Lines of Treatment of COVID-19 Infection

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LINES OF TREATMENT

Till the present time, there is no definitive treatment for COVID-19 infection. Various drugs are suggested for managing these cases, but none of them have proven efficacy. Many researches are currently going all over the world to optimize the outcome of the patients with COVID-19 infection.

Different lines for treatment of pregnant women with COVID-19 are summarized in Table 5.1.

ANTIVIRAL DRUGS

As COVID-19 infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), antiviral drugs were investigated in its management. Antiviral drugs work through many mechanisms. They prevent viral entry inside the target cells through angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2), prevent viral membrane fusion, and prevent 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase (Sanders et al., 2020).

TABLE 5.1
Lines of Treatment for Covid-19.

1. Antiviral drugs (remdesivir, lopinavir/ritonavir combination, umifenovir, and favipiravir)
2. Antibacterial drugs
3. Antimalarial drugs
4. Antiparasitics
5. Anticoagulants
6. Immune-based therapy
   a. Immunomodulatory therapy
      i. Steroids
      ii. Interleukin inhibitors
      iii. Interferons
   b. Human blood-derived products
      i. Convalescent plasma
      ii. Immunoglobulins
      iii. Mesenchymal stem cells
7. Host-directed therapy
   a. Metformin
   b. Statins
   c. Pioglitazones
8. Other therapeutic agents
   a. Angiotensin-converting enzyme inhibitors
   b. Nonsteroidal antiinflammatory drugs
   c. Vitamin C
   d. Vitamin D
   e. Zinc
   f. lactoferrin
   g. Melatonin
9. Oxygen therapy

These mechanisms suggest that antiviral treatment should start early in the disease to limit viral replications. The role of antiviral drugs is questionable after progression of the disease to the hyperinflammatory state, which characterizes advanced stages of the disease (Siddiqi and Mehra, 2020).

The commonly used antiviral drugs for treatment of COVID-19 include remdesivir, lopinavir/ritonavir combination, umifenovir, and favipiravir.

Remdesivir is an adenosine analog intravenous nucleotide that binds to the viral RNA-dependent RNA polymerase, preventing viral replication through premature termination of RNA transcription. It has a promising antiviral activity against RNA viruses such as SARS/MERS-CoV (Middle East respiratory syndrome coronavirus) and Ebola (Li et al., 2020). In vitro studies confirmed its efficiency in COVID-19 (Wang et al., 2020c), and its early administration after viral inoculation in a rhesus macaque model was associated with lower lungs virus load and less lung damage than the control animals (Williamson et al., 2020).

Side effects of remdesivir include gastrointestinal manifestations, elevated liver transaminases, prolonged prothrombin time, renal toxicity, and allergic reactions. Accordingly, liver function tests including liver enzymes and prothrombin time and concentration should be evaluated before the start of treatment and during it if clinically indicated, and discontinuation of treatment may be indicated if alanine transaminase (ALT) levels reached 10 folds of normal and should be done if ALT increase was associated with manifestations of liver inflammation (Wang et al., 2020c).

Treatment with remdesivir should not be started if glomerular filtration fraction is lower than 30 L/min (Sanders et al., 2020)

Remdesivir was not assigned to any Food and Drug Administration (FDA) category, as clinical trials evaluating its role in COVID-19 excluded pregnant women from participation. However, it was safely used in pregnant women for treatment of Ebola virus (Mulangu et al., 2019).

Remdesivir was approved by the FDA for the treatment of hospitalized COVID-19 cases on supplemental oxygen. Its use in patients on mechanical ventilation is questionable, as there was lack of evidence for its efficiency during these advanced stages (Beigel et al., 2020; Goldman et al., 2020; Spinner et al., 2020; Wang et al., 2020a,b,c,d,e,f).

A randomized controlled trial (RCT) included 1063 severely ill COVID-19 patients from 68 sites worldwide (47 in the United States and 21 in Europe and Asia).

Early reports revealed that remdesivir enhanced recovery time in these patients (from 15 to 11 days). After receiving the initial report, the FDA approved the emergency use of the drug for the treatment of severe hospitalized cases of COVID-19 (FDA, 2020a).

Remdesivir was used in 86 pregnant and postpartum hospitalized women with severe COVID-19, and it was found to be well tolerated, with a low rate of serious adverse events. The NIH recommended that remdesivir should not be withheld from pregnant patients if indicated (Williamson et al., 2020).

The currently recommended dose of remdesivir is 200 mg IV loading dose followed by 100 mg IV infusion daily for 9 days (Favilli et al., 2020).

Drug interactions with remdesivir were not studied in clinical trials. Gilead Sciences reported minimal to no reduction in remdesivir exposure when administered with dexamethasone (written communication, July 2020) and no significant interactions with oseltamivir or baloxavir (written communications, August and September 2020). Chloroquine or hydroxychloroquine (HCQ) may decrease the antiviral activity of remdesivir, so coadministration is not recommended (FDA, 2020b).

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Lopinavir/ritonavir (LPV/r), used in Chinese treatment schemes against COVID-19, are also known as "anti-HIV drugs" (Lee et al., 2007).

The replication of SARS-CoV-2 depends on two proteases that cleave polyproteins into an RNA-dependent RNA polymerase and a helicase. These proteases are named 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro) (Zumla et al., 2016a).

Lopinavir inhibits the division of HIV Gag-Pol, whereas ritonavir is a protease inhibitor. The combination of the two molecules reduces the replication of HIV by the production of immature particles that block viral replication (Chu et al., 2004).

LPV/r is an inhibitor of SARS-CoV 3CLpro in vitro, and this protease appears to be highly conserved in SARS-CoV-2 (Tahir ul Qamar et al., 2020; Liu and Wang, 2020). LPV/r has a poor selective in vitro activity against SARS-CoV. That may reflect the need for higher drug level than the tolerable levels to achieve the desired effect in vivo (Chen et al., 2004). Lopinavir is excreted in the gastrointestinal tract; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug (Chu et al., 2004).

Darunavir inhibits the 3CLpro enzyme and possibly the PLpro enzyme. However, in an in vitro study, darunavir did not show activity against SARS-CoV-2 (De Meyer et al., 2020).

Side effects of LPV/r include gastrointestinal manifestations such as anorexia, nausea, vomiting, abdominal pain, diarrhea, QTc prolongation, renal toxicity pancreatitis, cutaneous manifestation, and liver toxicity (Li et al., 2020; Cao et al., 2020). The last side effect is particularly important, as 20%—30% of COVID-19 patients have elevated levels of transaminases (Wu et al., 2020).

LPV/r is not assigned to any FDA category. However, ritonavir alone was assigned as FDA class B (Favilli et al., 2020).

There is extensive experience with the use of LPV/r in pregnant women with HIV, and the drug has a good safety profile with no evidence of teratogenicity. A RCT (Koss et al., 2014) conducted on 356 HIV-infected pregnant women showed no significant risk of preterm labor, even if Berghella reported that it crosses the transplacental barrier and may increase the risk of preterm delivery, but not the risk of teratogenic effects (Vincenzo and Hughes, 2020). That was confirmed in a study where 955 women with exposure to LPV/r during pregnancy were analyzed (Roberts et al., 2009).

For relative safety, LPV/r was suggested for treatment of COVID-19 in pregnant women. A treatment protocol could involve an oral administration of LPV/r 200 mg/50 mg, two capsules every 12 h with interferon-alpha (IFN-α) 5 million IU in 2 mL of nebulized physiologic solution (Liang and Acharya, 2020). Kim and colleagues recommend to avoid the nebulization of solutions for the risk of aerosolization of SARS-CoV-2 and, when possible, to administer inhaled medications by metered dose inhaler (Arthur and Kim, 2020). If the nebulized therapy is necessary, it is important to use some precautions during the nebulization, such as the positioning of the patient in an airborne infection isolation room, the use of adequate PPE, and not to reenter the room for 2—3 h after the therapy (George, 2020).

LPV/r plasma concentrations achieved using typical doses are far below the levels that may be needed to inhibit SARS-CoV-2 replication (Schoergenhofer et al., 2020). A moderately sized randomized trial failed to find a virologic or clinical benefit of LPV/r over standard of care (Cao et al., 2020). Results from a small RCT showed that darunavir/cobicistat was not effective for the treatment of COVID-19 (Chen et al., 2020c). There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.

DRUG–DRUG INTERACTIONS

LPV/r is a potent inhibitor of cytochrome P450 3A. Coadministration of LPV/r with medications that are metabolized by this enzyme may increase the concentrations of those medications, resulting in concentration-related toxicities.

LPV/r oral solution contains 42.4% alcohol and 15.3% propylene glycol and is not recommended for use during pregnancy, and the same is applied for the use of once-daily dosing.

The COVID-19 Treatment Guidelines Panel recommends against using LPV/r (AI) or other HIV protease inhibitors (AIII) for the treatment of COVID-19, except in a clinical trial, as it did not show efficacy in RCT with moderate sample size and the pharmacodynamics of the drug raise the doubts about the possibility of reaching enough blood concentration able to inhibit the virus proteases.

ANTIBACTERIAL DRUGS

Many reports found that most of the hospitalized cases with COVID-19 have received broad-spectrum antibiotics with unknown efficacy (Ding et al., 2020; Du et al., 2020; Zhou et al., 2020a,b; Chen et al., 2020a; Guan et al., 2020). Unnecessary antibiotics upon hospitalization may increase the individual risk of subsequent hospital-acquired pneumonia caused by resistant bacteria (Kalil et al., 2016; Stevens et al., 2011). On a population level, antibiotic administration for all hospitalized COVID-19 patients increase the antibiotic use during a pandemic and consequently an increase in antimicrobial resistance rates (Bell et al., 2014). Bacterial coinfection occurred in 3.5% of COVID-19 cases (Sieswerda et al., 2020).

The WHO recommends against the use of antibiotic therapy or prophylaxis in mild suspected or confirmed COVID-19. In moderate suspected or confirmed cases, antibiotics should not be prescribed unless bacterial infection is clinically suspected. In severe cases, the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors, and local epidemiology, should start as early as possible, ideally after withdrawal of blood cultures. Antimicrobial therapy should be assessed daily for deescalation. The choice of antibiotics with the least ecologic impact is based on data and guidance from local institution, region, or country (e.g., of the Access group of the AWaRe classification). The AWaRe classification categorizes antibiotics into three different groups (Access, Watch, and Reserve) based on their indication for common infectious syndromes, their spectrum of activity, and their potential for increasing antibiotic resistance (World Health Organization, 2019).

Treatment of other coinfections may be based on a laboratory-confirmed diagnosis or epidemiological criteria. Empiric antibiotic therapy should be deescalated on the basis of microbiology results and clinical judgment, and the duration of empiric antibiotic therapy should be shortened as much as possible, generally 5–7 days. Cautions should be taken, as the increase in the use of antibiotics during pandemics can enhance certain infections as Clostridioides difficile with clinical disease ranging from diarrhea and fever to colitis (Aldeyab et al., 2012).

Table 5.2 summarized evidence-based recommendations for antibacterial therapy in adults with COVID-19.

ANTIMALARIAL DRUGS

Chloroquine is an antimalarial drug that was developed in 1934. In 1946, its analog HCQ was developed. Chloroquine/chloroquine phosphate/HCQ are antimalarial drugs that have both antiviral and immunomodulatory activities. The three drugs differ in chemical structure but have the same clinical effects. However, HCQ has the least side effects (Favilli et al., 2020).

Chloroquine has a proven inhibitory effect on many viruses including HIV, MERS-CoV, and SARS-CoV. The needed dose of drug for treatment of a viral infection is lower than that used for treatment of malaria with subsequent lower side effects (Keyaerts et al., 2009).

Both chloroquine and HCQ increase the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes (Wang et al., 2020c). Chloroquine inhibits glycosylation of the cellular ACE2 receptor, which may interfere with binding of the virus to cell receptor (Vincent et al., 2005). Both chloroquine and HCQ prevent release of the viral genome through blocking of the transport of SARS-CoV-2 from early endosomes to endolysosomes (Liu et al., 2020a). However, administration of HCQ—alone or when combined with azithromycin—neither reduced upper or lower respiratory tract viral loads nor demonstrated clinical efficacy in a rhesus macaque model (Maisonnasse et al., 2020).

On March 28, 2020, the FDA authorized the emergency use of chloroquine and HCQ supplied from the Strategic National Stockpile to treat hospitalized adults and adolescents >50 kg body weight with COVID-19 for whom a clinical trial is not available, or participation is not feasible. On April 13, 2020, the Division of Anti-infective (DAI) products opened a priority Tracked Safety Issue (TSI) 2150 to assess the risk of cardiac toxicity with HCQ and chloroquine with or without azithromycin when used for the treatment of COVID-19.

TABLE 5.2 Summarized Evidence-Based Recommendations for Antibacterial Therapy in Adults With COVID-19 (Sieswerda et al., 2020).		
Recommendation	**Strength**	**Quality of Evidence**
Antibacterial drugs should be restricted in suspected or confirmed COVID-19 patients. This especially applies for mild and moderated cases.	Weak	Very low
Exceptions for the restrictive use of antibacterial drugs can be made for suspected or confirmed COVID-19 patients presenting with radiological findings and/or inflammatory markers compatible with bacterial coinfection, immunocompromised cases,[a] and those with severe illness.	Weak	GPS
Blood, sputum, and pneumococcal urinary antigen testing is better done upon admission before the start of empirical antibiotic therapy in suspected or confirmed COVID-19 patients.	Strong	GPS
In case of suspected bacterial coinfection, empirical antibiotic treatment covering atypical pathogens is better avoided in suspected or confirmed COVID-19 patients hospitalized at the general ward. Legionella urinary antigen testing should be performed according to local and/or national guidelines for CAP.	Weak	Very low
The empirical antibiotic regimens in case of suspected bacterial coinfection depend on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate severe CAP, following local and/or national guideline recommendations on antibacterial treatment in CAP is recommended.	Weak	Very low
Following local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection is recommended.	Strong	GPS
Stopping antibiotics is suggested when blood, sputum, and urinary antigen tests taken before start of empirical antibiotic therapy in patients with suspected or confirmed COVID-19 show no bacterial pathogens after 48 h of incubation.	Weak	GPS
Antibiotic treatment for 5 days is suggested in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms, and inflammatory markers.	Weak	GPS

[a] Immunocompromised is defined as the use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications. *GPS*, good practice statement.

On April 24, 2020, the FDA issued a Drug Safety Communication (DSC) cautioning against the use of HCQ or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of arrhythmias. The DSC described reports of serious cardiac events, including QT prolongation, in patients receiving HCQ or chloroquine, often in combination with azithromycin and other QT prolonging medicines, for the prevention or treatment of COVID-19.

The COVID-19 Treatment Guidelines Panel recommends against the use of chloroquine or HCQ with or without azithromycin for the treatment of COVID-19 patients except in a clinical trial (AI).

In a large RCT of hospitalized patients in the United Kingdom, the use of HCQ was associated with increased risk of intubation and death in patients on noninvasive mechanical ventilation and longer hospital stay without reduction of 28-day mortality when compared with the usual standard of care (Horby et al., 2020).

Further RCT failed to prove the efficacy of HCQ in treatment of mild to moderate (Cavalcanti et al., 2020) or severe COVID-19 cases (Furtado et al., 2020).

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for HCQ with or without azithromycin in hospitalized patients with COVID-19 (Geleris et al., 2020; Rosenberg et al., 2020).

Conversely, a large retrospective cohort study reported a survival benefit among hospitalized patients who received HCQ with or without azithromycin, compared with those who received neither drug (Arshad et al., 2020a,b). However, cases who did not receive HCQ had a lower rate of intensive care unit (ICU) admission, which suggests that these patients may have received less

aggressive care. Furthermore, a substantially higher percentage of patients in the HCQ arms also received corticosteroids (77.1% of patients in the HCQ arms vs. 36.5% of patients in the control arm), which is proved to improve the survival rate of patients with COVID-19 (Recovery Collaborative Group, 2020).

HCQ is administered orally as 400 mg every 12 h for 5 d or 400 mg twice a day for the first day and then 200 mg twice a day for 4 days (Li et al., 2020a). Chloroquine is used as 1 g for the first day of treatment and then 500 mg daily for 4−7 d depending on clinical response (Kim and Gandhi, 2020; Colson et al., 2020; Wei, 2020).

The COVID-19 Treatment Guidelines Panel recommends against using high-dose chloroquine to treat COVID-19 (AI). High-dose chloroquine (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days). An RCT compared high-dose and low-dose chloroquine in hospitalized severe COVID-19 patients. In addition, all participants received azithromycin, and 89% of the participants received oseltamivir. The study was terminated early because of the high rate of mortality and QTc prolongation in the high-dose group (Borba et al., 2020).

