Wani A, et al. J Pulm Med Respir Res 2022, 8: 072
DOI: 10.24966/PMRR-0177/100072

Journal of
Pulmonary Medicine and Respiratory Research

Opinion Article

Corona Virus Disease: A Comprehensive Review on Diagnosis and Management from 2022 Updated NIH, IDSA and ICMR Guidelines

Ahad Wani, Aamir Shafi* and Jawhar Ul Islam

Skims srinagar, Jammu and Kashmir valley, India

Introduction

Coronavirus Disease 2019 (COVID-19 has had a deleterius effect on the world's demographics resulting in more than 3.8 million deaths worldwide, emerging as the most devastating global health crisis since the era of the influenza pandemic of 1918. Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, limiting the continuing spread of this virus and its variants has become an issue of increasing concern, as SARS-CoV-2 continues to wreak havoc across the world, with many countries enduring a third wave of outbreaks of this viral illness attributed mainly due to the emergence of mutant variants of the virus currently being O-micron.

Clinical Manifestations of COVID-19

The median incubation period for SARS-CoV-2 is estimated to be 5.1 days, and the majority of patients will develop symptoms within 11.5 days of infection. It is estimated that 17.9% to 33.3% of infected patients will remain asymptomatic.

Conversely, the vast majority of symptomatic patients commonly present with fever, cough, and shortness of breath and less commonly with a sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhea. Stokes et al. reported that among 373,883 confirmed symptomatic COVID-19 cases in the US, 70% of them experienced fever, cough, shortness of breath, 36% reported myalgia and 34% reported headache. The relatively specific symptoms of O-micron variant are fever and night sweats.

***Corresponding author:** Aamir Shafi, Skims srinagar, Jammu and Kashmir valley, India, E-mail: amirshafi400@gmail.com

Citation: Wani A, Shafi A, Islam JU (2022) Corona Virus Disease: A Comprehensive Review on Diagnosis and Management from 2022 Updated NIH, IDSA and ICMR Guidelines. J Pulm Med Respir Res 8: 072.

Received: February 02, 2022; **Accepted:** February 10, 2022; **Published:** February 17, 2022

A large meta-analysis evaluating clinicopathological characteristics of 8697 patients with COVID-19 in China reported laboratory abnormalities that included lymphopenia (47.6%), elevated C-reactive protein levels (65.9%), elevated cardiac enzymes (49.4%), and abnormal liver function tests (26.4%). Other laboratory abnormalities included leukopenia (23.5%), elevated D-dimer (20.4%), elevated erythrocyte sedimentation rate (20.4%), leukocytosis (9.9%), elevated procalcitonin (16.7%), and abnormal renal function (10.9%).

A meta-analysis of 212 published studies comprising of 281,461 individuals from 11 countries/regions reported that severe disease course was noted in about 23% with a mortality rate of about 6% in patients infected COVID-19. The elevated Neutrophil-to-Lymphocyte Ratio (NLR), derived NLR ratio (d-NLR) [neutrophil count divided by the result of WBC count minus neutrophil count] and the platelet-to-lymphocyte ratio is indicative of a cytokine-induced inflammatory storm.

Based on the severity of presenting illness that includes clinical symptoms, laboratory and radiographic abnormalities, hemodynamics and organ function. The National Institutes of Health (NIH) issued guidelines that classify COVID-19 into following distinct types.

Asymptomatic COVID 19 infection: patients who test positive for COVID 19 and are free of COVID symptoms.

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

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

- Respiratory rate >24 breaths per minute
- Sp02 90% to 93% on ambient air

Severe illness: Individuals who have (SpO2) ≤ 94% on room air; a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO2/FiO2) <300 with respiratory rate>30 breaths/min or lung infiltrates >50%. However ICMR guidelines define severe disease as anyone of the two parameters

- Respiratory rate >30 breaths per minute
- Sp02 <90% on ambient air

Critical illness: Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunction. 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.

