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Review Article

AN EXTENSIVE REVIEW OF EXPLORING THE CONCEPT OF 3Rs (RIGHT TIME, RIGHT PATIENT, RIGHT DRUG) IN MANAGEMENT OF COVID-19

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ABSTRACT

Three devastating pandemics: SARS, Middle East respiratory disease (MERS), and COVID-19 are linked to new coronaviruses that have struck humans in the twenty-first century. All of the viruses that cause acute respiratory tract infections (ARTIs) are extremely infectious and/or have resulted in significant mortality rates. COVID-19 is a highly contagious viral infection caused by a zoonotic new coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Similar to the other two coronaviruses such as SARS-CoV-1 and MERS-CoV, SARS-CoV-2 is also likely to have originated from bats, which have long served as reservoirs for deadly coronaviruses. SARS-CoV-2 is thought to have originated as a spill over from an animal coronavirus and then evolved into a human-to-human transmission virus. The virus spreads quickly and evolves in the human population because it is extremely contagious. This review article specifies classification, current statistics, and various treatment approaches. And the ICMR guidelines for mild, moderate, and severe patients for COVID-19. The main pivotal area of my studied methodology is 3R's so that the right drug is given to the right patient at right time.

KEYWORDS: Covid-19, Management, Right Time, Right Patient, Right Drug

INTRODUCTION:

A new coronavirus was discovered in China in late December 2019, causing serious respiratory illness, including pneumonia. It was first known as Novel Coronavirus, and the World Health Organization (WHO) recommended the following terminology to describe the virus. The virus that causes the infection has been identified as SARS coronavirus 2 (severe acute respiratory syndrome coronavirus 2). (SARS-CoV-2). Coronavirus disease is the name of the infection-related disease (COVID-19). COVID-19 is a High Consequence Infectious Disease that is spread through the air. SARS-CoV-2 is spreading among people all across the world, as evidenced by the WHO's daily situation reports dashboard. Vaccines are now widely available. Antibiotics are ineffective in treating a viral illness.(1)

HISTORY OF COVID-19(2)(3):

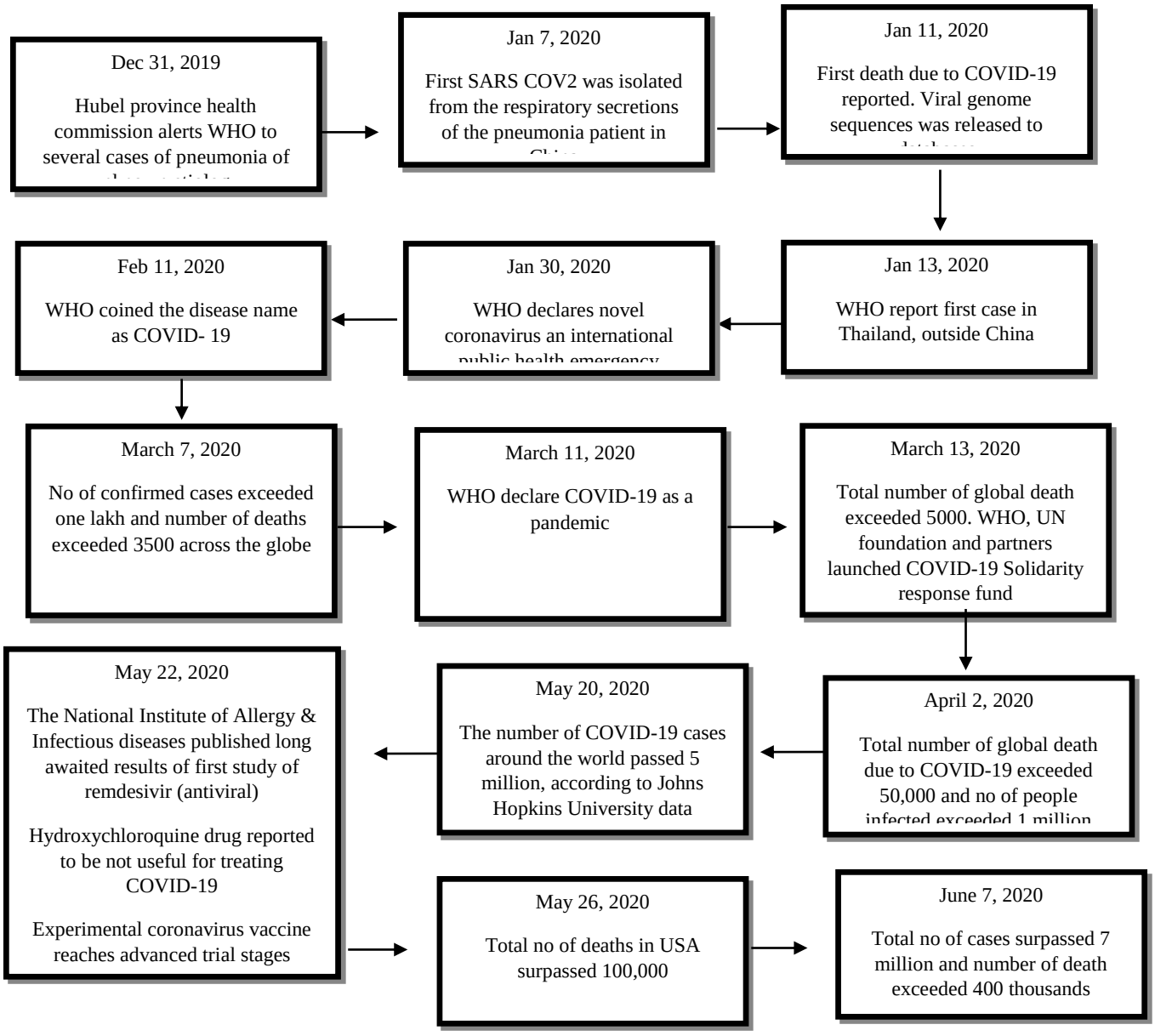


Fig. 1 Timeline in the key events of SARS-CoV-2

A virulent strain of COVID-19, SARS-CoV2, is the cause for COVID-19. Infection with COVID-19 usually results in mild to moderate respiratory illness that recovers without any special treatment. An undetermined cause of pneumonia was detected in Wuhan City, Hubei Province, on 31 December 2019. As of 3 January 2020, WHO has received reports from national authorities in China of 44 patients with pneumonia of unknown aetiology(4). SARS-CoV2 is originated in bats and transmitted to humans via an unknown intermediary host in Wuhan, China. Genomic analysis of SARS-CoV2 revealed that it is similar to MERS-CoV and SARS-CoV1, which supports the theory that the virus originated from bats(5). The coronavirus affects both birds and humans and it has a wide range of types.

