Covid-19 and Therapeutic Options for its Clinical Management: A Narrative Review

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Abstract

COVID- 19 caused by SARS-CoV-2 was declared a pandemic by the WHO on 11th March 2020. In Bangladesh, confirmed COVID-19 cases were detected on March 8, 2020 and since then, Bangladesh is also facing the toll of this highly transmissible viral infection. Though the main strategy to handle the pandemic is containment by isolation of cases, quarantine of contacts, physical distancing of people, wearing masks and sanitizing hand and other sources of contamination, the potential severity of the disease and its deadly complications require effective clinical management as well. In addition to optimized supportive and symptomatic therapy, drugs targeting the pathogenesis of this viral infection at different levels can be proved efficacious in COVID-19. Keeping this in mind, different anti-viral drugs which had been found effective in some pre-clinical and clinical studies against other viruses have been used against SARS-CoV-2. Immunomodulatory and anti-thrombotic agents have proved their own place in treating COVID-19 targeting SARS-CoV-2 induced cytokine storm and hypercoagulability. Some drugs used mainly against protozoal infection have also been used by the virtue of their additional anti-viral property. Use of vitamins and minerals to boost up the immunity is also widespread. This review provides an overview of current COVID-19 status, its ways of transmission and clinical presentation. Discussing the pathophysiology, the review explores how drugs used for the purpose of treating COVID-19 can modulate various stages and factors resulting beneficial outcome. Categorization of COVID-19 cases and their severity-wise management in perspective of Bangladesh have also been discussed. Drugs using worldwide and in Bangladesh have been overviewed in this review justifying their recommendation against SARS-CoV-2. [*Bangladesh Journal of Infectious Diseases, June 2023;10(1):38-51*]

Keywords: COVID-19; transmission; clinical presentation; pharmacotherapy

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Introduction

The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). An outbreak of SARS-CoV-2 was first reported in Wuhan, China in December 2019[1], but soon it had spread to the rest of the world. Reports said that the pandemic is going on in 214 countries and the situation is rapidly expanding with increased number of new cases and deaths every day. In light of the situation, COVID-19 was declared a Public Health Emergency of International Concern by the Director General of the World Health Organization on January 30, 2020 and subsequently declared a pandemic on March 11, 2020[2]. COVID-19

pandemic has become a global concern because of its extremely high potential for dissemination. Amidst this global crisis, Bangladesh has been identified as one of the 25 most vulnerable countries to be affected by this fast spreading virus[3].

Epidemiology

As of April 13, 2021, there are 137,442,147 confirmed cases of COVID-19 worldwide with 2,959,078 global death[4]. Among the global confirmed cases, US, India and Brazil are now ranked 1st, 2nd and 3rd respectively[4]. Three cases of COVID-19 were confirmed for the first time in Bangladesh on March 8, 2020 by Institute of epidemiology, disease control, and research (IEDCR)[5] and consequently by April 25, 2020, it was confirmed in 63 out of 64 districts. More than 80% of the SARS-CoV-2 infection detected in Bangladesh have been reported in the Dhaka division and nearly 60% of them are in the capital, Dhaka[3]. According to the Director General of Health service, 697985 COVID-19 confirmed cases have been reported till April 13, 2020 with total deaths of 9891[6].

Coronaviruses are genetically classified into four major genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. Six types of human coronaviruses have been identified, which include HCoV-NL63 and HCoV-229E belonging to the α-coronavirus genus and HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS CoV-2 belonging to the β-coronavirus genus[7].

In the 21st century, the world faced three major outbreaks caused by coronavirus including severe acute respiratory syndrome, SARS-CoV-1 or SARS-CoV in 2002-2003 in China, middle east respiratory syndrome, MERS CoV in 2011-2012 in Saudi Arabia and SARS-CoV-2 or coronavirus disease, COVID-19 in 2019[8]. Amongst these, COVID-19 was considered as a worldwide pandemic. In spite of being less deadly than SARS-CoV-1 and MERS CoV, this novel virus is termed as a pandemic because of its high transmissibility[9].