Diagnostic Testing In COVID-19

The standard diagnostic mode of testing is testing a nasopharyngeal swab for SARS-CoV-2 nucleic acid using a real-time PCR assay. Commercial PCR assays have been validated by the US Food and Drug Administration (FDA) with Emergency Use Authorizations (EUAs) for the qualitative detection of nucleic acid from SARS-CoV-2 from specimens obtained from nasopharyngeal swabs as well as other sites such as oropharyngeal, anterior/mid-turbinate nasal swabs, nasopharyngeal aspirates, Bronchoalveolar Lavage (BAL) and saliva. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period.

The sensitivity of PCR testing is dependent on multiple factors that include the adequacy of the specimen, technical specimen collection, time from exposure, and specimen source. However, the specificity of most commercial FDA-approved SARS-CoV-2 PCR assays is nearly 100%, provided that there is no cross-contamination during specimen processing. SARS-CoV-2 antigen tests are less sensitive but have a faster turnaround time compared to molecular PCR testing. Comprehensive testing for other respiratory viral pathogens should be considered for appropriate patients as well.

Serology Testing

An antibody test can evaluate for the presence of antibodies that occurs as a result of infection. Antibody tests play an important role in broad-based surveillance of COVID-19, and many commercial manufactured antibody testing kits are available to evaluate the presence of antibodies against SARS-CoV-2 are available. Despite the numerous antibody tests designed to date, serologic testing has limitations in specificity and sensitivity, and results from different tests vary. However, an antibody test with a specificity higher than 99% and a sensitivity of 96% has been developed by the CDC, which can identify past SARS-CoV-2 infection.

Other Laboratory Assessment

Complete Blood Count (CBC), a Comprehensive Metabolic Panel (CMP) that includes testing for renal and liver function and a coagulation panel should be performed in all hospitalized patients. Additional tests such as testing for inflammatory markers such as ESR, C-Reactive Protein (CRP), ferritin, lactate dehydrogenase, D-dimer and procalcitonin can be considered in hospitalized patients. However, their prognostic significance in COVID-19 is not clear.

Imaging Modalities

Considering this viral illness commonly manifests itself as pneumonia, radiological imaging has a fundamental role in the diagnostic process, management, and follow-up. Imaging studies may include chest x-ray, lung ultrasound, or chest Computed Tomography (CT). There are no guidelines available regarding the timing and choice of pulmonary imaging studies in patients with COVID-19, and the type of imaging should be considered based on clinical evaluation.

Chest X-ray

Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes; it can be completely normal in the initial stages of the disease. In the more advanced stages of infection, the chest X-ray examination commonly shows bilateral multifocal alveolar opacities, which tend to confluence up to the complete opacity of the lung. Pleural effusion can also be demonstrated.

Chest Computed Tomography (CT)

The American College of Radiology does not recommend Chest CT' routinely as an initial imaging study or screening. Given its high sensitivity, chest Computed Tomography (CT), particularly High-Resolution CT (HRCT), is the diagnostic method of choice in evaluating COVID-19 pneumonia, particularly when associated with disease progression.

Several non-specific findings and radiologic patterns can be found on Chest CT. Most of these findings may also be observed in other lung infections, such as Influenza A (H1N1), CMV, SARS, MERS, streptococcus, and Chlamydia, Mycoplasma. The most common CT findings in COVID-19 are multifocal bilateral "ground or Ground Glass" (GG) areas associated with consolidation areas with patchy distribution, mainly peripheral/subpleural and greater involvement of the posterior regions lower lobes. The "crazy paving" pattern can also be observed. This latter finding is characterized by GG areas with superimposed interlobular septal thickening and intralobular septal thickening. It is a non-specific finding that can be detected in different conditions. Other notable findings include the "reversed halo sign," a focal area of GG delimited by a peripheral ring with consolidation, and the findings of cavitations, calcifications, lymphadenopathies, and pleural effusion.