Several randomized trials have not shown a clinical benefit for HCQ in nonhospitalized patients with COVID-19. However, other clinical trials are still ongoing (Mitjà et al., 2020; Skipper et al., 2020).

Both chloroquine and HCQ have a similar toxicity profile, although HCQ is better tolerated and has a lower incidence of toxicity than chloroquine.

Adverse effects are mainly cardiac in the form of QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths (Nguyen et al., 2020). Other side effects included hypoglycemia, rash, nausea, and retinopathy. Bone marrow suppression may occur with long-term use.

Patients receiving chloroquine or HCQ should be monitored for adverse events, especially prolonged QTc interval (AIII). Baseline and follow-up electrocardiograms are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases. The risk−benefit ratio should be assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 bpm), or uncorrected hypokalemia and/or hypomagnesemia (American College of Cardiology, 2020).

DRUG−DRUG INTERACTIONS

Chloroquine and HCQ are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors. Use caution when administering these drugs with medications that are metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants, digoxin) (University of Liverpool, 2020). Chloroquine and HCQ may decrease the antiviral activity of remdesivir; coadministration of these drugs is not recommended (Food and Drug Administration, 2020e).

Concomitant medications that pose a moderate-to-high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, macrolides [including azithromycin] (Nguyen et al., 2020), fluoroquinolone antibiotics) (CredibleMeds, 2020) should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia. Multiple studies have demonstrated that concomitant use of HCQ and azithromycin can prolong the QTc interval (Bessière et al., 2020; Chorin et al., 2020; Mercuro al., 2020); in an observational study, the use of HCQ plus azithromycin was associated with increased odds of cardiac arrest (Rosenberg et al., 2020). The use of this combination warrants careful monitoring.

CONSIDERATIONS IN PREGNANCY

Both chloroquine and HCQ are not assigned to any FDA category, but they have mild effects when administered during pregnancy with no evidence of increased risk of preterm birth or fetal damage. Chloroquine is widely used in malaria areas. Klumpp et al. report that, in 20 years of utilization, about 1 billion people have used chloroquine, including pregnant women reporting no fetal damages or adverse effects on pregnancy, labor, and newborns (Theodore, 1965). HCQ is commonly used for the treatment of malaria in pregnant women and malaria in pregnant women (Vincenzo and Hughes, 2020), and it is reported that it passes the placental barrier and accumulates in fetal ocular tissues, but no toxicity or ocular damages have been found in human species.

The NIH stated that antirheumatic doses of chloroquine and HCQ have been used safely in pregnant women with SLE, and no changing of dose is necessary for chloroquine or HCQ during pregnancy.

ANTIPARASITICS
Ivermectin

Ivermectin is an FDA-approved broad-spectrum anti-parasitic drug (Canga et al., 2008) that has antiviral activity (Lundberg et al., 2013; Tay et al., 2013; Veronika et al., 2016) in vitro. It inhibits integrase protein (IN) nuclear import and HIV-1 replication (Kylie et al., 2012) and nuclear import of host and viral proteins, including simian virus SV 40 large tumor antigen (T-ag) and dengue virus (DENV) nonstructural protein 5 (Kylie et al., 2012). It also inhibits importin (IMP) $\alpha/\beta 1$ heterodimer responsible for IN nuclear import through which many RNA viruses can infect the host cells. Accordingly, it limits many RNA viruses infection as DENV 1−4, West Nile Virus, Venezuelan equine encephalitis virus, and influenza (Leon et al., 2020). Ivermectin has some inhibitory activity on some DNA viruses as pseudorabies virus.

Ivermectin inhibits the replication SARS-CoV-2 in cell cultures (Leon et al., 2020). However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans (Guzzo et al., 2002; Chaccour et al., 2020). Even though ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 in vitro (Arshad et al., 2020a,b; Bray et al., 2020).

Ivermectin is not approved for the treatment of any viral infection, including SARS-CoV-2 infection. The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans.

The available clinical data on the use of ivermectin to treat COVID-19 are limited.

A retrospective analysis of confirmed COVID-19 patients (27% of them had the severe form) who were admitted to four Florida hospitals compared patients who received at least one dose of ivermectin ($n = 173$) to those who received "usual care" ($n = 103$). Ivermectin was administered as a single dose of 200 μg/kg, to be repeated after 7 days if the patient was still hospitalized (13 patients received a second dose). In addition, 90% of the ivermectin cases and 97% of the usual care group received HCQ (in the majority in conjunction with azithromycin).

They found that all-cause mortality was significantly lower in the ivermectin group when compared with the usual care group (OR [odds ratio] 0.27; $P = .03$). That improved mortality appeared to be limited to severe cases. There was no difference between the groups for the median length of hospital stay (7 days in both groups) or the proportion of mechanically ventilated patients who were successfully extubated (36% and 15% in the ivermectin and the usual care groups respectively; $P = .07$). However, this study has many limitations. It is a retrospective one with no enough data given about oxygen saturation or radiographic findings or other therapeutic interventions (types and timing). The analyses of the durations of ventilation and hospitalization do not appear to account for death as a competing risk, and no virologic assessments were performed (Juliana et al., 2020).

A recent metaanalysis was conducted to assess the value of ivermectin for the treatment of COVID-19. A total of 629 (397 of them received ivermectin along with usual therapy) confirmed COVID-19 patients were included in four studies. The overall pooled OR to be 0.53 (95% CI [confidence interval]: 0.29 to 0.96, $P = .04$) for all-cause mortality. Ivermectin-received patients had a significant clinical improvement compared with usual therapy (OR = 1.98, 95% CI: 1.11 to 3.53, $P = .02$). However, the quality of evidence is very low (Padhy et al., 2020).

The COVID-19 Treatment Guidelines Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial (AIII).

ANTICOAGULANTS
Association Between COVID-19 and Thromboembolism

COVID-19 infection is associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers (Driggin et al., 2020; Han et al., 2020). The increased levels of these markers were reported to be associated with poor clinical outcomes (Guan et al., 2020; Tang et al., 2020).

Venous thromboembolism (VTE) was reported in 14.1% of hospitalized COVID-19 patients (95% CI: 11.6−16.9) (Nopp et al., 2020). The prevalence was higher when ultrasound screening was used (40.3%; 95% CI: 27.0−54.3 vs. 9.5%; 95% CI: 7.5−11.7). The incidence of VTE in non−COVID-19-hospitalized patients on VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall (Samama et al., 1999; Leizorovicz et al., 2004). That incidence increased to 5%−16% and reached 37% in critically ill non−COVID-19 patients who received prophylactic dose of anticoagulants and

critically ill septic patients, respectively (Fraisse et al., 2000; Shorr and Williams, 2009; Protect Investigators, 2011). VTE guidelines for non−COVID-19 patients have recommended against routine ultrasound screening in critically ill patients due to lack of evidence that this strategy reduces the rate of complications (Kahn et al., 2012).

In American Society of Hematology Guidelines Panel metaanalysis, there was no difference in overall VTE and related mortality when compared patients treated with prophylactic dose or higher doses of anticoagulation (American Society of Hematology, 2020). In critically ill patients, intermediate or therapeutic dose anticoagulation was associated with a lower odd of pulmonary embolism (OR 0.09; 95% CI: 0.02−0.57) but a higher odd of major bleeding (OR 3.84; 95% CI: 1.44−10.21). Incidences of symptomatic VTE between 0% and 0.6% at 30−42 days post− hospital discharge have been reported in patients with COVID-19 (Patell et al., 2020; Roberts et al., 2020). Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants in patients with COVID-19 to prevent VTE. A single-center retrospective analysis of 2773 hospitalized COVID-19 patients from a single reported in-hospital mortality in 22.5% and 22.8% of patients who received therapeutic anticoagulation and those who did not receive anticoagulation, respectively. Subgroup analysis of 395 mechanically ventilated patients reported mortality rate of 29.1% and 62.7% in those who received anticoagulation and who did not respectively. However, this study has many limitations: data about patient characteristics, indications for anticoagulant initiation, and other therapies were lacking. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19 (Paranjpe et al., 2020).

A single-center, randomized trial of 20 mechanically ventilated patients with D-dimers >1000 μg/L (as measured by the VIDAS D-dimer Exclusion II assay) found that patients treated with therapeutic anticoagulation showed improvement in $PaO_2:FiO_2$ ratio, higher number of ventilator-free days (15 days [IQR 6−16] vs. 0 days [IQR 0−11]; $P = .028$) when compared with those who received the prophylactic anticoagulation. However, there was no between-group difference in in-hospital or 28-day mortality. Two patients had minor bleeding in the therapeutic anticoagulation group, and two patients in each group experienced thrombosis (Lemos et al., 2020).

Guidelines about coagulopathy and prevention and management of VTE in COVID-19 have been released by multiple organizations, including the Anticoagulation Forum (Barnes et al., 2020), the American College of Chest Physicians(Moores et al., 2020), the American Society of Hematology (Adam et al., 2020), the International Society of Thrombosis and Haemostasis (ISTH) (Thachil et al., 2020), the Italian Society on Thrombosis and Haemostasis (Marietta et al., 2020), and the Royal College of Physicians. In addition, a paper that outlines issues related to thrombotic disease with implications for prevention and therapy has been endorsed by the ISTH, the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology (Bikdeli et al., 2020).

All guidelines agree that hospitalized patients with COVID-19 should receive prophylactic-dose anticoagulation for VTE. Some guidelines note that intermediate dose anticoagulation can be considered for critically ill patients (Barnes et al., 2020) (Spyropoulos et al., 2020a). Given the variation in VTE incidence and the unknown risk of bleeding in critically ill patients with COVID-19, the COVID-19 Treatment Guidelines Panel and the American Society of Hematology and the American College of Chest Physician Guidelines Panels recommend treating all hospitalized patients with COVID-19, including critically ill patients, with prophylactic dose anticoagulation (Moores et al., 2020). Participation in clinical trials is suggested to understand the safety and efficacy of different anticoagulant doses in patients with COVID-19.

MONITORING COAGULATION MARKERS IN PATIENTS WITH COVID-19

The NIH recommends against the routine testing of markers of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count (AIII) in nonhospitalized COVID-19 patients, as there is lack of evidence that these tests can predict the risk of VTE in asymptomatic and mild cases of COVID-19 infection. Although hematologic and coagulation parameters are commonly measured in hospitalized cases, there are currently insufficient data to recommend either for or against using such data to guide management decisions (National Institutes of Health, 2020a).

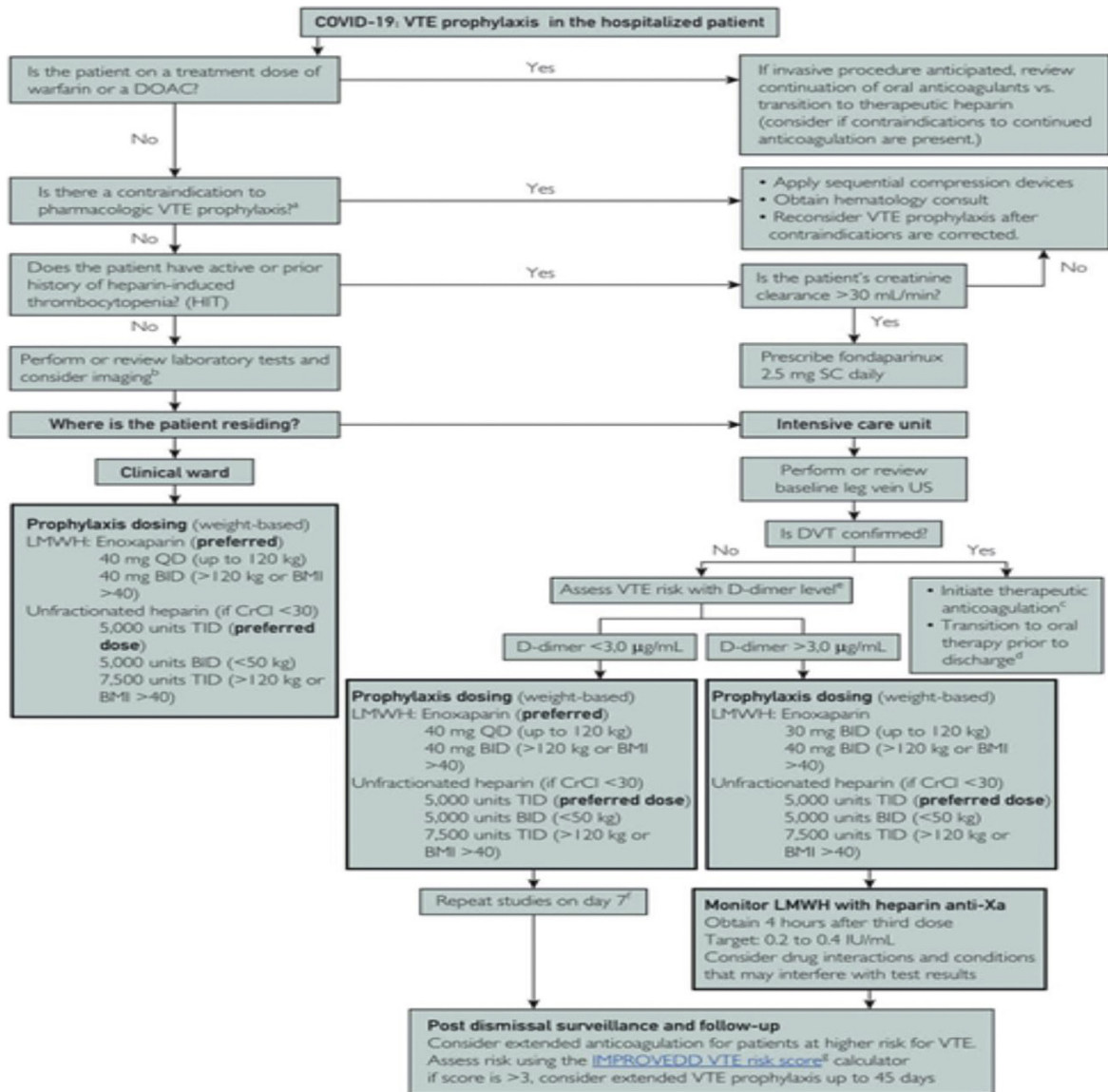Fig. 5.1 described the suggested approach to hospitalized COVID-19 cases.

COVID-19: VTE prophylaxis in the hospitalized patient

Is the patient on a treatment dose of warfarin or a DOAC? — **Yes** → If invasive procedure anticipated, review continuation of oral anticoagulants vs. transition to therapeutic heparin (consider if contraindications to continued anticoagulation are present.)

No ↓

Is there a contraindication to pharmacologic VTE prophylaxis?[a] — **Yes** → • Apply sequential compression devices • Obtain hematology consult • Reconsider VTE prophylaxis after contraindications are corrected.

No ↓

Does the patient have active or prior history of heparin-induced thrombocytopenia? (HIT) — **Yes** → Is the patient's creatinine clearance >30 mL/min? — **No** ↑

No ↓ / **Yes** ↓ Prescribe fondaparinux 2.5 mg SC daily

Perform or review laboratory tests and consider imaging[b]

Where is the patient residing? → **Intensive care unit**

Clinical ward / Perform or review baseline leg vein US

Prophylaxis dosing (weight-based)
LMWH: Enoxaparin (**preferred**)
40 mg QD (up to 120 kg)
40 mg BID (>120 kg or BMI >40)
Unfractionated heparin (if CrCl <30)
5,000 units TID (**preferred dose**)
5,000 units BID (<50 kg)
7,500 units TID (>120 kg or BMI >40)

Is DVT confirmed? — **No** → Assess VTE risk with D-dimer level[e] / **Yes** → • Initiate therapeutic anticoagulation[c] • Transition to oral therapy prior to discharge[d]

D-dimer <3.0 µg/mL | D-dimer >3.0 µg/mL

Prophylaxis dosing (weight-based)
LMWH: Enoxaparin (**preferred**)
40 mg QD (up to 120 kg)
40 mg BID (>120 kg or BMI >40)
Unfractionated heparin (if CrCl <30)
5,000 units TID (**preferred dose**)
5,000 units BID (<50 kg)
7,500 units TID (>120 kg or BMI >40)

Prophylaxis dosing (weight-based)
LMWH: Enoxaparin
30 mg BID (up to 120 kg)
40 mg BID (>120 kg or BMI >40)
Unfractionated heparin (if CrCl <30)
5,000 units TID (**preferred dose**)
5,000 units BID (<50 kg)
7,500 units TID (>120 kg or BMI >40)

Repeat studies on day 7[f]

Monitor LMWH with heparin anti-Xa
Obtain 4 hours after third dose
Target: 0.2 to 0.4 IU/mL
Consider drug interactions and conditions that may interfere with test results

Post dismissal surveillance and follow-up
Consider extended anticoagulation for patients at higher risk for VTE.
Assess risk using the IMPROVEDD VTE risk score[g] calculator if score is >3, consider extended VTE prophylaxis up to 45 days

FIG. 5.1 Suggested approach to patients requiring hospitalization for coronavirus disease 2019 (COVID-19)-related complications. [a]Active bleeding, platelet count <30 × 10^9/L, or congenital bleeding disorder including von Willebrand disease or hemophilia. [b]Laboratory tests: complete blood cell count and differential, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer. If PT and/or aPTT are prolonged, consider a special coagulation profile, which includes a lupus anticoagulant screen. Imaging: for patients presenting with a prolonged illness or those who have had a long hospital stay, consider obtaining bilateral lower extremity venous ultrasonography. [c]Initiate therapeutic anticoagulation therapy as follows: unfractionated heparin infusion is preferred. In a patient with a history of heparin-induced thrombocytopenia, use argatroban or bivalirudin (see direct thrombin inhibitors order set). [d]Continue oral anticoagulation for a minimum of 3 months with clinical reassessment thereafter. A direct oral anticoagulant (DOAC) is preferred unless the patient has another indication for the use of a vitamin K antagonist or low-molecular-weight heparin (LMWH). [e]Assess venous thromboembolism (VTE) risk using the D-dimer level as follows: low risk, <3.0 µg/mL; high risk, 3.0 µg/mL. This recommendation reflects a sixfold increase above the upper limit of normal. Precise cutoff requires external validation. [f]On day 7 of therapy (or earlier if clinical deterioration occurs), repeat the following studies: bilateral lower extremity venous ultrasonography; laboratory tests (complete blood cell count with differential, D-dimer, and fibrinogen). Consider alternating ultrasonography and laboratory tests every 3−4 days (McBane 2nd et al., 2020).