Transmission of corona virus

The emergence of SARS-CoV-2 from an animal market in Wuhan suggests its zoonotic origin[10]. Usually, the CoVs are commonly harbored in mammals and birds. The intermediate hosts of SARS-CoV and MERS-CoV were masked palm civets and dromedary camels, respectively, with human as the terminal hosts. SARS-CoV-2 has similarity of about 88% and 50% to bat-derived SARS and MERS CoVs, respectively, suggested by genome sequence analysis. The search is going on to determine a possible intermediate carrier that may have passed the SARS-CoV-2 infection onto human.

Although the mechanism of human to human transmission of COVID-19 is not fully understood, it has been widely observed in health care as well as community settings. The recent studies suggest that such transmission is through the respiratory droplets and surface contact. The droplets generated from an infected person through his coughs or sneezes, potentially infect others remaining in the close contact. Moreover, viability of the virus within the droplets on the surface of an object for a few days can infect others who touch those objects or surfaces and then consequently touch their eyes, nose or mouth. The symptomatic persons are thought to be the most contagious. But recent evidence suggests that an asymptomatic person could also potentially spread the pathogen during the incubation period. The median incubation time is 5–6 days, ranging from 1 to 14 days. After an interval of an average of 11.5 days, 97.5% of all cases become symptomatic[11]. Unlike other coronavirus, the risk of contamination by SARS-CoV-2 virus through feces of an infected person is low[2]. Though there is no evidence of airborne dissemination of SARS-CoV-2, it may take place during aerosol producing procedures such as endotracheal intubation, bronchoscopy, and nebulization, turning the patient to the prone position, open suctioning and cardiopulmonary resuscitation. Recently, a few outbreaks had been reported in indoor crowded places, suggesting the chances of aerosol transmission in combination with droplet transmission[9].

Environmental factors, such as- temperature, humidity, and wind speed were found to significantly affect the survival and transmission of human coronaviruses such as SARS CoV and MERS- CoV. But in spite of having similar origin, the role of temperature and absolute humidity in the transmission of novel SARS-CoV-2 virus is yet to be clearly understood[5].

Clinical Presentations

Although about 50% of patients with COVID-19 remain asymptomatic, ~14% of infected individuals present with serious symptoms requiring hospitalization and oxygen therapy, while 5% require intensive care. The median duration from

symptom onset to intensive care unit admission is ~10 days, while the duration between symptom onset and death ranges from 2-8 weeks[7], influenced by the patient's age (shorter in patients > 70 years of age) and immune response[9].

For the practical purpose of patient management, cases of COVID-19 have been categorized into mild - Influenza like illness, moderate - Pneumonia, severe - Severe Pneumonia and critical - ARDS, Septic shock [65]. As per the World Health Organization (WHO), May 27, 2020, most infected individuals develop mild (40%), moderate (40%) or severe symptoms (~15%), while only 5% suffer from critical disease. Patients with the symptoms, like- cough, fever, sore throat, running nose, headache, malaise, muscle pain, diarrhea, nausea and vomiting are considered as a case of mild infection. Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) and chest images with patchy opacities or consolidation, without manifestation of severe pneumonia or requirement for oxygen supply diagnosed as a case of moderate severity. Severe cases are those who have clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus respiratory rate > 30 breaths/min or severe respiratory distress or SpO2 < 93% on room air[7,9]. Onset within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms, chest imaging presented with ground glass opacities and can't be explained by cardiac failure or fluid overload or lung collapse and oxygenation impairment are the indicators of acute respiratory distress syndrome. Life-threatening organ dysfunction manifested as altered mental status, difficult or fast breathing, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling with laboratory evidence of coagulopathy, thrombocytopenia less than 50,000/cmm, raised lactate and hyperbilirubinemia indicate that patient has developed sepsis and a critical case of COVID-19[65]. Individuals with pre-existing comorbidities such as cardiovascular dysfunction, respiratory disease, or diabetes may experience more severe symptoms of COVID-19[12].

