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Management of Covid-19: An Illustrated Review from 2022 Updated NIH, IDSA and ICMCR Guidelines

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1. Abstract

Coronavirus disease 2019 (COVID-19 has had a deleterious effect on the world's demographics resulting in more than 3.8 million deaths worldwide, emerging as the most devastating global health crisis since the era of the influenza pandemic of 1918. The main concerns regarding the disease have been lack of specific antiviral therapies. Results from ongoing trials have given some promising results for the management of COVID-19 especially Molnupiravir, monoclonal antibodies, janus kinase inhibitors and remdesivir. This review article gives a comprehensive update on various pharmacological therapies in the light of recently published standard treatment guidelines for the management of COVID-19.

2. Introduction

Coronavirus disease 2019 (COVID-19 has had a deleterious effect on the world's demographics resulting in more than 3.8 million deaths worldwide, emerging as the most devastating global health crisis since the era of the influenza pandemic of 1918. Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, limiting the continuing spread of this virus and its variants has become an issue of increasing concern, as SARS-CoV-2 continues to wreak havoc across the world, with many countries enduring a third wave of outbreaks of this viral illness attributed mainly due to the emergence of mutant variants of the virus currently being O-micron. Based on the severity of presenting illness that includes clinical symptoms, laboratory and radiographic abnormalities, hemodynamics, and organ function. The National Institutes of Health (NIH) issued guidelines that classify COVID-19 into following distinct types;

2.1. Asymptomatic COVID-19 infection: patients who test positive for COVID-19 and are free of COVID symptoms [1,2].

2.2. Mild illness: Individuals who have any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging [3].

2.3. Moderate illness: Individuals who have clinical symptoms or radiologic evidence of lower respiratory tract disease and who have oxygen saturation (SpO2) ≥ 94% on room air [4]. However, ICMR guidelines define moderate disease as anyone of the two parameters [41].

1. Respiratory rate >24 breaths per minute.

2. SpO_2 90% to 93% on ambient air.

2.4. Severe illness: Individuals who have (SpO_2) ≤ 94% on room air; a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO_2/FiO_2) <300 with respiratory rate>30 breaths/min or lung infiltrates >50%.

However, ICMR guidelines define severe disease as anyone of the two parameters [41].

1. Respiratory rate >30 breaths per minute.

2. SpO_2 <90% on ambient air.

2.5. Critical illness: Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunctions. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS) which tends to occur approximately one week after the onset of symptoms.

2.6. Pharmacologic Therapies In The Management Of Adults With COVID-19: Currently, a variety of therapeutic options are available that include antiviral drugs (e.g., molnupiravir,-paxlovid,remdesivir), anti-SARS-CoV-2 monoclonal antibodies (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory drugs (e.g., dexamethasone), immunomodulators agents (e.g., baricitinib, tocilizumab) are available under FDA issued Emergency Use Authorization(EUA) or being evaluated in the management of COVID-19 [10]. The clinical utility of these treatments is specific and is based on the severity of illness or certain risk factors. The clinical course of the COVID-19 illness occurs in 2 phases, an early phase when SARS-CoV-2 replication is greatest before or soon after the onset of symptoms. Antiviral medications and antibody-based treatments are likely to be more effective during this stage of viral replication. The later phase of the illness is driven by a hyperinflammatory state induced by the release of cytokines and the coagulation system's activation that causes a prothrombotic state. Anti-inflammatory drugs such as corticosteroids, immunomodulating therapies, or a combination of these therapies may help combat this hyperinflammatory state than antiviral therapies. Below is a summary of the latest potential therapeutic options proposed, authorized, or approved for clinical use in the management of COVID-19.

