# PHAMRMACOTHERAPY OF COVID-19: A COMPREHENSIVE REVIEW FROM 2022 UPDATED NIH,IDSA AND ICMR GUIDELINES


## ABSTRACT

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



**KEYWORDS:** COVID-19, Monoclonal antibodies, Molnupiravir, Baricitinib.


**Abbreviations: IDSA ( infectious disease society of America),ICMR ( Indian council of medical research), COVID ( Corona virus disease).**

## INTRODUCTION

Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, limiting the continuing spread of this virus and its variants has become an issue of increasing concern, as SARS-CoV-2 continues to create havoc across the world, with some countries languishing in a third wave of outbreaks of this viral illness due to the emergence of mutant variants of the virus currently being O-micron.

Based on the severity of presenting illness that includes clinical symptoms, laboratory and radiographic abnormalities, hemodynamics, and organ function. The National Institutes of Health (NIH) classified COVID-19 into following distinct types; **Asymptomatic COVID-19 infection:** patients who test positive for COVID-19 and are free of COVID symptoms [1,2].

**Mild illness:** Individuals who have any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, nausea, vomiting, diarrhea, anosmia, or dysgeusia but no breathlessness and normal chest imaging [3].

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

1. Respiratory rate >24 breaths per minute.

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

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

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

1. Respiratory rate >30 breaths per minute.
2. $SpO_2$ <90% on ambient air.

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

**Pharmacologic Therapies In The Management Of Adults With COVID-19: At present** , a lot of pharmacological options are available that include antiviral drugs (e.g., molnupiravir,paxlovid,remdesivir), anti-SARS-CoV-2 monoclonal antibodies (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory medications (e.g., dexamethasone), immunomodulators agents (e.g., baricitinib, tocilizumab) under FDA Emergency Use Authorization( EUA) in the management of COVID-19[10].

The pharmacological use of these treatments is specific and is based on the severity of illness and specific risk factors. The clinical course of the COVID-19 illness traverses through 2 phases, an initial phase when SARS-CoV-2 replication is at its peak soon after the onset of symptoms. Antiviral medications and antibody-based treatments are effective during this stage. The later phase of the illness is characterized by a hyperinflammatory response due to outburst of cytokines and the coagulation system's activation leading to a prothrombotic state. Anti-inflammatory drugs such as corticosteroids, immunomodulating therapies, or a combination of these try to overcome this cytokine storm state.Folllwing medications have been the potential therapeutic options proposed, authorized, or approved for treating COVID-19 disease.

**Antiviral Therapies**

**Molnupiravir:** A directly acting broad-spectrum oral antiviral agent acting on the RdRp enzyme initially developed as a possible antiviral treatment for influenza, alphaviruses including Eastern, Western, and Venezuelan equine encephalitic viruses. Based on meta-analysis of available phase 1-3 studies, molnupiravir was noted to demonstrate a significant reduction in hospitalization and

death in mild COVID-19 disease [5]. Results from a phase 3 double-blind randomized placebo controlled trial (MOVE OUT) reported that early treatment with molnupiravir reduced the risk of hospitalization or death in at risk unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19 [6]. January 2022 updated ***IDSA guidelines recommend molnupiravir for ambulatory patients with mild to moderate disease at risk of progression to severe disease who have no other treatment options within 5 days of symptom onset*** [40]. ***Current ICMR guidelines do not recommend molnupiravir in the treatment of*** *COVID-19* [41].

Paxlovid (ritonavir in combination with nirmatrelvir) is an oral combination pill of two antiviral agents which on an interim analysis of phase 2-3 data (reported via press release) which included 1219 patients, found that the risk of -19 related hospital admission or all-cause mortality was 89% lower in the paxlovid group when compared to placebo when started within three days of symptom onset [7]. Further studies are ongoing to establish the efficacy reported [14]. On 22 December 2021, the FDA issued a EUA authorizing the use of Paxlovid for patients with mild to moderate COVID-19. January 2022 updated ***IDSA guidelines recommend paxlovid for ambulatory patients with mild to moderate disease at risk of progression to severe disease within 5 days of symptom onset*** [40]. ***ICMR guidelines do not recommend paxlovid in the treatment of COVID-19*** [41].