Mechanism of Disease

Cronaviruses are a large family of enveloped, positive-sense, single-stranded RNA viruses. The structural proteins include spike protein (S), nucleocapsid protein (N), membrane protein (M), and the envelope protein (E)[8].
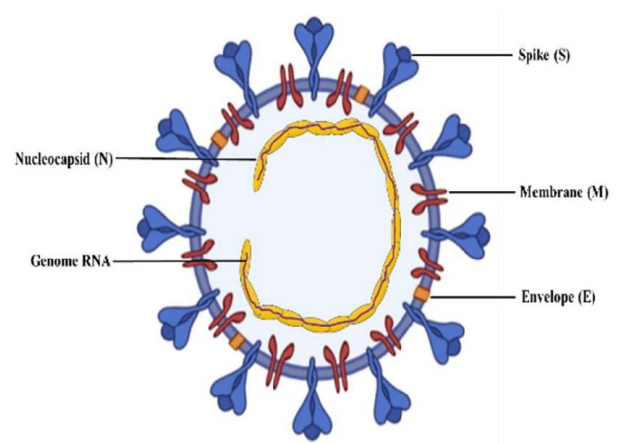
Figure I: Schematic Diagram of Coronavirus Particle[85]

The life cycle of SARS-CoV-2 can be categorized into nine major steps. Step-1: SARS-CoV-2 enters host target cells through either fusion or endocytosis. Step-2: In the endocytic pathway, the SARS-CoV-2 envelope fuses with the endosome membrane in the lysosomal acid environment, which promotes viral RNA genome release into the host cell cytoplasm. Step-3: Translation of viral polymerase protein. Step-4: Replication of genomic RNA. Step-5: The viral sub-genome is transcribed. Step-6: SARS-CoV-2 then undergoes viral RNA replication in the host cells. Step-7: Viral N, M, E and S proteins are translated through the endoplasmic reticulum and Golgi apparatus. Step-8: Structural proteins interact with viral genomic RNA to pack and form a novel virion. Step-9: The assembled virion is then released via exocytosis into the extracellular compartment. The released viral particles are infectious and may begin a new life cycle[7,8].

The entry of SARS-CoV-2 into the host cells is dependent on binding of its structural spike (S) protein to host cell receptors and S-protein priming via host cell proteases. SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2) receptors on the surface of human cells through its S-protein. Following this initial binding, 2 transmembrane serine protease (TMPRSS2) primes the S-protein by acid-dependent proteolytic cleavage at two specific sites of S protein, facilitating viral entry into the cell through endosomes[9,16]. Both ACE2 and TMPRSS2 proteins are expressed in nasal goblet secretory cells, lung type II pneumocytes, ileal absorptive enterocytes and also in kidneys and heart.
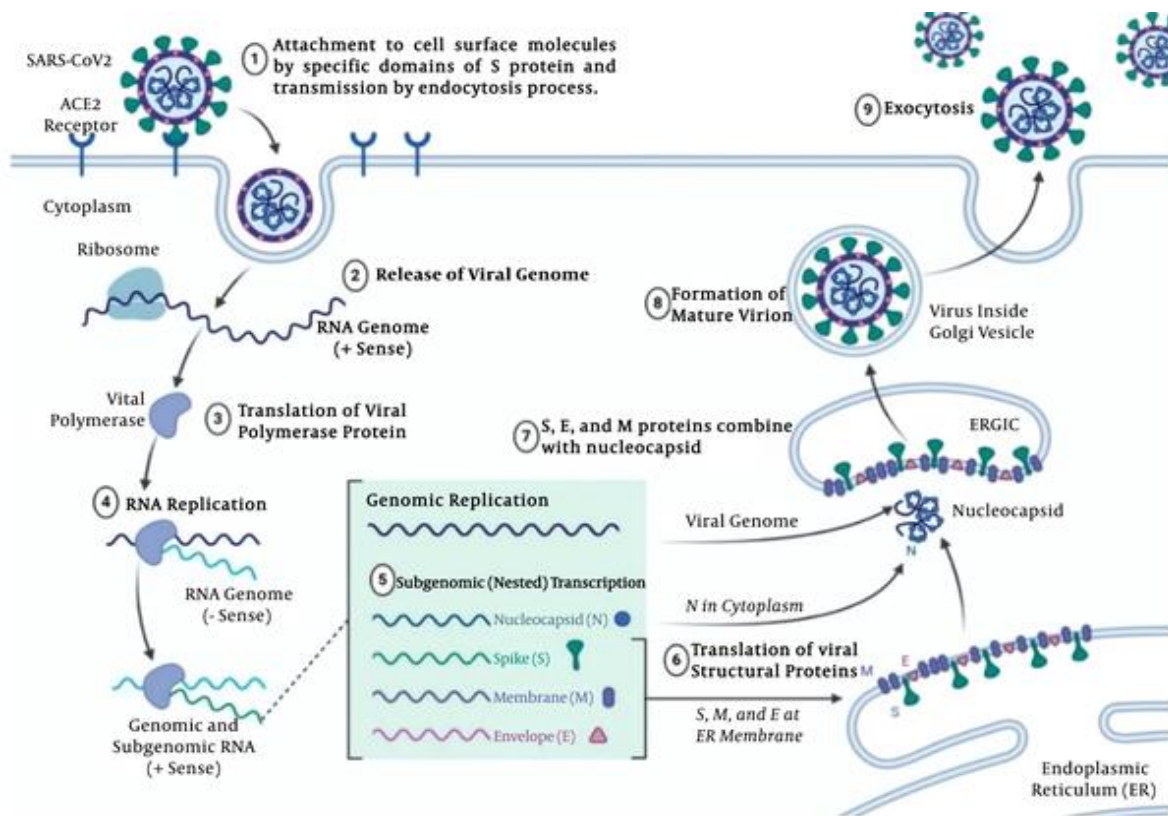
Figure II: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Lifecycle[86]