Ultrasonography of Lungs

Ultrasonographic examination of the lung allows evaluating the progression of the disease, from a focal interstitial pattern up to a "white lung" with evidence of subpleural consolidations. Considering its noninvasive nature and zero risks of radiation, it is a useful diagnostic modality for patient follow-up and assists in determining the setting of mechanical ventilation and prone positioning. The main sonographic features are:

Pleural lines: appear often thickened, irregular and discontinuous until it almost seems erratic; subpleural lesions can be seen as small patchy consolidations or nodules.

B lines: They are often motionless, coalescent and cascade and can flow up to the square of "white lung."

Thickenings: They are most evident in the posterior and bilateral fields, especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.

Perilesional Pleural Effusion

In summary, during the course of the illness, it is possible to identify the first phase with focal areas of fixed B lines followed by a phase of numerical increase of the lines B up to the white lung with small subpleural thickening, which progresses further until there is evidence of posterior consolidations.

Management

Pharmacologic therapies in the management of adults with COVID-19

Currently, a variety of therapeutic options are available that include antiviral drugs (e.g., molnupiravir, paxlovid, remdesivir),

anti-SARS-CoV-2 monoclonal antibodies (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory drugs (e.g., dexamethasone), immunomodulators agents (e.g., baricitinib, tocilizumab) are available under FDA issued Emergency Use Authorization (EUA) or being evaluated in the management of COVID-19.

The clinical utility of these treatments is specific and is based on the severity of illness or certain risk factors. The clinical course of the COVID-19 illness occurs in 2 phases, an early phase when SARS-CoV-2 replication is greatest before or soon after the onset of symptoms. Antiviral medications and antibody-based treatments are likely to be more effective during this stage of viral replication. The later phase of the illness is driven by a hyperinflammatory state induced by the release of cytokines and the coagulation system's activation that causes a prothrombotic state. Anti-inflammatory drugs such as corticosteroids, immunomodulating therapies, or a combination of these therapies may help combat this hyperinflammatory state than antiviral therapies. Below is a summary of the latest potential therapeutic options proposed, authorized, or approved for clinical use in the management of COVID-19.

Antiviral therapies

Molnupiravir (named after the Norse god Thor's hammer Mjölnir) is a directly acting broad-spectrum oral antiviral agent acting on the RdRp enzyme was initially developed as a possible antiviral treatment for influenza, alphaviruses including Eastern, Western, and Venezuelan equine encephalitic viruses. Based on meta-analysis of available phase 1-3 studies, molnupiravir was noted to demonstrate a significant reduction in hospitalization and death in mild COVID-19 disease. Results from a phase 3 double-blind randomized placebo controlled trial 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. Results from a phase 3 double-blind randomized placebo controlled trial 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. Current IDSA guidelines recommend molnupiravir for ambulatory patients with mild to moderate disease at risk of progression to severe disease who have no other treatment options within 5 days of symptom onset.

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. Further studies are ongoing to establish the efficacy reported. On 22 December 2021, the FDA issued a EUA authorizing the use of Paxlovid for patients with mild to moderate COVID-19.current IDSA guidelines recommend paxlovid for ambulatory patients with mild to moderate disease at risk of progression to severe disease within 5 days of symptom onset.

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, 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. However, results from the WHO SOLIDARITY Trial conducted at 405 hospitals spanning across 40 countries involving 11,330 in patients 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 reported an 87% lower risk of hospitalization or death than placebo when at-risk non hospitalized patients with COVID-19 were treated with a 3-day course of remdesivir. There is no data available regarding the efficacy of remdesivir against the new SARS-CoV-2 variants; however, acquired resistance against mutant viruses is a potential concern and should be monitored.current ICMR guidelines do not recommend remedsevir use in non hospitalized or mild disease patients. However in moderate and severe disease it is given EUA/off label use. Current IDSA guidelines recommend remdesvir for non hospitalized patients with mild to moderate disease at risk of progression to severe disease.