A suggested protocol for anticoagulation therapy in COVID-19 patients includes the following:

- Patients with suspected/confirmed thromboembolic events without possible ischemia or infarction should receive full dose of anticoagulation according to institutional protocols and those with possible ischemic events as myocardial infarction or strokes may be considered for thrombolytic therapy after consultation of pulmonary embolism response or stroke teams and have to receive full dose of anticoagulation according to institutional protocols if thrombolytic therapy is not available or recommended.
- Patients not suspected to have thromboembolic events and using anticoagulation for any other indication as atrial fibrillation (AF) should continue their current therapy if they do not need hospitalization or switch to short acting parenteral agent in those who need hospitalization. Those not using such therapy are not candidate for anticoagulation as long as they do not need hospitalization (prophylactic doses can be used in high-risk cases as patients with previous thromboembolic events, recent surgery or trauma, immobilization, or obese patients). In patients needing hospital admission for routine medical, surgical, or obstetric care, prophylactic dose of anticoagulation preferably low-molecular-weight heparin (LMWH) is used while those needing ICU admission should start anticoagulation. There are controversies of the used dose in these patients due to lack of sufficient data about their safety and efficacy and the risk of thromboembolic events. However, following the institutional protocol is recommended.

NIH Recommendations for Venous Thromboembolism Prophylaxis and Screening

Anticoagulants and antiplatelet therapy should not be administered in nonhospitalized patients for the prevention of venous or arterial thrombosis unless indicated for other reasons or as a part of a clinical trial (AIII) while prophylactic dose anticoagulation (AIII) should be given to all hospitalized nonpregnant adults with COVID-19. Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII).

There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.

Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis (AIII) unless being at high risk for VTE and low risk for bleeding. In these cases, continuing anticoagulation with an FDA-approved regimen for extended VTE prophylaxis after hospital discharge can be considered (BI).

There are currently insufficient data to recommend either for or against routine screening for VTE in COVID-19 patients without clinical manifestations of VTE, regardless of the status of their coagulation markers.

The possibility of VTE should be considered in hospitalized COVID-19 patients who experience rapid deterioration of respiratory, cardiac, and/or neurological function, or of sudden, localized loss of peripheral perfusion (AIII) (Piazza and Morrow, 2020).

The American College of Chest Physicians recommended the use of prophylactic dose of LMWH in critically ill patients and prophylactic-dose LMWH or fondaparinux in other patients and does *not* recommend routine prophylaxis in nonhospitalized cases or extended prophylaxis after hospital discharge. The International Society on Thrombosis and Hemostasis recommended the use of prophylactic-dose LMWH in critically ill and noncritically ill patients, half-therapeutic dose LMWH in high-risk critically ill patients, and LMWH or direct oral anticoagulant in patients with high risk of thrombosis and low risk of bleeding for 30 days after hospital discharge and does *not* recommend routine prophylaxis in nonhospitalized cases (Piazza and Morrow, 2020).

NIH Recommendations for Venous Thromboembolism Treatment

- When diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy (AIII).
- Patients with COVID-19 who require extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 (AIII).

Special Considerations During Pregnancy and Lactation

- Anticoagulants treatment that was administered during pregnancy before diagnosis of COVID-19 infection should be continued (AIII).
- For pregnant patients hospitalized for severe COVID-19, prophylactic-dose anticoagulation is recommended unless contraindicated (BIII).

- As for nonpregnant patients, VTE prophylaxis after hospital discharge is not recommended for pregnant patients (AIII). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, considering concomitant VTE and bleeding risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy (AIII).
- Unfractionated heparin, LMWH, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment (AIII). In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data (AIII) (Bates et al., 2018)

MANAGING ANTITHROMBOTIC THERAPY IN PATIENTS WITH COVID-19

- In hospitalized, critically ill patients, LMWH or unfractionated heparin is preferred over oral anticoagulants because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug–drug interactions (AIII). Potential drug–drug interactions with other concomitant drugs should be considered (AIII).
- COVID-19 outpatients receiving warfarin who are in isolation and thus unable to get international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular AF, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin (AIII).
- Hospitalized patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops, or other contraindications are present (AIII).
- For hospitalized patients with COVID-19, prophylactic-dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) (AIII). Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a

sepsis-induced coagulopathy score ≥4 (Tang et al., 2020). For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care (AIII). Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.
- When imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 (AIII).
- There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are hospitalized. Although there is evidence that multiorgan failure is more likely in patients with sepsis if they develop coagulopathy (Iba et al., 2017), there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19.
- After hospital discharge, VTE prophylaxis is not recommended for patients with COVID-19 (AIII) except in high-risk patients. The FDA approved the use of rivaroxaban 10 mg daily for 31–39 days in patients (Cohen et al., 2016; Spyropoulos et al., 2020b) with Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4 or Modified IMPROVE VTE risk score ≥2 and D-dimer level >2 times the upper limit of normal (Spyropoulos et al., 2020b).
- Any decision to use postdischarge VTE prophylaxis for patients with COVID-19 should consider the individual patient's risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged.

SPECIAL CONSIDERATIONS DURING PREGNANCY AND LACTATION

Pregnant and parturient women are at higher risk of VTE when compared with nonpregnant women as pregnancy is a well-known hypercoagulable state (Heit et al., 2005). It is not yet known whether COVID-19 increases this risk or not. In several cohort studies of pregnant women with COVID-19, VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic

anticoagulation varied across the studies (Breslin et al., 2020; Delahoy et al., 2020; Knight et al., 2020). The American College of Obstetricians and Gynecologists (ACOG) advises that although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease (American College of Obstetricians and Gynecologists, 2020). If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or LMWH in critically ill or mechanically ventilated pregnant patients (Society for Maternal Fetal Medicine, 2020). Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy (ACOG Practice Bulletin No. 196 Summary: Thromboembolism in Pregnancy, 2018; Bates et al., 2018). If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

There are no data on the use of scoring systems to predict VTE risk in pregnant individuals. Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation (Hu et al., 2020; Réger et al., 2013; Wang et al., 2013).

In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, LMWH is recommended rather than unfractionated heparin for the prevention and treatment of VTE in pregnancy (ACOG Practice Bulletin No. 196 Summary: Thromboembolism in Pregnancy, 2018).

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals (Bates et al., 2018). The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.

IMMUNE-BASED THERAPY

Hyperactive inflammatory response is responsible for many manifestations and complications in COVID-19 infection. Agents modulating the immune response were suggested as an adjunctive therapy in moderate, severe, and critical COVID-19 (Zhong et al., 2020). These agents include immunomodulatory and human blood-derived therapy.

Immunomodulatory agents include generalized antiinflammatory drugs as steroid therapy (Horby et al., 2020) and more targeted antiinflammatory therapy as interleukin (IL) inhibitors (Xu et al., 2020; Shakoory et al., 2016), IFNs (Zhou et al., 2020b), kinase inhibitors (Cao et al., 2020b), and others.

Human blood-derived products are obtained from recovered COVID-19-infected individuals (Mair-Jenkins et al., 2015; Wang et al., 2020d). These products can work through direct antiviral actions (as convalescent plasma [CP]) and/or immunomodulatory effects (as mesenchymal stem cells [MSCs]) (Shetty, 2020). Additionally, neutralizing monoclonal antibodies directed against the virus are currently investigated in clinical trials (Marovich et al., 2020).

STEROIDS

In severe COVID-19 infection, lung injury and multisystem organ dysfunction can complicate the condition as a result of exaggerated systemic inflammatory response. As corticosteroids have potent antiinflammatory effects, these drugs were evaluated to prevent or ameliorate these deleterious effects.

RATIONALE FOR USE OF CORTICOSTEROIDS IN PATIENTS WITH COVID-19

The use of corticosteroids in patients suffering from pulmonary infections has been studied and proved to have both beneficial and deleterious clinical outcomes. In patients with *Pneumocystis jirovecii* pneumonia and hypoxia, prednisone therapy reduced the risk of death (Bozzette et al., 1990). However, in outbreaks of previous coronavirus infections (as MERS and SARS), corticosteroid treatment led to delayed virus clearance (Stockman et al., 2006; Arabi et al., 2018). In severe influenza viruses' pneumonia, it was associated with poor clinical outcomes, including secondary bacterial infection and death (Rodrigo et al., 2016).

A metaanalysis of seven RCTs that included 851 patients with acute respiratory distress syndrome (ARDS) found that corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI: 0.59−0.95) and duration of mechanical ventilation (mean difference, −4.93 days; 95% CI: −7.81 to −2.06 days) (Mammen et al., 2020).

In January 2020, the WHO issued against the routine use of steroids for treatment of SARS-CoV-2. That was based on the previous experience in treatment of influenza, MERS, and SARS-CoV. They described a possible

role for steroids in ARDS based on their ability to suppress lung tissue inflammation but with a risk of delayed virus clearance (Zhang et al., 2020c).

The RCOG described that steroids administration for SARS-CoV-2 during pregnancy has no potential harms (RCOG Guideline, 2020).

As SARS-CoV-2 infection in pregnancy is associated with increased risk of preterm birth, administration of betamethasone was advised by many studies (Liang and Acharya, 2020; Dashraath et al., 2020; Poon et al., 2020).

RECOVERY trial randomized 2104 patients with SARS-CoV-2 to single dose of oral or intravenous dexamethasone 6 mg daily for 10 days and compared them with 4321 patients received usual care without steroids. The mortality rate was reduced in the dexamethasone ventilated patients by one-third (rate ratio 0.65 [95% CI 0.48 to 0.88]; $P = .0003$) and in dexamethasone oxygen receiving patients by one-fifth (0.80 [0.67 to 0.96]; $P = .0021$). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; $P = .14$). They concluded that dexamethasone could prevent 1 death if administered in eight ventilated patients or 25 patients requiring oxygen alone (Recovery Collaborative Group, 2020).

CORTICOSTEROIDS OTHER THAN DEXAMETHASONE

- Prednisone, methylprednisolone, or hydrocortisone can replace dexamethasone if not available. The dose should be titrated as 6 mg of dexamethasone is equivalent to 40 mg prednisone, 32 mg methylprednisolone, and 160 mg hydrocortisone (Czock et al., 2005).
- As the half-lives of different forms vary, the frequency of administration varies with it. Dexamethasone is a long-acting corticosteroid that has a half-life of 36−72 h, so administered once daily. Prednisone and methylprednisolone are intermediate-acting corticosteroids with a half-life of 12−36 h, once or twice daily. Hydrocortisone is a short-acting corticosteroid with a half-life of 8−12 h, so administered in two to four doses daily.
- Hydrocortisone is the commonest form of steroids used in management of septic shock in COVID-19 patients. Dexamethasone has the advantage over other corticosteroids studied in patients with ARDS of lacking mineralocorticoid activity and thus has minimal effect on fluid and electrolyte balance (Villar et al., 2020).

Monitoring, Adverse Effects, and Drug−Drug Interactions

- COVID-19 patients receiving dexamethasone should be closely monitor for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) (Lier et al., 2020; Stauffer et al., 2020) or fulminant reactivations of HBV (Liu et al., 2020b) should be considered.
- Dexamethasone may reduce the concentration and efficacy of drugs that are CYP3A4 substrates being a moderate cytochrome P450 (CYP) 3A4 inducer. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.

CONSIDERATIONS IN PREGNANCY

Steroids are used commonly during pregnancy for enhancement of fetal lung maturation a long time ago without hazards (Dashraath et al., 2020).

There is risk of potential deterioration of the clinical condition of already sick patients. So, 12-mg betamethasone single dose is recommended to minimize hazardous effects on maternal blood sugar and her clinical condition (Kakoulidis et al., 2020).

Betamethasone is not assigned to any FDA category. The use of steroids in management of SARS-CoV-2-infected pregnant women should be individualized according to clinical condition of the woman (Poon et al., 2020) with close monitoring of infected ones (Kakoulidis et al., 2020).

Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, the Panel

recommends using dexamethasone in hospitalized pregnant women with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but who are not mechanically ventilated (BIII).

Other steroids such as methylprednisolone are not recommended by the WHO as they delay virus clearance and cause maternal hyperglycemia without adding benefits on maternal survival (Li et al., 2020a).

The WHO recommended the use of systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence) and suggested not to use corticosteroids in the treatment of patients with nonsevere COVID-19 (conditional recommendation, based on low certainty evidence) (World Health Organization, 2020b).

One essential feature of corticosteroid treatment is its duration, especially in COVID-19 cases with persistent ground-glass lung opacities. At the present time, extended corticosteroids therapy beyond 10 days is considered only in selected patients of severe COVID-19 (Villar et al., 2020a,b).

Corticosteroid is a double-edged sword in the treatment of COVID-19 patients. Corticosteroids use and its duration should consider the risk–benefit ratio (Mishra and Mulani, 2020).

Long duration of treatment prevents postdisease fibrosis in COVID-19 patients but may be associated with poor outcomes. The steroid effects in the procoagulant environment of COVID-19 patients are to be considered. A hypercoagulable state with profound endothelial injury may be responsible for thrombosis that occurs in severe COVID-19 infection (Maiese et al., 2020).

Dexamethasone (6 mg per day) increases the clotting factors especially fibrinogen so it can precipitate clinical thrombosis (Brotman et al., 2006).

A protracted corticosteroid course contributes to the so-called long COVID syndrome that presents with fatigue and psychological symptoms, in which steroid-related adverse drug reactions such as myopathy, neuromuscular weakness, and psychiatric symptoms might have a part to play (Warrington and Bostwick, 2006; Steinberg et al., 2006).

INTERLEUKIN-6 INHIBITORS

Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. COVID-19 infection induces IL-6 production from bronchial epithelial cells in a dose-dependent pattern (Yoshikawa et al., 2009). Increased cytokine release in COVID-19 patients with systemic inflammatory response and hypoxic respiratory failure can be detected through elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin (Wang et al., 2020f; Zhou et al., 2020a). Controlling the elevated levels of IL-6 may alter the aggressive course of the disease.

The FDA-approved IL-6 inhibitors include anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) and anti-IL-6 monoclonal antibodies (e.g., siltuximab).

ANTI−INTERLEUKIN-6 RECEPTOR MONOCLONAL ANTIBODIES
Sarilumab

Sarilumab is an FDA-approved recombinant humanized anti-IL-6 receptor monoclonal antibody used in treatment of rheumatoid arthritis. The available form is subcutaneous injection that was not approved for the treatment of cytokine release syndrome (CRS).

The safety and efficacy of 400 and 200 mg IV sarilumab was compared with placebo in hospitalized COVID-19 patients in an adaptive Phase 2 and 3, randomized (2:2:1), double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier NCT04315298). Randomization was stratified by the severity of disease (i.e., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids for COVID-19. The Phase 2 component of the trial reported a reduced level of CRP in both doses of sarilumab. The primary outcome for Phase 3 of the trial was change on a seven-point ordinal scale, and this phase was modified to focus on the dose of sarilumab 400 mg among the patients in the critically ill group. During the conduct of the trial, there were numerous amendments that increased the sample size and modified the dosing strategies being studied, and multiple interim analyses were performed. Ultimately, the trial findings to date do not support a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. Additional detail (as would be included in a published manuscript) is required to fully evaluate the implications of these study findings (Sanofi and Regeneron, 2020).