3. Antiviral Therapies

3.1. Molnupiravir: A directly acting broad-spectrum oral antiviral agent acting on the RdRp enzyme was initially developed as a possible antiviral treatment for influenza, alphaviruses including Eastern, Western, and Venezuelan equine encephalitic viruses. Based on meta-analysis of available phase 1-3 studies, molnupiravir was noted to demonstrate a significant reduction in hospitalization and death in mild COVID-19 disease [5]. Results from a phase 3 double-blind randomized placebo controlled trial (MOVE OUT) reported that early treatment with molnupiravir reduced the risk of hospitalization or death in at risk unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19 [6]. Current IDSA guidelines recommend molnupiravir for ambulatory patients with mild to moderate disease at risk of progression to severe disease who have no other treatment options within 5 days of symptom onset [40]. Current ICMR guidelines do not recommend molnupiravir in the treatment of COVID-19 [41]. Paxlovid (ritonavir in combination with nirmatrelvir) is an oral combination pill of two antiviral agents which on an interim analysis of phase 2-3 data (reported via press release) which included 1219 patients, found that the risk of -19 related hospital admission or all-cause mortality was 89% lower in the paxlovid group when compared to placebo when started within three days of symptom onset [7]. Further studies are ongoing to establish the efficacy reported [14]. On 22 December 2021, the FDA issued a EUA authorizing the use of Paxlovid for patients with mild to moderate COVID-19. Current IDSA guidelines recommend paxlovid for ambulatory patients with mild to moderate disease at risk of progression to severe disease within 5 days of symptom onset [40]. ICMR guidelines do not recommend paxlovid in the treatment of COVID-19 [41].

Remdesivir is a broad-spectrum antiviral agent that previously demonstrated antiviral activity against SARS-CoV-2 in vitro. Based on results from three randomized, controlled clinical trials that showed that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with mild-to-severe COVID-19 [8,9]. The U.S. Food and Drug Administration (FDA) approved remdesivir for clinical use in adults and pediatric patients (over age 12 years and weighing at least 40 kilograms or more) to treat hospitalized patients with COVID-19 [10-12]. However, results from the WHO SOLIDARITY Trial conducted at 405 hospitals spanning across 40 countries involving 11, 330 inpatients with COVID-19 who were randomized to receive remdesivir (2750) or no drug (4088) found that remdesivir had little or no effect on overall mortality, initiation of mechanical ventilation, and length of hospital stay. A recently published randomized double blind placebo controlled trial [PINETREE] reported an 87% lower risk of hospitalization or death than placebo when at-risk non hospitalized patients with COVID-19 were treated with a 3-day course of remdesivir. There is no data available regarding the efficacy of remdesivir against the new SARS-CoV-2 variants; however, acquired resistance against mutant viruses is a potential concern and should be monitored. Current ICMR guidelines do

not recommend remdesivir use in non-hospitalized or mild disease patients. However, in moderate and severe disease it is given EUA/ off label use [41]. Current IDSA guidelines recommend remdesivir for non-hospitalized patients with mild to moderate disease at risk of progression to severe disease [40].

3.2. Anti-SARS-CoV-2 Neutralizing Antibody Products

Individuals recovering from COVID-19 develop neutralizing antibodies against SARS-CoV-2, and the duration of how long this immunity lasts is unclear. Nevertheless, their role as therapeutic agents in the management of COVID-19 is extensively being pursued in ongoing clinical trials. Convalescent Plasma therapy was evaluated during the SARS, MERS, and Ebola epidemics; however, it lacked randomized control trials to back its actual efficacy. The FDA approved convalescent plasma therapy under a EUA for patients with severe life-threatening COVID-19 [13,14]. Although it appeared promising, data from multiple studies evaluating the use of convalescent plasma in life-threatening COVID-19 has generated mixed results. One retrospective study based on a U.S. national registry reported that among patients hospitalized with COVID-19, not on mechanical ventilation, there was a lower risk of death in patients who received a transfusion of convalescent plasma with higher anti-SARS-CoV-2 IgG antibody than patients who received a transfusion of convalescent plasma with low antibody levels [15]. Data from three small randomized control trials showed no significant differences in clinical improvement or overall mortality in patients treated with convalescent plasma versus standard therapy [16-18]. Current ICMR guidelines recommend against CPT use in COVID-19 disease [41]. Current IDSA guidelines recommend against CPT use in patients hospitalized for COVID-19 [40].