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

however, acquired resistance against mutant viruses is a potential concern and should be monitored. January 2022 updated ICMR ***guidelines do not recommend remdesivir use in non hospitalized or mild disease patients. However, in moderate and severe disease it is given EUA/off label use*** [41].***IDSA guidelines recommend remdesivir for non hospitalized patients with mild to moderate disease at risk of progression to severe disease*** [40].

**Anti-SARS-CoV-2 Neutralizing Antibody Products**

Individuals recovering from COVID-19 develop neutralizing antibodies against SARS-CoV-2, and the duration of how long this immunity lasts is unclear. Nevertheless, their role as therapeutic agents in the management of COVID-19 is extensively being pursued in ongoing clinical trials.

Convalescent Plasma therapy was evaluated during the SARS, MERS, and Ebola epidemics; however, it lacked randomized control trials to back its actual efficacy. The FDA approved convalescent plasma therapy under a EUA for patients with severe life-threatening COVID-19 [13][14]. Although it appeared promising, data from multiple studies evaluating the use of convalescent plasma in life-threatening COVID-19 has generated mixed results. One retrospective study based on a U.S. national registry reported that among patients hospitalized with COVID-19, not on mechanical ventilation, there was a lower risk of death in patients who received a transfusion of convalescent plasma with higher anti-SARS-CoV-2 IgG antibody than patients who received a transfusion of convalescent plasma with low antibody levels [15]. Data from three small randomized control trials showed no significant differences in clinical improvement or overall mortality in patients treated with convalescent plasma versus standard therapy [16][17][18]. January 2022 updated ICMR ***guidelines recommend against CPT use in COVID-19 disease*** [41].***IDSA guidelines recommend against CPT use in patients hospitalized for COVID-19*** [40].

**REGN-COV2 (Casirivimab and Imdevimab):** REGN-COV2 is an antibody cocktail containing two noncompeting IgG1 antibodies (casirivimab and imdevimab) that target the RBD on the SARS-CoV-2 spike protein that has been shown to decrease the viral load in vivo. Results from an interim analysis of 275 patients from an ongoing double-blinded trial involving non hospitalized patients with COVID-19 who were randomized to receive placebo, 2.4 g of REGN-COV2 (casirivimab 1,200 mg and imdevimab 1,200 mg) or 8 g of REGN-COV2 COV2 (casirivimab 2,400 mg and imdevimab 2,400 mg) reported that the REGN-COV2 antibody

cocktail reduced viral load compared to placebo [19]. This interim analysis also established the safety profile of this cocktail antibody, similar to that of the placebo group [20]. IDSA guidelines recommend use of REGN-COV2 in patients with mild to moderate disease at risk of progression [40].

***January 2022 updated IDSA guidelines recommend sotrivimuab for non hospitalized mild to moderate disease at risk of progression*** [40].

**Immunomodulatory Agents**

Corticosteroids: Severe COVID-19 is associated with inflammation-related lung injury driven by the release of cytokines characterized by an elevation in inflammatory markers. During the pandemic's early course, glucocorticoids' efficacy in patients with COVID-19 was not well described. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, which included hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 who were randomly assigned to received dexamethasone (n=2104) or usual care (n=4321), showed that the use of dexamethasone resulted in lower 28-day mortality in patients who were on invasive mechanical ventilation or oxygen support but not in patients who were not receiving any respiratory support [22]. Based on the results of this landmark trial, dexamethasone is currently considered the standard of care either alone or in combination with remdesivir based on the severity of illness in hospitalized patients who require supplemental oxygen or non-invasive or invasive mechanical ventilation. January 2022 updated ***IDSA and ICMR guidelines also recommend methylprednisolone as an alternative to dexamethasone in a dosage of 0.5 to 1 mg/ kg for moderate disease and 1 to2 mg/kg for severe and critical disease respectively*** [40,41].