Adverse Effects

Side effects of sarilumab include dose-dependent transient and/or reversible liver enzymes elevations, rarely neutropenia and thrombocytopenia. Serious bacterial and/or fungal infections and intestinal perforations were reported with prolonged use of the drug.

Considerations in Pregnancy

There are insufficient data about the risk of teratogenicity or miscarriage. Monoclonal antibodies actively cross the placenta (with highest transfer during the third trimester), which may affect immune responses in utero in the exposed fetus.

TOCILIZUMAB

Tocilizumab is FDA-recombinant humanized anti-IL-6 receptor monoclonal antibody that is used in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell therapy. It is available in both IV and SQ injection. However, IV route should be used in treating CRS (Le et al., 2018).

Clinical Data for COVID-19

In the industry-sponsored Phase 3 COVACTA trial (ClinicalTrials.gov Identifier NCT04320615), 450 adults hospitalized with severe COVID-19-related pneumonia were randomized to receive tocilizumab or placebo. No statistically significant difference was found between the two study groups regarding improved clinical status, which was measured using a seven-point ordinal scale to assess clinical status based on the need for intensive care and/or ventilator use and the requirement for supplemental oxygen over a 4-week period (OR 1.19; 95% CI: 0.81−1.76; $P = .36$). At week 4, mortality rates did not differ between the tocilizumab and placebo groups (19.7% vs. 19.4%; difference of 0.3%; 95% CI: −7.6%−8.2%; $P = .94$). The difference in median number of ventilator-free days between the tocilizumab and placebo groups did not reach statistical significance (22 days for tocilizumab group vs. 16.5 days for placebo group; difference of 5.5 days; 95% CI: −2.8 to 13.0 days; $P = .32$). Infection rates at week 4 were 38.3% in the tocilizumab group and 40.6% in the placebo group; serious infection rates were 21.0% and 25.9% in the tocilizumab and placebo groups, respectively (Roche, 2020).

Adverse Effects

Tocilizumab has similar side effects such as dose-dependent liver enzymes elevations, uncommonly neutropenia and thrombocytopenia. Serious bacterial and/or fungal infections and intestinal perforations were reported with prolonged use of the drug.

Considerations in Pregnancy

Exactly as with sarilumab, there are insufficient data about the risk of teratogenicity or miscarriage. Monoclonal antibodies actively cross the placenta (with highest transfer during the third trimester), which may affect immune responses in utero in the exposed fetus.

ANTI−INTERLEUKIN-6 MONOCLONAL ANTIBODY
Siltuximab

Siltuximab is an FDA-approved recombinant human−mouse chimeric monoclonal antibody that binds IL-6 used in treatment of Castleman's disease. It inhibits the binding of IL-6 to its receptors (both soluble and membrane-bound receptors). Siltuximab is dosed as an IV infusion.

Clinical Data for COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19 (Gritti et al., 2020). There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (SARS or MERS).

Adverse Effects

The primary adverse effects reported for siltuximab have been related to rash. Additional adverse effects (e.g., serious bacterial infections) have been reported only with long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data about the risk of teratogenicity or miscarriage. Monoclonal antibodies actively cross the placenta (with highest transfer during the third trimester), which may affect immune responses in utero in the exposed fetus.

The Panel recommends against the use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) for the treatment of COVID-19, except in a clinical trial (BI) as preliminary, unpublished data from RCTs failed to demonstrate safety or efficacy of sarilumab or tocilizumab in COVID-19 patients and only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19 (Gritti et al., 2020).

INTERFERON

IFNs are a family of cytokines with antiviral properties. They have been suggested as a potential treatment for COVID-19 especially, type I (IFN-I) because of their in vitro and in vivo antiviral properties.

The IFN-I family includes IFN-α, IFN-β, and IFN-ω. These molecules provide innate immune initial rapid antiviral response. IFN-I proteins are induced when a cell detects viral RNA through protein sensors, e.g., TLR3, TLR7, and TLR8 that are found within the endosomes. The IFN-I molecules then bind to the cell surface receptor IFNAR (types 1 and 2) with transcription of many genes (Schoggins et al., 2011) that block viral replication (Meffre and Iwasaki, 2020).

CLINICAL DATA FOR COVID-19

In a double-blind, placebo-controlled trial conducted in the United Kingdom on hospitalized nonventilated COVID-19 patients. Compared with the patients receiving placebo (n = 50), the 48 patients receiving inhaled IFN-β1a (once daily for up to 14 days) were more likely to recover to ambulation without restrictions (HR [hazard ratio] 2.19; 95% CI: 1.03−4.69; $P = .04$), had decreased odds of developing severe disease (OR 0.21; 95% CI: 0.04−0.97; $P = .046$), and had less breathlessness when compared with the 50 placebo patients (Synairgen plc, 2020).

Another single center open-label, randomized trial conducted on severe COVID-19 patients found no difference between 42 patients who received subcutaneous IFN-β1a (three times weekly for 2 weeks) and 39 control patients regarding time to clinical response, overall length of hospital stay, length of ICU stay, or duration of mechanical ventilation. They reported a lower 28-day mortality in IFN group; however, four patients in this group were excluded from the analysis as they died before receiving the fourth dose of IFN-β1a, which may reflect biased results (Davoudi-Monfared et al., 2020).

INTERFERON-ALPHA-2B

A Chinese retrospective cohort study of 77 moderate COVID-19 adults patients compared treatment with nebulized IFN-α2b, umifenovir only versus combination of the two drugs. The time to viral clearance in the upper respiratory tract and reduction in systemic inflammation was shorter in the IFN groups. However, bias in these results as participants in the combined therapy group were younger (mean age 40 vs. 65 years old) and had less morbidity events (15 vs. 54%) when compared with participants in the umifenovir only group. The nebulized IFN-α2b formulation is not approved by the FDA for use in the United States (Zhou et al., 2020b).

A prospective observational study was conducted on 814 patients suffering from severe COVID-19 infection in Cuba. They were subjected to combination of oral antivirals (lopinavir/ritonavir and chloroquine) with intramuscular administration of IFN-α2b (761 patients) or the approved COVID protocol without IFN treatment (53 patients). The proportion of patients discharged from hospital (without clinical and radiological symptoms and nondetectable virus by real-time polymerase chain reaction) was higher in the IFN-treated compared with the non−IFN-treated group (95.4% vs. 26.1%, $P < .01$). The case fatality rate (CFR) for all patients was 2.95%, and for those patients who received IFN-α2b, the CFR was reduced to 0.92. Intensive care was required for 82 patients (10.1%), and 42 (5.5%) had been treated with IFN. The authors claimed that the use of Heberon Alpha R may be contributed to complete recovery of patients. The study has the limitation of unmatched demographic characteristics between treatment groups with huge difference in the number of participants between the two arms (Pereda et al., 2020).

CLINICAL DATA FOR SARS AND MERS

IFN-β used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes (Al-Tawfiq et al., 2014; Shalhoub et al., 2015; Omrani et al., 2014; Chu et al., 2004).

ADVERSE EFFECTS

The most frequent adverse effects of IFN-α include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression and suicidal ideation). IFN-β is better tolerated than IFN-α (Food and Drug Administration, 2018, 2019c).

DRUG−DRUG INTERACTIONS

The most serious drug−drug interactions with IFN are the potential for added toxicity with concomitant use of other immunomodulators and chemotherapeutic agents (Food and Drug Administration, 2018, 2019c).

CONSIDERATIONS IN PREGNANCY

No proven adverse birth outcomes as congenital malformations or miscarriage was associated with exposure to IFN-β1b whether in the preconception period or during pregnancy (Hellwig et al., 2020; Sandberg-Wollheim et al., 2011), and IFN exposure did not affect neonatal morphological characteristics such as birth weight, neonatal height, or head circumference (Burkill et al., 2019).

RECOMMENDATION

The COVID-19 Treatment Guidelines Panel recommends against the use of IFN for the treatment of severe or critical COVID-19 patients, except in a clinical trial (AIII). There are insufficient data to recommend either for or against the use of IFN-β for the treatment of early (within 1 week from onset of symptoms) mild and moderate COVID-19 cases.

CONVALESCENT PLASMA

Plasma collected from people recovering from infection, especially after severe form, may contain high levels of polyclonal, pathogen-specific antibodies. These antibodies can provide a rapid passive immunity to recipients and, in viral infection, can neutralize viral particles (Casadevall and Pirofski, 2020). The use of CP to passively transfer antibodies aiming to prevent or treat infections dates back almost 100 years and before the advent of vaccines, including during the influenza pandemic of 1918 (Mair-Jenkins et al., 2015). Hyperimmune globulin is still used for postexposure prophylaxis against various viral infections, including hepatitis B, varicella zoster, and rabies (Estcourt and Roberts, 2020).

During MERS and SARS coronavirus outbreaks, CP was used safely and efficiently to treat infected cases (although evidence was obtained from small case series). The efficacy may be related to faster viral clearance, particularly when administered early in the disease course (Casadevall and Pirofski, 2020). Most patients who recover from COVID-19 infection develop circulating antibodies to various SARS-CoV-2 proteins 14−21 days following infection, which are detectable by enzyme-linked immunosorbent assay or other quantitative assays and often correlate with the presence of neutralizing antibodies. These antibodies appear to be protective, based on several primate studies showing animals could not be reinfected with SARS-CoV-2 weeks to months later.

On August 23, 2020, the US FDA granted emergency use authorization (EUA) of CP in hospitalized COVID-19 patients. They suggested using high-titer CP during early stages of the disease. Titer was measured by specific antiviral Ig testing and titer threshold criteria (Food and Drug Administration, 2020c).

Both high-titer (i.e., Ortho VITROS SARS-CoV-2 IgG tested with signal-to-cutoff ratio ≥12) and low-titer COVID-19 CPs are authorized for use (Food and Drug Administration, 2020c).

The process of CP preparation is complex and requires cooperation between recovered patients, plasma collection centers, treating clinicians, receiving patients, and healthcare administrators. Plasmapheresis is used to collect large volumes of plasma. Clinical assays that measure the level of antibodies reacting against various SARS-CoV-2 protein are widely available and may correlate with neutralizing antibody titers, and thus might be used to predict the potency of CP units, although data on this relationship continue to evolve (Li et al., 2020b).

Potential donors must have had confirmed COVID-19 infection (documented through positive nasopharyngeal swab or positive serological tests), free of symptoms for at least 14 days, and have standard blood donor eligibility requirements. At the present time, patients treated with CP are not allowed to donate blood or its products including plasma for 3 months. Donations are accepted as frequently as weekly for several months following recovery before the decline in antibody titers (Li et al., 2020b).

ADVERSE EFFECTS

Before administering CP to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank.

Serious adverse reactions following the administration of CP are uncommon and similar to the usual risks associated with plasma infusions for any indications. These risks include blood transmitted diseases (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), circulatory overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described (Food and Drug Administration, 2020a).

Additional risks include a theoretical risk of antibody-dependent enhancement and a theoretical risk of suppressed long-term immunity.

CONSIDERATIONS IN PREGNANCY

The safety and effectiveness of COVID-19 CP during pregnancy have not been evaluated.

An open-label randomized trial of CP use in patients with severe or critical COVID-19 was conducted in Wuhan, China, from February 14 to April 1, 2020. Only plasma units with a SARS-CoV-2 viral spike receptor−binding domain-specific IgG titer of ≥1:640 were transfused. There was no significant difference

between the treatment and control groups in time to clinical improvement within 28 days (HR 1.40; 95% CI: 0.79−2.49; $P = .26$). 91% versus 68% in severe cases (difference of 23%; OR 1.34; 95% CI: 0.98−1.83; $P = .07$) and 21% versus 24% in life-threatening disease in CP and control groups, respectively. There was no significant difference in mortality (21% vs. 24% in CP and control groups, respectively; ($P = .30$). At 24 h, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the CP group (45%) than in the control group (15%; $P = .003$), and differences persisted at 72 h. The nonblinding and early termination of the trial are the main limitations of the study (Li et al., 2020b).

PLACID Trial is an open-label, randomized clinical trial of CP versus standard of care for hospitalized patients with COVID-19 conducted in 39 tertiary care centers in India between April 22 and July 14, 2020. Confirmed severe COVID-19 patients with hypoxia were eligible if matched donor plasma was available at the time of enrollment. Critically ill patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <200 mmHg or shock) were excluded. Participants in the intervention arm received two doses of 200 mL plasma, transfused 24 h apart. Antibody titer of transfused plasma was not assessed.

Among 454 participants, 235 were randomized into the CP arm and 229 were randomized into the standard of care arm. The arms were well balanced regarding age (median of 52 years in both arms) and days from symptom onset to enrollment (median of 8 days in both arms). There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the CP arm and 41 (17.9%) in the control arm. 34 (14.5%) in the CP arm and 31 patients (13.6%) in the control arm died. In each arm, 17 participants progressed to severe disease (7.2% in the CP arm vs. 7.4% in the standard of care arm) (Agarwal et al., 2020). The nonblinding and nontesting of the antibody titer in the donated plasma were the main limitations of the study.

The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program was an open-label, nonrandomized that was primarily designed to provide adult patients with severe or critical COVID-19 infection with access to CP. Secondary objectives were to obtain data on the safety of the intervention. Exploratory objectives included assessment of 7-day and 28-day mortality. The program was sponsored by the Mayo Clinic and included a diverse range of clinical sites. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential were not mandated. Patients were transfused with 1 or 2 units (200−500 mL) of CP. The main outcomes for the safety analysis were serious adverse events (including death) reported after 4 h and 7 days of transfusion (Joyner et al., 2020a,b).

A peer-reviewed publication described the safety outcomes for the first 20,000 EAP plasma recipients, enrolled between April 3 and June 2, 2020. One-third of the participants were aged ≥70 years, 60% were men, and 71% had severe or life-threatening COVID-19. 20% of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. Thirteen deaths were assessed as possibly or probably related to the CP treatment. The 83 nonfatal SAEs that were assessed as possibly or probably related to the CP treatment included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. The life-threatening events that were reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days (Joyner et al., 2020a,b).

Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of the efficacy of COVID-19 CP by using subsets of EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower titers of antibodies.

The FDA analysis included 4330 patients, and donor-neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay. The analysis revealed no difference in 7-day mortality between the patients who received high-titer plasma and those who received low-titer plasma, in the patient population overall, or in the subset of patients who were intubated. However, among nonintubated patients (approximately two-thirds of those analyzed), mortality within 7 days of transfusion was 11% for those who received high-titer plasma and 14% for those who received low-titer plasma ($P = .03$). In a post hoc analysis of patients aged <80 years who were not intubated and who were treated within 72 h of COVID-19 diagnosis, 7-day mortality was lower among the patients who received high-titer plasma than among those who received low-titer plasma (6.3% vs. 11.3%, respectively; $P = .0008$) (FDA, 2020a).

A similar efficacy analysis by the Mayo Clinic, which has not been peer reviewed, included 3082 participants

who received a single unit of plasma out of the 35,322 participants who had received plasma through the EAP by July 4, 2020. Antibody titers were measured by using the Ortho Clinical Diagnostics COVID-19 IgG assay, and outcomes in patients transfused with low- (lowest 18%), medium-, and high- (highest 17%) titer plasma were compared. After adjusting for baseline characteristics, the 30-day mortality in the low-titer group was 29% and 25% in the high-titer group. This difference did not reach statistical significance. Similar to the FDA analyses, post hoc subgroup analyses suggested a benefit of high-titer plasma in patients aged <80 years who received plasma within 3 days of COVID-19 diagnosis and who were not intubated (Joyner et al., 2020a,b).

Limitations of the Study

- The lack of an untreated control arm limits interpretation of the safety and efficacy data. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded.
- The EAP data may be subject to multiple confounders, including regional differences and temporal trends in the management of COVID-19.
- There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in CP from patients who have recovered from COVID-19 are highly variable.
- The efficacy analyses rely on a subset of EAP patients who only represent a fraction of the patients who received CP through the EAP.
- The subgroup that demonstrated the largest estimated effect between high-titer and low-titer CP— patients aged <80 years who were not intubated and who were transfused within 3 days of COVID-19 diagnosis—was selected post hoc by combining several subset rules, which favored subgroups that showed a trend toward benefit of high-titer plasma. This approach tends to overestimate the treatment effect.
- The FDA analysis relied on 7-day mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. Because participants in this observational study were not rigorously followed after they were discharged from the hospital, the 30-day mortality estimates are uncertain.

A randomized trial was conducted in hospitalized adult patients with severe COVID-19 pneumonia in a 2:1 ratio to receive CP or placebo. A total of 228 patients were assigned to receive CP and 105 to receive placebo. The median titer of the infused CP was 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1: 3200]. After 30 days, no significant difference was detected between the two groups regarding the distribution of clinical outcomes according to the ordinal scale (OR 0.83; 95% CI: 0.52 to 1.35; $P = .46$). Overall mortality was 10.96% and 11.43% in CP and placebo group, respectively, for a risk difference of −0.46 percentage points (95% CI: −7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the CP group at day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups (Simonovich et al., 2020).