3.3. REGN-COV2 (Casirivimab and Imdevimab): REGN-COV2 is an antibody cocktail containing two noncompeting IgG1 antibodies (casirivimab and imdevimab) that target the RBD on the SARS-CoV-2 spike protein that has been shown to decrease the viral load in vivo. Results from an interim analysis of 275 patients from an ongoing double-blinded trial involving non hospitalized patients with COVID-19 who were randomized to receive placebo, 2.4 g of REGN-COV2 (casirivimab 1,200 mg and imdevimab 1,200 mg) or 8 g of REGN-COV2 COV2 (casirivimab 2,400 mg and imdevimab 2,400 mg) reported that the REGN-COV2 antibody cocktail reduced viral load compared to placebo [19]. This interim analysis also established the safety profile of this cocktail antibody, similar to that of the placebo group [20]. IDSA guidelines recommend use of REGN-COV2 in patients with mild to moderate disease at risk of progression [40].

Bamlanivimab and Etesevimab (LY-CoV555 or LY3819253 and LY-CoV016 or LY3832479) are potent anti-spike neutralizing monoclonal antibodies. Bamlanivimab is a neutralizing monoclonal antibody derived from convalescent plasma obtained from a patient with COVID-19. Like REGN-COV2, it also targets the RBD of the spike protein of SARS-CoV-2. In Phase 2 of the BLAZE-1 trial, bamlanivimab/etesevimab was associated with a significant reduction in SARS-CoV-2 viral load compared to placebo [39]. Data from the Phase 3 portion of BLAZE-1 is pending release, but preliminary information indicates that therapy reduced the risk of hospitalization and death by 87%. Sotrovimab (VIR-7831) is a potent anti-spike neutralizing monoclonal antibody that demonstrated in vitro activity against all the four VOCs Alpha (B.1.1.7), Beta (B.1.351), Gamma(P1), and Delta (B.1.617.2). Results from a preplanned interim analysis (not yet peer-reviewed) of the multicenter, double-blind placebo-controlled Phase 3, COMET-ICE trial by Gupta et.al that evaluated the clinical efficacy and safety of sotrovimab demonstrated that one dose of sotrovimab (500 mg) reduced the risk of hospitalization or death by 85% in high-risk non hospitalized patients with mild to moderate COVID-19 compared with placebo. Current IDSA guidelines recommend sotrivimuab for non-hospitalized mild to moderate disease at risk of progression [40].

3.4. Immunomodulatory Agents

Corticosteroids: Severe COVID-19 is associated with inflammation-related lung injury driven by the release of cytokines characterized by an elevation in inflammatory markers. During the pandemic's early course, glucocorticoids' efficacy in patients with COVID-19 was not well described. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, which included hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 who were randomly assigned to received dexamethasone (n=2104) or usual care (n=4321), showed that the use of dexamethasone resulted in lower 28-day mortality in patients who were on invasive mechanical ventilation or oxygen support but not in patients who were not receiving any respiratory support [22]. Based on the results of this landmark trial, dexamethasone is currently considered the standard of care either alone or in combination with remdesivir based on the severity of illness in hospitalized patients who require supplemental oxygen or non-invasive or invasive mechanical ventilation. Current IDSA and ICMR guidelines also recommend methylprednisolone as an alternative to dexamethasone in a dosage of 0.5 to 1 mg/ kg for moderate disease and 1 to2 mg/kg for severe and critical disease respectively [40,41].

Tocilizumab is an anti-interleukin-6 receptor alpha receptor monoclonal antibody that has been indicated for various rheumatological diseases. The data regarding the use of this agent is mixed. A randomized control trial involving 438 hospitalized patients with severe COVID-19 pneumonia, among which 294 were randomized to receive tocilizumab and 144 to placebo, showed that tocili-

zumab did not translate into a significant improvement in clinical status or lower the 28-day mortality compared to placebo [23,24]. Results from another randomized, double-blind placebo-controlled trial involving patients with confirmed severe COVID-19 that involved 243 patients randomized to receive tocilizumab or placebo showed that the use of tocilizumab was not effective in preventing intubation or death rate [25,26,27]. The REMAP-CAP and RECOVERY trials two large randomized controlled trials, showed a mortality benefit in patients exhibiting rapid respiratory decompensation [28]. Current IDSA and ICMR guidelines recommend tocilizumab for severe covid disease with rapid decompensation and high inflammatory markers (IL6 and CRP) in absence of bacterial or TB infection [40,41]. In the largest clinical trial on the treatment of tocilizumab criterion for systemic inflammation was defined as CRP> 75 mg/L.