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. 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. 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. An in vitro analysis of convalescent plasma obtained from individuals previously infected with the ancestral SARS-CoV-2 strains demonstrated significantly reduced neutralization against SARS-CoV-2 variant B.1.351/ 501Y.V2. Another in vitro study reported B.1.351 variant exhibited markedly more resistance to neutralization by convalescent plasma obtained from individuals previously infected with the ancestral SARS-CoV-2 strains compared to the B.1.1.7 variant, which was not more resistant to neutralization. Current ICMR guidelines recommend against CPT use in COVID 19 disease. Current IDSA guidelines recommend against CPT use in patients hospitalized for COVID 19.

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, preventing virus-induced pathological sequelae when administered prophylactically or therapeutically in non-human primates. 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. This interim analysis also established the safety profile of this cocktail antibody, similar to that of the placebo group. Preliminary data from a Phase 3 trial of REGN-COV (casirivimab/imdevimab) revealed a 70% reduction in hospitalization or death in nonhospitalized patients with COVID-19. In vitro data is available regarding the effect of REGN-COV2 on the two new SARS-CoV-2 variants of concern (B.1.1.7; B.1.351 variants) that reveal retained activity. A recent preprint study by Wilhelm et al. reported that SARS-CoV-2 Omicron variant was resistant to casirivimab and imdevimab in their in-vitro study. Current IDSA guidelines recommend use of REGN-COV2 in patients with mild to moderate disease at risk of progression.

Bamlanivimab and Etesevimab (LY-CoV555 or LY3819253 and LY-CoV016 or LY3832479) are potent anti-spike neutralizing monoclonal antibodies. Bamlanivimab is a neutralizing monoclonal antibody derived from convalescent plasma obtained from a patient with COVID-19. Like REGN-COV2, it also targets the RBD of the spike protein of SARS-CoV-2 and has been shown to neutralize SARS-CoV-2 and reduce viral replication in non-human primates. In vitro experiments revealed that etesevimab binds to a different epitope than bamlanivimab and neutralizes resistant variants with mutations in the epitope bound by bamlanivimab. In Phase 2 of the BLAZE-1 trial, bamlanivimab/etesevimab was associated with a significant reduction in SARS-CoV-2 viral load compared to placebo. Data from the Phase 3 portion of BLAZE-1 is pending release, but preliminary information indicates that therapy reduced the risk of hospitalization and death by 87%. In vitro data is available regarding the effect of bamlanivimab/etesevimab on the new SARS-CoV-2 variants of concern (B.1.1.7; B.1.351) reveals retained activity.

Sotrovimab (VIR-7831) is a potent anti-spike neutralizing monoclonal antibody that demonstrated in vitro activity against all the four VOCs Alpha (B.1.1.7), Beta (B.1.351), Gamma (P1), and Delta (B.1.617.2). Results from a preplanned interim analysis (not yet peer-reviewed) of the multicenter, double-blind placebo-controlled Phase 3, COMET-ICE trial by Gupta et.al that evaluated the clinical efficacy and safety of sotrovimab demonstrated that one dose of sotrovimab (500 mg) reduced the risk of hospitalization or death by 85% in high-risk non hospitalized patients with mild to moderate COVID-19 compared with placebo. Current IDSA guidelines recoomend sotrivimuab for non hospitalized mild to moderate disease at risk of progression.

REGN-COV2 (casirivimab and imdevimab) and sotrovimab were approved for clinical use by the FDA under two separate EUAs issued in November 2020 and May 2021, respectively, that allowed the use of these drugs only in nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with laboratory-confirmed SARS-CoV-2 infection and mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. On March 25th, the U.S. government stopped recent treatment study distribution of bamlanivimab alone, citing that the increasing emergence of coronavirus variants makes the treatment ineffective. Ongoing local vigilance regarding the prevalence of emerging variants will be necessary to determine which antibody treatments retain efficacy.Current ICMR guidelines do not approve monoclonal antibody use in covid 19 pts.

