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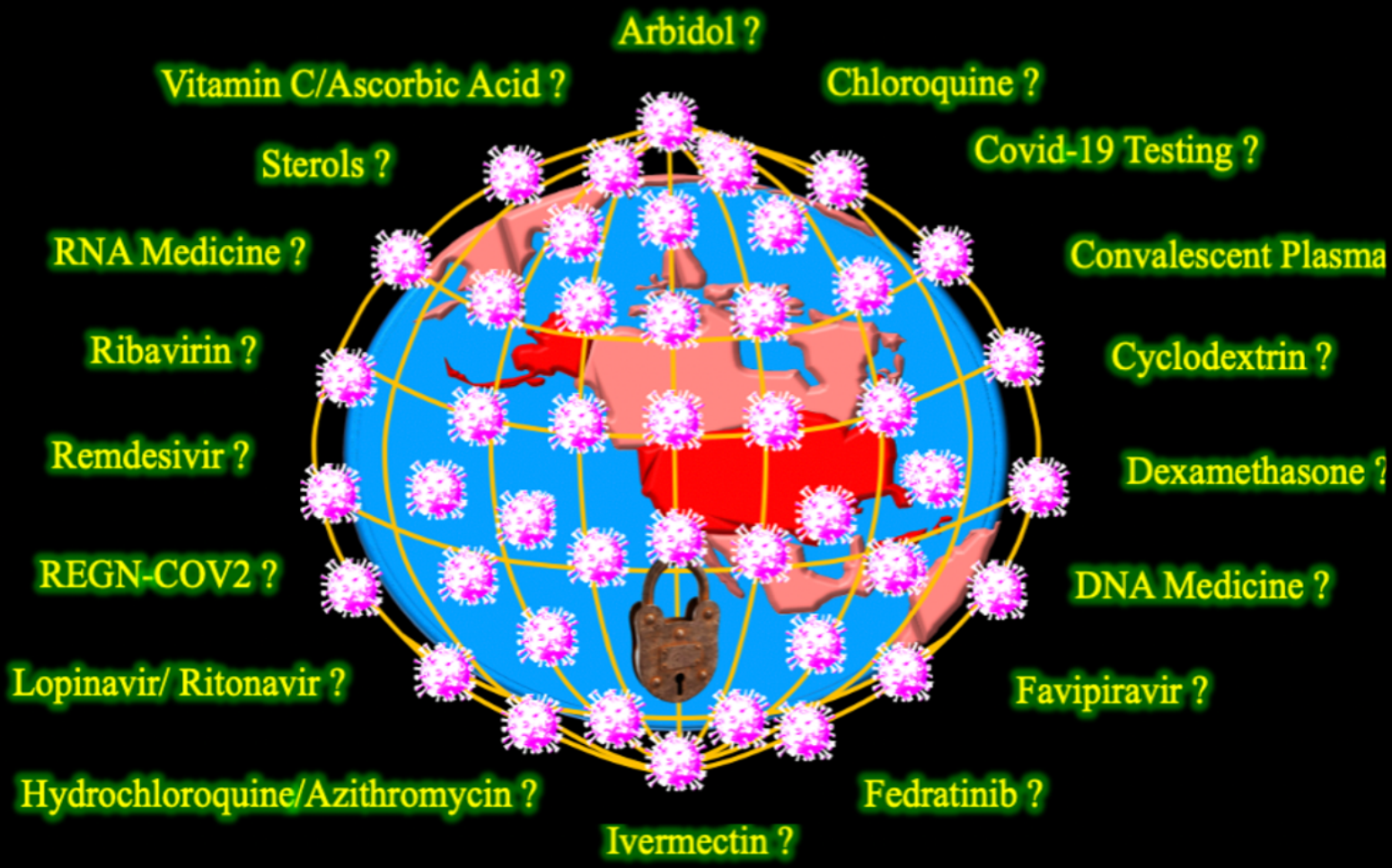

Fear of coronavirus locks down the world and resets activities on the earth

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Review Article

Corona Virus Disease (Covid-19) Management- A Review

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Introduction

Corona Virus Disease 2019 (COVID-19) is an infection caused by Corona Virus identified in 2019. Although it is a systemic disease, most of the morbidity and mortality comes from the involvement of the lungs and the body's exaggerated immune response in an attempt to fight off this infection. Corona Virus may cause an acute respiratory syndrome-like picture and therefore often labeled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2).

