordingly, the down-regulation of ACE2 by binding of SARS-CoV-2 leaves the angiotensin II unopposed, causing it to exacerbate lung damage. Therefore, ARBs are advantageous because they upregulate ACE2, which degrades Angiotensin II and directly block the action of angiotensin II at the angiotensin II receptor [57, 58]. For the aforementioned reasons, and also because of direct binding and neutralization of SARS-CoV-2, some have suggested directly administering soluble ACE2 [59].

Convalescent Plasma

Plasma (immunoglobulins) from patients recovering from viral infections can be considered in COVID-19 due to prior clinical success without serious adverse events. Indeed, immunoglobulins have been used in SARS-CoV, H1N1 and Ebola [60-62]. Also, in a meta-analysis, convalescent plasma has been associated with shorter hospitalization and lower mortality in previous outbreaks, but most of these studies have been considered poor quality [63]. Since viremia typically reaches peak within the first 7-10 days of infection, administration of immune plasma is probably the most effec-

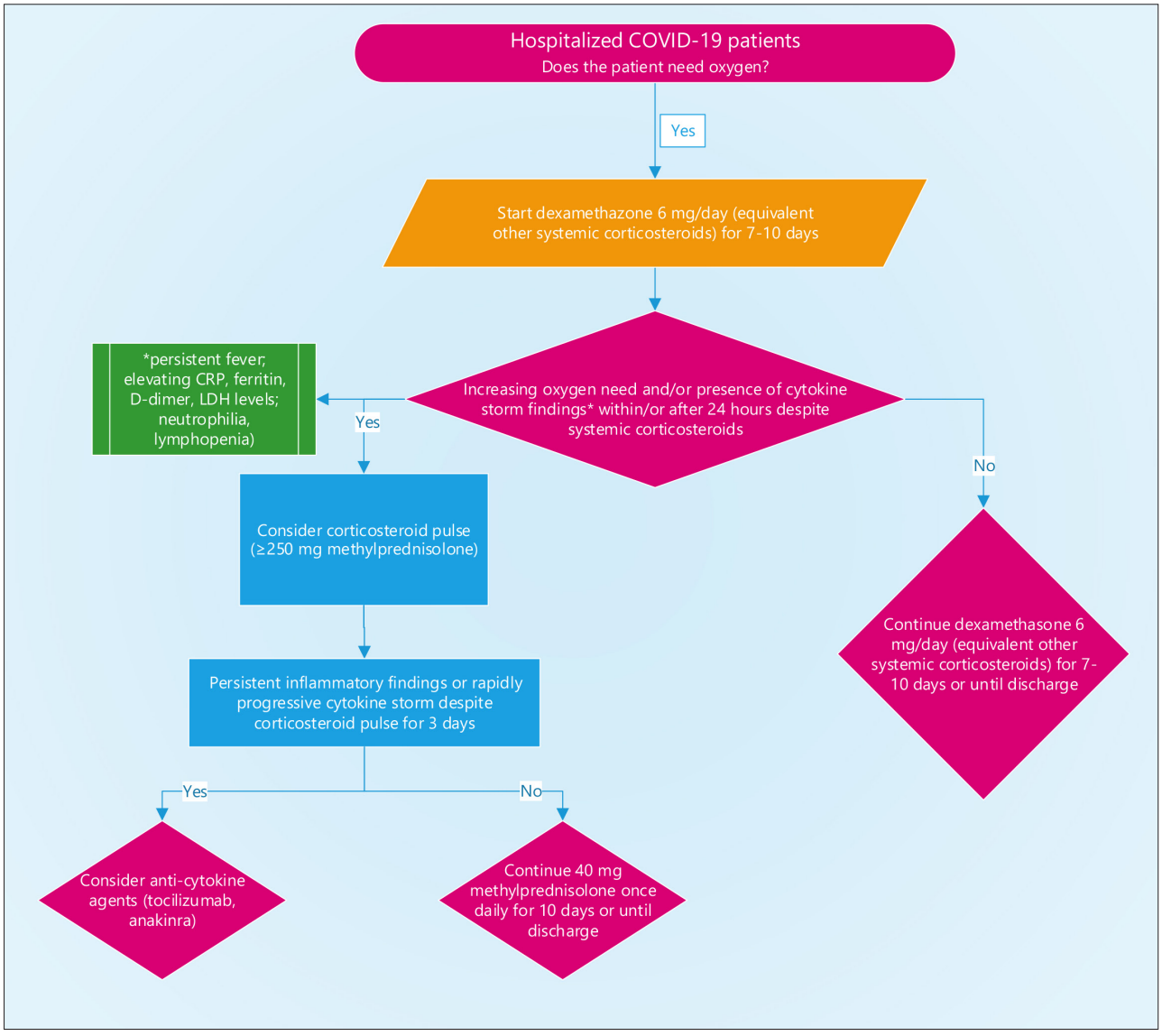

Figure 1. Current recommendation scheme for hospitalized COVID-19 patients

tive when administered early. SSC guidelines do not routinely recommend using convalescent plasma in SARS-CoV-2 [6]. 5000 patients were evaluated in the largest study regarding use of convalescent plasma in COVID-19, but neutralizing antibody titer was not evaluated. In this study convalescent plasma was found to be safe with less than 1% serious adverse events [64]. In a recent study, the outcomes of thirty-nine hospitalized patients with severe to life-threatening COVID-19 who received convalescent plasma transfusion were compared against a cohort of retrospectively matched controls. Plasma recipients demonstrated improved survival, compared to control patients [65]. However, in a recent meta-analysis authors were skeptical about effectiveness of convalescent plasma in patients hospitalized for COVID-19. Moreover, a contemporary randomized trial of convalescent plasma in severe COVID-19 pneumonia failed to show any significant difference in clinical status or overall mortality [66].

Supportive Treatments

As for hypoxemic respiratory failure related to COVID-19, the SSC panel recommends titrating supplemental oxygen therapy to achieve a saturation of 92% to 96% based on a recent meta-analysis of non-COVID-19 patients showing that liberal oxygen therapy is associated with increased mortality [6]. However, the authors also highlighted a new study showing potential damage in ARDS patients treated with conservative oxygen therapy [67]. When hypoxemic respiratory failure develops despite traditional oxygen therapy, high flow nasal cannula (HFNC) should be considered due to data showing that it reduces the rate of intubation compared to traditional oxygen therapy. In addition, treatments that reduce intubation should be preferred because mechanical ventilation is a limited resource in pandemics. The FLORALI trial provides some data to prefer HFNC before noninvasive positive pressure ventilation (NIPPV) in addition to a meta-analysis showing that compared with NIPPV, HFNC reduces the need for intubation and mechanical ventilation [68, 69]. Finally, there is a report regarding infection control, with an increased rate of SARS-CoV transmission during NIPPV [70]; however, environmental contamination for HFNC was not found greater than the conventional oxygen mask in a small cohort of in vitro and critical patients [71, 72].

Management of invasive mechanical ventilation should comply with standard ARDS care, ie lower tidal volumes (4-8 mL/kg estimated body weight) and lower inspiratory pressures (plateau pressure <30 cmH_2O). Higher positive end-expiratory pressure without stepwise recruitment maneuvers is probably the best strategy recommended by the SSC guidelines [6].

The prone position is recommended for COVID-19 patients with severe ARDS by both the SSC guidelines and WHO while the SSC guidelines also suggest prone positions for moderate ARDS [5]. They stated that in order to obtain maximum benefit, the prone position should be applied 12-16 hours a day [6].

The recommendation for fluid treatment in the WHO guideline is to re-evaluate the patient's physiology constantly and not deliver more than 250-500 mL of fluid. Similarly, the SSC guidelines endorse a conservative approach given the absence of benefit for liberal fluid administration in sepsis and the risk of ARDS in COVID-19.

Treatment and prophylaxis studies have been initiated rapidly all over the world. In the coming period, according to the results of studies, vital issues such as the effectiveness or ineffectiveness of the drugs and whether they are reliable or not, will be clarified.

In this dark time when the evidence is ambiguous, developments in treatment should be followed continuously and management guidelines should be updated in line with these developments. However, it should not be forgotten that supportive treatments in intensive care are the basis of the treatment and the management of diseases requires customized care tailored to each patient's unique physiological response, rather than following a protocol blindly.

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