In Depth Review

A Pathophysiologic Approach to COVID-19 Management and Current Status of Treatment and Recommendations

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Abstract: A multipronged approach is needed to manage COVID-19 illness, caused by SARS-CoV-2. It includes preventive strategies such as masking, physical distancing, sanitizing (CAB-COVID appropriate behavior) and vaccines & therapeutic strategies targeting (a) viral replication and (b) host immunological responses which injure the host due to collateral damage in containing the virus. An effective chemoprophylactic antiviral compound along with better clinical management by properly classifying the disease pathology and targeting therapy will lead to judicious use of medications to treat COVID-19. To achieve these goals several measures, include development of vaccines and repurposing of drugs to thwart viral replication and mitigate exuberant host immunological/inflammatory responses. Each measure has its own importance in addressing the threat posed by SARS-CoV-2 to the health of an individual and the community. This review describes relevant biology of the virus and key therapeutic interventions targeting SARS-CoV-2 entry, replication, and the inflammatory host immunological pathways, as part of prevention and treatment of COVID-19 to reduce pill burden for disease management as per recent recommendations. We are also reminded of the classical quote by Dr. David Ho an eminent virologist and AIDS researcher, "It is the Virus Stupid" and it must be contained with counter measures that target the virus and disease progression. Dr. David Ho's groundbreaking work to combat replicating HIV in patients with hard hitting antiretrovirals changed the death sentence of HIV/AIDS into a manageable problem and likewise provides us clue to effectively manage COVID-19.

Keywords: COVID-19, Clinical management, Immunity, Cytokine storm, Pill burden, Dr. David Ho

List of Abbreviations Used	
ACE	Angiotensin-converting Enzyme
ACE2	Angiotensin-Converting Enzyme 2
ACEIs	Angiotensin-converting Enzyme Inhibitors
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AECII	Alveolar Epithelial Type II Cells
ALI	Acute Lung Injury
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
CAB	COVID appropriate behavior
CoV	Coronaviruses
CP	Convalescent Plasma
CQ	Chloroquine
CRP	C-reactive Protein
DAMPs	Damage Associated Molecular Patterns
DIC	Disseminated Intravascular Coagulation
ECMO	Extracorporeal Membrane Oxygenation
EMPACTA	Evaluating Minority Patients with Actemra
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
HCQ	hydroxychloroquine
IFN	Interferons IFN
IL-6	Interleukin 6
IMP	Importin
JAB	COVID-19 Vaccination
LDH	Lactate Dehydrogenase
mAbs	Human Monoclonal Antibodies
MAS	Macrophage Activation Syndrome
MERS	Middle East Respiratory Syndrome
Mil6r	Transmembrane IL-6 Receptors
NK	Natural Killer
NLRP3	Nucleotide-binding domain (NOD)-like Receptor Protein 3
NTD	N-terminal Domain
PAMPs	Pathogen Associated Molecular Patterns
PE	Pulmonary Embolism
PEP	Postexposure Prophylaxis
PrEP	Preexposure Prophylaxis
PRRs	Pattern-Recognition Receptors
RAAS	Renin–angiotensin–aldosterone System
RAS	Renin Angiotensin System Modulation
RBC	Red Blood Cell
RBD	Receptor Binding Domain
SARS	Severe Acute Respiratory Syndrome
TH1	T Helper 1

Background: Historically Coronaviruses (CoV) were discovered in chicken in 1930s and it was not until 1960s that they were reported to cause disease in humans. Two crucial years (2002, 2012) saw the emergence of zoonotic human CoVs-Severe Acute Respiratory Syndrome (SARS) CoV (Total cases 8098; mortality rate 9.5%) and Middle East Respiratory Syndrome (MERS) CoV (Total cases 2519 cases; mortality rate 34.4%) respectively (1-2). However, neither escalated to pandemic proportions comparable in scale to SARS-CoV-2, causative agent for COVID-19 (3) declared as a Public Health emergency of international concern. Like its other family members SARS-CoV-2 is probably enzootic and jumped the species barrier in 2019 transmitting in humans with over 569 million people infected worldwide and over 6 million deaths as of July 2022, and still superseding the damage done by other human CoVs (4).

Biology of a Quasi-species SARS-CoV-2: SARS-CoV-2 high replication rate early in the infection cycle leads to emergence of viral quasi species and high genetic recombination to generate a population of heterogenous viral particles (5). These variants get notoriously designated either as Variants of Concern (VOC), Variants of Interest (VOI) or Variant of High Consequence (VOHC) based on their virulence and transmission dynamics that ensue public health interventions. Most intriguing aspect is that the continuous emergence of variants in the same individual spring forth evolution to more transmissible viral populations that may be virulent and potentially overcome immunity provided by wild type infection and existing vaccines. The recommendations of COVID-19 management are evolving based on our understanding of virus biology and host immune response. Hence, an ongoing human endeavor is to renew our line of COVID-19 management and viable treatment options.

COVID-19 infection manifests either as asymptomatic or symptomatic disease with illness ranging from mild, moderate, and severe that may necessitate hospitalization. Early symptoms include dry cough, fever or chills, shortness of breath, new loss of smell and/or taste, sore throat, congestion or runny nose, fatigue, muscle or body aches, headache, nausea or vomiting, and diarrhea while severe illness usually manifests after 7-10 days characterized by dyspnea and hypoxemia. The list of symptoms is evolving with the emergence of SARS-CoV-2 variants and disease sequelae christened as "Long COVID-19" with new/persisting symptoms in recovered individuals.

Severely ill patients show progressive respiratory failure with onset of bilateral infiltrates, severe hypoxemia and lung exudates fulfilling criteria of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Multi organ dysfunction and inflammation sets in with lymphopenia, thrombocytopenia, thromboembolic complications, coagulation disorders, acute kidney injury, cardiac arrhythmias, liver injury, disorders of the central and peripheral nervous system, hyperferritinemia with

elevated D-dimer, high levels of interleukin-6 (IL-6), LDH (Lactate dehydrogenase), and C-reactive protein (CRP). Disease severity induced by SARS-CoV-2 is attributed to a mix of factors that include virus inoculum, host age and underlying comorbidities like obesity, diabetes and existing heart ailments, respiratory diseases, cancer, and renal failure in affected host (5, 6). The uncertainty in disease presentation is not only due to infectivity of the virus but its consequent immune/inflammatory response to the viral replication in the host.

Pathogenesis of SARS-CoV-2: Pathogenesis of SARS-CoV-2 involves virus-host interactions, entry and egress from host cell, orchestration of innate and adaptive immune regulation (6, 7). After entry, virus proliferation is facilitated by taking over the host cellular machinery. The host's innate and adaptive immune system is activated to eliminate the virus. On entry of SARS-CoV-2, the first line of host defense by innate immune response is triggered. Macrophages and monocytes recruited to the site respond to infection, release cytokines and prime adaptive T and B cell immune responses (7). To mount the innate antiviral immune response (6), pattern-recognition receptors (PRRs) present on alveolar epithelial cells and alveolar macrophages detect the released pathogen-associated molecular patterns (PAMPs), such as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP, DNA and oligomers. Among PRRs, NLRP3 inflammasome activated by PAMPS or DAMPs catalyzes recruitment of caspases leading to activation of interleukins (6, 7). Recognition by innate immune cells lead to activation of downstream signaling cascade which results in the upregulation of expression of type I IFN and other pro-inflammatory cytokines and chemokines, caspases, IL-6, IFN-gamma, MCP1 and IP-10 into extracellular compartments of infected tissues. These cytokine responses are indicators of a T helper 1 (TH1) cell-polarized response (8).