Epidemiology

By the time of this writing, more than 122 million cases of Covid-19 have been reported and it has resulted in more than 2.7 million deaths worldwide according to the World Health Organization[1] and an interactive map managed by John Hopkins University[2] The United States of America leads the number of cases followed by Brazil and India. The studies estimating the prevalence and incidence of Covid-19 tend to underestimate the true burden of the disease.[3,4]

COVID-19 symptoms

Initial symptoms of Covid-19 are like any other viral illness i.e. prodromal symptoms. Fever, cough, and fatigue are the most common symptoms in Covid-19 patients.[5, 6] According to CDC, the vast majority of Covid-19 patients manifest the following symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Signs of worsening disease

Symptoms are mild to moderate in nearly 80% of patients and the vast majority of them can be managed in an outpatient setting. There are however several symptoms that may indicate more severe disease and deserve more close monitoring or in-hospital care. These symptoms are considered high risk and should prompt immediate medical attention:[7,8]

- Trouble breathing
- Persistent pain or pressure in the chest
- New confusion
- Inability to wake or stay awake
- Bluish lips or face

High-risk factors

Various studies have documented high-risk clinical factors for worse Covid-19 outcomes. These are known or possible risk factors for poor prognosis in Covid-19 patients:[9,10]

- Advancing age
- Cardiovascular disease i.e. hypertension and hypotension
- Diabetes mellitus
- Obesity
- Cancer
- Chronic Obstructive Pulmonary Disease
- Immunotherapy after solid organ transplant
- Chronic kidney disease
- Smoking
- Cystic fibrosis
- Cerebrovascular accident
- Severe bronchial asthma
- Oxygen saturation less than 94%

Similarly, some of the laboratory markers which have proven to be of prognostic value include ferritin, D Dimers, ALT, Interleukin-6, Troponin, high urea nitrogen and creatinine, C Reactive Protein and procalcitonin levels.[11]

Role of testing

During the course of the pandemic and the high prevalence of Covid-19, suspected patients should be tested if feasible. This is not only for diagnostic purposes but also for epidemiological surveillance and contact tracing. In the setting of the pandemic, patients with suggestive symptoms are considered to be Covid- 19 positive and are treated as such if they have not been tested, or even if they test negative due to the possibility of a false negative. In real life, many factors determine the testing rates including the patient's out-of-pocket expenses and if the health care system is properly equipped and not overwhelmed. The most reliable form

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of Covid testing is the direct detection of SARS-CoV-2 RNA by nucleic acid amplification (NAATs) by reverse transcription-polymerase chain reaction (RT-PCR).[12] A positive NAAT test generally confirms the Covid-19 diagnosis. However, continued detection of SARS-CoV-2 mRNA weeks after symptoms resolution does not indicate infectiousness or ongoing illness, rather only non-viable viral fragments.[13]

CoV-2 antigens can be performed quickly and at the bedside as a point of care test. The antigen-based testing is also becoming available for the consumer for home testing. They are less sensitive and can have high false-negative rates. In clinical trials, the average sensitivity was 56%.[14-16] The patient should be treated as having Covid-19 despite a negative test -either NAATs or Covid antigen testing- if clinical suspicion for disease continues and until a new PCR test can be performed. The CoV-2 antibody has a limited role if any in the diagnosis or management of suspected Covid-19 patients in an acute setting. Though Covid-19 antibody testing has FDA emergency use authorization, CDC guidelines recommend using viral testing as a preferred diagnostic test in the acute clinical setting.[17] This is due to the fact that there is a delay of several days before antibodies become positive,[18] that there is cross-reactivity with other viral antibodies.[19] As of yet there is no standardization and the viral neutralization assays also require a very high level of expertise and equipment.