RECOMMENDATION

There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 CP for the treatment of COVID-19.

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of CP for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 CP through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational CP and thus did not include an untreated control arm. Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that CP with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 h of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and non-randomized studies, observational cohorts, and animal experiments—met the criteria for EUA issuance (Food and Drug Administration, 2020d). Despite meeting the "may be effective" criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of CP due to the lack of a randomized,

untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable with those of plasma donors, potentially limiting the benefit of CP in this patient population (Gharbharan et al., 2020; Agarwal et al., 2020). Several randomized, placebo-controlled trials of COVID-19 CP are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the CP EUA documents (FDA, 2020a).

IMMUNOGLOBULINS: SARS-COV-2 SPECIFIC

Intravenous immunoglobulins (IVIGs) are commonly used immunotherapeutic agents for treatment of various autoimmune and inflammatory diseases. These are normal IgG isolated from the pooled plasma of several thousand healthy donors (Perez et al., 2017). The therapeutic dose of IVIG is 2 g/kg infused over one, two, or five consecutive days. IVIGs are used to treat many diseases including Kawasaki disease, immune thrombocytopenic purpura, inflammatory myopathies, Guillain–Barré syndrome, graft-vs-host disease, and blistering diseases. IVIG exerts its therapeutic effects through targeting the inflammatory immune response mediators (both soluble and cellular mediators). That can be achieved through complement scavenging, autoantibodies neutralization; enhancement of autoantibodies degradation by neonatal Fc receptor saturation; inhibition of activation of various innate immune cells, including dendritic cells, monocytes, macrophages, and neutrophils, and secretion of inflammatory mediators; suppression of effector T helper cells Th1 and Th17, and reciprocal enhancement of immunoprotective regulatory T cells (Tregs); and blockade of B cell activation (Galeotti et al., 2017).

The possible mechanisms of action of IVIGs in COVID-19 are through reduction in the inflammatory mediators. IVIGs target cytokine storm in severe and critically ill COVID-19 patients (Fig. 5.2). Although IVIGs could neutralize seasonal coronavirus, they could not provide cross-neutralizing antibodies against SARS-CoV-2 (Schwaiger et al., 2020). Therefore, the benefits of IVIGs cannot be explained by passive virus neutralization. SARS-CoV-2 encodes a superantigen motif near its S1/S2 cleavage site that might trigger cytokine storm (Cheng et al., 2020). As IVIG contains antibodies reacting against SARS-CoV-2 antigens (Díez et al., 2020), IVIG might inhibit superantigen-mediated T cell activation and cytokine release.

Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

CONSIDERATIONS IN PREGNANCY

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

RECOMMENDATION

There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against SARS-CoV-2 IG for the treatment of COVID-19. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with SARS or MERS.

IMMUNOGLOBULINS: NON-SARS-COV-2 SPECIFIC
Recommendation

The COVID-19 Treatment Guidelines Panel recommends against the use of non-SARS-CoV-2)-specific IVIG for the treatment of COVID-19, except in a clinical trial (AIII). This recommendation should not prevent the use of IVIG when otherwise indicated for the treatment of COVID-19 complications.

RATIONALE FOR RECOMMENDATION

It is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

CLINICAL DATA FOR COVID-19

This study has not been peer reviewed.

A retrospective, non–peer-reviewed nonrandomized cohort study of IVIG for the treatment of
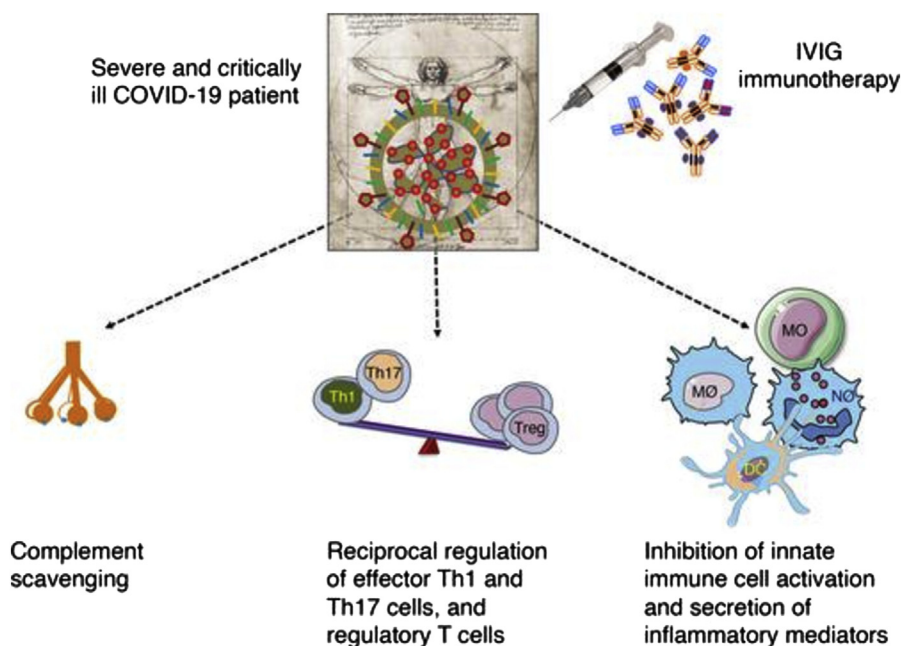
FIG. 5.2 Possible mechanisms of action of intravenous immunoglobulin (IVIG) in coronavirus disease-19 (COVID-19). It is not yet clear how IVIG benefits severe and critically ill COVID-19 patients. Several studies have reported that IVIG reduces IL-6 and C-reactive protein in the COVID-19 patients suggesting that IVIG targets inflammatory process. Based on the known mechanisms of IVIG demonstrated in autoimmune and inflammatory diseases, and considering the pathophysiology of COVID-19, we propose that IVIG might target cytokine storm in COVID-19 patients by complement scavenging; reciprocal regulation of effector Th1 and Th17 cells, and regulatory T cells (Treg); and inhibition of innate immune cell activation and secretion of inflammatory mediators. *DC*, dendritic cell; *MO*, monocyte; *MØ*, macrophage; *NØ*, neutrophil (Galeotti et al., 2020).

COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG. More patients in the IVIG group had critical disease at study entry (41% vs. 21% in IVIG and control groups respectively). The median hospital stay was longer in the IVIG group (24 vs.16 days), and the median duration of disease was also longer in the IVIG group (31 vs. 23 days). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days (Shao et al., 2020). Interpretations of these results are difficult as it was nonrandomized, unbalanced arms as patients in the IVIG group were older with higher proportion of them had more severe disease when compared with non-IVIG arm and nonbalancing of concomitant therapeutic drug administration among the two groups.

CONSIDERATIONS IN PREGNANCY

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile (ACOG Practice Bulletin No. 207: Thrombocytopenia in Pregnancy, 2019; Neunert et al., 2011).

MESENCHYMAL STEM CELLS

Stem cell–based therapies, especially MSCs, are currently used to treat many diseases (Wang et al., 2012; Murphy et al., 2013). MSC-based therapy is used for management of cases of ARDS based on its property of secretion of antiinflammatory, antifibrosis, and antiapoptosis cytokines, which eventually reduce the cytokine storm (Sadeghi et al., 2020a; Leng et al., 2020).

MSCs can inhibit and control the cytokine storm through their immunomodulatory properties through both cellular actions and release of soluble factors (Leng et al., 2020).

These two mechanisms modulate the proliferation and activation of T cells and induce the polarization of the mononuclear cells to an antiinflammatory phenotype (Lee et al., 2009). MSCs can inhibit T cell activation through several immunomodulatory factors (e.g., transforming growth factor-beta 1 (TGF-β1), prostaglandin E2 (PGE2), and HLA-G5) and membrane-bounded molecules (e.g., PD-L1, VCAM-1, and Gal-1) (Wang and Ma, 2008).

MSCs also increase regulatory T cells (TReg) and antiinflammatory TH2 cells. MSCs release NO and IDO that suppress the T cell cytokine production (Pittenger et al., 2019). MSCs suppress NK cell cytotoxicity with a decrease in IFN-γ expression and prevent dendritic cells maturation (by downregulating the surface expression of CD80, CD86, and MHC class II molecules), thus retaining the dendritic cells in a tolerogenic phenotype and also inducing antiinflammatory M2-macrophage polarization with the increased levels of PGE2, TSG-6, and IL-1RA (Lee et al., 2019).

Unlike other therapeutic options used as immunomodulators, MSCs create an immunomodulated environment via the secretion of many immunomodulatory factors. The unique immunomodulatory property of MSCs is reflected in many clinical trials; it has been shown that MSCs reduce the inflammatory responses and defend the host against cytokine storm with lowered mortality, without serious side effects (Lee et al., 2019; Pittenger et al., 2019). As a result, MSC therapy has emerged as an attractive strategy through several favorable changes in the management of respiratory models such as H7N9-induced ARDS (Trounson and McDonald, 2015; Squillaro et al., 2016; Han et al., 2019). Since H7N9 and COVID-19 have similar complications, MSC therapy could be an alternative approach in COVID-19 treatment (Chen et al., 2020a,b,c).

Furthermore, MSCs lack the ACE2 receptor that SARS-CoV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection (Shetty, 2020; Lukomska et al., 2019). The protective effects of MSCs in COVID-19 are shown in Fig. 5.3.

Clinical Data

Data supporting the use of MSCs in patients with viral infections, including COVID-19 infection, are limited to case reports and small, open-label studies.

A pilot study of intravenous MSC transplantation in China enrolled 10 patients with confirmed COVID-19. Seven of them (one has critical, four have severe, and two have common form). Seven patients received MSCs, and the other three (all have critical form) received placebo. All patients in the MSCs group recovered. Among the three control patients, one died, one developed ARDS, and one remained stable with severe disease (Leng et al., 2020).

A small clinical trial was conducted on 41 patients with severe COVID-19 infection, 12 of them received human umbilical cord mesenchymal stem cell (hUC-MSC) infusion, and 29 received standard of care therapies only. The groups were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All participants in the hUC-MSC group recovered without requiring mechanical ventilation, whereas four patients in the standard care group progressed to critical illness requiring mechanical ventilation (three of them died). These results are statistically nonsignificant, and interpretation of the study is limited by nonrandomization and small sample size (Shu et al., 2020).

A case report of a 65-year-old female with critical COVID-19 infection mentioned that she had severe pneumonia, respiratory, and multiorgan failure. She received allogeneic human umbilical cord blood-derived MSCs for three times (5×10^7 cells each time). After the second dose, the patient was off the ventilator and discharged from the ICU 2 days after the third dose and testing for SARS-CoV-2 turned negative (Liang et al., 2020).

Adverse effects of MSC transfusion are uncommon. These include failure to produce the desired effects and its potential to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions (Center for Disease Control and Prevention, 2019).

Considerations in Pregnancy

There are insufficient data to assess the risk of MSC use during pregnancy (Sadeghi et al., 2020b).

Recommendation

The COVID-19 Treatment Guidelines Panel recommends against the use of MSCs for the treatment of COVID-19, except in a clinical trial (AII). No MSCs are approved by the FDA for the treatment of COVID-19. There are insufficient data to assess the role of MSCs for the treatment of COVID-19.

The FDA has recently issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful (Food and Drug Administration, 2019b). Several cord blood-derived products are currently licensed by the FDA for indications such as the treatment of cancer (e.g., stem cell transplant) or rare genetic diseases, and as scaffolding for cartilage defects and wound beds. None of
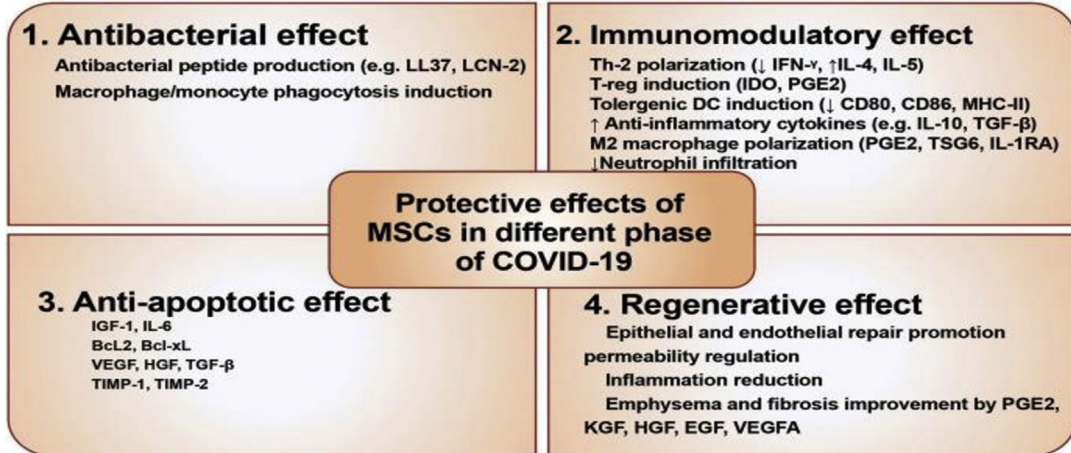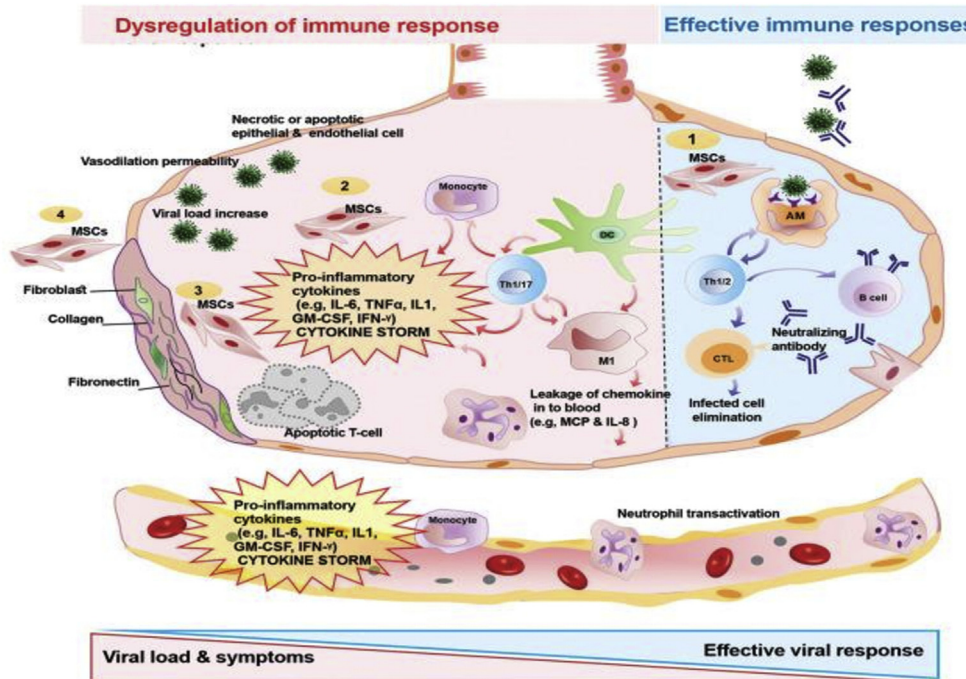
FIG. 5.3 Protective effects of MSCs in different phases of COVID-19 (Sadeghi et al., 2020b). *MSCs*, mesenchymal stem cells.

these products are approved for the treatment of COVID-19 or any other viral disease (Food and Drug Administration, 2019a). In the United States, MSCs should not be used for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access programs, or an Emergency Investigational New Drug application (AII).

For the use of immunotherapy in treatment of COVID-19 infection, the Treatment Guidelines Panel (the Panel) does not have recommendations either for or against the use of COVID-19 CP or SARS-CoV-2 immunoglobulins as the available data are insufficient, but the Panel recommends against the use MSCs (AII) or non-SARS-CoV-2-specific IVIG (AIII) outside the

clinical trials. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

HOST DIRECTED THERAPY

Host-directed therapy (HDT) is a term used to describe therapeutic agents that do not act directly against the virus itself but modulate the host immune system to minimize tissue damage resulted from intense inflammatory reactions (Zhao et al., 2020). HDT use in acute inflammation is safe and efficient and includes treatment with metformin, statins, and glitazone (Zumla et al., 2016).

METFORMIN

Metformin was originally introduced as an antiinfluenza therapy, and its glucose-lowering ability was described as side effect of treatment (Amin et al., 2019). Some scientists described metformin as the aspirin of the 21st century because of its many pleiotropic effects and its widespread utility in medicine (Romero et al., 2017).