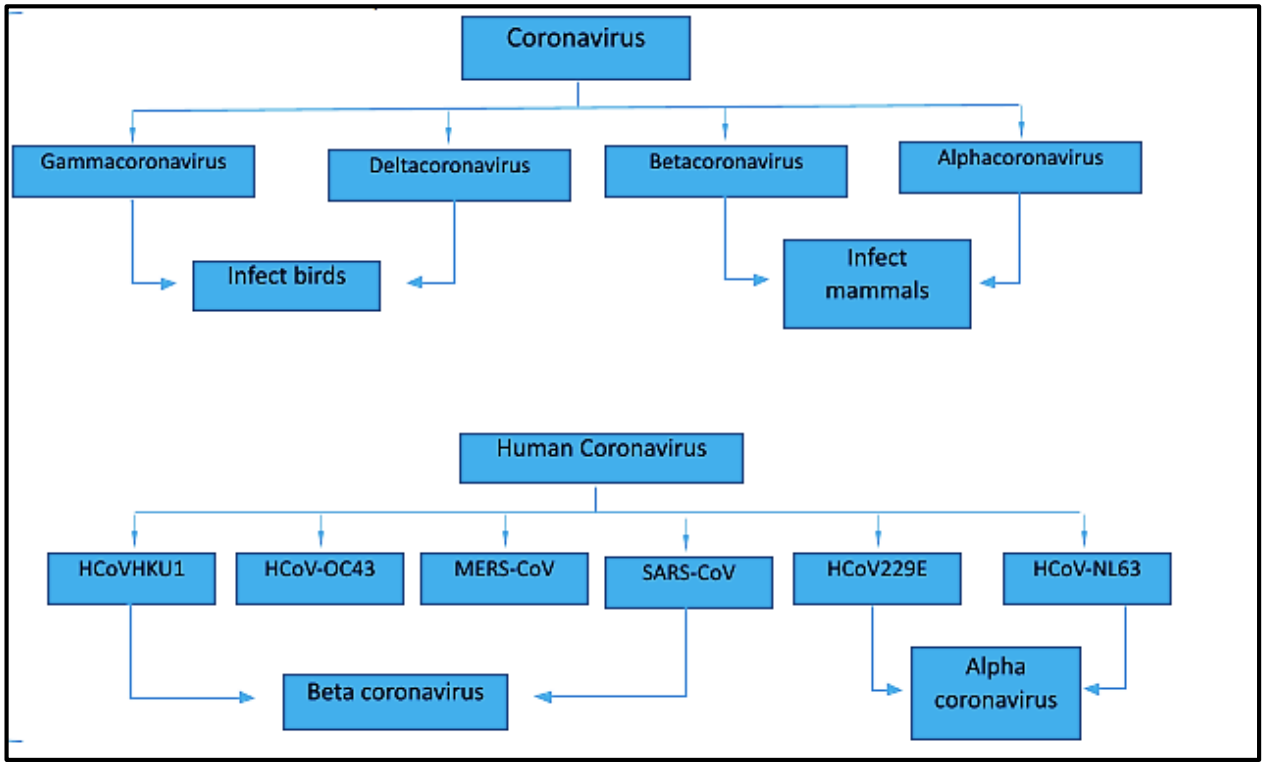


Fig.2 Classification of coronavirus(6)(7)

Different strains of coronavirus:

Culture, electron microscopy, and serological studies are typically used to classify viruses. Crown-shaped Coronaviruses have a diameter between 120 and 160 nm.

The name “coronavirus” is derived from the Greek κορώνα, meaning crown. Coronaviruses are divided into three groups based on their antigenic relationships: group 1 and 2 are composed of mammalian coronaviruses, and group 3 is composed of avian coronaviruses(8)

SARS-related coronavirus (SARSr-CoV) was classified as a subgroup of group 2, group 2b, coronavirus, and group 2c, 2d, 3b, and 3c coronaviruses were discovered using phylogenetic approaches. The International Committee for Virus Taxonomy has recommended three genera to replace the three traditional groups of coronaviruses: Alpha coronavirus, Beta coronavirus, and Gamma coronavirus. Only ten coronaviruses with full sequences were available before the SARS crisis in 2003, including. Up till April 2010, 15 new coronaviruses were discovered with their genomic sequences following the SARS epidemic. And various care and facility is given by government(9)

Current statistics:

- Currently total number of cases of COVID-19 is 23,84,62, 521.Till date 48,65,002 people lost life due to COVID-19.21,56,16,007 patients recovered from COVID-19
- The USA has the highest number of cases 4,51,79,209
- India has second highest cases of COVID-19 3,39,53,475
- Brazil has 2,15,67,181 cases of COVID-19
- Highest number of deaths occurred in USA 7,33,058
- Second highest death occurred in brazil6,00,880
- 4,50,621 people lost life due to COVID-19 in India

Non-reliability of rapid test, RT-PCR, CT scans:

Rapid tests for COVID-19 may provide comfort and convenience, but our concern is with the result. There are two types of rapid tests: One which detects coronavirus and the other which detects the genetic material of coronavirus in the sample which is collected by inserting a cotton swab up the nose, collecting material is then added to a tube of fluid. Toa certain degree, rapid testing sacrifices accuracy with speed(9).They can be helpful in screening symptomatic individuals during an outbreak in resource-limiting settings. Someone with a positive test should be treated as infected with COVID-19, but the negative test is less reliable and may need to be confirmed by a more sensitive molecular assay. Real-time reverse transcriptase PCR (RT-PCR) is of great interest today for the detection of SARS-CoV2.it is considered as the “Gold standard” for the detection of viruses. An important issue with the real-time RT-PCR test is the risk of eliciting false-negative and false-positive results. It is reported that many ‘suspected’ cases with typical clinical characteristics of COVID-19 and identical specific computed tomography (CT) images were not diagnosed(10). Thus, a negative result does not exclude the possibility of COVID-19 infection and should not be used as the only criterion for treatment or patient management decisions. It is well known that results from real-time RT-PCR using primers in different genes can be affected by the variation of viral RNA sequences.

False-negative results may occur by mutations in the primer and probe-target regions in the SARS-CoV-2 genome. Although it was attempted to design the real-time RT-PCR assay as precisely as possible based on the conserved regions of the viral genomes, variability causing mismatches between the primers and probes and the target sequences can lead to a decrease in assay performance and potential false-negative results. According to the natural history of the COVID-19 and viral load kinetics in different anatomic sites of the patients, sampling procedures largely contribute to the false-negative results. Optimum sample types and timing for peak viral load during infections caused by SARS-CoV-2 remain to be fully determined(11).

A study has reported sputum as the most accurate sample for laboratory diagnosis of COVID-19, followed by nasal swabs, while throat swabs were not recommended for the diagnosis.

They also suggested the detection of viral RNAs in Broncho alveolar lavage fluid (BALF) for the diagnosis and monitoring of viruses in severe cases. However, a gathering of BALF needs both a suction tool and an expert operator, in addition to being painful to the patients. While BALF samples are not practical for the routine laboratory diagnosis and monitoring of the disease, collection of other samples such as sputum, nasal swab, and throat swab is rapid, simple, and safe(12).