Symptom's severity and activity level

Symptom's severity point towards the severity of Covid-19. The day of the onset of symptoms is considered as Day 1. The patient is actively asked about dyspnea including the number of days since dyspnea began and the severity of dyspnea symptoms. These are all important determinants of the severity of Covid- 19. Most patients develop dyspnea on Days 4-8 after the onset of symptoms but there is large variability. Helpful inquiries may also include about any changes in baseline activity levels or any new limitations from the prior day. Even in the absence of respiratory symptoms, any notable episodes such as chest pain, dizziness, weakness, fainting or falls must be properly addressed Similarly, changes in mental status, confusion, drowsiness, cyanosis are concerning. These symptoms are concerning due to underlying coronary or myocardial involvement, hypotension, orthostasis, and hypoperfusion.

Dyspnea severity

If a patient has symptoms of dyspnea, it is most important to assess the severity. Dyspnea severity can be classified based on limitations i.e. mild if there are no limitations, moderate if there are some limitations, and severe if the patient is short of breath even at rest.

Oxygen assessment

Transcutaneous oxygen saturation can be an important clinical parameter which if available, can help assess a patient's respiratory status. Oxygen saturation of 95% or more is reassuring while a saturation of 93-94% warrants frequent checks. Oxygen saturations at 92% or lower should require a hospital level evaluation Oxygen saturation can be surprisingly low in a relatively asymptomatic or minimally symptomatic patient. This should raise concerns and should escalate the level of care from outpatient to ER evaluation and/or inpatient admission.

Social factors

The main social factors which impact the decision about place of care are physical support at the home with a healthy and caring companion and the ability to safely isolate. CDC guidelines recommend the assessment for appropriate home settings to assist care, recovery, and isolation [20].

Monoclonal antibody treatment

The BLAZE-1 study is a randomized phase 2/3 trial at 49 US centers including ambulatory patients (N = 613) who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms. In the first stage of the study, patients were randomly assigned to receive a single intravenous infusion of bamlanivimab in one of three doses (700 mg, 2800 mg, or 7000 mg) or a placebo. At a later stage, patients received bamlanivimab 2800 mg and etesevimab and were compared to those who received the placebo.

The primary outcome was the change from baseline in the viral load at Day 11. Authors concluded that among non-hospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with the placebo, was associated with a mild statistically significant reduction in SARS-CoV-2 viral load at Day 11. No significant difference in viral load reduction was observed for bamlanivimab monotherapy [21]. In earlier post hoc analysis, the rate of hospitalization among patients who were older than 65 years and those who had BMI>35 had the admission rate reduced to 4% compared to 15% in the placebo group [22].

Another candidate is the Casirivimab-Imdevimab combination. Data from this ongoing, double-blind, phase 1/3 trial involving non-hospitalized patients with Covid-19 was published in January 2021. Patients were randomly assigned (1:1:1) to receive a placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2. Patients were prospectively characterized at baseline for the

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endogenous immune response against SARS-CoV-2 (serum antibody-positive or serum antibody-negative).

The primary endpoint was the time-weighted average change in viral load from Day 1 to Day 7. Another endpoint was at least one Covid-19 related visit with a healthcare provider in the first 29 days after the transfusion. Data from 275 patients were reported. In the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody-negative at baseline, the corresponding percentages were 15% and 6% (difference, -9 percentage points; 95% CI, -29 to 11) [23]. This evidence from the above two trials made the basis for the emergency use authorization by the FDA for the above agents in recently diagnosed mild or moderate Covid-19 patients. Participants must not require supplemental oxygen and also need to meet the following additional criteria:

- Age 65 years or more
- Age 55 years or older but with cardiovascular disease, and/or hypertension, and/or chronic pulmonary disease
- BMI >35
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppressive disease or on immuno-suppressants

On similar lines, the Infectious Disease Society of America guidelines also recommend using, rather than not using bamlanivimab/etesevimab in outpatients (and few selected inpatients) who have additional risk factors and are at risk of worsening Covid-19, though admitting evidence is weak and it is a conditional recommendation [24].

Indications of hospitalization

It can be challenging to predict the precise percentage of Covid-19 patients who may require hospitalization. In the beginning of pandemic, roughly 80% of Covid-19 patients were managed as outpatients. The remaining 20% percent of patients required close, in-person care and a proportion of them required hospitalization. Based on the severity of patient symptoms, a clinical decision is made to admit the patient to a dedicated Covid-19 medical floor or an intensive care setting.