The Th1 type immune response plays a dominant role in adaptive immunity to viral infections. Cytokine microenvironment generated by antigen presenting cells dictates the direction of T cell responses. Helper CD4 T cells orchestrate the overall adaptive response, while cytotoxic CD8 T cells essentially kill the viral infected cells and aid in viral clearance (9, 10). This initial response comprises the first line of defense against SARS-CoV-2 at the entry site. In majority of COVID-19 infected patients, activated immune cells can clear the infection, the immune/ inflammatory response tapers off, and patients recover. Interferons limit virus spread and play an immune-modulatory role to promote macrophage phago-cytosis of antigens and Natural Killer (NK) cells mediate restriction of infected target cells and modulate exuberant macrophage activation. The initial immune response is the key to containing disease severity as inappropriate dampening immune response early on can be treacherous. Regarding B-cell activation, total levels of IgG and IgM have been reported to be similar between severe and mild COVID-19 cases suggesting no major general impairment in B-cell activity; IgM response peaks around day 9 after disease onset and the switching to IgG by week two (6).

SARS-CoV-2 virus can circumvent host antiviral responses resulting in uncontrolled viral replication, which is an area of immense study. The sudden clinical worsening in severely affected hospitalized COVID-19 patients is driven by a unique pattern of immune dysfunction. The immunopathology of lung leading to ALI and ARDS results from overdrive of inflammatory responses or "cytokine storm" as witnessed by soaring levels of blood inflammatory markers and excessive unabated oxidation stress that results in the activation of the cytokine storm (Figure 1) (6-8). The advent of cytokine storm in COVID-19 infection is derived from our understanding of cytokine storm in other human coronavirus infections (11). High influx of pro-inflammatory factors leads to increased vascular permeability and entry of fluid and blood cells into the alveoli, resulting in dyspnea and in severe cases respiratory failure due to impaired oxygenation and alveolar gas exchange. Pro-inflammatory cytokines also lead to increase in von Willebrand factor aggregation into multimers in activated endothelial cells along with release of chemokines, clumping of platelets (thrombus formation) and activation of the complement cascade. Furthermore, myriad COVID-19 clinical manifestations and long-lasting sequelae involve Multisystem Inflammatory Syndrome (MIS) orchestrated either by inflammatory factors and/or deposition of immune complexes/ Ig mediated complement activation leading to vasculitis, acute kidney injury, myocarditis, involvement of Central Nervous System and Peripheral Nervous System with neurological manifestations and Kawasaki-like disease in children and adults with SARS-CoV-2 infection (12).

Like SARS-CoV, SARS-CoV-2 prefers binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2) to gain entry to the host cell (13, 14), although this may not be the receptor of choice in some variants. ACE-2 is proven to be present on vascular endothelial cells, the renal tubular

epithelium, Leydig cells in the testes, lung, kidney, and gastrointestinal tract and in some hematopoietic cells, (AECII) express 83% of ACE2, hence the lung tissue is most susceptible to the virus (14). The N-terminal domain (NTD) of SARS-CoV-2 Spike (S) protein also engages with 9-*O*-acetylated sialic acid-containing receptors. The Receptor Binding Domain (RBD) recognizes ACE2 while the NTD binds a lipid raft rich in ganglioside at the cell surface; S glycoprotein priming by host serine protease-TMPRSS2 leads to viral fusion with the cell membrane (5, 14, 15). Widespread presence of ACE2 also explains the multi-organ involvement in SARS-CoV-2 as virus-receptor interaction modifies the local microenvironment of immune complexes in blood vessels and alveoli causing immune complex related endothelitis (12); Abundant ACE2 gene expression has been recently reported in subcutaneous and visceral adipose tissue compared to the lung tissue (16). As per an experimental study, SARS-CoV-2 infection impaired insulin/IGF (Insulin-like Growth Factor) signaling in adipose tissue and several other organs (17). Obese patients with abundant adipose tissue are hence more susceptible to virus entry into cells and proliferation leading to multi organ involvement with severe COVID-19 disease (18). Also, affinity to human gut epithelium has long term implications in viral fecal-oral transmission of the virus and will impact its containment due to persistence in wastewater from households and treatment facilities (19). This indeed makes an interesting surveillance tool to detect presence of SARS-CoV-2 in wastewater samples as a surrogate marker to predict possible outbreaks.

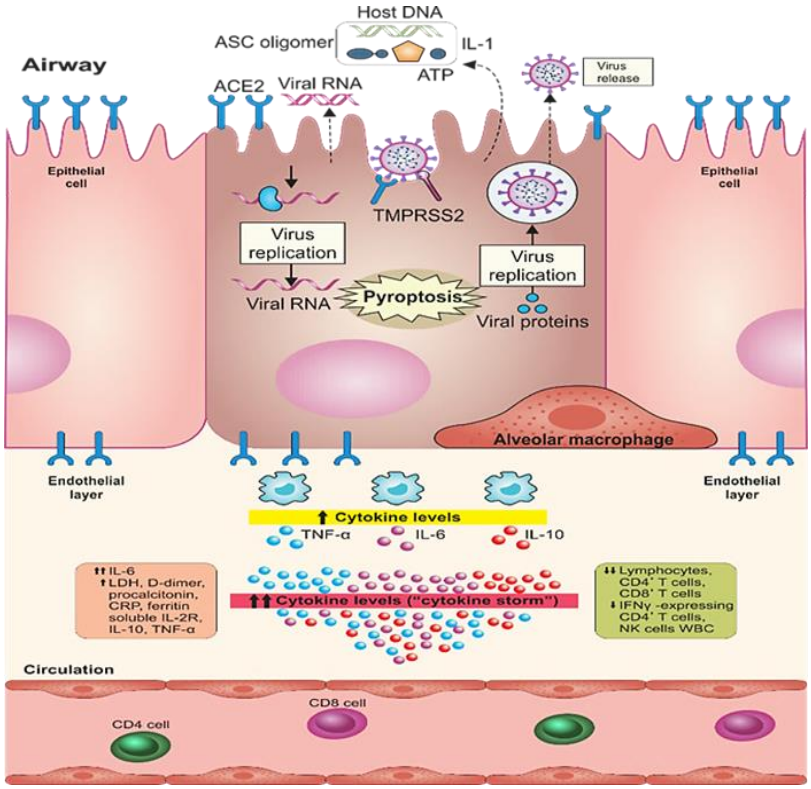

Figure 1: Pathophysiology of Cytokine Storm: SARS-CoV-2 entry is facilitated by binding to ACE2 receptor. Since respiratory epithelial cells abundantly express ACE2 receptor they demonstrate high levels of damage caused by inflammasome induced pyroptosis. Acute lung injury and inflammation promotes neutrophil infiltration and further burst of cytokines. Patients with severe infection manifest decreased lymphocyte count (including marked depletion of NK cells) while secretion of inflammatory cytokines contributes to the cytokine storm. Dysregulated immune response in severe SARS-CoV-2 infection is marked by decreased lymphocyte counts, increased neutrophil counts, a higher neutrophil-lymphocyte ratio and an increased percentage of monocytes and macrophages that infiltrate the lung responsible for lung disease with eventual fibrosis.