Tocilizumab is an anti-interleukin-6 receptor alpha receptor monoclonal antibody that has been indicated for various rheumatological diseases. The data regarding the use of this agent is mixed. A randomized control trial involving 438 hospitalized patients with severe COVID-19 pneumonia, among which 294 were randomized to receive tocilizumab and 144 to placebo, showed that tocilizumab did not translate into a significant improvement in clinical status or lower the 28-day mortality compared to placebo [23,24]. Results from another randomized, double-blind placebo-controlled trial involving patients with confirmed severe COVID-19 that involved 243 patients randomized to receive tocilizumab or placebo showed that the use of tocilizumab was not effective in preventing intubation or death rate {25,26,27}. The REMAP-

CAP and RECOVERY trials two large randomized controlled trials, showed a mortality benefit in patients exhibiting rapid respiratory decompensation [28]. January 2022 updated ***IDSA and ICMR guidelines recommend tocilizumab for severe covid disease with rapid decompensation and high inflammatory markers (IL6 and CRP) in absence of bacterial or TB infection[ 40,41]. In the largest clinical trial on the treatment of tocilizumab criterion for systemic inflammation was defined as CRP> 75 mg/L.***

Sarilumab and Siltuximab are IL-6 receptor antagonists that may potentially have a similar effect on the hyperinflammatory state associated with COVID-19 as tocilizumab. Currently, there no known published clinical trials supporting the use of siltuximab in severe COVID-19. Conversely, a 60-day randomized, double-blind placebo control multinational phase 3 trial that evaluated the clinical efficacy, mortality, and safety of sarilumab in 431 patients did not show any significant improvement in clinical status or mortality rate [29]. Another randomized, double-blind placebo-controlled study on sarilumab's clinical efficacy and safety in adult patients hospitalized with COVID-19 is currently ongoing (NCT04315298). January 2022 updated ***IDSA guidelines recommend sarilumab when tocilizumab is not available and patient qualifies for later*** [40].

**Janus kinase (JAK) inhibitors**

Baricitinib is an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2 currently indicated for moderate to severely active rheumatoid arthritis(RA) patients. Baricitinib was considered a potential treatment for COVID-19 based on its inhibitory effect on SARS-CoV-2 endocytosis in vitro and on the intracellular r signaling pathway of cytokines that cause the late-onset hyperinflammatory state that results in severe illness [39,40]. This dual inhibitory effect makes it a promising therapeutic drug against all stages of COVID-19. A multicenter observational, retrospective study of 113 hospitalized patients with COVID-19 pneumonia who received baricitinib combined with lopinavir/ritonavir (baricitinib arm, n=113) or hydroxychloroquine and lopinavir/ritonavir (control arm, n=78) reported significant improvement in clinical symptoms and 2-week mortality rate in the baricitinib arm compared with the control arm. Results from the ACTT-2 trial, a double-blind, randomized placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adult patients with COVID-19, reported that the combination therapy of baricitinib plus remdesivir was superior to remdesivir therapy alone in not only reducing recovery time but also accelerating clinical

improvement in hospitalized patients with COVID-19, particularly who were receiving high flow oxygen supplementation or noninvasive ventilation [31,32] Baricitinib, in combination with remdesivir, has been approved for clinical use in hospitalized patients with COVID-19 under a EUA issued by the FDA. The efficacy of baricitinib alone or in combination with remdesivir has not been evaluated in the SARS-CoV-2 variants, and there is limited data on the use of baricitinib with dexamethasone. January 2022 updated ***ICMR guidelines do not recommend baricitinib for use in COVID-19 irrespective of severity***[41].***IDSA guidelines recommend use of barictinib for severe and critical disease patients with high inflammatory markers*** [40]. ***Patients who can receive steroids IDSA guidelines recommend use of baricitinib in combination with remdesivir.***

**Prognosis**

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

**CONCLUSION:**

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

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