Metformin works through activation of AMP-activated protein kinase (AMPK) in hepatocytes by causing its phosphorylation, which results in favorable effects on glucose and lipid metabolism (Zhou et al., 2001).

AMPK activation caused by metformin leads to phosphorylation of ACE2 (Liu et al., 2019), which results in conformational and functional changes in the ACE2 receptor (Plattner and Bibb, 2012). This could lead to decreased its binding with SARS-CoV-2.

Entry of the SARS-CoV-2 inside the host cells causes downregulation of ACE2 receptors with the resultant imbalance in the renin—angiotensin—aldosterone system (RAS) promoting the harmful effects of its proinflammatory and profibrotic arm, further giving rise to the lethal cardiopulmonary complications (Wang et al., 2020a,b,c,d,e,f). By upregulating ACE2, the imbalance in RAS is corrected. So, metformin is not just working through prevention of viral cell entry but also prevents the damaging sequelae by causing activation of ACE2 (Sharma et al., 2020).

A well-known risk factor for development of the severe form of COVID-19 and its complications includes diabetes and obesity. High levels of tumor necrosis factor α (TNFα), which contribute to insulin resistance, were found in the lungs of COVID-19 patients; IL-6 is linked in COVID-19 complications (Blüher et al., 2005).

Metformin decreases TNFα and IL-6, raises IL-10 (an antiinflammatory cytokine), and has been found to cause these beneficial effects significantly more in females than males in both animal and human studies (Matsiukevich et al., 2017; Park et al., 2017; Quan et al., 2016).

Metformin enhances the production of mitochondrial reactive oxygen species and the macrophages autophagy (Beigel et al., 2019), lowering the lung damage in murine models (Zmijewski et al., 2008).

In a retrospective cohort analysis of 6256 hospitalized confirmed COVID-19 patients who have type 2 diabetes or obesity, Metformin use was not associated with significantly decreased mortality in the overall sample of men and women by either Cox proportional hazards stratified model (HR $0\cdot887$; 95% CI: $0\cdot782-1\cdot008$) or propensity matching (OR $0\cdot912$; 95% CI: $0\cdot777-1\cdot071$; $P = 0\cdot15$). Metformin was associated with decreased mortality in women by Cox proportional hazards (HR $0\cdot785$; 95% CI: $0\cdot650-0\cdot951$) and propensity matching (OR $0\cdot759$; 95% CI: $0\cdot601-0\cdot960$; $P = 0\cdot021$). There was no significant reduction in mortality among men (HR $0\cdot957$; 95% CI: $0\cdot82-1\cdot14$; $P = 0\cdot689$ by Cox proportional hazards) (Bramante et al., 2020).

Gilbert and colleagues studied the use of metformin during the first trimester of pregnancy (Gilbert et al., 2006) and seemed safe as regarding congenital malformations. Li et al. found that the use of metformin in treatment of women with gestational diabetes reduced the risk of complications as gestational hypertension, hyperglycemia, and the need of neonatal ICU (Li et al., 2015). Metformin is not assigned to any FDA category (Favilli et al., 2020).

HMG-COA REDUCTASE INHIBITORS (STATINS)

Statins are commonly used to treat hyperlipidemia, and they have the ability to decrease cytokines in numerous noninfective conditions (Fang et al., 2005). Long-term statin therapy improves the outcome in patients with bacterial pneumonia (Novack et al., 2009; Mortensen et al., 2005) and influenza (Vandermeer et al., 2012).

There is controversy about the effect of statins on the course of COVID-19 infection. Dysregulation of the myeloid differentiation primary response protein (MYD) 88 pathway with resultant overwhelming inflammation is associated with poor prognosis in previously studied coronaviruses but is still not proved for SARS-CoV-2 (Yuan, 2015)

Statins are known inhibitors of MYD88 and its level in the presence of external stressors, so they can protect COVID-19 patients from the development of hyperinflammatory reaction (Totura et al., 2015).

On the other hand, statins cause deficiency of endogenous cellular cholesterol with upregulation of low-density lipoprotein receptors with subsequent increase of exogenous cholesterol transfer through the cell membrane and formation of multiple lipid bundles increasing the accessibility for coronaviruses (Shrestha, 2020).

Statins might promote the development of a more severe course of COVID-19 due to activation of the inflammasome pathway in ARDS leading to increased proinflammatory interleukin-18 (IL-18) levels and subsequent cytokine storm (Goldstein et al., 2020)

A retrospective cohort study analyzed 717 patients admitted to a tertiary center in Singapore for COVID-19 infection. Clinical outcomes of interest were the need for supplemental oxygen (PO$_2$ ≤ 94%), ICU admission, invasive mechanical ventilation, and death. Patients were considered to have dyslipidemia if they were receiving dyslipidemia medications (statins, fibrates, or ezetimibe) for a long time. One hundred fifty-six (21.8%) patients had dyslipidemia, and 97% of these were on statins. ICU admission rate was lower in statin when compared with nonstatin users (ATET: Coeff [risk difference]: − 0.12 [−0.23, − 0.01]; *P* = .028). There are no significant differences between statin and nonstatin users regarding other clinical outcomes. The authors described that these findings support to continue statins prescription for COVID-19 patients (Tan et al., 2020).

A metaanalysis involved four studies with a total of 8990 COVID-19 patients: three of them were of good quality. The pooled analysis revealed a significantly reduced hazard for fatal or severe disease with the use of statins pooled (HR 0.70; 95% CI: 0.53−0.94) compared with nonuse of statins in COVID-19 patients. They suggested that the use of statins was associated with 30% reduction in fatal or severe disease (Kow and Hasan, 2020).

Considerations in Pregnancy

Data about the use of statins during pregnancy are limited. Its use was linked to major congenital malformations (Pollack et al., 2005). They are currently assigned, as FDA class thus contraindicated in pregnancy based on animal studies in which the dose administered was much higher than that normally used in human. A systematic review reported the need of evidence for safety of statins use during pregnancy. It should be avoided during the first trimester, as they carry a major teratogenic risk (Karalis et al., 2016).

Both metformin and statins can be used with antiviral drugs as adjuvants to reduce the needed dose of antiviral and consequently its side effects (Zumla et al., 2015). However, no data are available regarding their clinical use with antiviral purpose in pregnant women (Favilli et al., 2020).

Recommendations

- Persons on statin therapy for the prevention or treatment of cardiovascular disease should continue their medications if they become infected with COVID-19 (AIII).
- The Panel recommends against the use of statins for the treatment of COVID-19, except in a clinical trial (AIII)

Pioglitazone

Pioglitazone belongs to the family of thiazolidinediones (TZDs). These drugs are used in treatment of insulin resistance (Lebovitz, 2019). Insulin resistance is associated with numerous cardiovascular risk factors; increases in C-reactive protein, IL-6, and TNF-α (Liu et al., 2016a); and produces a procoagulant state with increased fibrinogen and plasminogen activator inhibitor (PAI-1) (King et al., 2016). These effects ma of insulin resistance raise many concerns about the response of patients with type 2 diabetes to COVID-19 infection (Pfützner et al., 2010). Pioglitazone inhibits the secretion of proinflammatory cytokines (e.g., IL-1b, IL-6, and IL-8) and enhances the secretion of antiinflammatory ones (e.g., IL-4 and IL-10) in astrocytes stimulated with lipopolysaccharide (Qiu and Li, 2015). Pioglitazone decreases ferritin in angiotensin II−induced hypertension in a rat model (Sakamoto et al., 2012).

Administration of pioglitazone at a dose of 30−45 mg/day for 3 months can significantly reduce IL-6 and TNFα (Xie et al., 2017), and a 4-month course of 45 mg/day reduces the monocyte gene and protein expression of IL-1b, IL-6, and IL-8 and lymphocyte IL-2, IL-6, and IL-8 (Zhang et al., 2008).

It was found that pioglitazone decreases lung injury when modulating adipose inflammation in a cecal ligation puncture (CLP) model in mice (Kutsukake et al., 2014). It has a direct effect on lung inflammation and fibrosis (Aoki et al., 2009) and can reduce the lung fibrotic reaction to silica-exposed rats (Barbarin et al., 2005).

The safety of glitazones in pregnancy was not studied, and most data came from case reports of accidental use or therapeutic use for PCOS, which ended in normal outcome (Yaris et al., 2004) or spontaneous abortion (Ota et al., 2008). They were not assigned to any FDA category.

OTHER THERAPEUTIC AGENTS

Concomitant drugs used include ACE inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs (NSAIDs), vitamin C, vitamin D, zinc, lactoferrin, and melatonin.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Upregulation of ACE2 expression has been shown in several animal models but a limited number of human studies showing mixed results on plasma ACE2 levels (Vaduganathan et al., 2020; Mehta et al., 2020). These findings suggested that the use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) may enhance SARS-CoV-2 cell entry and its replication (Fang et al., 2020). Conversely, ACE2 expression is downregulated following SARS infection. ACE2 serves as the key enzyme for balance between two pathways: one is the classic ACE/angiotensin II, whereas the other is the angiotensin1−7/Mas/"anti−renin angiotensin system pathway (RAS)." Downregulation of ACE2 then leads to overactivation of the classic angiotensin II pathway, which is normally counteracted by the anti-RAS pathway, which can result in excessive RAS activation and lung damage, vessel leakage, inflammation, and fibrosis. Therefore, ACEI/ARB administration may block ACE2 downregulation-induced hyperactivation of RAS with the resultant acute lung injury and risk of ARDS (Sarzani et al., 2020; Zhang et al., 2020a).

A recent metaanalysis that included 21 studies was done to investigate the impact of ACEI/ARB on COVID-19 disease severity and mortality. For mortality with ACEI/ARB use, the pooled OR was 1.29 [0.89−1.87] $P = .18$ with heterogeneity of 91%, while the pooled OR for COVID-19 severity was 0.94 [0.59−1.50] $P = .81$ with heterogeneity of 89%. In combining both mortality and severe disease outcomes, the pooled OR was 1.09 [0.80−1.48] $P = .58$ but with heterogeneity of 92%. The authors concluded that the use of ACEI/ARB was not associated with increased mortality or severe COVID-19 (Lo et al., 2020).

RECOMMENDATIONS

- Persons receiving ACEI and/or ARB for cardiovascular disease (or other indications) should continue these medications if they got infected with COVID-19 (AIII).

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial (AIII).

It is unclear whether these medications are helpful, harmful, or neutral in the pathogenesis of SARS-CoV-2 infection.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs are one of the most common medications used as antipyretics and analgesics (Cleveland Clinic, 2020). NSAIDs work by inhibiting cyclooxygenase (COX), an enzyme-converting arachidonic acid to prostaglandins, which play an important role in mediating the inflammatory response (Kirkby et al., 2016).

The use of NSAID in patients with COVID-19 is controversial. On March 14, 2020, the French Minister of Health recommended the use of acetaminophen instead of ibuprofen based on a trial hypothesizing the worsening effects of ibuprofen on COVID-19 infection (Picheta, 2020). Rinott et al. conducted a large retrospective cohort study on 403 confirmed COVID-19 patients who received ibuprofen versus acetaminophen versus no antipyretic medication and found no significant differences in mortality rates or need for respiratory support between the groups (Rinott et al., 2020).

One study conducted by Fu et al. showed an upregulation of ACE2 receptors with the use of NSAIDs, which may facilitate SARS-CoV-2 entry inside the cells (Fu et al., 2020). On the contrary, several NSAIDs as indomethacin and naproxen have antiviral activity (Russell et al., 2020; Lejal et al., 2013). Furthermore, the antiplatelet and antiinflammatory properties of select NSAIDs may be instrumental in symptomatically treating patients with COVID-19 and reducing the risk of morbidity and mortality (Liu et al., 2016b; Toner et al., 2015).

The common side effects of COX-2 inhibition are related to a decrease in prostaglandin 2 production in the gastrointestinal tract, leading to mucosal injury (Tai and McAlindon, 2018) and nephrotoxicity (Little, 2020). The reduced production of other prostaglandins, particularly prostacyclin (PGI2), is linked to an increased risk of adverse cardiovascular events in patients taking NSAIDs (Grosser et al., 2017). The long-term use of NSAIDs, such as selective COX-2 inhibitors and diclofenac, has also been shown to increase the risk of major vascular events, whereas other NSAIDs such as naproxen did not increase the risk of vascular events (Bhala et al., 2013).

RECOMMENDATIONS

- Persons taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician if they get infected with COVID-19 (AIII).
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (AIII).

The FDA stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use NSAIDs as directed (Food and Drug Administration, 2020b).

VITAMIN C

Vitamin C (ascorbic acid) is a water-soluble vitamin that has beneficial effects in patients with severe and critical illnesses. It has an antioxidant property and acts as a free radical scavenger that has antiinflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines (Fisher et al., 2011; Wei et al., 2020).

More than 100 animal studies have indicated that a daily dose of a few grams of vitamin C may alleviate or prevent infections (Hemilä, 2017). Already during the outbreak of SARS-CoV-1 in 2003, vitamin C was used as a nonspecific treatment for severe cases (Hemilä, 1997, 2003). Vitamin C supports cellular functions of both the innate and adaptive immune systems with modification of susceptibility viral infections and manipulation of inflammatory process (Ang et al., 2018; Carr and Maggini, 2017). Vitamin C was proved to increase resistance to infection by a coronavirus in chick embryo tracheal organ cultures (Atherton et al., 1978). It also restores the stress response and improves the survival of stressed humans (Marik, 2020).

Because serious COVID-19 may cause sepsis and ARDS, the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied.

CLINICAL DATA ON VITAMIN C IN CRITICALLY ILL PATIENTS WITHOUT COVID-19

A small, three-arm pilot study compared two regimens of intravenous (IV) vitamin C to placebo in 24 critically ill patients with sepsis. Over the 4-day study period, patients who received vitamin C 200 mg/kg per day and those who received vitamin C 50 mg/kg per day had lower sequential organ failure assessment scores and levels of proinflammatory markers than patients who received placebo (Fowler et al., 2014).

In an RCT in 167 critically ill patients with sepsis induced ARDS, patients who received IV vitamin C 200 mg/kg per day for 4 days had sequential organ failure assessment (SOFA) scores and levels of inflammatory markers that were similar to those observed in patients who received placebo. However, 28-day mortality was lower in the treatment group (29.8% vs. 46.3%; $P = .03$), coinciding with more days alive and free of the hospital and the ICU (Fowler et al., 2019). A post hoc analysis of the study data reported a difference in median SOFA scores between the treatment group and placebo group at 96 h; however, this difference was not present at baseline or 48 h (Fowler et al., 2020).

Two small studies that used historic controls reported favorable clinical outcomes in patients with sepsis or severe pneumonia who received a combination of vitamin C, thiamine, and hydrocortisone. These outcomes include lowered mortality, lesser risk of progression to organ failure, and improved radiographic findings (Kim et al., 2018; Marik et al., 2017).

In three RCTs in patients with septic shock treated with vitamin C and thiamine (with or without hydrocortisone), no survival benefit was reported. In two trials reduction in organ dysfunction (as measured by a SOFA score at Day 3) (Chang et al., 2020; Fujii et al., 2020) was observed, and the third reported reduction was observed in the duration of shock (Iglesias et al., 2020) without an effect on clinical outcomes. Two other trials found no differences in any physiologic or outcome measure between the treatment and placebo groups (Moskowitz et al., 2020; Hwang et al., 2020).

RECOMMENDATION FOR NONCRITICALLY ILL PATIENTS WITH COVID-19

There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in noncritically ill patients, as these patients are less likely to experience oxidative stress or severe inflammation so the role of vitamin C in this setting is unknown.

There are insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in critically ill patients, as there are only sparse and inconclusive observational trials with no completed controlled trials of vitamin C in patients with COVID-19, and the studies of vitamin C in sepsis and ARDS patients have reported variable efficacy and few safety concerns.

VITAMIN D

Vitamin D is a fat-soluble vitamin required for bone and mineral metabolism. It reduces the risk of microbial infection through three main mechanisms: physical barriers, cellular natural immunity, and adaptive immunity (Rondanelli et al., 2018). Vitamin D enhances innate cellular immunity through the induction of antimicrobial peptides, including the human cathelicidin LL-37 and by 1,25-dihydroxyvitamin D and defensins, while maintaining tight junctions, gap junctions, and adherens junctions (Schwalfenberg, 2011; Laaksi, 2012). Cathelicidins also have direct antimicrobial effects against various microbes including bacteria (both gram-positive and gram-negative ones), viruses (both enveloped and nonenveloped viruses), and fungi (Herr et al., 2007). Cathelicidins also induce a variety of proinflammatory cytokines, stimulation of the chemotaxis of neutrophils, monocytes, macrophages, and T lymphocytes into the site of infection, and promotion of the clearance of respiratory pathogens by inducing apoptosis and autophagy of infected epithelial cells (Greiller and Martineau, 2015). Furthermore, 1,25(OH)2D−vitamin D receptor complex acts on the cathelicidin gene promoter vitamin D response elements to enhance transcription of cathelicidin (Wang et al., 2004). Vitamin D reduces the production of proinflammatory T-helper (Th)1 cytokines (TNF-α and IFN-γ) and increases the expression of antiinflammatory cytokines by macrophages (Gombart et al., 2020). It increases cytokine production by Th2 lymphocytes causing suppression of Th1 cells (Cantorna et al., 2015). It also favors induction of the T regulatory (Treg) cells, thereby inhibiting inflammatory processes (Murdaca et al., 2019). With advancement of age, serum vitamin D concentrations tend to decrease as a result of lower levels of 7-dehydrocholesterol in the skin and less sun exposure (Vásárhelyi et al., 2011).