Cytokine Storm: Neutrophilia and lymphocytopenia have been suggested as risk factors for the development of cytokine storm, ARDS, and progression from ARDS to death in severe COVID-19 (20). The mechanisms by which SARS-CoV-2 subverts the body's innate antiviral cytokine responses are under investigation as multiple viral structural and non-structural proteins can antagonize interferon responses. Antagonism or inadequate type I interferon response allows unchecked viral replication triggering the intracellular processes that lead to increased pyroptosis with further aberrant inflammatory responses as part of massive cell destruction. The damaged cell products in-turn recruit proinflammatory macrophages and granulocytes and unrestrained inflammatory cell infiltration can itself mediate tissue damage through excessive secretion of proteases and reactive oxygen species, besides the direct damage resulting from the virus (21). Besides causing local damage in the lung, cytokine

storm also has ripple effects across the body. Elevated levels of cytokines can cause shock and multi-organ failure which can lead to myocardial injury and circulatory failure as observed in many patients with severe infection. People with severe COVID-19 seem to exhibit a phenomenon consistent with the "Macrophage Activation Syndrome" (MAS), a life-threatening condition that requires immediate medical attention (22). MAS is characterized by hyper stimulation and proliferation of macrophages and T cells causing an inflammatory cytokine storm by mediation of hemophagocytosis and hyper-cytokinemia (22-24). Red blood cell (RBC) destruction in hemophagocytosis leads to release of high levels of ferritin. High ferritin levels are classically associated with inflammatory diseases and septic shock (23). Cytokine cocktail consisting of tumor necrosis factor and interferon-gamma and several interleukins (IL-1, IL-6, IL-10, IL-18, IL-33) are part of cytokine storm. Hence dampening of a hyper stimulated immune response using anti-inflammatory agents and steroids is an attractive therapeutic option besides novel treatments that modulate the release of cytokines. Anti-inflammatory therapies that attenuate NLRP3 inflammasome upstream or downstream, modulation of cytokines and/or agents that neutralize macrophages and neutrophils that work alone or in combination are also under evaluation as therapeutic agents.

In summary, pathology of severe COVID-19 infection involves multiorgan-hepatorenal, myocardial, lung damage attributable to multiple reasons like immune complexes, cytokine storm, vascular/endothelial dysfunction, coagulation disorders, and hypoxic injury (22). Old age and people with co-morbidities are more likely to develop such a dysfunctional immune response and may fail to eradicate the pathogen (25, 26). To demarcate the bane from the boon, we need to focus on aspects of the COVID-19 pandemic crucial to understand the disease severity and hence the considerations for clinical management of mild-moderate-severely ill patients and post COVID-19 sequalae. This review brings forth the scientific learnings to manage COVID-19 with the key thrust of decreasing pill burden and reducing morbidity and mortality based on current recommendations.

The Changing Landscape and Current Status of Recommendations to Manage COVID-19: The main strategy of clinical management of COVID-19 disease is focused on novel inhibitors, alleviating clinical symptoms and supportive care (27). The clinical therapeutic agents and mechanism in COVID-19 management are summarized in Table 1 (28). Figure 2 summarizes clinical management of hospitalized and non-hospitalized COVID-19 patients (28). For hospitalized patients, the supportive treatment including oxygen therapy, conservation fluid management, and the use of broad-spectrum antibiotics to cover secondary bacterial infection, whereas anti-thrombotic and concomitant medication remains important in management strategy and decision should be made on case-by-case basis.

Pre-exposure Prophylaxis (PrEP) for COVID-19: The United States Food and Drug Administration (FDA) has granted Emergency Use Authorization (EUA) to Long-acting antibody (LAAB) treatment (29). LAAB is a pre-exposure prophylaxis (PrEP) beneficial for individuals not exposed to COVID-19 but are at high risk for severe COVID-19 and hospitalization, once infected (30). Combination of monoclonal antibodies Tixagevimab and Cilgavimabis is a LAAB treatment provided EUA by FDA (31). This cocktail can be administered to persons ≥12 years old, weight ≥40 kg with history of immune compromise or allergy to currently available vaccines against COVID-19 (31).

Clinical Management and Treatment for Mild to Moderate Disease: Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) do not initially require hospitalization, and maybe able to manage their illness at home. The decision to monitor a patient as inpatient or outpatient is made case-by-case. Home care for COVID-19 entails isolation in well ventilated room, adequate hydration, following respiratory etiquettes, hand hygiene, use of mask with frequent change for patient and caretakers, monitoring temperature, and oxygen saturation daily (32).

Patients at higher risk of severe illness should be monitored closely given the possible risk of progression to severe illness in the second week after symptom onset and may benefit from administration of monoclonal antibodies in outpatient or under hospital settings. Also, availability of new antivirals for patients with possibility of progression to severe disease/hospitalization/death and their current recommendation status (28) are elaborated below.

Table 1: Clinical Therapeutic Agents, Mechanism in COVID-19 Management and Current Status

No	Types of Therapeutic Strategies/Agents	Therapeutic Mechanism	Current Recommendation (https://www.covid19treatmentguidelines.nih.gov/)
1	**Antivirals:** Nirmatrelvir 300 mg (two 150 mg tablets) and Ritonavir 100 mg	Nirmatrelvir is a protease inhibitor preventing viral replication. Ritonavir increases plasma concentrations of Nirmatrelvir	Emergency Use Authorization granted for early treatment of patients aged ≥12 years and weighing ≥40 kg within five days of onset of symptoms who possess high risk for progression to severe COVID-19, hospitalization or death
	Molnupiravir 800 mg (four, 200-mg capsules)	As synthetic cytidine nucleoside, Molnupiravir introduces errors during viral replication and thereby producing defective viral elements	Emergency Use Authorization granted for early treatment of patients aged ≥18 years within five days of onset of symptoms who possess high risk for progression to severe COVID-19, hospitalization or death
	Remdesivir 200mg IV on Day 1 followed by 100mg IV from Day 2	Acts by shutting down viral replication by inhibiting a key viral enzyme, the RNA polymerase	Emergency Use Authorization for hospitalized adults and emergency use in individuals *aged ≥28 days and weighing ≥3 kg* Not recommended for mild -moderate COVID-19
	Ivermectin 200–600 µg/kg	Blocks transmission of viral proteins into host nucleus by inhibiting the importin (IMP) α/β receptor	Not recommended for treatment of COVID-19, for PrEP or PEP for prevention of SARS-CoV-2 infection, except in a clinical trial
	Chloroquine or Hydroxychlo-roquine 800 mg loading dose followed by 400 mg	Chloroquine and hydroxychloroquine inhibit fusion of SARS-CoV-2 with host membrane/binding to receptor for cell entry/prevent release of viral genome thus exerting antiviral role. Also have immunomodulatory role.	Not recommended for treatment of mild-moderate-severe COVID-19. Their Emergency Use Authorization was withdrawn in mid-2020
2	**Anti-inflammatory Agents:** Systemic Corticosteroids: Dexamethasone 6mg, Hydrocortisone 10mg, Prednisone 40mg, Methylprednisolone 32 mg Inhaled Corticosteroids: Budesonide 800mcg Ciclesonide 160mcg	Directly target the key cytokines, dampens cytokine storm and alleviate hyperinflammation	To use Dexamethasone over other systemic corticosteroids for the treatment of hospitalized patients with severe or critical COVID-19 requiring supplemental oxygen. If Dexamethasone is not available, other systemic corticosteroids at dosages equivalent to Dexa-methasone 6 mg daily may be used. However, Dexamethasone is not recommended in mild to moderate COVID-19 and in clinically severe patients not requiring supplemental oxygen Currently, inhaled corticosteroids (Budesonide, Ciclesonide) are not recommended for treatment of COVID-19
3	**Monoclonal antibodies (mAbs):** Casirivimab 600mg plus Imdevimab 600 mg IV Bamlanivimab 700 mg plus Etesevimab 1400 mg IV Sotrovimab 500 mg IV Bebtelovimab 175 mg IV Tixagevimab 300 mg plus Cilgavimab 300 mg IM	Neutralizing antibodies that block viral attachment and binding to the SARS-CoV-2 receptor-binding domain of the Spike protein thus blocking virus entry	Initially, Emergency Use Authorization granted for Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab and Sotrovimab for post exposure prophylaxis (PEP) and treatment of mild to moderate cases of COVID-19. However, in January 2022, use of these monoclonal antibodies was withdrawn as found ineffective against different Omicron COVID-19 variant. Bebtelovimab effective against Omicron variants is still recommended for treatment of high-risk outpatients with mild to moderate COVID-19 Tixagevimab plus Cilgavimab is recommended as preexposure prophylaxis (PrEP) of COVID-19 for patients at high risk of infection