But the primary target is human lung epithelial cells. After proteolytic cleavage, the S protein facilitates viral envelope fusion with the host cell membrane through the endosomal pathway. The coronavirus uses the vesicular trafficking system of the secretory pathway of the host cell to release newly synthesized viral particles by exocytosis[8]. COVID-19 has a staged progression in the course of events after the incubation period. At one end of the spectrum, a balanced immune response keeps the infection under control, but at the other end there is an exaggerated immune response with consequent lung injury. Lung injury initiates at the epithelial-interstitial-endothelial level, with exudation of neutrophils and macrophages, which, in turn reduces the alveolar surfactant, thereby reducing the patency and the gas exchange. Infected cellular debris further augments the release of inflammatory cytokines like TNF-a, interleukin-1 and 6, further accentuating the 'cytokine storm". The second phase begins with uncontrolled viral replication induced angiotensin-converting enzyme 2 (ACE2)-directed cytotoxicity, that triggers a vicious circle of immune activation with consequent worsening of the hyper-inflammatory state. The accompanying "cytokine storm" leads to a massive vascular inflammation, disseminated coagulation, shock and hypotension, leading to multi organ failure and

death[8,13,14]. Reports suggested host innate immune response as higher neutrophil, C-reactive protein, interleukin-6 (IL-6) and reduced lymphocyte counts were observed in infected individuals. Neutrophilia and lymphocytopenia resulted in increased disease severity Severe patients exhibited elevated creatinine, erythrocyte sedimentation rate and blood urea nitrogen levels[9,15]. Associated hypercoagulability in patients with severe COVID-19 is reflected by increased D-dimer concentration, prolonged prothrombin time, increased fibrin degradation products, and thrombocytopenia[12].

Pharmacotherapy

As the detrimental consequences of COVID-19 continue to impact nations globally, the need for a safe and effective treatment is paramount. Successfully implemented pharmacotherapy that slows or kills SARS-CoV-2 has the potential to save COVID-19 patients and ease the burden of the pandemic on healthcare systems[12]. Prophylactic treatment has been suggested, particularity to frontline workers and those at higher risk of susceptibility[17]. Pharmacotherapy has been aimed at alleviating symptoms, combined with various attempts to prevent the spread and complications of

COVID-19. At present, repurposing of available medications has been the standard of care for treatment of SARS-CoV-2 patients[17].

Anti-viral agents

Various antiviral agents including remdesivir, lopinavir/ritonavir, ribavirin, favipiravir, chloroquine/ hydroxychloroquine, arbidol have been repurposed specifically for the management of COVID-19.