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. Based on the results of this landmark trial, dexamethasone is currently considered the standard of care either alone or in combination with remdesivir based on the severity of illness in hospitalized patients who require supplemental oxygen or non-invasive or invasive mechanical ventilation. Current IDSA and ICMR guidelines also recommend methylprednisolone as an alternative to dexamethasone in a dosage of 0.5 to 1 mg/ kg for moderate disease and 1 to2 mg/kg for severe and critical disease.

Anti-IL-6 receptor Monoclonal Antibodies: Interleukin-6 (IL-6) is a proinflammatory cytokine that is considered the key driver of the hyperinflammatory state associated with COVID-19. Targeting this cytokine with an IL-6 receptor inhibitor could slow down the process of inflammation based on case reports that showed favorable outcomes in patients with severe COVID-19(33,34,35) The FDA approved three different types of IL-6 receptor inhibitors for various rheumatological conditions (Tocilizumab, Sarilumab) and a rare disorder called Castleman's syndrome (Siltuximab).

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. 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. The REMAP-CAP and RECOVERY trials (not yet published), two large randomized controlled trials, showed a mortality benefit in patients exhibiting rapid respiratory decompensation. Current IDSA and ICMR guidelines recommend tocilizumab for severe covid disease with rapid decompensation and high inflammatory markers (IL6 and CRP) in absence of bacterial or TB infection.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. Another randomized, double-blind placebo-controlled study on

sarilumab's clinical efficacy and safety in adult patients hospitalized with COVID-19 is currently ongoing (NCT04315298).Current IDSA guidelines recommend sarilumab when tocilizumab is not available and patient qualifies for later.

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. 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. Baricitinib, in combination with remdesivir, has been approved for clinical use in hospitalized patients with COVID-19 under a EUA issued by the FDA. The efficacy of baricitinib alone or in combination with remdesivir has not been evaluated in the SARS-CoV-2 variants, and there is limited data on the use of baricitinib with dexamethasone. Current ICMR guidelines do not recommend baricitinib for use in covid 19 irrespective of severity. Current IDSA guidleines recommend use of barictinib for severe and critical disease patients with high inflammatory markers.

Patients who can receive steroids IDSA guidelines recommend use of baricitinib in combination with remedesvir. Ruxolitinib is another oral selective inhibitor of JAK 1 and 2 that is indicated for myeloproliferative disorders, polycythemia vera, and steroid-resistant GVHD. Similar to baricitinib, it has been hypothesized to have an inhibitory effect on cytokines' intracellular signaling pathway, making it a potential treatment against COVID-19. Results from a small prospective multicenter randomized controlled phase 2 trial evaluating the efficacy and safety of ruxolitinib reported no statistical difference than the standard of care. However, most of the patients demonstrated significant chest C.T. improvement and faster recovery from lymphopenia. A large randomized, double-blind, placebo-controlled multicenter trial (NCT04362137) is ongoing to assess ruxolitinib's efficacy and safety in patients with severe COVID-19.

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

Bruton's tyrosine kinase inhibitors such as acalabrutinib, ibrutinib, rilzabrutinib are tyrosine kinase inhibitors that regulate macrophage signaling and activation currently FDA approved for some hematologic malignancies. It is proposed that macrophage activation occurs during the hyperinflammatory immune response seen in severe COVID-19. Results from a small off-label study of 19 hospitalized patients with severe COVID-19 who received acalabrutinib highlighted the potential clinical benefit of BTK inhibition. Clinical trials are in progress to validate the actual efficacy of these drugs in severe COVID-19 illness.

Current IDSA guidelines recommend use of FLUVOXAMINE, IVERMECTIN and FAMOTIDINE only in the context of clinical trials. Oxygenation and Ventilation Management in COVID-19.