With a panel of esteemed laboratory experts, the ICMR has discussed the issue of correlating COVID-19 disease severity with Ct values and, as a result, deciding on patient management protocol. The "Expert Group" of the ICMR has made the following recommendations:

1. There are no conclusive studies that show a direct link between disease severity/infectiousness and Ct values. In terms of patient care, viral load plays a minor role (13).
2. The Ct values vary from one kit to the next. Because our labs currently use a mixed basket of kits with variable Ct cut-offs and gene targets, comparing Ct results amongst kits is a difficulty(13).
3. Ct values are also affected by how the sample was taken. Inadequate Ct values may be shown in a poorly obtained sample. In addition, the technical competency of the individual doing the test, the calibration of equipment and pipettes, and the interpreters' analytical skills all influence Ct readings(14).
4. The Ct values of nasal and oropharyngeal specimens taken from the same person may differ(14).
5. Similarly, the temperature of transportation, as well as the period between collection and receipt in the lab, might affect Ct readings(15).
6. Patients with early symptomatology may have a high Ct value, which may vary with time. High Ct values will create a false sense of security in such instances(15).
7. Aside from the viral load, the severity of covid 19 infections is mostly determined by the host factor. Due to the triggering of an immune response, some patients with low virus loads may develop very severe illness. As a result, high CT values create a false sense of security(15).

So, to treat patients there is a need to provide treatment to the right **patient at right and with the right drugs.**

1. TREATMENT APPROACHES:

As per **the National Institute of Health (NIH):**

Table 1 various treatment approaches for COVID-19:

Disease severity	Panel's recommendations	References
Not hospitalized, Mild to moderate COVID-19	For patients who are not at high risk for developing disease progression supportive care and symptomatic management. (All) For patients who are at high risk of disease progression using one of the following combinations: • **Bamlanivimab+Eteseviamab** • **Casirivimab+Imdevimab**	(16)
Hospitalized but does not require supplemental oxygen	There are insufficient data to recommend either for or against routine use of remdesivir. For patients at high risk for disease progression, use of remdesivir may be appropriate	(17)(18)
Hospitalized and requires supplemental oxygen	Use one of the following options: • **Remdesivir-**For patients who require minimal supplemental oxygen (Blla) • **Dexamethasone+Remdesivir-**For patients who require an increasing amount of supplement oxygen (Blll) • **Dexamethasone-**When combination therapy with remdesivir cannot be used or is not available	(19)
Hospitalized and require oxygen delivery through high flow device or noninvasive ventilation	Use one of the following options: • **Dexamethasone (Al)** • **Dexamethasone Remdesivir (Blll)** For patients who were not recently hospitalized with rapidly increasing oxygen needs and systemic inflammation: • Add **tocilizumab** to one of two options above **(B‖a)**	(19)
Hospitalized and requires invasive mechanical ventilation or ECMO	• **Dexamethasone (Al)** For patients who are within 24 hours of admission to ICU: • **Dexamethasone+Tocilizumab(B‖a)**	(20)

As per **the Indian Council of Medical Research (ICMR):**(13)(21)(22)(23)

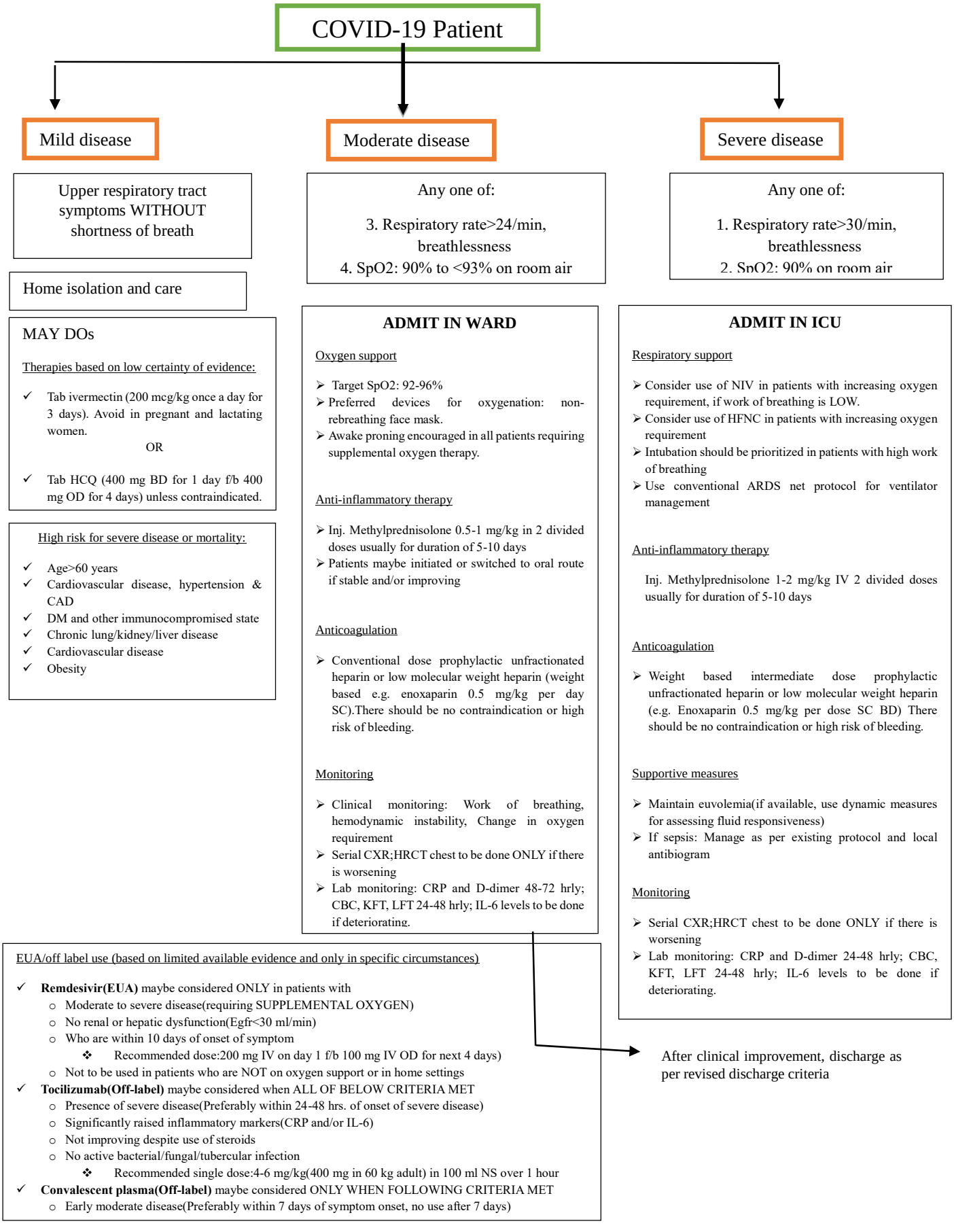
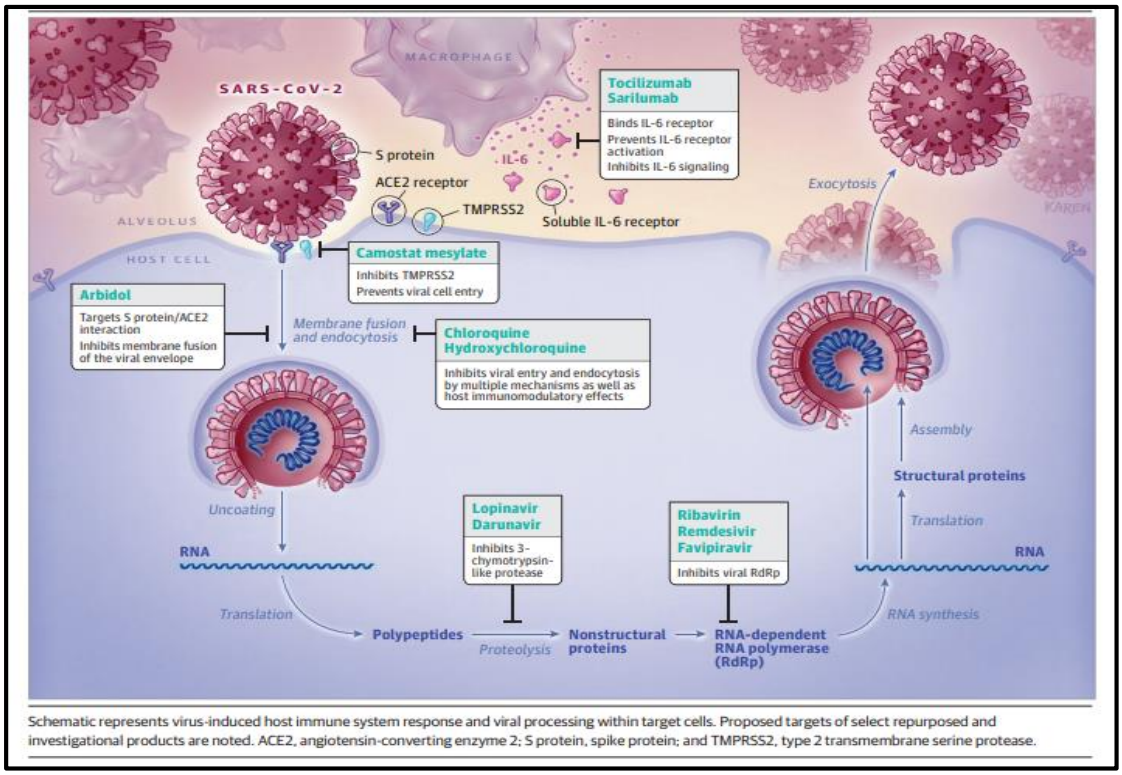