Sarilumab and Siltuximab are IL-6 receptor antagonists that may potentially have a similar effect on the hyperinflammatory state associated with COVID-19 as tocilizumab. Currently, there no known published clinical trials supporting the use of siltuximab in severe COVID-19. Conversely, a 60-day randomized, double-blind placebo control multinational phase 3 trial that evaluated the clinical efficacy, mortality, and safety of sarilumab in 431 patients did not show any significant improvement in clinical status or mortality rate [29]. Another randomized, double-blind placebo-controlled study on sarilumab's clinical efficacy and safety in adult patients hospitalized with COVID-19 is currently ongoing (NCT04315298). Current IDSA guidelines recommend sarilumab when tocilizumab is not available and patient qualifies for later [40].

3.5. Janus kinase (JAK) inhibitors

Baricitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2 currently indicated for moderate to severely active rheumatoid arthritis(RA) patients. Baricitinib was considered a potential treatment for COVID-19 based on its inhibitory effect on SARS-CoV-2 endocytosis in vitro and on the intracellular signaling pathway of cytokines that cause the late-onset hyperinflammatory state that results in severe illness [39,40]. This dual inhibitory effect makes it a promising therapeutic drug against all stages of COVID-19. A multicenter observational, retrospective study of 113 hospitalized patients with COVID-19 pneumonia who received baricitinib combined with lopinavir/ritonavir (baricitinib arm, n=113) or hydroxychloroquine and lopinavir/ritonavir (control arm, n=78) reported significant improvement in clinical symptoms and 2-week mortality rate in the baricitinib arm compared with the control arm. Results from the ACTT-2 trial, a double-blind, randomized placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adult patients with COVID-19, reported that the combination therapy of baricitinib plus remdesivir was superior to remdesivir therapy alone in not only reducing recovery time but also accelerating clinical improvement in hospitalized patients with COVID-19, particularly who were receiving high flow oxygen supplementation or noninvasive ventilation [31,32] Baricitinib, in combination with remdesivir, has been approved for clinical use in hospitalized patients with COVID-19 under a EUA issued by the FDA. The efficacy of baricitinib alone or in combination with remdesivir has not been evaluated in the SARS-CoV-2 variants, and there is limited data on the use of baricitinib with dexamethasone. Current ICMR guidelines do not recommend baricitinib for use in COVID-19 irrespective of severity [41]. Current IDSA guidelines recommend use of barictinib for severe and critical disease patients with high inflammatory markers [40]. Patients who can receive steroids IDSA guidelines recommend use of baricitinib in combination with remdesivir.

Tofacitinib is another oral selective inhibitor of JAK 1 and JAK3 that is indicated for moderate to severe RA, psoriatic arthritis, and moderate to severe ulcerative colitis. Given its inhibitory effect on the inflammatory cascade, it was hypothesized that its use could ameliorate the viral inflammation-mediated lung injury in patients with severe COVID-19. Results from a small randomized controlled trial that evaluated the efficacy involving 289 patients who were randomized to receive Tofacitinib or placebo showed that Tofacitinib led to a lower risk of respiratory failure or death (PMID:34133856). Current IDSA guidelines recommend against use of Tofacitinib in COVID-19 hospitalized patients not on NIV or IMV [40]. Current IDSA guidelines recommend use of FLUVOXAMINE,IVERMECTIN and FAMOTIDINE only OUTSIDE the context of clinical trials [40].

4. Oxygenation and Ventilation Management In COVID-19

4.1. Conventional oxygen therapy: COVID-19 patients with associated respiratory insufficiency should be monitored closely with continuous pulse oximetry. Supplemental oxygen supplementation via nasal cannula or Venturi mask must be administered to maintain oxygen saturation (SpO2) between 92 to 96% (< 88-90% if COPD). If there is improvement in clinical and oxygen saturation, supplemental oxygen should be continued with periodic reassessment. If there is no clinical improvement or worsening of symptoms and/or oxygen saturation, non-invasive treatments such as High-Flow Nasal Cannula (HFNC) or Noninvasive Positive Pressure Ventilation(NIPPV) are recommended.