Conventional Oxygen Therapy

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

Management of Acute Hypoxemic Respiratory Failure in COVID-19

Acute hypoxemic respiratory failure is the most common complication in adult patients with COVID-19, and conventional oxygen therapy is not helpful to address the oxygen demand in these patients. These patients should be managed with enhanced respiratory support modalities such as high-flow nasal cannula (HFNC), Noninvasive Positive Pressure Ventilation (NIPPV), endotracheal intubation, and Invasive Mechanical Ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

High-Flow Nasal Cannula (HFNC) and Noninvasive Positive Pressure Ventilation (NIPPV)

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

Noninvasive Positive-pressure Ventilation (NIPPV)

NIPPV (Bilevel Positive Airway Pressure [BiPAP]/Continuous Positive Airway Pressure [CPAP]) is instrumental in the management of COVID-19-associated acute hypoxemic respiratory failure and may help avoid invasive mechanical ventilation in carefully selected patients. NIPPV should be restricted to hospitalized patients with COVID-19 who develop respiratory insufficiency due to COPD, cardiogenic pulmonary edema, or have underlying Obstructive Sleep Apnea (OSA) rather than ARDS.

A helmet is preferred for minimizing the risk of aerosolization. In NIPPV with face masks (full-face or oronasal), the use of masks integrated with an expiratory valve fitted with an antimicrobial filter is recommended. Results from the HENIVOT trial, an Italian open-label multicenter randomized clinical trial, reported that there was no significant difference in the number of days free of respiratory support with the utilization of helmet noninvasive ventilation treatment compared to high flow nasal oxygen in COVID-19 patients hospitalized with moderate to severe degree of hypoxemia.

Endotracheal Intubation and Lung Protective Invasive Mechanical Ventilation

Impending respiratory failure should be recognized as early as possible, and a skilled operator must promptly perform endotracheal intubation to maximize first-pass success. Clinicians and other healthcare staff must wear appropriate PPE that includes gowns, gloves, N95 masks, and eye protection when performing endotracheal intubation and manual ventilation before intubation, physical proning of the patient, or providing critical patient care such as upper airway suctioning, disconnecting the patient from the ventilator. Pre oxygenation (100% O2 for 5 minutes) should be performed via HFNC. Invasive mechanical ventilation in COVID-19 associated acute hypoxemic respiratory failure and ARDS should be with lower tidal volumes (V.T.) (4 to 8 ml/kg predicted body weight, PBW) and lower inspiratory pressures reaching a plateau pressure (Pplat) < 30 cm of H_2O.

Positive End-Expiratory Pressure (PEEP) must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible (< 14 cmH2O). Use of Neuromuscular Blocking Agents (NMBA) should be used as needed to facilitate lung-protective ventilation. In patients with refractory hypoxemia (PaO2:FiO2 of <150 mm Hg), prone ventilation for > 12 to 16 hours per day and the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion are strongly emphasized. The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel recommends against inhaled pulmonary vasodilators such as nitric oxide.

Lung-protective ventilation can also reduce the risk of new or worsening AKI by preventing ventilator-induced hemodynamic effects. ECMO should be considered in carefully selected patients with refractory hypoxemia despite lung-protective ventilation and patients who fail to respond to prone position ventilation. Management of COVID-19 Based on the Severity of Illness.

Asymptomatic or Presymptomatic Infection

Individuals with a positive SARS-CoV-2 test without any clinical symptoms consistent with COVID-19 should be advised to isolate themselves and monitor clinical symptoms.

Mild Illness

- Based on the NIH guidelines, individuals with mild illness is manageable in the ambulatory setting with supportive care and isolation.
- Laboratory and radiographic evaluations are routinely not indicated.
- Elderly patients and those with pre-existing conditions should be monitored closely until clinical recovery is achieved.
- SARS-CoV-2 neutralizing antibodies such as REGN-COV2 (casirivimab and imdevimab) or bamlanivimab/etesevimab or sotrovimab can be considered for outpatients who are at risk of disease progression with a low threshold to consider hospitalization for closer monitoring.
- The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel recommends against dexamethasone in mild illness.