Initial hospital management and diagnostic workup

The basic principles of care in the initial hospital assessment and management are very similar to other acutely sick patients. Special attention is given to support the patient's hydration status, caloric intake, and managing fever and body aches as well as close monitoring and managing of respiratory status. Secondary bacterial infections are uncommon but common illnesses like COPD flareup, CHF exacerbation, and community or healthcare-associated pneumonia should be kept in mind and managed accordingly, even in the setting of the pandemic. Many patients who require hospitalizations often present with a positive test prior to their admission. In those ill patients who have yet to be tested, the standard nucleic acid amplification testing (NAATs), mostly using reverse transcription-polymerase chain reaction, should be performed [12]. PCR testing time varies from place to place but many places have the return time down to 5 or 6 hours in the United States.

The routine testing in most institutions for patients other than the Covid-19 test include
- Complete blood count
- Comprehensive metabolic panel
- Creatinine phosphokinase (CPK)
- Coagulation profile (PT and aPTT)
- D- Dimers.

CXR is commonly performed in these patients while CT chest is reserved only for patients with moderate to severe symptoms or when another competing pulmonary diagnosis such as pneumonia or pulmonary embolism is suspected.

Prevention of venous thromboembolism

The incidence of thromboembolism in Covid-19 patients is high and arterial and venous thromboembolism is a pathological hallmark of the disease. Additionally, many Covid-19 patients have severe body aches and pains and a severe lack of energy resulting in reduced mobility. In a meta-analysis of studies, the weighted mean prevalence of VTE was 31.3% (95% CI: 24.3-39.2%) [25].

Though ambulation should be encouraged whenever feasible, pharmacological thromboprophylaxis for hospitalized patients is recommended unless contraindicated.

COVID-19 specific therapies

A. Dexamethasone & other steroids

Major support for the recommendation to use dexamethasone comes from a pivotal open-label trial performed in the UK. A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. There was a significant difference in mortality. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). There were also significant differences in the outcome depending on the oxygen and respiratory

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support needed by patients. The difference in the incidence of death was most pronounced in patients on invasive ventilation. Death in this group receiving mechanical ventilation compared to the usual care group was 29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94). This improved outcome was not seen among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55)[26].

Similarly, a metanalysis including data from 7 trials, with a total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; P < .001 based on a fixed-effect meta-analysis). Different trials have different steroids i.e. dexamethasone, hydrocortisone, and methylprednisone, and this improved survival was observed with every steroid used compared to control [27]. The above mortality benefits were not observed in mild to moderate Covid-19 cases not requiring supplemental oxygen or ventilatory support. Steroids are not recommended in such patients.

B. Remdesivir

Remdesivir is an antiviral agent. It is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after being distributed into cells.

In a double-blinded, randomized trial, a total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to a placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received the placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). The Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with the placebo by Day 15, and 11.4% with remdesivir and 15.2% with placebo by Day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) [28]. In this study, the most benefit was noticed in patients requiring supplemental oxygen, but no benefit was observed in patients on mechanical ventilation, requiring ECMO, high flow oxygen and non-invasive ventilation. It is important to note that the study was not powered to assess these differences in subgroups.

Another randomized, double-blind, placebo-controlled, multi-center trial was performed in ten hospitals in Hubei, China. It enrolled adult Covid-19 patients with oxygen saturation of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on Day 1 followed by 100 mg on Days 2-10 in single daily infusions) or placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir-ritonavir, interferons, and corticosteroids. In this trial, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87-1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving the placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95-2·43])[29].

There have been multiple meta-analyses published combining data from various trials but with varying differing results [30-32]. Though remdesivir has FDA emergency use authorization for any Covid-19 patients older than 12 years, most guidelines recommend using remdesivir in hospitalized Covid-19 patients who require supplemental oxygen and not in severe patients requiring non-invasive, invasive ventilation or ECMO [33 34]. When remdesivir is used, 200 mg are administered on the first day followed by 100 mg daily for 5 days or until the time of discharge- whatever may be earlier. This can be extended up to 10 days in certain patients.