4	**IL-6 Inhibitors:** Anti-IL-6 receptor mAbs: Tocilizumab: <30 kg: 12 mg/kg IV (maximum 800 mg) ≥30 kg: 8 mg/kg IV (maximum 800 mg) Sarilumab 400 mg SQ in 100 cc 0.9% NaCl administered IV anti-IL-6 mAbs: Siltuximab	Anti-Interleukin-6 Receptor Monoclonal antibodies	Tocilizumab use recommended with Dexamethasone for hospitalized patients with COVID-19 who are receiving invasive mechanical ventilation or ECMO and who are within 24 hours of ICU admission with rapid respiratory decompensation Recommended only when Tocilizumab is not available or is not feasible to use Not recommended for COVID-19 patients except under clinical trials
5	**Interleukin-1 Inhibitors** Anakinra 300 mg/200 mg/100 mg IV Canakinumab 450 mg/ 600 mg/ 750mg	IL-1 inhibitors	Anakinra and Canakinumab are not recommended in the treatment of COVID-19, except in clinical trials
6	**Kinase inhibitors:** Baricitinib 4 mg/2 mg/1mg Tofacitinib 10 mg Ruxolitinib 5 mg-20 mg	Involved in signaling pathways that can regulate cytokines responsible for cytokine storm	Baricitinib and Tofacitinib are recommended in certain hospitalized patients while Ruxolitinib is not recommended. In rare circumstances when corticosteroids cannot be used, the use of Baricitinib/ Tofacitinib in combination with Remdesivir and Dexamethasone for the treatment of COVID-19 in hospitalized non intubated patients who require oxygen supplementation is recommended
7	**Angiotensin Receptor Blockers (ARB)**	Potentially beneficial vasodilatory and anti-inflammatory properties, blocking enzymatic activity that aids in viral clearance	Patients receiving an ACE inhibitor or ARB for cardiovascular disease (or other non-COVID-19 indications) should not discontinue these drugs during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition. However, ACE inhibitors or ARBs should not be used to treat COVID-19 except in the context of a clinical trial
8	**Antithrombotic Agents**	Reduces the formation of blood clots by inhibiting platelet activity	It is recommended to use a venous thromboembolism (VTE) prophylactic dose of low molecular weight heparin for patients in ICU or requiring high flow oxygen. Patients hospitalized with COVID-19 already receiving anticoagulant or antiplatelet therapy should not discontinue use unless contraindications are present or significant bleeding develops. Patients with no signs or symptoms of VTE should not be given any antithrombotic therapy. VTE prophylaxis for patients with COVID-19 after hospital discharge is not recommended.
9	**Convalescent Plasma**	Modifying the inflammatory response, provides immediate immunity	The use declined in early 2021 due to mixed results from randomized clinical trials. Recommended for use based on individualized assessment of risk and benefit/ immunosuppressed patients with aberrant antibody responses
10	**Adjunct Therapies**	Immunomodulatory role	Vitamin and mineral supplements like Vitamin C, D and Zinc are not recommended as adjunct therapies for treatment of COVID-19

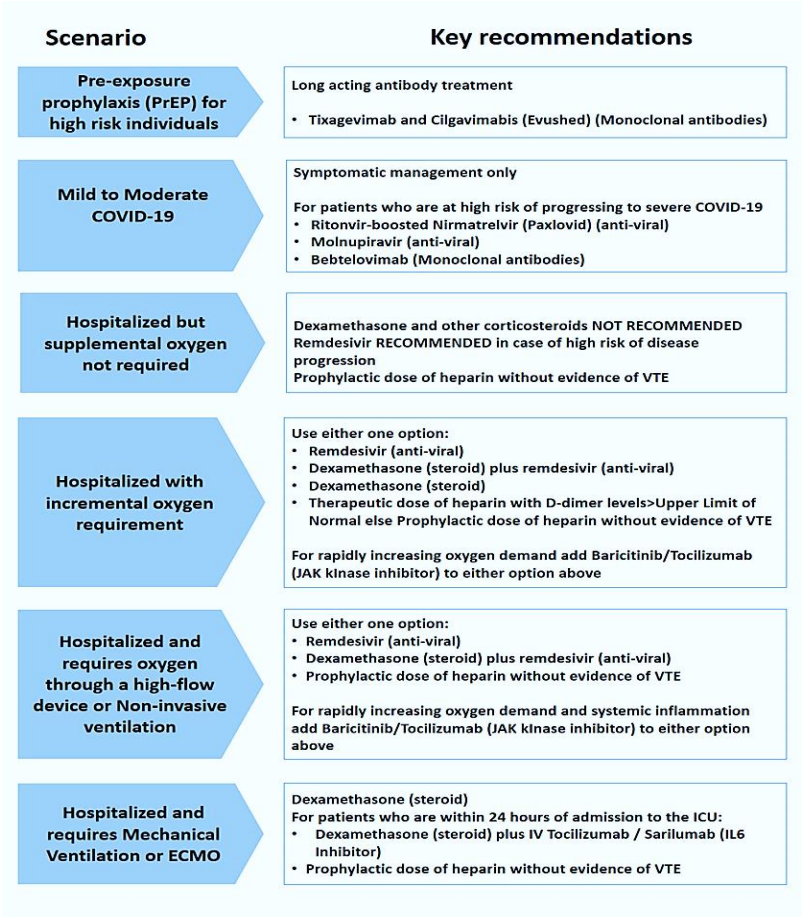

Figure 2: Recommendations to Manage Different COVID-19 Scenarios: Long acting antibody treatment is recommended for high risk individuals on pre-exposure prophylaxis. Symptomatic management to be considered for mild to moderate cases of COVID-19 but if the condition can transform to severe COVID-19 then treattment with Ritonvir- boosted Nirmatrelvir, Molnupiravir, and Bebtelovimab is recommended whereas when a patient is hospitalized due to COVID -19 but doesn't require supplemental oxygen then Dexamethasone and other corticosteroids are not recommended but Remdesivir is recommended in case of high risk of disease progression. Patients hospitalized due to COVID -19 and require incremental oxygen can be treated with various options such as Remdesivir, Dexamethasone, combination of both Remdesivir and Dexamethasone, and therapeutic dose of heparin when D-dimer levels are greater than upper limit of normal, else prophylactic dose of heparin without evidence of VTE is recommended. However, in case patient needs oxygen with high flow device or non-invasive ventilation then treatment will be the same as done for the patient requiring incremental oxygen excluding therapeutic dose of heparin. Dexamethasone is recommended for patient hospitalized and requiring mechanical ventilation or ECMO but when patient have been admitted to ICU within 24 hours then Dexamethasone with IV Tocilizumab / Sarilumab (IL6 Inhibitor) and Prophylactic dose of heparin without evidence of VTE is recommended.

a) Antibody Preparations: Immunotherapy is regarded as an effective method for clinical treatment of infectious diseases. Human monoclonal antibodies are promising therapeutic molecules successfully used for the prevention or treatment of viral infectious diseases (33). Recent years have seen major advances in human B cell isolation techniques and have led to the identification of large numbers of therapeutic monoclonal antibodies candidates against many life-threatening viral pathogens.