Moderate illness

- Patients with moderate COVID-19 illness should be hospitalized for close monitoring.
- Clinicians and healthcare staff should don appropriate Personal Protective Equipment (PPE) while interacting or taking care of the patient.
- All hospitalized patients should receive supportive care with isotonic fluid resuscitation if volume-depleted, and supplemental oxygen therapy must be initiated if SpO2 and be maintained no higher than 96%.
- Empirical antibacterial therapy should be started only if there is a suspicion of bacterial infection and should be discontinued as early as possible if not indicated.
- Patients with COVID-19 are at risk of developing venous and thromboembolic events and should be maintained on thromboembolic prophylaxis with appropriate anticoagulation.
- Remdesivir and dexamethasone can be considered for patients who are hospitalized and require supplemental oxygen.
- The National Institutes of Health (NIH) Covid-19 treatment guidelines panel recommends the use of either remdesivir alone or dexamethasone plus remdesivir or dexamethasone alone if combination therapy (remdesivir and dexamethasone) is not available in hospitalized patients who require supplemental oxygen but are not receiving HFNC or NIPPV or IMV or ECMO.

Severe/Critical illness

- Patients with severe/critical COVID-19 illness require hospitalization.
- Considering that patients with severe COVID-19 are at increased risk of prolonged critical illness and death, discussions regarding care goals, reviewing advanced directives, and identifying surrogate medical decision-makers must be made.
- All patients should be maintained on prophylactic anticoagulation, considering COVID-19 is associated with a prothrombotic state.

- Clinicians and other healthcare staff must wear appropriate PPE that include gowns, gloves, N95 masks, and eye protection when performing aerosol-generating procedures on patients with COVID-19 in the ICU, such as endotracheal intubation, bronchoscopy, tracheostomy, manual ventilation before intubation, physical proning of the patient or providing critical patient care such as nebulization, upper airway suctioning, disconnecting the patient from the ventilator, and noninvasive positive pressure ventilation that may potentially lead to the aerosol generation.
- Renal replacement therapy should be considered in renal failure when indicated.
- HFNC or NIPPV can be considered in patients who do not require intubation.
- Having awake patients self-prone while receiving HFNC can improve oxygenation if endotracheal intubation is not indicated. However, the efficacy of performing this maneuver on awake patients is not clear and more data from clinical trials is needed.
- The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel strongly recommends using dexamethasone in hospitalized patients who require oxygen via noninvasive or invasive ventilation. Combination therapy with dexamethasone plus remdesivir or baricitinib or tocilizumab in combination with dexamethasone alone is also recommended in hospitalized patients on HFNC or NIPPV with evidence of disease progression. If corticosteroids cannot be used, baricitinib plus remdesivir may be used in non intubated patients.
- The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel also recommends tocilizumab (as a single intravenous dose) in recently hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19.
- Impending respiratory failure should be recognized as early as possible, and endotracheal intubation with IMV must be initiated as described earlier.
- Vasopressors should be started to maintain Mean Arterial Pressure (MAP) between 60 mmHg and 65 mmHg. Norepinephrine is the preferred initial vasopressor.
- Empiric antibacterial therapy should be considered if there is a concern for a secondary bacterial infection. Antibiotic use must be reassessed daily for de-escalation, and the duration of the treatment requires evaluation for appropriateness based on the diagnosis.
- Management of COVID-19 patients with ARDS should be similar to classical ARDS management from other causes, including prone positioning as per The Surviving Sepsis Campaign guidelines for managing COVID-19.
- ECMO should be
- considered in patients with refractory respiratory failure as previously described

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.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752