Vitamin D enhances expression of genes glutathione reductase and the glutamate−cysteine ligase modifier subunit linked to antioxidation (Lei et al., 2017), which in turn spares the use of vitamin C enhancing its antimicrobial activities (Mousavi et al., 2019; Colunga Biancatelli et al., 2020).

Drug Interactions

Vitamin D serum levels are reduced by antiepileptics, antineoplastics, antibiotics, antiinflammatory agents, antihypertensives, antiretrovirals, endocrine drugs, and some herbal medicines, through the activation of the pregnane-X receptor (Gröber and Kisters, 2012).

Adverse Effects

Most people do not commonly experience side effects with vitamin D, unless too much is taken. High levels of vitamin D may cause weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting, hypercalcemia, and nephrocalcinosis (Ross et al., 2011)

The role of vitamin D supplementation in the prevention or treatment of COVID-19 is not known. The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. Some investigational trials on the use of vitamin D in people with COVID-19 are using vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency.

Vitamin D deficiency is more common in old age, obese, and hypertensive patients; these factors were confirmed to be associated with poor outcomes in COVID-19 patients. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults (Lu et al., 2018) and children (Science et al., 2013).

In a metaanalysis of RCTs, vitamin D supplementation was proven to be protective against acute respiratory tract infection (Martineau et al., 2017). However, in two RCTs that were double-blind and placebo-controlled, high-dose vitamin D administration to critically ill (non- Covid-19) patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the mortality rate when compared with placebo (Ginde et al., 2019).

Considerations in Pregnancy

Vitamin D is *likely safe* during pregnancy and breastfeeding when used in daily amounts below 4000 units (100 mcg). Higher doses are better avoided unless instructed by healthcare provider. Vitamin D is *possibly safe* when used in higher amounts during pregnancy or while breast-feeding. Using higher doses might cause serious harm to the infant (Webmed, 2020a).

RECOMMENDATION

- There are insufficient data to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.

ZINC SUPPLEMENTATION AND COVID-19

Zinc can reduce the risk of viral respiratory tract infections, including COVID-19 and shorten the duration and severity of these infections. Zinc inhibits the enzymatic activity, replication of SARS-CoV RNA polymerase, and ACE2 activity as shown in in vitro studies (Velthuis et al., 2010; Skalny et al., 2020).

Zinc can modify the host's response to infections as it is an essential cofactor element for many functions in the body. Most of the beneficial effects of zinc occur at the cell membrane. Zinc (Zn^{2+}) reduces the cell membrane permeability and alters the capillary epithelium, thus inhibiting transcapillary movement of plasma protein that in turn may reduce local edema, inflammation, exudation, and mucus secretion (Novick et al., 1996).

Zinc enhances cytotoxicity and induces apoptosis when used in vitro with a zinc ionophore like chloroquine. Chloroquine, in turn, enhances intracellular zinc uptake in vitro (Xue et al., 2014). The relationship between zinc and COVID-19, including how zinc deficiency affects the severity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation (Calder et al., 2020). Zinc levels are difficult to measure accurately, as it is a component of various proteins and nucleic acids (Hambridge, 2007).

The optimal dose of zinc for the treatment of COVID-19 is not established. The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women. There are variability of zinc doses used in registered clinical trials for treatment of COVID-19 with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily (National Institutes of Health, 2020b).

Side Effects

Routine zinc supplementation is not recommended without healthcare professional advice. In some people, zinc might cause nausea, vomiting, diarrhea, metallic taste, kidney and stomach damage, and other side effects. Zinc is *possibly safe* when taken by mouth in doses greater than 40 mg daily, especially when these doses are taken only for a short period of time (Webmed, 2020a).

Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects such as anemia, leukopenia, and potentially irreversible neurologic manifestations such as myelopathy, paresthesia, ataxia, and spasticity (Myint et al., 2018). Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency (Hoffman et al., 1988). In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations (National Institutes of Health, 2020b).

Because zinc has not been shown to have clinical benefit and may be harmful, the Panel recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII).

CLINICAL DATA

A non–peer-reviewed retrospective observational study was conducted on 932 hospitalized COVID-19 patients to compare zinc supplementation (n = 411) with no zinc supplementation (n = 521) in patients who received HCQ and azithromycin. Patients who received zinc had higher absolute lymphocyte count and lower troponin and procalcitonin levels at baseline than those who did not receive zinc. In univariate analysis, no differences were observed between the two groups regarding duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO_2 while in bivariate logistic regression analysis, zinc supplementation was associated with a decreased mortality rate; however, the association with a decreased mortality rate was no longer significant when analysis was limited to patients who were treated in the ICU. Limitations of the study included the following: it is retrospective nonrandomized one, the statistical methods used do not account for confounding variables or patient differences, and no details on the timing of zinc initiation or patients' condition at the start of treatment were clarified (Carlucci et al., 2020). Given the nature of the study design and its limitations, the authors do not recommend using this study to guide clinical practice.

Considerations in Pregnancy

Zinc is *likely safe* for most pregnant and breastfeeding women when used in the recommended daily amounts (RDA) but possibly unsafe and likely unsafe if used in high doses by breastfeeding and pregnant women, respectively. Pregnant and breastfeeding women aged 14 to 18 and over 18 should not take more than 34 and 40 mg per day, respectively (Webmed, 2020b).

RECOMMENDATIONS

- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII).

LACTOFERRIN

Lactoferrin (LF) is an iron-binding glycoprotein with a molecular weight in the range of 70–80 kDa, which transports iron in the blood and serum (Wang et al.,

2019). LF has two symmetrical lobes of a polypeptide chain; each lobe contains two domains, which can bind a metal atom (Baveye et al., 1999). The antiviral effect of LF is mediated by binding iron and is not affected by unsaturated iron levels (Lönnerdal and Iyer, 1995). LF is produced by mucosal epithelial cells in several different mammalian and fish species and is found in mucosal secretions, body fluids, and secondary neutrophil granules (González-Chávez et al., 2009). LF has antifungal, antiviral, and antiinflammatory activities, along with its effects on the immune response (Hao et al., 2019). These activities are mediated through the capacity of LF to bind iron and to interact with components of the host and the pathogens (González-Chávez et al., 2009). LF is positively charged in vivo and can bind large molecules with negative charges, such as lipopolysaccharides and glycosaminoglycans, which is one of the key mechanisms underlying its antiviral activity (Elass-Rochard et al., 1998). The protective effects of LF were first confirmed in 1987 in mice infected with the polycythemia-inducing strain of friend virus complex (Lu et al., 1987). LF has been identified to be effective against several viruses including influenza A virus, adenovirus, SARS-CoV, dengue virus, and others (Pietrantoni et al., 2015; Chen et al., 2017; Oda et al., 2020; Ishikawa et al., 2013).

Two promising in vitro studies, one conducted in 2011 on SARS-CoV and the other conducted in 2020 on SARS-CoV-2, have shown that lactoferrin can inhibit viral infection in the early stages and is effective against SARS-CoV-2 in the postinfection phase (Mirabelli et al., 2020).

A preprint study was conducted by teams at university hospitals in Rome to evaluate the role of oral and intranasal administration of lactoferrin in 32 COVID-19 patients with mild to moderate symptoms, as well as an asymptomatic form of the disease. The study also used a control group of 32 healthy volunteers. A dose of 1 g of liposomal apolactoferrin in 10 capsules per day was administered orally for 30 days, in addition to the same form administered nasally three times per day.

All patients demonstrated improvement in every symptom except fatigue, which continued in about a third of the group. Other very promising data have emerged from these studies, such as a drop in D-dimer concentration, which is crucial in prognosis for the disease, as well as regulation of IL-6, one of the three proinflammatory cytokines (Campione et al., 2020).

Lactoferrin is *likely safe* for pregnant and breastfeeding women when taken in food amounts. Lactoferrin is *possibly safe* in doses of 250 mg daily in women who are in the second or third trimester of pregnancy.

Lactoferrin can cause diarrhea. In very high doses, skin rash, loss of appetite, fatigue, chills, and constipation have been reported (Webmed, 2020c).

MELATONIN

Melatonin, the main hormone secreted by the pineal gland, has various properties. These include antioxidant, antiinflammatory, antiexcitatory, sleep initiation, and immunoregulation effects (Juybari et al., 2019). Melatonin affects mitochondrial function through its protection against free radicals, modulating its permeability transition pore, changing its electron flux, and influencing energy metabolism (Mehrzadi et al., 2020). Melatonin is effective therapy in sleep disturbances, cardiovascular diseases, and eye diseases and acts as a complementary therapy in neonatal care, in vitro fertilization hemodialysis, and anesthesia (Sánchez-Barceló et al., 2010).

The antioxidative and antiinflammatory properties of melatonin counter acute lung injury (ALI) and ARDS induced by viral and bacterial infections. In critically ill patients, melatonin reduces vessel permeability, induces sedation, decreases agitation, and increases sleep quality. These beneficial effects support the hypothesis that melatonin may exert further clinical outcomes for COVID-19 patients (Zhang et al., 2020b).

The innate resistance of bats to viral disease is poorly understood. Melatonin production level in humans is significantly lower than in bats, particularly in the elderly ones (Tresguerres et al., 2006). Given that the elderly people were excessively affected by SARS-CoV-2 than people under the age of 20; besides other factors, it could be hypothesized that high levels of melatonin exert protective properties in bats against the severity of SARS-CoV-2 (Bahrampour Juybari et al., 2020).

Due to a positive correlation between immune dysfunction and disease severity in patients with COVID-19, it is necessary to consider this condition for preparing the optimal vaccine. The safety of melatonin profile has been broadly examined in different preclinical and clinical studies on wide-range doses. Because of the lack of an available vaccine or effective antiviral treatment for COVID-19, the use of melatonin as an adjuvant might be worth consideration. Although the direct protective action of melatonin against COVID-19 is unknown, its extensive application in animal studies and human clinical trials has repeatedly verified its efficacy and safety in a broad range of disorders. Therefore, melatonin practical usage in the current COVID-19 outbreak is suggested to be beneficial (Bahrampour Juybari et al., 2020).

Information regarding safety and efficacy in pregnancy and lactation is lacking.

Possible adverse effects include dizziness, enuresis, excessive daytime somnolence, headache, nausea, insomnia, nightmares, and transient depression. Drowsiness may be experienced within 30 min after taking melatonin and may persist for approximately 1 h; as a result, melatonin may affect driving ability. Use of the animal tissue-derived product is discouraged because of the risk of contamination or viral transmission (Drugs.com, 2020).

OXYGENATION AND VENTILATION

Oxygen therapy targets vary according to the clinical condition of the patient with COVID-19. The aim of oxygen therapy in severe COVID-19 patients with respiratory distress, hypoxemia, or shock is to keep $SpO_2 >$ 94% (World Health Organization, 2020a). After initial stabilization, SpO_2 should be stabilized above 90% and 92%–95% in nonpregnant (World Health Organization, 2020a) and pregnant (The Queensland Health, 2020) adults, respectively, but not above 96% (Alhazzani et al., 2020).

NONMECHANICALLY VENTILATED ADULTS WITH HYPOXEMIC RESPIRATORY FAILURE

Although the optimal oxygen saturation in adults with COVID-19 is not exactly known, uncertain. However, it is known that an SpO_2 below 92% or above 96% may be harmful.

An RCT was conducted on ARDS patients without COVID-19 compared a conservative oxygen strategy with a target SpO_2 of 88%–92% or to a liberal oxygen strategy (target $SpO_2 \geq 96$%). It was terminated after enrollment of 205 patients, as there was an increased mortality at 90 days (risk difference was 14%; 95% CI: 0.7%–27%) and at 28 days (risk difference was 8%; 95% CI: −5%–21%) in the conservative oxygen group (Barrot et al., 2020).

A metaanalysis of 25 randomized trials involving patients without COVID-19 found that a liberal oxygen strategy (median SpO_2 of 96%) was associated with an increased risk of in-hospital mortality compared with a lower SpO_2 comparator (relative risk 1.21; 95% CI: 1.03–1.43) (Chu et al., 2018).

Acute Hypoxemic Respiratory Failure

Conventional oxygen therapy may be insufficient to reach the target oxygenation in adults with acute hypoxemic respiratory failure and COVID-19 infection.

Proper respiratory support can be provided through high-flow nasal cannula (HFNC), noninvasive positive-pressure ventilation (NIPPV), intubation and invasive mechanical ventilation, or ECMO.

High-Flow Nasal Cannula and Noninvasive Positive-Pressure Ventilation

Data from clinical trial in non-COVID-19 patients with acute hypoxemic respiratory failure suggested that HFNC is preferred over NIPPV. The study participants of this unblind study were randomized to HFNC, conventional oxygen therapy, or NIPPV. The ventilator-free days were 24, 22, and 19 days ($P = .02$) in the HFNC, conventional oxygen therapy, and NIPPV groups, respectively. The 90-day mortality was lower in the HFNC group compared with both the conventional oxygen therapy group (HR 2.01; 95% CI: 1.01−3.99) and the NIPPV group (HR 2.50; 95% CI: 1.31−4.78). In more severely hypoxemic patients with PaO_2/FiO_2 mm Hg ≤ 200, the intubation rate was lower for HFNC when compared with the conventional oxygen therapy or NIPPV patients (HR 2.07 and 2.57, respectively) (Frat et al., 2015).

A metaanalysis of eight trials that involved 1084 patients conducted to assess the efficacy of oxygenation strategies prior to intubation. HFNC reduced the rate of intubation (OR 0.48; 95% CI: 0.31−0.73) and ICU mortality (OR 0.36; 95% CI: 0.20−0.63) when compared with NIPPV (Ni et al., 2018).

NIPPV carries a high risk for aerosol spread of SARS-CoV-2 (Yu et al., 2007; Tran et al., 2012). The risk of aerosol spread for HFNC is undetermined.

Prone Positioning for Nonintubated Patients

In ARDS patients receiving mechanical ventilation, prone position improves oxygenation and clinical outcomes in patients with moderate-to-severe ARDS (Fan et al., 2017). The benefit of prone position in awake patients on supplemental oxygen without mechanical ventilation is less evident. A case series of patients with COVID-19 requiring oxygen or NIPPV have reported that awake prone positioning is well tolerated and improves oxygenation (Elharrar et al., 2020; Sartini et al., 2020), with some series also reporting low intubation rates after proning (Sartini et al., 2020; Sun et al., 2020).

A single-center prospective study of awake prone positioning in 56 COVID-19 patients on HFNC or NIPPV reported that prone positioning for ≤ 3 h was feasible in 84% of the patients, and it was associated with significant improvement in oxygenation (PaO_2/FiO_2 286 and 181 mm Hg in prone and supine position,

respectively). However, when compared with baseline oxygenation before initiation of prone positioning, this improvement in oxygenation was not sustained (PaO_2/FiO_2 of 181 and 192 mm Hg at baseline and 1 h after resupination, respectively). Among patients put in the prone position, there was no difference in intubation rate between patients who maintained improved oxygenation and others (Caputo et al., 2020).

A prospective, multicenter observational cohort study was conducted on 199 COVID-19 patients with acute respiratory failure receiving HFNC to evaluate the effect of prone positioning on the rate of intubation. Although the time to intubation was 1 day (IQR 1.0−2.5) in patients receiving HFNC and prone positioning (55 patients) versus 2 days [IQR 1.0−3.0] in patients receiving only HFNC ($P = .055$), the use of awake prone positioning did not reduce the risk of intubation (RR 0.87; 95% CI: 0.53−1.43; $P = .60$) (Ferrando et al., 2020).

It is unclear to which patients and for how long should prone position be applied in nonintubated patients with COVID-19 pneumonia. Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone. Awake prone positioning is contraindicated in patients with respiratory distress, as they require immediate intubation, in hemodynamically unstable patients, patients with recent abdominal surgery, and those having an unstable spine (Bamford et al., 2020). Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position (especially in late pregnancy) or the fully prone position (Society for Maternal Fetal Medicine, 2020).