Using monoclonal antibodies in infectious disease prevention may overcome many drawbacks associated with serum therapy and intravenous immunoglobulins preparations in terms of specificity, purity, low risk of blood-borne pathogen contamination and safety. In recent years, many monoclonal antibodies against viruses are being developed and some are already in clinical pipeline (34- 36). Harnessing and identifying cells producing neutralizing antibodies from sera of recovered individuals and generating blocking monoclonal antibodies is an attractive strategy (37).

The spike protein present on the surface of the coronavirus is one of the principal antigenic components against which immune responses are generated. The specific neutralizing monoclonal antibodies either against receptor-binding domain in spike protein or specific antibody that binds to ACE2 could effectively block the virus entry. Hence, these were a key target to develop potential effective therapeutics against Coronavirus infection (37).

Two monoclonal antibody cocktail- Casirivimab and Imdevimab - bind to different epitopes of the RBD of spike protein non-competitively and have shown potent virus neutralization by blocking the interaction of the viral protein with ACE2 (38). This would be helpful as both prophylaxis and as a treatment measure especially in high-risk groups. The antibody cocktail was approved by USA FDA under EUA in adults with mild-to-moderate COVID-19 to prevent progression to severe disease in high-risk individuals with poor prognosis.

The BLAZE trial-Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies showed relevance of anti-spike neutralizing monoclonal anti-bodies- Bebtelovimab alone or with Bamlanivimab and Etesevimab in reducing viral loads in mild-moderate patients leading to their EUA (39). Sotrovimab, another neutralizing monoclonal antibody inhibiting SARS-CoV-2 replication and prevented disease progression to severe COVID-19 was granted EUA after successful results of TICO-ACTIV-3 trial (40).

In January 2022, the EUA of Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, and Sotrovimab for post exposure prophylaxis (PEP) and treatment of mild to moderate cases of COVID-19 was withdrawn due to their ineffectiveness against Omicron COVID-19 variants. Bebtelovimab effective against Omicron variants is still recommended for treatment of high-risk outpatients with mild to moderate COVID-19 (28). The recommendations for monoclonal antibodies therapy remains fluid and requires cognizance of prevailing COVID-19 variants and subvariants.

b) Antiviral Agents: With onset of symptom less than 5 days, The FDA recommends Nirmatrelvir and Ritonavir or Molnupiravir for patients with possibility of progression to severe disease/hospitalization/death (26). Dual pill Nirmatrelvir and Ritonavir is the recent most addition to the EUA list of COVID-19 drugs. In a phase 2/3 EPIC-HR clinical trial involving 2224 non-hospitalized adult patients with confirmed diagnosis of COVID-19 with risk of progression to severe disease, Nirmatrelvir and Ritonavir reduced hospitalization time and death by 86% compared to placebo group (41). The drug was most effective in clearing the virus within three days of symptom onset. The combination drugs are authorized for use amongst the age group above 12 years weighing 40 kg, while it is not advised in patients with renal and hepatic impairment.

Molnupiravir, an oral, small-molecule antiviral pro-drug was evaluated in 1433 participants in a Phase 3 MOVe-OUT randomized, placebo-controlled, double-blind clinical trial (42). The participants included non-hospitalized, mild-to-moderate confirmed COVID-19 cases at risk for progressing to severe COVID-19. Early treatment, before 5 days of symptoms onset, with Molnupiravir reduced the risk of hospitalization or death by COVID-19 in at-risk, unvaccinated adults (42).

Clinical Management and Treatment for Severe Disease: Severe illness management revolves around the supportive management of the complications of severe COVID-19 that include sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury and complications from prolonged hospitalization including secondary bacterial/ fungal infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy. Acute hypoxemic respiratory failure from ARDS is the most common complication in patients admitted to the ICU, followed by shock, myocardial dysfunction, and acute kidney injury. In a small proportion of these, the illness may be severe enough leading towards death. Besides therapeutic interventions, proning for 12 hours a day with side switching every two hours has reduced mortality in ARDS patients with severe hypoxia. Use of therapeutic agents to manage disease progression or to manage advent of severe disease are elaborated below along with their current status of recommendations (28).

a) Antiviral Agents: The dilemma is whether to "Target Virus or Target Ourselves" for COVID-19 (43). Several clinical trials are being conducted to determine which therapeutic targeting could potentially present more effective and broad-spectrum treatment modalities for COVID-19. One strategy adopted is to repurpose approved drugs known to act on different stages of both the infection and host response. Most of these drugs were originally designed for other pathogens and now repurposed for treatment of COVID-19 as these drugs are reported to have favorable safety profiles. These therapies can be divided into two categories depending on their target. One therapeutic approach primarily target virus directly either by blocking viral entry to human cells or by inhibiting viral enzymes responsible for replication. The other approach includes drugs that interfere with signaling pathways involved in viral replication or host innate immune responses.

Most antiviral drugs are small-molecule inhibitors and exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoded enzyme, blocking virus particle formation, or targeting a host factor required for replication (44). Repurposed existing drugs include an experimental antiviral Rem-desivir; the malaria medication Chloroquine (or its chemical cousin Hydroxychloroquine); a combination of the HIV drugs Lopinavir and Ritonavir; and combination of Lopinavir and Ritonavir plus interferon-beta, which acts

as an immune system messenger, that can help cripple viruses. These treatments may stop the virus replication by different mechanisms, but each has drawbacks.

Remdesivir: Remdesivir is a monophosphoramidate pro-drug of an adenosine analogue with a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. *In vitro*, Remdesivir has shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV including SARS-CoV-2 infections (45). Remdesivir has been found to inhibit coronavirus replication and improve pulmonary functions prophylactically and therapeutically (in early stage of infection) based on evidence from both *in vitro* and *in vivo* experiments. Remdesivir was developed by Gilead Sciences (USA) originally against the Ebola virus. While not effective against Ebola, the drug proved its safety in humans, and this allowed repurposing of the drug in clinical trials immediately in COVID-19 on an emergency basis (46). Remdesivir acts by shutting down viral replication by inhibiting a key viral enzyme, the RNA polymerase. The drug, which is given intravenously, has been issued FDA and EU Emergency Use Authorization to treat hospitalized patients aged ≥28 days and weighing ≥3 kg (26). Clinical studies showed that patients treated with Remdesivir had higher recovery rates and were associated with better rates of hospital discharge, but there was no significant reduction in mean time to clinical improvement or mortality (47). When mortality risk is low, using Remdesivir is not recommended (28).