Fig3. Classification of COVID-19 Patient based on Mild, moderate and severe response

Overall mortality, beginning of ventilation, and length of hospital stay showed that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized Covid-19 patients(24).



Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

Fig.4 Simplified representation of severe acute respiratory syndrome coronavirus 2 and potential drug targets(24)

Table 2 Various agent's contraindication and toxicities(25)(26)(27)

Agent	Target	Adult dose	Contraindications	Toxicities	Special populations
Repurposed agents					
Chloroquine phosphate	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing and endosomal acidification.	500 mg orally every 12-24h×5-10d. Available as:250 mg tablets(salt),500 mg tablets(salt)=300 mg chloroquine base	Hypersensitivity to chloroquine,4-aminoquinoline compounds or any component of formation. Presence of retinal or visual field changes of any etiology	Common::Abdominal cramps,anorexia,diarrhea,nausea,vomiting Major:CVS effects(QTc prolongation),hematological effect,hypoglycemia,retinal toxicity,neuropsychiatric and CNS effects	Maybe used in pregnancy if benefit overweighs risk
Hydroxycholoroquine	Hydroxychloroquine shares at same mechanism of action as chloroquine	400 mg orally every 12h×1d,then 200 mg orally every 12h×4d Available as:200 mg tablets of hydroxycholoroquine sulfate(salt)=155 mg hydroychloroquine base	Known hypersensitivity to hydroxychloroquine,4-aminoquinoline derivative or any component of formulation	Adverse drug reactions similar to chloroquine but less common	Maybe used in pregnancy if benefit overweighs risk
Lopinavir/ Ritonavir	3CL protease	400 mg/100 mg orally every 12h×14d Available as:200 mg/50 mg tablets;400 mg/100 mg per 5 mL oral solution	Hypersensitivity to lopinavir/ritonavir or any of its ingredients,including ritonavir.Co-administration with drugs highly dependent on CYP4503A.Co-administration with potent CYP450 A inducers	Common:Gastrointestinal intolerance,nausea,vomiting,diarrhea Major:Panreatitis,hepatotoxocity,cardiac conduction abnormalities	Maybe used in pregnancy;avoid oral solution if possible due to ethanol content
Jmifenovir	S protein/ACE2 membrane fusion inhibitor	200 mg every 8 hours orally×7-14h. Available as:50 mg and 100 mg tablets,capsules and granules	Known hypersensitivity to umifenovir	Allergic reaction,gastrointestinal upseet,elevated transaminase	Contraindicated in children <2 years of age(increased hypersensitivity)
Investigational agents					
Remdesivir	RNA polymerase inhibitor	200 mg×1,100 mg every 24 h IV infusion. Available as:5 mg/mL vial	Exclusion criteria based on specific protocols	Elevated transaminases(reversible),kidney injury	Safety in pregnancy unknown,currently recommended to avoid
Favipiravir	RNA polymerase inhibitor	Doses vary based on indication, limited data available. Available as:200 mg tablet	Exclusion criteria based on specific protocols	Hyperuricemia,diarrhea,eelvated transaminases,reduction in neutrophil count	Contraindicated during pregnancy,metabolite found in breast milk
Adjunctive therapies					
Tocilizumab	IL-6 inhibition-reduction in cytokine strom	400 mg IV or 8mg/kg×1-2 doses.Second dose 8-12 h after first dose if inadequate response. Available as:IV infusion injection:800 mg/4 mL(20 mg/mL);200 mg/10mL(20 mg/mL) in single dose vials for further dilution prior to IV infusion	Known hypersensitivity to tocilizumab or any components of formulation.Caution in patients with neutropenia(<500 cells/microliter) or thrombocytopenia(<50,000/microliter)	Common:Increase in upper respiratory tract infections(including tuberculosis),nasopharyngitis,headache,hypertension,increased AST,infusion related reactions. Major:Hematologic effects,infections,hepatotoxicity,gastrointestinal perforations,hypersensitivity reactions	Ssafety in pregnanacy unknown;may cause harm to fetus