In patients with COVID-19, there is a possibility of rapid deterioration of hypoxia with increased needs for intubation and invasive mechanical ventilation, so close monitoring is advised (Meng et al., 2020).

Recommendations

- The Panel recommends HFNC oxygen over NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy (BI).
- In the absence of an indication for endotracheal intubation and HFNC, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure (BIII).
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial

of awake prone positioning to improve oxygenation (CIII).
- The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of SARS-CoV-2 exposure to healthcare practitioners during intubation (AII).

MECHANICALLY VENTILATED ADULTS
Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:
- The Panel recommends using low tidal volume (VT) ventilation (VT 4−8 mL/kg of predicted body weight) over higher VT ventilation (VT > 8 mL/kg) (AI).
- The Panel recommends targeting plateau pressures of <30 cm H_2O (AII).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (BII).
- The Panel recommends against the routine use of inhaled nitric oxide (AI).

The rationale behind these recommendations is related to the absence of **evidence that ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from ventilator management of patients with hypoxemic respiratory failure due to other causes.**

Recommendations

For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (BII).
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12−16 h per day over no prone ventilation (BII).
- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBAs) or continuous NMBA infusion to facilitate protective lung ventilation (BIII).
- In the event of persistent patient−ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high

plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 h as long as patient anxiety and pain can be adequately monitored and controlled (BIII).

The beneficial effects of PEEP in patients with ARDS include prevention of alveolar collapse, improvement of oxygenation, and reduction of atelectotrauma, a source of ventilator-induced lung injury. A metaanalysis of three large trials in patients without COVID-19 found lower rates of ICU and in-hospital mortality with higher PEEP in those with moderate (PaO_2/FiO_2 100−200 mm Hg) and severe ARDS (PaO_2/FiO_2 <100 mm Hg) (Briel et al., 2010).

High level of PEEP is not definitely defined but usually considered if > 10 cm H_2O (Alhazzani et al., 2020). Recent reports have suggested that, in contrast to non-COVID-19 ARDS patients, some COVID-19 patients with moderate or severe ARDS have normal static lung compliance so that higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance (Tsolaki et al., 2020; Marini and Gattinoni, 2020). Other studies reported that COVID-19 patients with moderate-to-severe ARDS had low compliance as patients with non-COVID-19 ARDS (Ziehr et al., 2020; Schenck et al., 2020; Bhatraju et al., 2020; Cummings et al., 2020). These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population, and assessment for responsiveness to higher PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as barotrauma and hypotension.

The recommendation for intermittent boluses of NMBA or continuous infusion of NMBA to facilitate lung protection may require a healthcare provider to enter the patient's room frequently for close clinical monitoring. Therefore, in some situations, the risks of SARS-CoV-2 exposure and the need to use personal protective equipment for each entry into a patient's room may outweigh the benefit of NMBA treatment.

Recommendations

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation, and other rescue strategies:
- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (CII).
- If recruitment maneuvers are used, the Panel recommends against using staircase (incremental PEEP) recruitment maneuvers (AII).

- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (CIII).

There are no studies to assess the effects of recruitment maneuvers on oxygenation in COVID-19 patients with severe ARDS. A metaanalysis of six studies in non-COVID-19 patients with ARDS found that recruitment maneuvers reduced mortality, improved oxygenation 24 h after the maneuver, and decreased the need for rescue therapy (Goligher et al., 2017). Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of 8 RCTs in 2544 non-COVID-19 patients, which found that recruitment maneuvers did not reduce hospital mortality (RR 0.90; 95% CI: 0.78−1.04). Subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (RR 0.85; 95% CI: 0.75−0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (RR 1.06; 95% CI: 0.97−1.17) (Alhazzani et al., 2020).

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide use in patients with ARDS found no mortality benefit (Gebistorf et al., 2016). Because the review showed a transient benefit in oxygenation, it is reasonable to attempt inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.

Oxygen nasal cannula

Nasal oxygen cannula is easy, cheap, and easily used oxygen supplying system. It is the most initially used method for oxygen therapy in patients with mild hypoxia. It has a minimal aerosol generation and a low risk of spreading the virus in COVID-19 patients. However, it can only provide up to 40% inspired fraction of oxygen (FiO_2) and requires humidification when oxygen flow is above 6 L per minute. Therefore, nasal oxygen cannula typically cannot provide efficient oxygen therapy in a patient with severe hypoxia due to significant lung damage (Auriant et al., 2001).

Oxygen face mask

Oxygen face masks, especially nonrebreathing face masks, can provide high FiO_2 oxygen therapy, but does not increase oral pharyngeal pressure, and is therefore not efficient enough to treat hypoxia due to severe lung damage and significant alveolar collapse (Jiang and Wei, 2020).

High-flow nasal oxygenation

High-flow nasal oxygenation (HFNO) therapy is used increasingly before invasive ventilation in adults with acute respiratory failure (Weingart and Levitan, 2012; Levy et al., 2016; Koga et al., 2020). It supplies warm, humidified oxygen through the pliable nasal cannula with a fraction of inspired oxygen (FiO_2) up to 1.0 and maximum flow rate up to 70 L/min. At the beginning of the COVID-19 pandemic, the lack of resources named invasive mechanical ventilators, critical care providers, and the easiness of use of HFNO resulted in its use in some COVID-19 patients for oxygen therapy (Xie et al., 2020). A one study 85% of the survivors and 50% of the nonsurvivors received HFNO. Additionally, 14% of patients were treated with HFNO before intubation, and 34.5% of patients who died of COVID-19 received HFNO (Xie et al., 2020).

HFNO use has a higher efficiency than conventional oxygen therapy provided through nasal cannula or oxygen face mask (Zhu et al., 2019) with better tolerability and comfortability (Stéphan et al., 2015). The risks of treatment failure and 30-day mortality were not significantly different between HFNO and noninvasive ventilation (NIV) as first-line therapy in respiratory failure (Koga et al., 2020). HFNO was recommended over NIV, as it has less side effects (Leone et al., 2020) and more reduction in intubation rates in acute respiratory failure (Huang et al., 2018). HFNO was associated with lower 90-day mortality (Frat et al., 2015) and 30-day mortality (Koga et al., 2020) in patients with pneumonia or patients without hypercapnia.

The use of HFNO is associated with less risk of lung injury, as it has a clearing effect on the upper airway without increasing tidal volume (Mauri et al., 2017). This clearing effect makes it more suitable for patients with excessive secretion (Hasani et al., 2008) (28%—34% of COVID-19 cases and 35%—42% in ICU COVID-19 cases) (Guan et al., 2020). However, most protocols for airway management for patients with COVID-19 now consider HFNO a relative contraindication (Brewster et al., 2020) for fear of increase risk of virus aerosol spread. A systematic review of aerosol-generating procedures in SARS patients suggested that HFNO did not increase the risk of SARS transmission significantly (Tran et al., 2012). Besides, it was reported that HFNO with good interface fitting was associated with a low risk of airborne transmission (Hui et al., 2019).

HFNO could be applied in mild and moderate non-hypercapnia cases, but patients should be assessed for respiratory failure. It is also suggested that if there is no improvement within 1 or 2 h, endotracheal intubation and mechanical ventilation should be considered (Li, 2020).

Noninvasive ventilation

Traditional NIV is primarily composed of continuous positive airway pressure or bilevel positive airway pressure ventilation (García-de-Acilu et al., 2019).

NIV has been used in oxygen/ventilation therapy in SARS- and H1N1-infected patients. In recent studies (Yao et al., 2020; Wang et al., 2020a), NIV was used up to 70% in COVID-19 patients before tracheal intubation for invasive mechanical ventilation. However, it seemed that the mortality in these patients was high. It has also been reported that NIV may delay the intubation in patients with severe respiratory failure and is not recommended (Meng et al., 2020).

Recent international expert recommendations suggested that HFNO should be used before NIV in critically ill COVID-19 patients. If NIV is used, it should be limited to short periods with close monitoring of pulmonary failure and decision for early tracheal intubation for invasive ventilation (Alhazzani et al., 2020).

Helmet ventilation

Helmet ventilation is an alternative mode of NIV, with a helmet to replace a commonly used face mask (Lucchini et al., 2020). Its main advantages over the face mask in COVID-19 patients include the reduction of air leakage during positive-pressure ventilation that makes NIV more efficient, reduction of the aerosol spreading of the SARS-CoV-2 virus, and its high tolerability by the patients. Its main disadvantages include the need for high flow of gases (>100 L per minute and high consumption of oxygen supplies), with the difficulty of humidification, the potential rebreathing causing carbon dioxide retention especially at low inspiratory flow and the patient's movement of head and body. Although Helmet seemed to be widely used in COVID-19 patients in Italy, its effectiveness and side effects to treat pulmonary failure and reduce mortality are not clear at this time. No international expert recommendation could be provided (Alhazzani et al., 2020).

Conventional mechanical ventilation

A conventional mechanical ventilator is needed in 10% −17% of COVID-19 patients (Huang et al., 2020). High mortality in COVID-19 patients was reported after tracheal intubation and CMV (Bhatraju et al., 2020). That may be related to late intubation after severe hypoxia and its subsequent multiple organ damage (Sorbello et al., 2020) or complications associated with high-pressure ventilation such as pneumothorax during CMV, which increase the lung damage (Yao et al., 2020).

However, the consistent high mortality after tracheal intubation during this pandemic around the world has inspired alternative techniques, such as HFNO, for oxygen/ventilation treatment in COVID-19 patients and avoiding CMV, although there is no clear conclusion at this moment (Jiang and Wei, 2020).

High-frequency jet ventilation

High-frequency jet ventilation (HFJV) is characterized by its open system, high frequency (respiratory rate >60/minutes), small tidal volume, and low airway pressures (Ihra et al., 2000). High frequency can minimize the diaphragm movement and therefore benefit the AF ablation. Low airway pressure and low tidal volume may benefit the oxygen/ventilation in ARDS treatment or during hypovolemic shock. HFJV at a frequency close to heart rate or synchronized with heart rate also assists cardiovascular function (Angus et al., 1997).

Previous studies suggested that HFJV may provide better oxygenation than CMV in the treatment of respiratory failure or ARDS caused by various reasons. Although there was no improvement of mortality in HFJV over CMV, it acts as an alternative mechanical ventilation with similar efficacy (Bingold et al., 2012).

HFJV is not widely used now for the treatment of pulmonary failure or ARDS as it is difficult to monitor FiO_2, airway pressure, $PetCO_2$ due to its open system, and the difficulty of humidification of the inhaled gases. With its characteristics of better oxygenation under the condition of small tidal volume and low airway pressure, HFJV is expected to treat hypoxia in COVID-19 patients efficiently, especially for those with severe pulmonary failure or ARDS (Jiang and Wei, 2020).

High-frequency two-way jet ventilation

High-frequency two-way jet ventilation (HFTJV) is composed of both active inspiratory and expiratory phases. During the inspiratory phase, a jet pulse is injected into the lung, while a jet pulse is injected out of the lung during the expiratory phase (Wei et al., 1992).

Compared with regular HFJV, the active exhalation by the reverse jet pulse during the expiratory phase not only further decreases mean airway pressures but also enhances oxygenation/ventilation and improvement of circulatory function (Wei et al., 1992). HFTJV theoretically provides the greater capability of improving cardiopulmonary functions than CMV or regular HFJV. Additionally, the reverse jet pulse inside the trachea generates active expiration and may eliminate the SARS-CoV-2 virus out of the lungs due to the Venturi effects generated by the reverse jet pulses. HFTJV is expected to lower mortality in COVID-19 patients, compared with traditional CMV. Therefore, it is important and urgent to investigate the effectiveness and side effects of HFTJV in the treatment of COVID-19 patients with ARDS.

Supraglottic jet oxygenation and ventilation

HFJV is an infraglottic jet ventilation, with jet pulses originated below the vocal cord, which necessitates tracheal intubation and deep patients' sedation. Many studies (Liang et al., 2019a, 2019b; Li et al., 2017; Wu et al., 2017) suggested that supraglottic jet oxygenation and ventilation (SJOV) with jet pulses originated above the vocal cords can also maintain similar efficacy of oxygenation/ventilation as HFJV, as long as the jet pulses are directed toward vocal cord. Compared with the regular infraglottic HFJV, SJOV has the following advantages: (1) easy, quick, and convenient to set up and use; (2) easy to learn and train, even patients can do it themselves through synchronizing their inhalation with the inspiratory jet pulses; (3) monitoring of breathing function with the ability to monitor $PetCO_2$; and (4) minimizing the barotrauma complications frequency seen in the transtracheal jet ventilation (up to 30% in emergent airway management) (Craft et al., 1990), due to its guarantee of opening systems by opened mouth and nose during SJOV.

SJOV is expected to treat hypoxia in COVID-19 patients, especially during the early phase of the disease. Beside the aforementioned advantages, SJOV may have other advantages in the treatment of hypoxia in COVID-19 patients. These include the following: it can be easily adjusted from treating mild hypoxia to moderate or severe hypoxia by increasing driving pressures and change of position of Wei Nasal Jet (WNJ) from mouth to nose under mild sedation (Qin et al., 2017); it requires less sedation than NIV but provides efficient oxygenation/ventilation and may be used to avoid tracheal intubation; it may provide similar efficacy on oxygenation and ventilation, but reduced use of sedation requirement compared with the CMV.

Similar to HFNO, SJOV is a ventilation technique that has the potential to generate aerosol transmission of the SARS-CoV-2 virus. If SJOV is used to treat hypoxia/hypercapnia in COVID-19 patients, it should be performed in a negative pressure room with an anteroom between patients' rooms and clean area. Adequate PPE should be worn to protect healthcare workers from cross-infection (Jiang and Wei, 2020).

EXTRACORPOREAL MEMBRANE OXYGENATION

In ECMO, blood is pumped outside the body to a heart−lung machine that removes carbon dioxide from the blood, supplies it with oxygen, and pumps it again to the tissues. Blood flows from the right side of the heart to the membrane oxygenator in the heart−lung machine and then is rewarmed and sent back to the body. This method allows the blood to "bypass" the heart and lungs, allowing these organs to rest and heal from any injury. ECMO is used in critical care situations, when the heart and/or the lungs are injured and need time to repair so it may be used in care for COVID-19, ARDS, and other infections (MayoClinic, 2020).

The WHO recommended that well-equipped expert health places with sufficient ECMO volume to maintain proficiency consider ECMO support in COVID-19-related ARDS with refractory hypoxemia if lung protective mechanical ventilation (Brower et al., 2000) was insufficient to support the patient (World Health Organization, 2020a). Despite such optimism for a possible role for ECMO in both acute respiratory and cardiac failure, early reports of patients with COVID-19 requiring ECMO suggested that mortality could be greater than 90% (Henry and Lippi, 2020).

High mortality in the initial published experience led some clinicians and investigators to recommend withholding ECMO support in patients with COVID-19 (Ñamendys-Silva, 2020).

RECOMMENDATION

There are insufficient data to recommend either for or against the use of ECMO in patients with COVID-19 and refractory hypoxemia.

RATIONALE

ECMO has been used as a short-term rescue therapy in patients with ARDS caused by COVID-19 and refractory hypoxemia. However, there is no conclusive evidence that ECMO is responsible for better clinical outcomes regardless of the cause of hypoxemic respiratory failure (Combes et al., 2018; Munshi et al., 2019).

The clinical outcomes for patients with ARDS who are treated with ECMO are variable and depend on multiple factors including the cause of respiratory failure, the severity of lung injury, the presence of comorbidities, and the ECMO experience of the healthcare providers (Henry and Lippi, 2020; Bullen et al., 2020; Mustafa et al., 2020). A recent case series of 83 COVID-19 patients in Paris reported a 60-day mortality of 31% for patients on ECMO (Schmidt et al., 2020). This mortality was similar to the mortality observed in a 2018 study of non-COVID-19 patients with ARDS who were treated with ECMO during the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial; that study reported a mortality of 35% at day 60 (Combes et al., 2018).

The Extracorporeal Life Support Organization (ELSO) Registry provides the largest multicenter outcome data set of patients with confirmed COVID-19 who received ECMO support. A recent cohort study evaluated ELSO Registry data for 1035 COVID-19 patients who initiated EMCO between January 16 and May 1, 2020, at 213 hospitals in 36 countries. This study reported an estimated cumulative in-hospital mortality of 37.4% in these patients 90 days after they initiated ECMO (95% CI: 34.4%−40.4%) (Barbaro et al., 2020). Without a controlled trial that evaluates the use of ECMO in patients with COVID-19 and hypoxemic respiratory failure (e.g., ARDS), the benefits of ECMO cannot be clearly defined for this patient population (National Institutes of Health, 2020a).

Rating of recommendations: A = strong; B = moderate; C = optional rating of evidence: I = one or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = one or more well-designed, nonrandomized trials or observational cohort studies; III = expert opinion (National Institutes of Health, 2020a).

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