Lopinavir-Ritonavir Combination with or without Interferon: Lopinavir is an antiretroviral drug and acts as a protease inhibitor and is usually formulated with another protease inhibitor Ritonavir which decreases the metabolism of Lopinavir by the inhibition of cytochrome P450. Lopinavir-Ritonavir is approved to treat HIV/AIDS (48). Although preliminary clinical trials using Lopinavir-Ritonavir to treat SARS-CoV-2 have been disappointing (49), it is being evaluated combined with other antiviral drugs (50). No significant benefit was observed with Lopinavir-Ritonavir treatment beyond standard care. Diarrhoea, nausea, and asthenia were the most frequently reported adverse effects in patients receiving Lopinavir-Ritonavir based regimen (51). Results from various clinical studies have shown there was no benefit of using Lopinavir-Ritonavir in reducing mortality rate, hospital time nor progression to mechanical ventilator intervention in COVID-19 patients. Hence not recommended for treatment of COVID-19.

Favipiravir: Favipiravir is a non-nucleoside RNA polymerase inhibitor and acts by dysregulating viral RNA replication. Favipiravir showed antiviral activity against infectious diseases caused by RNA viruses such as Influenza, Ebola, and Norovirus Influenza A, yellow fever, and Ebola (52-53). Favipiravir was repurposed as an experimental agent for COVID-19. A randomized control trial showed that COVID-19 patients treated with Favipiravir had better recovery rate (71.43%) than those treated with Umifenovir (55.86%), and the relief from fever and cough was significantly faster in Favipiravir group than in Umifenovir group (54). In a study from India, early virological clearance was observed in adults with mild to moderate COVID-19 that received Favipiravir, although not statistically significant and requires more evaluation for long-term use (55), hence not recommended for treatment of COVID-19.

Oseltamivir: Oseltamivir is a well-tolerated neuraminidase inhibitor drug approved for treatment of Influenza A and B that reduces viral shedding and severity of illness (56). An early study from Wuhan reported no improvement in COVID-19 patients administered different doses of Oseltamivir (57) and thus not used in COVID-19 treatment.

Chloroquine: Chloroquine (CQ) and the 4-aminoquinoline drug hydroxychloroquine (HCQ), amine acidotropic form of natural quinine is an approved front-line drug for the treatment and prophylaxis of malaria (58). CQ and HCQ were initially touted as potential broad-spectrum antiviral drugs and can block virus infection by increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cellular receptors of SARS-CoV (59). CQ has been shown to interfere with the terminal glycosylation of ACE2, and thus negatively influences the virus-receptor binding in SARS-CoV infection (59-61). CQ and HCQ can also inhibit major histocompatibility complex class II expression, antigen presentation and immune activation (reducing CD154 expression by T cells) via Toll-like receptor signaling and cGAS stimulation of interferon genes. Thus, CQ and HCQ can reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon-α and tumor necrosis factor, which are involved in the cytokine storm. The immunomodulatory effects of CQ may synergize its antiviral effects in the treatment of COVID-19 (62). Whether HCQ is as efficacious as CQ in treating SARS-CoV-2 infection still lacks experimental evidence. Medical opinion has cautioned that HCQ can prove more harmful than doing any good as it poses numerous side effects. As in controlled clinical trials CQ and HCQ have failed to demonstrate benefit for treating

COVID-19, these are not recommended for treatment of COVID-19 (28).

Ivermectin: Macrocyclic lactone Ivermectin is reported to have antiparasitic, antiviral and immunomodulation roles in human host. Regarding COVID-19, Ivermectin blocks transmission of viral proteins into host nucleus by inhibiting the importin (IMP) α/β receptor (63). Ivermectin was considered a potential anti-viral when tested as a prophylactically (NCT04422561) in early stages of COVID-19 infection as a host directed therapy to reduce viral load to levels where the host immunity can control the infection. Some observational and case control studies and small randomized clinical trials suggest a potential benefit of Ivermectin. The pilot study report that in group treated with ivermectin there was marked reduction of self-reported anosmia/hyposmia, a reduction of cough, lower viral loads and lower IgG titers (64). Although seems promising, larger trials needed to support use of Ivermectin for the early treatment of COVID-19. To date controlled clinical trials have failed to substantiate the clinical benefit in COVID-19 illness and hence not recommended for treatment of COVID-19 (28).

Azithromycin: A macrolide with an established safety profile, Azithromycin has exhibited *in-vitro* antiviral activity by acting at different stages of the viral cycle and immunomodulatory activities of dampening the cytokine storm. The drug can achieve therapeutic concentrations in the lung is useful in community acquired pneumonia. The RECOVERY trial, however reported that Azithromycin 500 mg for 10 days may benefit individuals with bacterial infections only and did not reduce 28-day mortality in patients hospitalized with COVID-19 (65), an eye opener to prevent resistance development by rampant misuse of such macrolide antibiotics.

b) Anti-inflammatories and Immunomodulators: In SARS-CoV-2 infection, infiltration of large number of inflammatory cell and cytokine storm lead to acute lung injury, ARDS and death (66-70). Most of severe COVID-19 patients have persistent high levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and high level of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, TNFα associated with ARDS, hypercoagulation and disseminated intravascular coagulation (DIC), manifested as thrombosis, thrombocytopenia, gangrene of extremities. Maybe cytokine storm exacerbates lung damage and leads to other fatal complications. In severe illness, abrupt deterioration is noticed within 1–2 weeks after disease onset. As cytokine storm occurs in critically ill patients leading to the immune-mediated damage and even death in some cases, giving priority to targeting the inflammatory response could blunt the inflammatory cytokine storm and help in checking further tissue injury.

Several approaches including immunomodulatory agents that directly target the key cytokines involved in COVID-19 may help to alleviate hyperinflammation symptoms in severe cases and cope with cytokine storm. Monoclonal antibodies blocking cytokines associated with hyper-inflammation is a promising therapeutic avenue to limit systemic inflammation before it results in multi-organ dysfunction in COVID-19 patients. Certain immune-modulatory agents with good safety profiles may be considered for combination with antiviral drugs to treat severe or critical cases of COVID-19 as elaborated below.

IL-6 Inhibitors: Among the increased level of cytokines produced, elevated levels of the inflammatory indicator IL-6 in the blood have been reported to be predictive biomarker for disease severity. IL-6 binds to trans-membrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and the resulting complex can combine with signal transducing component gp130 to activate the inflammatory response. Tocilizumab is a specific monoclonal antibody IL-6 receptor antagonist that can bind specifically to sIL-6R and mIL-6R, and block signal transduction (71). Thus, monoclonal antibodies against IL-6 could theoretically dampen cytokine storm process and improve clinical outcomes. Dose of 8 mg per kilogram of body weight intravenous Tocilizumab was evaluated in phase 3 EMPACTA (Evaluating Minority Patients with Actemra) clinical trial in hospitalized COVID-19 patients without mechanical ventilation (72). The results showed that Tocilizumab added to benefits of antivirals and glucocorticoids in saving lives as also substantiated by many trials globally including the RECOVERY trial. Tocilizumab is recommended in critical patients with high oxygen demand and acute inflammatory response (28). Likewise, Sarilumab another anti-IL-6 receptor mAbs is approved for use in hospitalized patients when Tocilizumab is not available while Siltuximab- anti-IL-6 mAbs is not recommended in COVID-19 treatment except in clinical trial (28).

IL-1 Inhibitors: There is a battery of other biological agents available that target various other critical cytokines in the inflammatory network and repurpose their anti-inflammatory activities to treat COVID-19. The recombinant IL-1 receptor antagonist, Anakinra was originally developed

to control cytokine storm and associated tissue damage in sepsis patients and has subsequently been successfully used in patients with cytokine storm syndrome secondary to autoimmune/ inflammatory infectious or malignant disease (73). Anakinra was thought to have potential for controlling hyper-inflammation in severe COVID-19 disease (74) but is not currently recommended along with another IL-1 mAbs-Canakinumab (28).