Three traditional rights in the sequence should include(28)(29)(30)

(A) Right patient:

Identifying whether or not the patient being treated is the intended recipient of the drug. It's best to get the patient's name before giving them medication, and if necessary, check the medical wristband for a match with the name and ID number on the chart. If there are two or more patients in a unit with the same or similar names, it is best not to address them by their first name or surname alone. Some patients, such as psychiatric patients, may not wear wristbands or have altered mutation to the point that they are unable to identify themselves appropriately, depending on the unit they are in. Nurses are recommended to authenticate a patient's identity using alternate methods with proper due diligence in these situations(28)

(B) Right drug:

Ascertaining that the medication to be taken is the same as the one prescribed. Due to a prefix, suffix, or starting with the same first letter, some brand names or generic names may have very similar spelling or pronunciation. Beta-blocker drugs, for example, all finish in '-lol' to indicate their mechanism of action. It's crucial to distinguish between two pharmaceuticals with similar names since the two treatments may have significantly different modes of action or prescribing indications. Recent evidence-based studies support the practice of prescribing complete generic names of pharmaceuticals rather than brand names, coupled with the justification for prescribing, to assist reduce confusion.

Many medical errors are caused by misreading letters or digits that seem differently to various people due to poor handwriting and abbreviations. For example, if a brand name is written incorrectly, it is easy for a recipient of an order to become confused, resulting in the administration of medication for a different indication than that intended. Nursing practitioners should make it a practice to openly question patients about known allergies or a history of an allergic reaction to a drug they are about to administer after confirming the name and expiration date of the desired drug. A potential stumbling block for nurses is a patient's misinterpretation of what constitutes a hypersensitive reaction versus a poor symptom that they mistook for a bad experience(29)

(C) Right time:

Administering drugs at the time the prescriber planned. To maintain a therapeutic effect or level, many medications have defined intervals or window periods during which another dose should be given. One of the main principles of this 'right' is that medications should be prescribed as near to the time as possible, and

nurses should not stray from this time by more than half an hour to avoid side effects such altered bioavailability or other chemical mechanisms. A patient's health could be jeopardized if a medicine isn't delivered at the proper rate. Vancomycin, for example, must be given as a slow intravenous infusion to avoid a consequence known as "red man syndrome," a hypersensitive reaction that can be treated by decreasing the infusion rate even further(30)

2.1 AS PROPHYLAXIS (PREVENTIVE PURPOSE)

2.1.1 Nutraceuticals in COVID-19:

Nutraceuticals are those nutrients contained in foods that have beneficial effects on health.

It is possible to define as functional foods those foods that, due to their natural prerogative or supplementing, can provide vitamins, mineral salts, fibers, and fatty acids in such quantities as to positively influence specific functions or avoid the onset of diseases.

However, the causal link between the intake of a certain substance, such as a vitamin, and the prevention of infectious events is not always demonstrated, so even today, the intake of nutraceuticals to prevent infections, especially respiratory infections, is the subject of debate. This concept becomes even more important in the context of the ongoing COVID-19 pandemic since we are certainly at the center of an epochal historical event that is marking our lives(31)

2.1.2 Probiotics and prebiotics:

Probiotics are living microorganisms that can have beneficial effects on the host if ingested in a certain quantity. Prebiotics are non-digestible micronutrients, often oligosaccharides, which selectively stimulate the growth and activity of one or a limited number of bacterial species of the intestinal bacterial flora, contributing to the reduction of intestinal pH, thus making the environment inhospitable for pathogenic bacteria. Symbiotic are a mixture of probiotics and prebiotics. Probiotics seem to have a hitherto undefined role in modulating mucosal immunity. They can regulate the activity of many cells of the immune system, including both innate immunity (NK cells, macrophages, granulocytes, dendritic cells, and epithelial cells) and adaptive immunity (Th1, Th2, Th17, Treg cells, and lymphocytes B. Regarding COVID-19, experience with other viral strains, such as influenza, rhinovirus, and respiratory syncytial virus, has led some to conclude that probiotic supplementation can be considered for the prevention of SARS-CoV-2 infection. However, there is no specific evidence on the subject and specifically in children(32)

2.1.3 **Hesperidin:**

Hesperidin is a flavanone glycoside commonly found in citrus fruit, such as sweet oranges and lemons. Hesperidin has been tested for several pharmacological activities, such as anti-atherogenic, antihyperlipidemic, antidiabetic, cardioprotective, antioxidant, and anti-inflammatory actions. Hesperidin prevented the influenza A virus replication by inhibiting viral sialidase activity that is involved in the entry and releases stages of virus infection. Results showed that, among a range of natural substances with potential antiviral effects, hesperidin was the most suited to binding the Angiotensin-converting enzyme 2 (ACE2) interface, highlighting hesperidin's capability to disrupt the interaction of ACE2 with the receptor-binding domain (RBD)(33)

2.1.4 **Lactoferrin:**

It is a basic glycoprotein; it belongs to the transferrin family and comprises 692 amino acids. Lactoferrin is found in breast and bovine milk and is particularly concentrated in colostrum. Lactoferrin has antibacterial, antiviral, antioxidant, and immunomodulatory functions. As for viral infections, lactoferrin appears to inhibit the attack of viruses on their receptors on human cells. The potential spectrum of activity of lactoferrin against SARS-CoV-2 comes from observations on SARS-CoV. Based on these observations, a clinical study was proposed for symptomatic and asymptomatic COVID-19 patients to evaluate the efficacy and safety of an innovative liposomal formulation of lactoferrin administered for oral and intranasal use(34).

2.1.5 **Vitamin C:**

It is also known as ascorbic acid. Vitamin C shows efficient antioxidant activity. Vitamin C also scavenges reactive oxygen species, products of physiological cell metabolism, or associated with inflammatory diseases and oxidative damage. The clinical and biological importance of vitamin C is further confirmed by many studies reporting its adjuvant properties towards viral infections, such as herpes virus (HSV), influenza type 1, HIV, and rhinovirus but also sepsis and inflammation. In the context of the ongoing COVID-19 pandemic and while there is still no effective antiviral therapy, this antiviral hallmark has a new significance. In this regard, many authors have reported a strong affinity between the beneficial properties of vitamin C towards the complex pathological onset due to SARS-CoV-2 infection(35)