Remdisivir: Remdesivir is an adenosine nucleotide analogue. It is a pro-drug. It requires intracellular activation by phosphorylation to convert into active metabolite. Such conversion also improves intracellular delivery of the drug[18]. It targets and inhibits viral RNA-dependent RNA polymerase (RdRp) which terminates the transcription of viral RNA[7,18]. Moreover, coronaviruses have a "proofreading" enzyme named exoribonuclease which correcting the errors in the RNA sequence, limits the effects of such nucleotide analogues. But remdesivir has the ability to evade this proofreading. Remdesivir has suboptimal oral bioavailability and therefore can be administered only by intravenous infusion in the actual formulation[18].Remdesivir was 1st developed by Gilead Sciences during the peak of the Ebola virus outbreak in 2016[7]. It has a broad-spectrum antiviral activity against filoviruses, paramyxoviruses, pneumoviruses and pathogenic coronaviruses, like SARS-CoV and MERS-CoV[18,19,20]. There is evidence that remdisivir can inhibit the replication of coronaviruses in tissue cultures. Efficacy in nonhuman animal models had also been explored[20]. Animal study of remdisivir against Ebola virus showed limited plasma stability of the drug in rodents due to high serum esterase activity. For this reason, antiviral activity against coronaviruses was evaluated in a mouse model[17]. In this model of SARS-CoV pathogenesis, remdesivir was administered before and after inoculation of the virus. It showed significant reduction of the lung viral load. As well as it improved the clinical signs of the disease and respiratory function in comparison to untreated control animals[19]. Another study evaluating the efficacy of prophylactic and therapeutic remdesivir treatment in rhesus macaque model of MERS-CoV infection revealed prevention of replication in respiratory tissues, which reduces the formation of lesions in the lungs. In this study, prophylactic remdesivir treatment was initiated 24 hours before inoculation, whereas therapeutic treatment was initiated after 12 hours of virus inoculation[21].

The first human study evaluating the efficacy of remdesivir against COVID-19 (ClinicalTrials.gov identifier NCT04257656) was started in February 2020 in Wuhan. It was a phase 3 randomized, double-blind, placebo-controlled trial. Hospitalized COVID-19 patients with hypoxia and radiological findings of lung involvement were enrolled in the study, where 158 patients were treated with remdesivir (200 mg on day 1 and 100 mg on days 2 to 10) and 79 patients were given a placebo for 10 days. This study revealed that treatment with remdisivir can reduce 5 days in the time to clinical improvement[18]. Another randomized, placebo-controlled clinical trial involving 1000 COVID-19 patients, also demonstrated a significant faster recovery time in the remdisivir treatment arm compared to placebo arm[22]. Similar results were found enrolling 1062 patients randomly in a study. The study showed that a median recovery time is 10 days in remdisivir-treated group as compared to 15 days in placebo group[23]. This study also revealed that treatment with remdesivir prevented the progression to more severe respiratory disease which was reflected by less serious adverse events due to respiratory failure, lower incidence of new oxygen use and a less requirement of higher levels of respiratory support during study. Treatment with remdesivir reduced the duration of subsequent use of oxygen, mechanical ventilation or ECMO in those patients receiving such interventions at enrollment. Researchers compared 5-day dosing regimen with 10-day regimen and found similar clinical improvement.

Four phase 1 clinical trials were conducted by Gilead Sciences, the manufacturer of remdesivir, to evaluate the pharmacokinetics and safety-tolerability of remdesivir. The drug was found to be generally well tolerated. A few cases of adverse effects were reported including phlebitis, constipation, headache, ecchymosis, nausea, and pain in extremities. Transient raised level of liver enymes, mild prolongation of the prothrombin time mild hyperglycemia were the detected laboratory abnormalities. There were no findings of renal involvement in healthy subjects. No clinically relevant abnormalities were found in electrocardiograms[18]. In VigiAccess of Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, 5935 adverse drug reactions were found to be reported till April 1, 2021 including 1470 cases of general physical health deterioration and injection site complications, 722 cardiac adverse reactions and 672 respiratory, thoracic and mediastinal disorders ranking 1st, 2nd and 3rd, respectively. Thirty percent of all ADRs reported in the age group of 45-64

years with a male predominance (60%).Considering the preliminary results about remdesivir, US FDA issued an emergency authorisation to remdesivir on May 1, 2020 for the treatment of suspected or laboratory-confirmed COVID-19 adults and children who are hospitalized, irrespective of their severity of disease[24]. Later US FDA approved remdesivir for the treatment of hospitalized COVID-19 patients on October 23, 2020[24]. In Bangladesh, Injection remdesivir has been advocated for moderate to severe cases who need oxygen therapy and/ or hospitalisation. Dosage of remdesivir used is 200 mg IV infusion (within 30 min-2 hours) on Day 1 followed by 100 mg infusion (within 30 min to 2 hours) from Day 2 to Day 5[11].