C. Baricitinib

Baricitinib is a Janus Kinase Inhibitor that is approved for rheumatoid arthritis. It also seems to have antiviral properties by it's affinity for AP2-associated protein AAK1, reducing SARS-CoV-2 endocytosis [35]. In a randomized, double-blinded trial, a total of 1033 patients underwent randomization (with 515 assigned to a combination of baricitinib and remdesivir treatment and 518 to control with standard care including remdesivir). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P = 0.03), and a 30% higher odds of improvement in clinical status at Day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were less

frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, -5.0 percentage points; 95% CI, -9.8 to -0.3; P = 0.03), as were new infections (5.9% vs. 11.2%; difference, -5.3 percentage points; 95% CI, -8.7 to -1.9; P = 0.003).

Authors concluded that the use of baricitinib plus remdesivir was superior to the use of remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. [36] In this trial, 223 patients were on glucocorticoids. In this group, no additional benefit of baricitinib was observed. Other than this trial there is a relative lack of good randomized trials. For that reason and especially after the pivotal steroid trial, more clinicians are using a steroid and remdesivir combination rather than adding baricitinib to remdesivir. Due to a lack of data, the NIH panel took no position, for or against it's use in hospitalized patients in whom steroids can be used. The panel also recommended that in rare instances where steroids cannot be used in Covid patients not on mechanical ventilation but requiring oxygen, baricitinib can be an option in combination with remdesivir[37]. The Infectious Disease Society of America favored this combination of baricitinib and remdesivir, but only in patients in whom steroids cannot be used [34].

D. Convalescent plasma

Smaller nonrandomized studies at the beginning of Covid-19 have suggested better outcomes and survival by adding convalescent plasma to the standard of care [38 39]. Unfortunately, more robust randomized trials performed later on failed to show these improved outcomes.

In an open-label, multicenter, randomized clinical trial performed in 7 medical centers in Wuhan, China, 103 patients were randomized and 101 completed the study. Clinical improvement occurred within 28 days in 51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, -10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; P = .26). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.59 [95% CI, 0.22-1.59]; P = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.95]; P = .12). Authors concluded that convalescent plasma failed to improve clinical improvement at 28 days compared to standard of care. The trial had planned to enroll 200 patients and was terminated early which might have limited it's results [40].

Another open-label, parallel-arm, phase II, multicenter, randomized controlled trial was performed. It enrolled 646 adult Covid-19 patients with respiratory rate of 24 or more per minute and oxygen saturation 93% or lower. Progression to severe disease or all-cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval -0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54). In short, the use of convalescent plasma failed to show a reduction in progression to more severe disease or all-cause mortality [41]. An important limitation of the trial appears to be large variability for neutralizing antibody titer among convalescent plasma donors.

Due to a lack of enough supporting data, the NIH guidelines panel stated that they have no recommendation for or against the use of a convalescent plasma [33]. The expanded access program in the US has ended but physicians can recommend this treatment under FDA emergency access authorization. However the Infectious Disease Society of America's guideline panel and most experts recommend COVID-19 convalescent plasma only in the context of a clinical trial [34].

E. Interleukin-6 Blockers

Various monoclonal antibodies in Covid- 19 patients have been tested for their role in Covid-19. Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1k subclass directed against soluble and membrane-bound interleukin 6 receptors (IL-6R). It is approved as a disease-modifying anti-rheumatic drug (DMARD) to treat adults with moderate to severe rheumatoid arthritis, children over 2 years of age with the systemic form of juvenile idiopathic arthritis, or children over 2 years of age with the polyarticular form of juvenile idiopathic arthritis. A small study conducted in China randomized patients in three arms, Tocilizumab plus Favipravir, Tocilizumab alone, and Favipravir alone. The primary endpoint was the cumulative lung lesion remission rate at Day 14. The lung lesion remission rate at Day 14 was higher in the combination group as compared with the Favipiravir group (P = 0.019, HR 2.66 95 % CI [1.08-6.53]) and similarly, there was a difference between Tocilizumab and Favipiravir (P = 0.034, HR 3.16, 95 % CI 0.62-16.10). There was no difference between the use of the combination and Tocilizumab alone [42]. Unfortunately, no such benefit was replicated in randomized studies performed later which enrolled more patients.