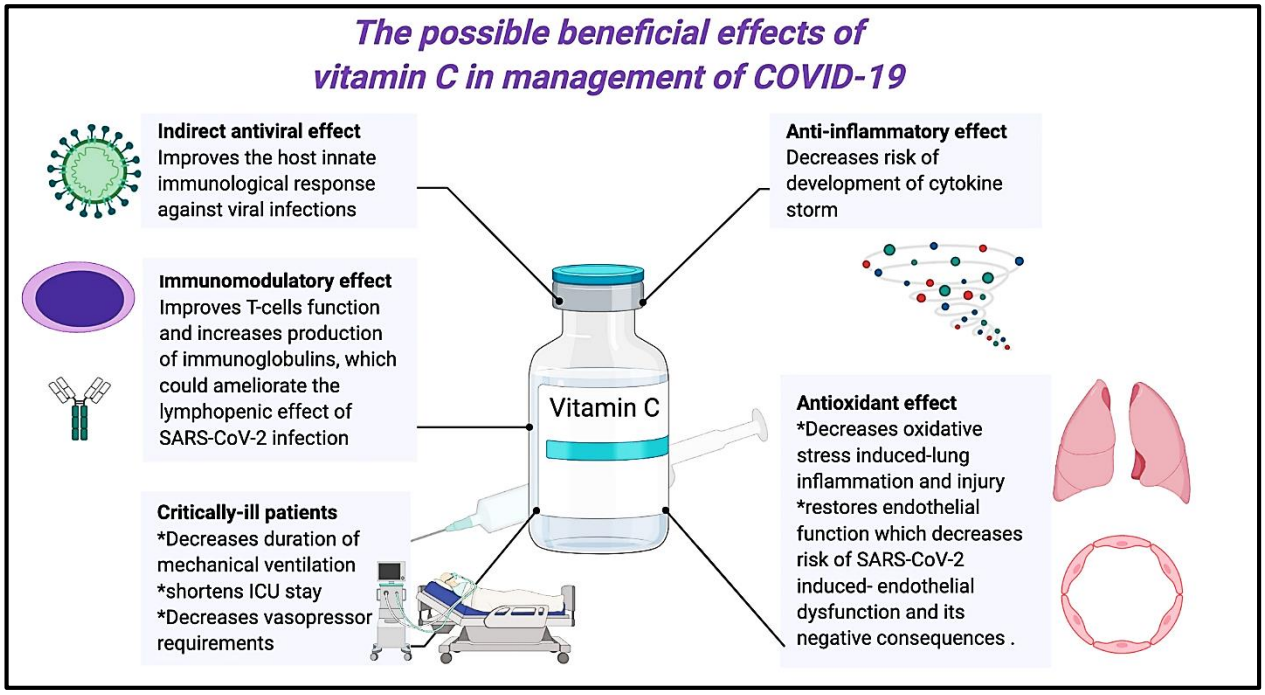


Fig. 5 Vitamin C in management of COVID-19

2.1.6 **Zinc:**

Zinc is an essential mineral present in the body in quantities greater than that of any other trace element other than iron. Zinc performs various functions: it is essential for the functioning of many enzymes; it is necessary for the functioning of some cellular mediators and regulates apoptosis by lymphocytes in vitro and in vivo. Zinc contributes to the inhibition of the replication of some viruses, such as influenza and rhinoviruses, and for this reason, it might also be effective in inhibiting the replication of SARS-CoV-2(36)

2.1.7 **Omega 3 fatty acids:**

They are a type of polyunsaturated fatty acids characterized by the presence of a double bond at the Ω-3 carbon atom. Severe COVID-19 could manifest as a hyper inflammatory syndrome, which is characterized by an important hypercytokinemia (cytokine storm) with multi organ failure and ARDS in approximately 50% of patients. Several studies have been done to determine if Ω-3 fatty acids could modulate the systemic inflammatory response, affecting plasma cytokine production(37)

2.1.8 **Vitamin K:**

Vitamin K is a cofactor for numerous proteins in the coagulation system, including prothrombin, factors VII, IX, and X. Several investigations have hypothesized an intriguing link between vitamin K and COVID-19 clinical outcome and related consequences, such as thromboembolism and coagulopathy, based on these findings. This study implies a link between vitamin K insufficiency and a worsening clinical course in COVID patients due to increased fibre mineralization. Vitamin K insufficiency has been linked to admission to the intensive care unit (ICU)(38)

2.1.9 **Routine food habits and exercise:**

The association between the changes in lifestyle during coronavirus disease 2019 (COVID-19) confinement and body weight has not been studied deeply. This pandemic has led to strict decisions to control the chain of virus transmission, indicating physical distancing and a significant reduction in mobility as the primary prevention measure, calling on nations to implement quarantines and state plans that promote teleworking. Food habits can be protective factors for health and body weight increase(39). The association of food quality and exacerbation of the clinical scenario in patients with malnutrition due to excess consumption has been presented in developing countries, identifying westernization of the diet (WD) as one of the causes. WD is characterized by high contributions of sugars and refined flours, high consumption of saturated fats, low levels of fibre, low consumption of unsaturated soils, and consequently, low contributions of micronutrients and antioxidants, which are the main regulators of metabolism and the immune system, these poor habits and an unbalanced diet cause chronic activation of the innate system and an inhibition of the adaptive immune system response by increasing oxidative stress, eventually creating a delayed adaptive response as a defense against pathogens(40)

2.1.10 **Preventive measures:**

Masks should be used as part of a comprehensive strategy of measures to suppress transmission and save lives; the use of a mask alone is not sufficient to provide an adequate level of protection against COVID-19. If you are fully vaccinated and have a condition or are taking medications that weaken your immune system, you may need to keep taking steps to protect yourself, like wearing a mask. Avoid close contact with people who are sick. Put 6 feet of distance between yourself and people who don’t live in your household. Wash your hands often with hand sanitizer for at least 20 seconds especially after you have been in a public place, or after blowing your nose, coughing, or sneezing. Cover all surfaces of your hands and rub them together until they feel dry(41)

Avoid touching your eyes, nose, and mouth with unwashed hands. If you are wearing a mask: You can cough or sneeze into your mask. Put on a new, clean mask as soon as possible and wash your hands. Clean high-touch surfaces daily. This includes tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks(41)

The most important strategy for the population to undertake is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment. To reduce the risk of transmission in the community, individuals should be advised to wash their hands diligently, practice respiratory hygiene (i.e., cover their cough), and avoid crowds and close contact with ill individuals, if possible(42)

For people without respiratory symptoms, the WHO does not recommend wearing a medical mask in the community, since it does not decrease the importance of other general measures to prevent infection. The single use of a mask does not obstruct the disease; the improper use of the mask increases the risk of COVID-19 infection. In the WHO's "Advice on the use of masks in the context of COVID-19" interim guidance, the prioritized use of medical masks by health personnel was emphasized. The rationale for the face covering is primarily to contain secretions of and prevent transmission from individuals who have an asymptomatic or pre symptomatic infection. Another important point in preventing the spread of the disease throughout society is to increase the number of tests and thus pinpoint more cases, isolate them, and trace those who have been in contact. For this reason, increasing laboratories' test capacity and developing new testing strategies are of utmost importance(42)

In South Korea, which acted quickly to administer free-of-charge and extensive public testing for COVID-19, "drive-through testing" was initiated for the first time. Several different containment measures were implemented by the Turkish government. Turkey put into place several measures to limit the movement of people. Citizens 65 years old or older, patients with immune system deficiency, chronic lung disease, asthma, COPD, chronic cardiovascular disease, chronic renal disease, hypertension, chronic liver disease as well as users of drugs that disrupt the immune system were restricted from leaving their homes and using public transportation.