Lopinavir/ Ritonavir: Lopinavir is a protease inhibitor and are widely used for treating HIV infection. Due to its poor oral bioavailability and extensive biotransformation, lopinavir is combined with ritonavir to increase the half-life of lopinavir and thus prolong the action of the drug in the human body. Ritonavir does this by inhibiting cytochrome P450 3A4 enzyme of the host[17,25]. As studies had demonstrated that lopinavir/ritonavir had inhibitory activity, tested both in vitro and in an animal model, against MERS-CoV and SARS-CoV, it was assumed that the virus that causes SARS in humans can also be inhibited by the drug. But lopinavir/ritonavir alone was found ineffective in lowering virus load of SARS-CoV-2 in humans. A study was conducted enrolling hospitalized adult patients with severe Covid-19, where no benefit was observed with lopinavir/ritonavir therapy beyond standard care. There was no difference in the time to clinical improvement in patients treated with lopinavir/ritonavir compared to standard care. Mortality at 28 days was shown similarity in both the lopinavir/ritonavir and the standard-care group. Viral RNA at various time points were measured and found similar in both group of patients[25]. Not only in severe COVID-19 patients, clinical outcomes for hospitalized patients with mild to moderate COVID-19 did not reveal any improvement with lopinavir-ritonavir monotherapy compared to standard of care[26]. Though lopinavir/ritonavir alone did not show any demonstrable benefits for COVID-19, combining lopinavir/ ritonavir with other agents might play roles in the eradication of SARS-CoV-2[84].A trial was carried out in Hong Kong, where one group of SARS-CoV-2-infected human subjects were treated with interferon beta-1b, ribavirin and lopinavir/ritonavir therapy and other group with lopinavir/ritonavir alone. Median time from the beginning of the treatment to negative

nasopharyngeal swab was recorded and it revealed that patients treated with combined therapy had a shorter time (7days) in comparison to the control group (12 days)[27]. An open-label study was carried out in 2004 in which 41 patients were treated with a combination of lopinavir/ritonavir and ribavirin. The clinical progress and virological outcomes were monitored and compared with a historical control group that received only ribavirin. The addition of lopinavir/ritonavir to ribavirin reduced the adverse outcomes, like- acute respiratory distress syndrome (ARDS) or death. The study also demonstrated reduction of viral load among patients with SARS-CoV[28].Another study combining ribavirin and interferon alfa with lopinavir/ritonavir suggested virologic clearance and survival in a 64- years old patient[29].Study exploring the efficacy of prophylactic and therapeutic lopinavir/ritonavir and interferon-beta revealed that prophylactic therapy reduced viral loads only slightly where therapeutic lopinavir/ritonavir and interferon-beta improved pulmonary function with no effect on virus replication or severe lung pathology [19].Addition of lopinavir/ ritonavir did not show any mortality benefit with ribavirin and corticosteroids, but lopinavir/ritonavir accompanying arbidol augmented the SARS-CoV-2 eradication[25].Taking adverse reactions into consideration, lopinavir/ritonavir alone caused more diarrheal events [25,30] than lopinavir/ ritonavir, ribavirin and corticosteroids combined treatment. Vigiaccess showed that among total 12792 reported adverse effects for lopinavir till 19 April, 2020, gastrointestinal adverse reactions are reported mostly (3839 reports). As convincing data about the efficacy of lopinavir/ritonavir in humans are lacking, it is not recommended to treat COVID-19.

Ribavirin: Ribavirin is a guanosine analogue. It tightly binds to SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) and thus may be used against COVID-19[31].Evidence suggests that it had been used to treat several viral infections, like respiratory syncytial virus, hepatitis C virus, and some viral hemorrhagic fevers [7,20,30]. As there is no established definitive therapeutic benefit of ribavirin, explored during the 2003 SARS-CoV and 2012 MERS-CoV outbreaks, very limited clinical testing has been done against COVID-19 [32]. But combining ribavirin with interferon-α, lopinavir-ritonavir or corticosteroid may provide clinical benefits [26,33]. Although testing ribavirin with IFN-2b in a MERS-CoV rhesus macaque model exhibited promising results[34], testing in patients with MERS-CoV infections revealed conflicting result[35]. Combination of ribavirin and corticosteroids showed significant reduction of

mortality in a study[12]. The major concern with ribavirin was significantly higher incidence of adverse events, especially reduction of hemoglobin concentrations[20,30], hematologic and liver toxicity[12,33] and bradycardia [26]. Vigiaccess search showed as the most common adverse drug reaction of ribavirin. So considering both efficacy and safety, ribavirin has limited value as a therapeutic agent against COVID-19. It is not recommended to treat SARS-CoV-2 in Bangladesh.