Another multicenter, open-label, randomized clinical trial investigated the role of Tocilizumab in patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or

admission to the intensive care unit. On Day 14, fewer patients needed noninvasive ventilation or mechanical ventilation or died in the TCZ group than in the control group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00). The HR for mechanical ventilation or death was 0.58 (90% CrI, 0.30 to 1.09). Unfortunately, on Day 28, there was no difference between the two groups in terms of mortality. 7 patients had died in the Tocilizumab group and 8 in the control group (adjusted HR, 0.92; 95% CI 0.33-2.53). The authors concluded that Tocilizumab did not reduce the severity level in these patients on Day 4 nor did it improve survival at Day 28 but might have reduced the likelihood of mechanical or non-invasive ventilation and death at Day 14[43].

Similar trends were observed in another trial; randomly assigned (in a 2:1 ratio) patients hospitalized with Covid-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either Tocilizumab or a placebo. The cumulative percentage of patients who had received mechanical ventilation or who had died by Day 28 was 12.0% (95% confidence interval [CI], 8.5 to 16.9) in the Tocilizumab group and 19.3% (95% CI, 13.3 to 27.4) in the placebo group (hazard ratio for mechanical ventilation or death, 0.56; 95% CI, 0.33 to 0.97; P = 0.04 by the log-rank test). This difference was primarily led by fewer patients requiring mechanical ventilation. This, unfortunately, did not lead to improved survival and death from any cause by Day 28 occurred in 10.4% of the patients in the Tocilizumab group and 8.6% of those in the placebo group (weighted difference, 2.0 percentage points; 95% CI, - 5.2 to 7.8). The guidelines of the Infectious Disease Society of America favor using Tociluzimab in combination with dexamethasone in selected patients with rapidly declining respiratory status [24].
Similarly, the Institute of Health guidelines favor using Tociluzimab with the standard of care (including dexamethasone) in patients with high levels of inflammatory markers [44].

F. Hydroxychloroquine/chloroquine with or without azithromycin

Hydroxychloroquine is an immune modulator, frequently used in rheumatoid arthritis. There is some evidence of antiviral property in vitro. During the initial phase of Covid-19 small case studies raised hopes that Hydroxychloroquine or quinine might help control the pandemic [45]. There was a randomized small study from China that showed a survival benefit with the use of Hydroxychloroquine vs standard of care and a placebo. Unfortunately, later studies performed at a bigger scale and under stricter quality control have failed to show similar benefits.

In a double-blind, randomized trial, 821 asymptomatic participants were enrolled. Overall, 719 of 821 (86.9%) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of a new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine 11.8% and those receiving a placebo 14.3%; the absolute difference was -2.4 percentage points (95% confidence interval, -7.0 to 2.2; P

= 0.35). It was noted that the side effects were more common with hydroxychloroquine than with the placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported. The authors concluded that hydroxychloroquine did not reduce the likelihood of developing Covid-19 or testing positive for Covid-19 after high-risk exposure [46]. Similarly, in another multicenter, in a randomized, open-label study, 667 mild to moderate Covid- 19 patients were enrolled to the standard of care, the standard of care plus hydroxychloroquine or standard of care, hydroxychloroquine plus azithromycin on 1:1:1 ratio. The primary outcome in this study was the clinical status on Day 15. This trial failed to show any improvement in primary outcome and there were more side effects that included prolongation of QTc and abnormal liver functions with the use of hydroxychloroquine with or without azithromycin [47].

G. Azithromycin

Azithromycin is commonly used in community-acquired pneumonia and has a relatively good safety profile. Many clinicians had started using azithromycin with or without hydroxychloroquine in the initial phases of the Covid-19 pandemic. Later on, we have learned that secondary bacterial infections are rare in Covid-19, and the role of antibiotics is questionable unless there is a culture-proven bacterial infection. 447 patients were enrolled from March 28 to May 19, 2020. COVID-19 was confirmed in 397 patients who constituted the mITT population, of whom 214 were assigned to the azithromycin group and 183 to the control group. In the mITT population, the primary endpoint was not significantly different between the azithromycin and control groups (OR 1·36 [95% CI 0·94-1·97], p=0·11). Rates of adverse events, including clinically relevant ventricular arrhythmias, resuscitated cardiac arrest, acute kidney failure, and corrected QT interval prolongation, were not significantly different between groups.