Corticosteroids: Dexamethasone used in severe asthma, allergies, painful and swollen joints, systemic lupus erythematosus and rheumatoid arthritis was repurposed as an easily available and affordable drug to treat severe cases of COVID-19. Dexamethasone lessens the cytokine storm and dampens the immune response thus preventing the huge inflammation evident in lung and heart leading to acute respiratory issues in severely ill patients. Dexamethasone has been tested in the largest COVID-19 drug trial called the Randomized Evaluation of COVID-19 Therapy or RECOVERY trial (75). As part of the trial, researchers studied the effect of 6 mg daily dose of dexamethasone for 10 days in patients and compared that to the patients who did not receive it. The results of the trial showed the greatest benefit was in those patients on ventilators, where dexamethasone reduced the risk of death. In the cohort, 29.3% vs. 41.4% deaths respectively were reported in dexamethasone group compared to subjects on mechanical ventilation: 23.3% vs. 26.2% respectively in the group receiving dexamethasone and oxygen without mechanical ventilation and 17.8% vs 14.0% respectively in the group with dexamethasone and with no respiratory support (75). This translates to one life saved for every eight on ventilators and one in every 20-25 treated with oxygen. The drug is not proven to be beneficial in those with mild symptoms who do not require respiratory support. Brazil CoDEX trial also showed that Dexamethasone is the drug of choice to reduce mortality from COVID-19 (76). Use of alternative corticosteroids like hydrocortisone, prednisone, methylprednisolone for patients with severe COVID-19 are also recommended while inhaled corticosteroids Budesonide and Ciclesonide are not recommended (28). A word of caution that use of corticosteroids in the treatment of COVID-19 can cause immune suppression and may delay the elimination of virus and increase the risk of secondary infections.

Janus Kinase (JAK) Inhibitors: Given the nature of the COVID-19 cytokine storm and considering substantial impairment of host immune system in severe cases, it is critical to balance the risk and benefit before starting anti-inflammation therapy. In addition, timely anti-inflammation treatment initiated at the right window time is pivotal and should be tailored to individual patients to achieve the most favorable effects. However, there are many concerns with anti-inflammatory medications. The critical issue is balancing the risk and benefit ratio of anti-inflammatory therapy in COVID-19 infection. Anti-inflammation therapy that specifically target one set of pro-inflammatory cytokines may inhibit that specific inflammatory factor but fail in curbing the cytokine storm in COVID-19 in which other cytokines maybe of significant importance. Third, some anti-inflammation medication such as Janus kinase (JAK) inhibitor like Tofacitinib block INF-a production, which is important in controlling virus replication, and theoretically may not be suitable to treat inflammatory cytokine storm caused by COVID-19. On the contrary, other JAK inhibitors like Baricitinib was useful in managing cytokine storm by blocking cytokine signaling pathways and reducing hospital stay when co-administered with Remdesivir (77). Baricitinib/ Tofacitinib and Tocilizumab is recommended with Dexamethasone alone or Dexamethasone with Remdesivir to treat COVID-19 in critically ill hospitalized patients requiring high flow oxygen with systemic inflammation (28).

c) Antithrombotic Therapy: COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and venous thromboembolism (VTE). Both thrombotic risk assessment and VTE prevention are important components of the complex and comprehensive treatment of COVID-19 infection. Given that some COVID-19 patients' conditions may rapidly change, resulting in dynamic modifications of thrombotic risk and bleeding during treatment, repeated assessment and optimized strategies are crucial to reduce VTE and prevent fatal pulmonary embolism (PE) and effectually safeguard patients and promote early recovery. Experts have expressed consensus on management of COVID-19 associated VTE and preferential thrombo-prophylaxis measures based on VTE risk scoring, kidney function, creatinine clearance and severity of diseases along with anticoagulants (78-80). Low molecular weight heparin is recommended as the first line of treatment in severe and critically ill COVID-19 patients with low risk of bleeding (28). The experts have also recommended against non-heparin drug use like rivaroxaban or fondaparinux in presence of co-morbidities in critically ill COVID-19 patients. As coagulation parameters like D-dimer provide prognostic values, they are valuable to determine the risk

of developing VTE and may prompt consideration of full therapeutic dose regimens. It is not advised to continue VTE prophylaxis for discharged COVID-19 patients (28). The decision to continue post-discharge VTE prophylaxis should be based on case-by-case risk assessment for VTE, and bleeding.

d) HMG Co A Reductase Inhibitors (Statins), ACE Inhibitors, and Angiotensin Receptor Blockers (ARBs): Patients who suffer from hypertension and heart disease are treated with renin-angiotensin system (RAS) blockers, angiotensin receptor blockers (ARBs) and HMG-CoA reductase inhibitors/statins. RAS inhibitors and statins act by up-regulating ACE2 receptors and theoretically this could enhance viral entry leading to worsening outcomes. They were proposed to have a potential role in managing patients with severe COVID-19 due to immunomodulatory and anti-inflammatory role to reduce tissue injury through production of angiotensin [1-7] (81-82). The controversy regarding statins in treating severe COVID-19 along with ACE inhibitors and ARBs has finally been put to rest. Patients receiving these as concomitant medications for an underlying medical condition should not discontinue such therapy (28, 83). It is suggested that statins/ACEIs/ARBs should not be initiated in those patients with COVID-19 without clinical indications of cardiovascular diseases (28).

Acute treatment with statins had no significant effect on the course of SARS-CoV-2 infection. However, if a COVID-19 patient is earlier exposed or treated with statins then it can decrease the death risk in a patient who is hospitalized but not admitted in ICU (84). There is consensus on the fact that when cholesterol is lowered with statins, it has an advantageous impact on COVID-19 as presence of high amount of cholesterol in cell membranes eases the entry of SARS-CoV-2 through pushing ACE2 into endocytic vesicles, potentially becoming one phenomenon of age-related risk for COVID-19 (85). Thus, long term therapy with statins ae being evaluated for COVID-19 outcomes in high-risk groups.

Agents Under Lens for Management of COVID-19

Convalescent Plasma: Convalescent Plasma (CP) therapy is a classic adaptive immunotherapy and has been applied to the prevention and treatment of many infectious diseases. Convalescent serum was used during H1N1 pandemic, SARS, MERS and Ebola outbreaks with effective efficacy and safety (86-89). A general principle of CP therapy states it proves to be effectual to a greater extent when not used in treatment but for prophylaxis. If using in the therapy, antibodies are touted to be effective when regulated in a shorter span of time right after the first day of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease (90-91). A different explanation could be that modification of inflammatory response could be possibly the reason to how antibody works, since inflammatory can easily be obtained in the commencing of the immune response (91). Convalescent plasma therapy was hence considered as an option to treat the disease since it had demonstrated possible benefit in other coronaviruses outbreaks (92-94). Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of CP.