Steam inhalation is traditionally used as a home remedy for common colds and upper respiratory tract infections. The evidence base of the practice is weak, with unproven theories that the steam loosens mucus, opens nasal passages, and reduces mucosal inflammation, or that the heat inhibits replication of viruses. The common misconception is that steam inhalation is beneficial in preventing and treating respiratory tract symptoms. Studies have shown that there is no additional symptomatic relief from the use of steam inhalation therapy to treat the common cold. However, a survey of general practitioners in 2016 showed that 80% of general practitioners have recommended steam inhalation as a home remedy to their patients(43)

2.2 VACCINE:

2.2.1 **Different vaccines in use:**(44)

Table 5 Various type of vaccine:

Vaccine name	Type of vaccine	Doses	Price*	Efficacy	Manufacturer(Country)
Covishield (ChAdOx1)	Viral vector	2,28 days apart	7.2	90%	Serum Institute of India(India)
Comirnaty(BNT162)	RNA vaccine	2,21 days apart	37.5**	95%	BioNTech(UK)
Moderna(mRNA-1273)	RNA vaccine	2,28 days apart	36.5	94%	Moderna
Janssen(Ad26.COV2.S)	Viral vector vaccine	1	10	66%	Janssen pharmaceutical companies
Gamelya(Sputnik,Gam-COVID-Vac)	Viral vector vaccine	2	20	91.6%	Gamaleya research institute (Russia)
Covaxin(BBV152)	Inactivated vaccine	2,28 days apart	2	78%	Bharat biotech (India)
Sinovac(CoronaVac	Inactivated vaccine	2	27.2	51	Sinovac biotech, China

*-In US dollar in the US

**-For first 100 million doses

2.3 ANTIVIRAL AGENTS:

There are mainly three antiviral agents approved for the treatment of COVID-19 by the US FDA and NIH: Remdesivir, Ivermectin, and Nitazoxanide.

Remdesivir:

Remdesivir((initially named GS-5734) is an intravenous nucleotide prodrug of adenosine analogue that has a broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1).Remdesivir is approved by the Food and Drug Administration (FDA) for the

treatment of COVID-19 in hospitalized adult and paediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized paediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.

The safety and efficacy of combination therapy of remdesivir with corticosteroids have not been rigorously studied in clinical trials; however, there are theoretical reasons that combination therapy may be beneficial in some patients with severe COVID-19(45)

MOA: Remdesivir undergoes intracellular metabolic conversion to its active metabolite nucleoside triphosphate (NTP).NTP directly targets machinery responsible for replication of the viral genome, a highly conserved element of the viral life cycle. Nucleoside analogues are synthetic compounds that work by competition with endogenous natural nucleoside pools for incorporation into replicating viral RNA. While these compounds mimic their physiological counterparts, the incorporation of the analogue molecule disrupts subsequent molecular processes.

The drug target and the exact processes that lead to the inhibition of viral replication have been studied extensively in ebolavirus. ViralRdRp is the target protein for the active metabolite NTP.NTP acts as the substrate for RdRp where it competes with ATP for incorporation into new strands(46)

Fabiflu:

Favipiravir was originally used to treat SARS-CoV-2 in Wuhan, the pandemic's epicentre. The medicine was then approved for emergency use in Italy as the epidemic expanded to Europe, and it is now used in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Saudi Arabia and the United Arab Emirates have just granted approval. Following that, commercial launches were made in Turkey, Bangladesh, and, most recently, Egypt. Favipiravir was approved by the DCGI in India in June 2020 for mild and moderate COVID-19 infections. There are 32 studies listed on clinicaltrials.gov to examine the efficacy of this medication in the management of COVID-19 as of July 23, 2020(47)

Pharmacology: Favipiravir (T-705) is a synthetic prodrug that was initially identified in Toyoma chemicals' chemical library while testing the antiviral efficacy of chemical agents active against the influenza virus. T-1105's pyrazine moiety is chemically modified to produce favipiravir. In Japan, it was licensed in 2014 for the treatment of developing pandemic influenza infections(48)

Pharmacokinetics and pharmacodynamics

Favipiravir is given in the form of a prodrug. It has a high bioavailability (94%) and protein binding (54%) as well as a limited volume of distribution (10–20 L). After a single dose, it reaches Cmax in 2 hours. The

hydroxylated version of favipiravir has a short half-life (2.5–5 hours), resulting in fast renal clearance. Aldehyde oxidase and, to a lesser extent, xanthine oxidase are involved in elimination. The pharmacokinetics of favipiravir are both dosage and time dependent. The cytochrome P450 system does not metabolize it, but it does block one of its components (CYP2C8). As a result, it should be used with caution when combined with medications that are processed by the CYP2C8 system(47)

MOA: Favipiravir is a purine base analogue that is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation. It is a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir is incorporated into the nascent viral RNA by error-prone viral RdRp, which leads to chain termination and viral mutagenesis. After RNA viral incorporation, favipiravir-RTP works as a mutagen, which is capable of fleeing coronavirus repair machinery(47)(48)

2.4 ANTI-INFLAMMATORY AGENTS:

Dexamethasone:

On September 7, 2020, electronic searches were made on the Google Scholar database, MEDLINE, and PubMed. A search of the World Health Organization's COVID-19 research article database was also done. The results of recent studies that demonstrated corticosteroids' in vitro and in vivo action against COVID-19 and other coronavirus-related pneumonia were discussed. Low doses of corticosteroids (dexamethasone) were found to lower mortality in patients with severe COVID-19 disease, but had no effect on the mortality rate in those with a mild version of the disease. Corticosteroid medications are a type of synthetic steroid hormone produced in the adrenal cortex of healthy people. Glucocorticoids and mineralocorticoids are two types of corticosteroids that are used to treat a variety of disorders and symptoms(49) Dexamethasone is a steroid that belongs to the corticosteroid class, specifically the glucocorticoid class. It's used to treat a variety of ailments, including chronic obstructive pulmonary disease, severe allergies, rheumatic disorders, asthma, many skin illnesses, brain oedema, and tuberculosis when combined with antibiotics(50)

Pharmacokinetics and pharmacodynamics:

Corticosteroids are classed based on their potency, mineralocorticoid effects, and length of suppression of the hypothalamic-pituitary-adrenal axis. Potency is measured in terms of hydrocortisone and is useful for comparing doses. When these agents are used in pharmacologic doses to prevent or treat allergic, inflammatory, or immune responses, mineralocorticoid activity is also described in relation to hydrocortisone, and structural modifications to the steroid molecule are designed to increase potency while minimizing mineralocorticoid effects. Although stronger treatments have fewer mineralocorticoid effects, all current

medications have side effects in the levels that are commonly employed. Finally, depending on how long the hypothalamic-pituitary-adrenal axis is suppressed, these drugs are classed as short, medium, or long-acting. Because of the intracellular mechanism, the duration of action is not well connected with the duration of effect. Because corticosteroids have an intracellular mechanism, their effects last even after they are no longer in circulation. As a result, the duration of action for certain corticosteroids is frequently determined by how long the effects on the hypothalamic-pituitary-adrenal axis last, rather than the actual therapeutic action. Regardless of the method of administration, the onset of impact of systemic corticosteroids is frequently delayed for 3–8 hours(51)

MOA: The steroid molecule diffuses across cell membranes and attaches to glucocorticoid receptors, causing the receptor to undergo a conformational change. The receptor- glucocorticoid complex can enter the nucleus and dimerize, binding to glucocorticoid response elements. Trans repression and transactivation are terms used to describe the effects of glucocorticoid response elements on genes that suppress or promote transcription, resulting in ribonucleic acid and protein production. In the end, these drugs stop macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells from making pro-inflammatory mediators. The suppression of phospholipase A2, which is responsible for the generation of various inflammatory mediators, is another major impact. Corticosteroids inhibit genes responsible for the expansion of cyclooxygenase-2, inducible nitric oxide synthase, and pro-inflammatory cytokines, including tumour necrosis factor-alpha and various interleukins(51)

2.5 MULTIVITAMINS:

Vitamin and mineral supplementation, often known as "immune nutrition," has been studied in a number of clinical trials in intensive care units, and there are numerous hypotheses to back up their routine usage. Immuno nutrition is the process of altering dietary nutrients to influence the immune system. Because ARDS is characterized by a proinflammatory condition, it has long been assumed that raising the level of antioxidant substances in the body will be advantageous. Additionally, increasing lymphocyte, macrophage, and neutrophil activity by supplementing with nutrients like glutamine has been characterized as useful. Nutrient supplementation has been shown to improve the clinical outcome in a variety of patients, including those who are critically ill.

The data on the positive effects of immunonutrition in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is contradictory and frequently skewed. Patients with ARDS had decreased baseline plasma levels of beta-carotene, retinol, alpha-tocopherol, and total radical antioxidant capacity, according to clinical investigations. When compared to a control group that did not receive supplementation, this might be

corrected following four days of feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants. However, no clinical consequences were reported(52)

RECENT TREND:

Molnupiravir

Molnupiravir is an experimental ribonucleoside analogue inhibitor that inhibits SARS-CoV2 replication when taken orally. Molnupiravir was created by Merck & Co. Inc. in partnership with Ridgeback Biopharmaceutics and was invented at Drug Innovation at Emory (DRIVE), a non-profit organization completely owned by Emory University(53)

Results of planned interim analysis

The results from 775 participants who were initially enrolled in the phase 3 trial on August 5, 2021 were analyzed in a planned interim analysis. More than 170 planned sites in Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Philippines, Poland, Russia, South Africa, Spain, Sweden, Taiwan, Ukraine, United Kingdom, and United States were included in Phase 3 of the study. The trial's admission criteria were mild to moderate COVID-19 symptoms that appeared within 5 days after the study's randomization. Molnupiravir reduced the risk of hospitalization and mortality by 50% in the interim study. On day 29, no deaths were reported in Molnupiravir-treated individuals, compared to 8 deaths in placebo-treated patients(53)

Molnupiravir was found to be effective against the gamma, delta, and mu virus strains. Adverse drug reactions were reported in 13% of cases and 1.3 percent of patients stopped taking their medication because of them. A suggestion from an independent data monitoring committee, as well as interaction with the US Food and Drug Administration Merck chose to cease enrolling patients for the trial early due to the excellent results, and the phase 3 sample sizes of 1550 patients was approaching full recruitment, with more than 90% of the anticipated sample size already enrolled.

Merck’s efforts to enable access to Molnupiravir:

After receiving EUA permission from the USFDA, Merck plans to supply 1.7 million courses of Molnupiravir for the US government, with a goal of producing 10 million courses by the end of 2021.

Lowered expectations: The US Food and Drug Administration has failed to grant Molnupiravir emergency use authorization despite promising preliminary clinical trial results. The FDA advisory committee convened on November 30th and decided 13 to 10 to recommend emergency approval of the medication candidate. Between May and early August, 762 patients were randomly assigned to either four antiviral tablets or a placebo for five days. Between August and early October, 646 participants in the second group received the same treatment. Merck's senior vice president of clinical development, Nicholas Kartsonis, told an FDA advisory committee that the company couldn't explain the wildly disparate results. During the first half of the study, the highly transmissible delta version of coronavirus had not yet become prevalent internationally, according to some committee members. This might mean that molnupiravir isn't as effective against delta as it is for some other variants.

Omicron variant of SARS-CoV2:

On November 11, 2021, the first sequenced omicron case was reported in Botswana, and a few days later, another sequenced case was discovered in a traveller from South Africa in Hong Kong. On November 26th, the World Health Organization (WHO) identified variant B.1.1.529, also known as omicron, which was first discovered in South Africa, as a variety of concern. It is unknown whether omicron is more transmissible than other variations such as delta. It's unclear whether omicron infection causes more severe sickness than infections with other variations, such as delta. According to preliminary data, hospitalization rates in South Africa are rising. Omicron infection is still detectable using widely used PCR testing(54). Patients with severe COVID-19 will still benefit from corticosteroids and IL6 receptor blockers. Omicron possesses multiple deletions and over 30 mutations, many of which are similar to those found in alpha, beta, gamma, or delta. Higher transmissibility can be achieved by mutating the furin cleavage site in spike protein. There are currently no efficacy data on the effect of monoclonal antibodies on the omicron variant. The serum antibody-containing portion of blood from 12 people who received Pfizer-BioNTech vaccine was around 40 times less potent against omicron on average than against an earlier strain of SARS-CoV2, according to a study led by virologist Alex Sigal at Africa Health Research Institute in Durban, South Africa(55)

That finding was similar to results from two other studies: one reported by Pfizer and BioNTech in the 8th December press release and other released on Twitter and later posted on goethite university Frankfurt, Germany(55).

CONCLUSION:

Recent researches on COVID-19 treatment have provided more understanding of treatment options for COVID-19. Different countries have specific guidelines for management of COVID-19 and specific considerations for hospitalization. Many drugs and vaccines are still in pipeline for development. Although we don't know everything about disease, research is still going on. COVID-19 can be managed by providing right drug at right time to right patient.

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