In a multicenter, open-label, and randomized trial 447 patients were enrolled; COVID-19 was confirmed in 397 patients who constituted the mITT population. Of these patients, 214 were assigned to the azithromycin group and

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183 to the control group. The primary endpoint was the clinical status at 15 days after randomization. The primary endpoint was not significantly different between the azithromycin and control groups (OR 1·36 [95% CI 0·94-1·97], p=0·11). Rates of adverse events, including clinically relevant ventricular arrhythmias, resuscitated

cardiac arrest, acute kidney failure, and corrected QT interval prolongation were not significantly different between the groups [48]. Similarly, metanalysis of chloroquine or hydroxychloroquine monotherapy or in combination with azithromycin failed to show significant improvement in outcomes [49]. Due to this data, most guidelines and expert panels advise against empirical or routine use of azithromycin unless there is evidence of or a high suspicion of another diagnosis with a clear indication for azithromycin use like atypical pneumonia.

H- Favipiravir

Favipiravir is an RNA polymerase inhibitor and is being investigated as one of the treatment options for Covid-19. A Chinese study randomized patients in three arms, Tocilizumab plus Favipiravir, Tocilizumab alone, and Favipravir alone. The primary endpoint was the cumulative lung lesion remission rate at Day 14. The lung lesion remission rate at Day 14 was higher in the combination group as compared with the Favipiravir group (P = 0.019, HR 2.66 95 % CI [1.08-6.53]) and similarly, there was a difference between Tocilizumab and Favipiravir (P = 0.034, HR 3.16, 95 % CI 0.62-16.10). There was no difference between the use of the combination and Tocilizumab alone [42]. Another study tested a combination of Favipiravir and interferon or hydroxychloroquine in moderate to severe Covid-19 patients. The study design was randomized, open-label, and the primary endpoints included: discharge, mortality, level of inflammatory markers, and the length of stay. It was a negative study with no difference between the two groups in the levels of inflammatory markers at discharge, length of stay, mortality, or discharge rates [50]. Currently, there are simply no good trials or evidence to support the use of Favipiravir for Covid-19.

I- Interferon

In another randomized, open-label, phase 2 trial conducted in the UK, 101 patients were enrolled. It revealed that between March 30 and May 30, 2020, 101 patients were randomly assigned to SNG001 (n=50) or to a placebo (n=51). 48 received SNG001 and 50 received the placebo and were included in the intention-to-treat population. 66 (67%) patients required oxygen supplementation at baseline: 29 in the placebo group and 37 in the SNG001 group. Patients receiving SNG001 had greater odds of improvement on the OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033) on Day 15 or 16 and were more likely than those receiving the placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). SNG001 was well tolerated. The most frequently reported treatment-emergent adverse event was a headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). There were three deaths in the placebo group and none in the SNG001 group. [51]

There was a large study conducted under the WHO umbrella in which four antiviral drugs were repurposed for Covid-19 treatment. It was a multi-national, multi-center study conducted at 405 hospitals in 30 countries; 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. The authors concluded that there was no clear mortality, avoidance of ventilation, or reduction in hospital duration benefit with any of the drugs [52]. There are no other good-quality randomized, blinded trials comparing interferon with the standard of care. Some studies combined multiple agents and interferon was one of the agents used which made interpretation of results difficult [53]. For said reason, interferon is not a part of guideline recommendations and is not a commonly used treatment agent.

J- Lopinavir/ritonavir

Lopinavir and Ritonavir are protease inhibitors used in the treatment of HIV. This combination is known to have antiviral properties in vitro and preclinical studies. They have been tested as investigational drugs in Covid-19. Many initial studies have used these agents in combination with interferon and other agents, making interpretation difficult. Lately, two randomized trials have been published. The first trial was under the auspices of the WHO solidarity consortium. At 405 hospitals in 30 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94 to 96% midway through treatment, with a 2 to 6% crossover. 148 deaths were reported out of 1399 patients receiving lopinavir and in 146 of 1372 receiving it's control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P = 0.97), showing no difference in mortality rate. Similarly, there was no effect on the initiation of ventilation and the duration of hospital stay. A second randomized, controlled, open-label, followed a pattern similar to the above studies and randomized patients between various Covid-19 re-purposed treatment options and standard of care. A total of 1616 patients were randomly allocated to

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receive lopinavir-ritonavir and 3424 patients to receive usual care. Overall, 374 (23%) patients allocated to lopinavir-ritonavir and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1·03, 95% CI 0·91-1·17; p=0·60). Trial organizers observed similar negative results when it came to the duration of hospitalization (average 11 days), initiation of mechanical ventilation, discharge alive, or mortality at 28 days [52].