4.2. Management of acute hypoxemic respiratory failure in COVID-19: Acute hypoxemic respiratory failure is the most common complication in adult patients with COVID-19, and conventional oxygen therapy is not helpful to address the oxygen demand in these patients. These patients should be managed with enhanced respiratory support modalities such as high-flow nasal cannula

(HFNC), noninvasive positive pressure ventilation (NIPPV), endotracheal intubation, and invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)

4.3. High-Flow nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV)

HFNC and NIPPV are noninvasive enhanced respiratory support modalities available in managing COVID-19-associated acute hypoxemic respiratory failure and are instrumental in avoiding invasive mechanical ventilation in carefully selected patients. A meta-analysis study evaluating the effectiveness of HFNC compared to conventional oxygen therapy and NIPPV before mechanical ventilation reported that HFNC, when used before mechanical ventilation, could improve the prognosis of patients compared to conventional oxygen therapy and NIPPV.[34] The use of HFNC or NIPPV is associated with decreased dispersion of exhaled air especially when used with a good interface fitting, thus creating a low risk of nosocomial transmission of the infection. However, these treatment modalities are associated with a greater risk of aerosolization and should be used in negative pressure rooms.

4.4. Noninvasive positive-pressure ventilation (NIPPV)

NIPPV (bilevel positive airway pressure BiPAP/continuous positive airway pressure CPAP) is instrumental in the management of COVID-19-associated acute hypoxemic respiratory failure and may help avoid invasive mechanical ventilation in carefully selected patients. NIPPV should be restricted to hospitalized patients with COVID-19 who develop respiratory insufficiency due to COPD, cardiogenic pulmonary edema, or have underlying obstructive sleep apnea (OSA) rather than ARDS. A helmet is preferred for minimizing the risk of aerosolization [35]. In NIPPV with face masks (full-face or oronasal), the use of masks integrated with an expiratory valve fitted with an antimicrobial filter is recommended. Results from the HENIVOT trial, an Italian open-label multicenter randomized clinical trial, reported that there was no significant difference in the number of days free of respiratory support with the utilization of helmet noninvasive ventilation treatment compared to high flow nasal oxygen in COVID-19 patients hospitalized with moderate to severe degree of hypoxemia.

4.5. Endotracheal intubation and lung protective invasive mechanical ventilation

Impending respiratory failure should be recognized as early as possible, and a skilled operator must promptly perform endotracheal intubation to maximize first-pass success [36]. Pre oxygenation (100% O_2 for 5 minutes) should be performed via HFNC. Invasive mechanical ventilation in COVID-19 associated acute hypoxemic respiratory failure and ARDS should be with lower tidal volumes (V.T.) (4 to 8 ml/kg predicted body weight, PBW) and lower inspiratory pressures reaching a plateau pressure (Pplat) < 30 cm of H2O [36, 37]. Positive end-expiratory pressure (PEEP) must be as high as possible to maintain the driving pressure as low as possible (< 14 cmH2O). Use of neuromuscular blocking agents (NMBA) should be used as needed to facilitate lung-protective ventilation. In patients with refractory hypoxemia (PaO2:FiO2 of <150 mm Hg), prone ventilation for > 12 to 16 hours per day and the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion are strongly emphasized. The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel recommends against inhaled pulmonary vasodilators such as nitric oxide. Lung-protective ventilation can also reduce the risk of new or worsening AKI by preventing ventilator-induced hemodynamic effects. ECMO should be considered in carefully selected patients with refractory hypoxemia despite lung-protective ventilation and patients who fail to respond to prone position ventilation. Empirical antibacterial therapy should be started only if there is a suspicion of bacterial infection and should be discontinued as early as possible if not indicated [38]. Patients with COVID-19 are at risk of developing venous and thromboembolic events and should be maintained on thromboembolic prophylaxis with appropriate anticoagulation.