Favipiravir: Favipiravir is a guanine-derived nucleoside analogue which converts into a phosphoribosylated form in the body to act. Being a substrate of viral RNA polymerase in many RNA viruses, after incorporating into nascent viral RNA, Favipiravir inhibits the RNA-dependent RNA polymerase enzyme (RdRp) resulting premature termination of the viral RNA chain which consequently halts the replication of the viral genome [30,35].Antiviral activity of Favipiravir against SARS-CoV-2 was found modest in the cell culture[9,36]. Favipiravir had been compared with other anti-viral agents for its efficacy against SARS-CoV-2. A prospective randomized clinical trial carried out in China compared favipiravir with arbidol. The study demonstrated that reduction of symptoms, like- fever, cough, and respiratory problems were significantly more in the favipiravir-treated group (71.4%) than arbidol-treated group (55.9%). These results were found in non-critical COVID-19 patients. But this effect was not promising among critically ill COVID-19 patients[37,38]. A study comparing favipiravir with lopinavir/ritonavir found significantly greater improvement in chest findings in favipiravir-treated (91.4%) COVID-19 patients in comparison to lopinavir/ritonavir (91.4% improvement with favipiravir (62.2%). Viral clearance was also found faster (4 days versus 11 days), whereas fewer adverse events (11.4% versus 55.6%) were observed in patients taking favipiravir compared to those taking lopinavir/ritonavir[39]. Another open labelled, non-randomized trial showed shorter viral clearance time in favipiravir treated patients than the control group treated with a combination of lopinavir/ritonavir and IFN-α [39]. Adverse events reported in Uppsala monitoring center for favipiravir is 506, which is very low in comparison to other anti-viral agents. Considering promising potency of favipiravir, found in preliminary results of clinical studies on Chinese COVID-19 patients, it was approved for the treatment of COVID-19 in China in March, 2020[30]. In Bangladesh, though the use of favipiravir is not recommended, it is used to prescribe both in indoor and outdoor COVID-19 patients.

Hydroxychloroquine: It had been found several times that a drug approved to treat a particular disease showed its efficacy in treating other diseases as well. Chloroquine and hydroxychloroquine is one of the examples of such drug. Having immune-regulatory, antithrombotic and anti-inflammatory properties, this drug had been used treating systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and malaria. Its broad spectrum anti-viral activity was also identified in the late 1960s [8,33,40,41,83]. Hydroxychloroquine is a derivative of Chloroquine. The hydroxyl group added in chloroquine has made Hydroxychloroquine less toxic than chloroquine, tested in animal studies. Anti-viral efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 in vitro had been explored both in cell culture and in animal (mouse model)[38,42,43,44]. It also proved to be effective in treating patients with COVID-19 [41].Chloroquine or hydroxychloroquine act in various ways to display its anti-viral effect. Being an alkaline drug it increases the pH of the endosome, blocking fusion and entry of the virus inside the cell. Inhibiting interaction between viral spike protein and cellular angiotensin-converting enzyme 2 receptor, it interrupts viral attack. It can also counteract cytokine storm in patients with severe COVID-19 disease[26]. A study in France explored the efficacy of hydroxychloroquine in clearing nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients and found a greater percentage of viral clearance in hydroxychloroquine treated patients[45]. Another study found a significant reduction in the recovery time from fever and cough in hydroxychloroquine treated group of patients. CT scan of chest also revealed more improvement in patients treated with hydroxychloroquine in this study. Moreover, there was no patient in the hydroxychloroquine group progressing to severe illness but there were 4 patients in the control group not receiving hydroxychloroquine treatment. Mild adverse effects were reported in two patients[36,41].Considering the anti-viral properties of chloroquine and hydroxychloroquine, FDA approved the drug for emergency use in March, 2020 but later withdrew the approval in June, 2020 as serious adverse effects (dysrrythmia with QT prolongation) were reported. As a consequence, FDA issued a safety warning regarding its use outside of the hospital setting for COVID-19. Adverse effects involving haematologic, hepatic and renal system also discouraged its random use[7,30].