The administration of CP was initially recommended to treat or prevent ARDS induced by SARS-CoV-2 infection and to accelerate virus clearance. The infusion of hyperimmune convalescent plasma having anti-IgG specific SARS-CoV-2 antibodies obtained from PCR-negative, COVID-19 recovered patients were an attractive approach in newly infected subjects. Duan et al reported that one dose of 200 mL CP transfusion was well tolerated by the critically ill patients with laboratory confirmed COVID-19 (95). After receiving plasma transfusion, the clinical symptoms significantly improved with the increase of oxyhemoglobin saturation within 3 days, increased lymphocytes count, and reduced level of C-reactive protein accompanied by rapid neutralization of viremia and with no adverse effects. However, there are various downsides to this approach which includes the difficulty in scaling up for widespread use as well as the risk of transmission of other diseases that would come along with the plasma of recovered patients. Also, the antibodies present in the plasma generally are in lesser concentration that may not be enough for the treatment. Use of CP therapy is investigational; clinical trials are assessing the true effectiveness of this therapeutic strategy (96-98). The current recommendations are against CP collected before the emergence of Omicron variants to treat COVID-19 (28, 98). Also, using CP in immunocompetent hospitalized patients is not recommended, yet immunocompromised COVID-19 patients with aberrant immune response may benefit from CP (28, 99). In such a case, individualized response to CP must be monitored carefully.

Experimental Therapeutics for COVID-19: Purinergic signaling pathway modulated through extracellular purine

nucleotides and adenosine/ATP nucleosides hold promise as therapeutic strategy to address cytokine storm, especially through adenosine A2a, A2b and P2X7 receptors (100, 101). Extracellular ATP being part of DAMPs may have key role in cell signaling and is also suggested to be part of NLRP3 inflammasome activation that stimulates caspases and proinflammatory cytokines in response to cellular damage (102). Deregulation of the activity of CD39, a vascular ectonucleotidase, is involved in the thrombo-inflammation in COVID-19 (103). Change in CD39/CD73 axis, which helps in maintaining the balance between the activities of P1 and P2 purinergic receptors through sequential hydrolysis of extracellular ATP to adenosine, plays a role in the regulation of T cells in COVID-19 (104). These recent findings present very promising therapeutic strategies to tame or suppress cytokine storm in COVID-19.

The battle with COVID-19 lead to unprecedented attempts at repurposing plethora of drugs for existing diseases. Though repurposed drugs are reported to be predominantly safe, the human endeavors to win COVID-19 resulted in exceptional activity of repurposing drugs. The infamous drug thalidomide known for its teratogenicity showed promise in suppressing cytokine storm in severe COVID-19 (105). Thalidomide potentially inhibited chemotaxis of neutrophils and suppressed neutrophils and monocytes. It acts on several factors to downregulate the cytokine storm and independently suppressed the associated oxidative stress. Thalidomide being an up-regulator for NK and T cells can also reverse the downregulatory effect of COVID-19 (105).

Suramin, another highly neurotoxic drug used to treat parasitic infections, viral diseases and cancers has demonstrated remarkable ability to suppress SARS-CoV-2 entry and replication in cell cultures and thus merits evaluation in clinical trials (106).

The human saga to save lives of COVID-19 patients have brought forth many unconventional therapeutic approaches, yet their utility and adoption must be justified by strong scientific evidence and ethics.

Summary and Conclusions: As COVID-19 pandemic intensified, showed blips and ripples due to emergence of new variants, the disease is not yet eliminated. Global vaccination efforts along with the search for effective treatments and vaccines to control the disease are at the forefront of medical research. Globally, all possibilities are being explored including repurposing existing drugs used to treat HIV/AIDS, malaria, cancer, immune disorders and evaluating them in well-planned clinical studies. Besides, new drugs in the form of small molecules targeting SARS-CoV-2 receptors, protease inhibitors, monoclonal antibodies, immunomodulators, antivirals, stem cell therapies and gene silencing approaches that prevent SARS-CoV-2 replication are being explored along with vaccine development. The ever-evolving pipelines with their current status are available at clinical trial database (https://clinicaltrials.gov/ct2/who_table).

As the hunt for best remedies continue, the clinical management practice should include evaluation of all COVID-19 patients for the risk of developing cytokine storm and VTE. Antivirals would provide greatest benefit in the early course of the disease when viral replication can be slowed down. Once cytokine storm develops, antiviral treatment alone will not be enough and immune-suppressive/anti-inflammatory treatment will be necessary to dampen the cytokine storm. Early recognition and treatment of cytokine storm will decrease the morbidity and mortality in COVID-19 infection. We propose "800 rule"-Ferritin over 800 ng/ml and absolute lymphocyte count below 800 cells per cubic millimeter of blood. Combination of the "800 rule" and evidence for fever and organ dysfunction portends a high risk regardless of age. COVID-19 can cause pneumonia due to infiltration of macrophages and neutrophils; can lead to vasculitis with veno-occlusive pulmonary disease; *in-situ* pulmonary arterial thrombosis leading to profound refractory hypoxemia and in some individuals permanent end organ lung damage due to fibrosis and fibro-cavitary disease; systemic arterial and venous thromboembolism, cryptogenic strokes, and acute kidney injury. A graded approach to management of COVID -19 patients would thus include (a) low risk individuals will benefit from isolation, symptomatic management, prevention of transmission strategies and monoclonal antibodies therapy in non-hospitalized patients if at risk for severe disease, (b) all hospitalized patients (including mild and moderate with hypoxia) would benefit from an effective anti-viral (most likely combination therapy) as this is an RNA virus with a high replication rate that is a risk factor for serious disease, (c) at risk for cytokine storm (800 rule and fever) require use of Dexamethasone/anti-inflammatory to dampen the immune response besides standard treatment and antivirals. Furthermore, the sequelae of COVID-19 regarding vasculitis, cardiac, neurological, psychiatric manifestations, secondary bacterial and fungal infections need to be managed case-by-case as per existing standards of care and treatment.

The guidelines for management of severe COVID-19 are continuously evolving as new data from clinical trials emerge. As of now, hospitalized patients with severe COVID-19 with oxygen requirement without delivery through a high flow device or noninvasive ventilation would benefit from Remdesivir or Dexamethasone plus Remdesivir if the requirement for oxygen increases or Dexamethasone alone Remdesivir is not available. While alternative corticosteroid can be used if Dexamethasone is not available or Baricitinib plus Remdesivir can be used in absence of corticosteroids. Tocilizumab could be added to Dexamethasone treatment with C-reactive protein (CRP) levels ≥75 mg/L and increasing oxygen needs without need of noninvasive ventilation. However, benefits of addition of Tocilizumab need to be ascertained as it may lead to increased risk of opportunistic infections. Proning position facing ventilator, upto 12 hours in a day with switching sides every two hours, has benefited ARDS patients on sedatives. However, proning with low tidal volume (6 cc per kg body weight) with muscle and nerve relaxants is justified when the patient is hemodynamically stable. For hospitalized patients requiring Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation (ECMO), monotherapy with Dexamethasone or alternative corticosteroids is the best option. For patients who advanced to invasive ventilation or ECMO, it is recommended to start Dexamethasone and continue Remdesivir till the end of treatment.

Concomitant medications for underlying conditions that necessitate use of ARBs, ACE inhibitors, statins, systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs should not be discontinued. Using off-label treatment for COVID-19 should not be encouraged unless safety and efficacy of the therapy has been proven in clinical trials. Plethora of agents such as macro and micronutrient supplementation have also not contributed to obtaining any result in treatment for COVID-19. It has been noted that the pill burden should not be increased by indiscriminate use of macro and micronutrients i.e., zinc, vitamin C, vitamin D etc. as they have yielded no gains in combating COVID -19.

The emphasis should be on CAB (COVID-19 behavior) and JAB (COVID-19 Vaccination) as prevention strategies, till an ultimate solution for the pandemic is attained. Finally, one is reminded of Dr. David Ho's most elegant comment *"It is the Virus Stupid";* we need to step up and tame it.

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