4.6. Prognosis

The prognosis of COVID-19 is largely dependent on various factors that include the patient's age, the severity of illness at presentation, pre-existing conditions, how quickly treatment can be implemented, and response to treatment. As previously described, the WHO's current estimate of the global case fatality rate for COVID-19 is 2.2%. However, the case fatality rate is affected by factors such as age, underlying pre-existing conditions, and severity of illness. Results from a European multicenter prospective cohort study that included 4000 critically ill patients with COVID-19 reported a 90-day mortality of 31%, with higher mortality noted in elderly, diabetic, obese, and severe ARDS patients [38].

5. Conclusion

Pharmacotherapy for covid 19 continues to emerge with extensive research going on. Promising results have been seen with some pharmacological therapies like molnupiravir, monoclonal antibodies, remdesivir and baricitinib in latest clinical trials. This review aims to give comprehensive and consolidated update on recent standard guidelines for management of COVID-19.

6. Conflict of Interest

The authors declare there is no conflict of interest.

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References

1. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020; 25(10): 2000180.
2. Nishiura H, Kobayashi T, Miyama T, Suzuki A, Jung SM, Hayashi K, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020; 94: 154-155.
3. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020; 383(18): 1757-1766.
4. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020; 383(18): 1757-1766.
5. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab Syndr. 2021; 15(6): 102329.
6. Bernal AJ, Silva MMGD, Musungaie DB, Kovalchuk E, Gonzalez A, Reyes VD, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2021; 386(6): 509-520.
7. Mahase E. Covid-19: Pfizer›s paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ. 2021; 375: n2713.
8. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30(3): 269-271.
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19-Final Report. N Engl J Med. 2020; 383(19): 1813-1826.
10. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020; 383(19): 1827-1837.
11. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020; 324(11): 1048-1057.
12. 19. Zhang R, Mylonakis E. In inpatients with COVID-19, none of remdesivir, hydroxychloroquine, lopinavir, or interferon β-1a differed from standard care for in-hospital mortality. Ann Intern Med. 2021; 174(2): JC17.
13. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022; 386(4): 305-315.
14. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv. 2020.
15. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc. 2020; 95(9): 1888-1897.
16. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, et al. PlasmAr Study Group. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2021; 384(7): 619-629.
17. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA. 2020; 324(5): 460-470.
18. Agarwal A, Mukherjee A, Kumar G. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020; 371: m4232.
19. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021; 27(4): 622-625.
20. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science. 2020; 370(6520): 1110-1115.
21. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021; 384(3): 238-251.
22. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. bioRxiv. 2021.
23. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384(8): 693-704.
24. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020; 34(2): 327-331.
25. Cellina M, Orsi M, Bombaci F, Sala M, Marino P, Oliva G, et al. Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab. Diagn Interv Imaging. 2020; 101(5): 323-324.
26. Michot JM, Albiges L, Chaput N, Saada V, Pommeret F, Griscelli F, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol. 2020; 31(7): 961-964.
27. Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021; 384(16): 1503-1516.
28. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020; 383(24): 2333-2344.
29. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill

Patients with Covid-19. N Engl J Med. 2021; 384(16): 1491-1502.

30. Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab COVID-19 Global Study Group. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021; 9(5): 522-532.
31. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020; 395(10223): e30-e31.
32. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020; 20(4): 400-402.
33. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021; 384(9): 795-807.
34. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol. 2020; 146(1): 137-146.
35. Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, et al. Exhaled air dispersion during high-flow nasal cannula therapy *versus* CPAP *via* different masks. Eur Respir J. 2019; 53(4): 1802339.
36. Grieco DL, Menga LS, Cesarano M, Rosa T, Spadaro S, Bitondo MM, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA. 2021; 325(17): 1731-1743.
37. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2022; 383(25): 2451-2460.
38. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A, et al. Consensus guidelines for managing the airway in patients with COVID-19: Guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists. Anaesthesia. 2020; 75(6): 785-799.
39. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020; 48(6): e440-e469.
40. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2021; 325(7): 632-644.
41. Infectious Disease Society of America. 2022.
42. AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group [Dte.GHS]. Ministry of health and Family Welfare, Government of India. Clinical guidance for management of adult covid 19 patients 2022.