K- Ivermectin

Ivermectin is an antiparasitic drug that is known to have antiviral properties in vitro[54]. During the initial days of Covid-19, Ivermectin was empirically used and benefits were reported in non-randomized studies. In a retrospective study from South Florida, US authors reported mortality benefits in patients receiving Ivermectin compared to the control group (15·0% versus 25·2%, OR 0·52, CI 0·29-0·96, P=0·03) [55]. A small randomized study enrolled 72 patients into three arms, Ivermectin 12 grams a day for 5 days, Ivermectin 12 grams on Day 1 combined with doxycycline from Day 1 for 5 days, and a control group. The authors concluded that the use of Ivermectin was a safe option and they observed an earlier viral clearance in Ivermectin for the group which took the drug for 5 days (9.7 days vs 12.7 days; p = 0.02) compared to the control group. No such benefit was noticed in the second group which received Ivermectin only on Day 1 plus doxycycline [56]. Other studies have not shown clinically important benefits [57]. Randomized studies carried on later have not replicated said benefits [58]. There were more studies conducted, but unfortunately with a relatively smaller number of patients, with varying endpoints, many times combined with other now un-approved treatments like hydroxychloroquine, the interpretation of the results has been made difficult . This is the reason why the NIH guideline panel stated that there is insufficient data for the panel to recommend for or against it's the use of Ivermectin [59]. The Infectious Disease Society of America (ISDA) Covid guidelines recommend against the use of Ivermectin for inpatients or outpatients outside the context of clinical trials [60].

Summary of management based on disease severity

Various clinical markers have been used to determine the severity of Covid-19 and predict patients' likelihood of worsening, requiring high flow oxygen or ventilation and prognosis. The most accepted prognostic clinical factors for Covid-19 were detailed above. Recently, clinical features have been validated in various statistical models, and online calculators and phone-based apps have been designed. Based on a multicenter, retrospective, cohort study, the Quick Covid Severity Index (qCSI) has been validated to predict critical respiratory illness in 24 hours following presentation to the Emergency Department [61]. Authors found the clinical markers which predict severity of Covid-19 include:

- Respiratory rate
- Oxygen saturation
- Oxygen flow rate for patients requiring supplemental oxygen.

Other clinical markers which predict prognosis are; aspartate transaminase, alanine transaminase, ferritin, procalcitonin, chloride, c-reactive protein, glucose and urea nitrogen.

Mild disease

Patients without viral pneumonia or hypoxemia are generally categorized as having mild Covid-19. Oxygen saturation in this group is mostly 95% or above. The vast majority of these patients can be managed at home with the help of telemedicine or telephone as long as the social circumstances of the patient allow for the isolation and support needed. Symptoms like fever, rigors, body aches, and fatigue are mostly managed with drugs on an as required basis.

Moderate disease

Symptoms in this group are worse than in the mild group. Still, dyspnea is mild without much limitations, and oxygen saturation is generally between 93-95%. Many of these patients can be managed on an outpatient basis but frequent checks with a healthcare professional may be required, and patients are quickly transferred to the hospital in case of deterioration. Emphasis is on hydration and proper feeding and encouraging ambulation as much as possible. Patients in mild to moderate groups with additional risk factors such as age over 65 years, BMI over 35, chronic kidney disease, diabetes mellitus, or cardiovascular history may also be considered for monoclonal antibodies.

Severe disease

These patients have more severe symptoms often involving respiratory compromise with hypoxia limiting daily activities due to shortness of breath and oxygen saturation 92% or less. The focus should be on supporting hydration and volume status, vitals, and work of breathing. Many patients who are symptomatic but do not need supplemental oxygen should be started on remdesivir and dexamethasone. Tocilizumab can also be considered if inflammatory markers are high or the patient displays quick deterioration in pulmonary status. Baricitinib can also be considered for those patients who cannot tolerate dexamethasone for any reason.

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