Ivermectin: Ivermectin is a broad-spectrum anti-parasitic agent. But its anti-viral property had also been proved against both different RNA and DNA

viruses[46]. Recent studies revealed its effect against SARS-Co-V-2[47]. In a randomized, double-blind, placebo-controlled trial, 72 hospitalized patients were enrolled and were assigned ivermectin alone (12 mg once daily for 5 days), ivermectin with doxycycline, and a placebo control group. Rapidity of viral clearance was determined and it was found earlier in the 5-day ivermectin treatment group in comparison to placebo group but not in the combination [48].Other study found combination of ivermectin and doxycycline to be very effective in viral clearance in mild and moderate COVID-19 patients and the researchers recommend this combination therapy to include in the national guideline[46]. Enrolling 118 healthcare providers in an observational study, 12 mg of ivermectin was given for 4 months (once monthly) to the experimental group. Both groups were exposed to confirmed COVID-19 cases. After the study period, 73.3% subjects in control group became positive for COVID-19, whereas only 6.9% subjects in the experimental group were diagnosed with COVID-19[46]. Small sample size, short duration of the studies, various strength-frequency and duration of treatment and variable outcome of the studies failed to prove its efficacy and thus not recommended in the national guideline of COVID-19 management. In spite, a single dose of 18 mg ivermectin is being prescribed now-a-days in outdoor basis.

Others Drugs

A number of anti-viral agents can also be used to treat SARS-CoV-2 infection, but inconclusive reports have limited their wide use, like- camostat mesylate, arbidol, nitazoxanide.

Immunomodulatory agents: Immune modulation is more than just boosting the body's immune system. It involves bringing the ratio of the different immune cells back into balance to enable the immune system to function correctly.

Interferon: IFN-α, pegylated IFNα-2a and α-2b and IFN-β are the type-1 interferon. Viral infection induces type-1 interferon synthesis and secretion which phosphorylates STAT/2 transcription factors activating interferon-stimulating genes. Type-1 interferon activates both cellular and humoral immune response against the virus. Secreted interferon induces activation of natural killer cell and cytotoxic T cells (CD8+ T cells) which destroy infected cells. Type-I interferon stimulating B cells, induces the production of neutralizing antibodies and thus limits infections in later-phase and prevents future re-infections[7].

Studies demonstrated reduced type-1 activity in cells infected with SARS-CoV and MERS-CoV. Treatments with type 1 interferon improves anti-viral activity amongst infected mice[49]and so interferon had been widely used through SARS and MERS epidemic[26]. As such, it can be hypothesized that type-1 interferons are a good option to treat infection with SARS-CoV-2[50]. IFN-α2b had been proved to reduce the duration of SARS-CoV-2 infection in the upper respiratory tract. It was also found to reduce the levels of inflammatory cytokine and C-reactive protein in COVID-19 patients[51]. There are several studies where efficacy of interferon combining with antiviral drugs had been explored. Many other clinical trials on interferons for the treatment of COVID-19 are ongoing worldwide[7].

Tocilizumab: In addition to type-1 interferon, COVID-19 also induces the release of pro-inflammatory cytokine, interleukin-6 (IL-6) which mediates inflammation in lung and other tissues leading to fibrosis. Tocilizumab is a recombinant humanized IL-6 receptor antagonist. It has been approved for treating rheumatoid arthritis and systemic variety of juvenile idiopathic arthritis. But till now, evidence to recommend tocilizumab to treat COVID-19 is not sufficient[12]. Retrospective studies have reported some efficacy in critically ill COVID-19 patients with significantly elevated levels of IL-6. 21 critically ill COVID-19 patients were enrolled in an observational study and were given tocilizumab. The therapy reduced body temperature with improvement of respiratory function in all patients. No adverse drug reactions were reported[52]. Considering the result of this study, China approved the use of tocilizumab to treat severe and critical COVID-19 patients with high IL-6 levels[30,38]. In Bangladesh, Tocilizumab is indicated to manage severe cases of COVID-19 who had met the criteria, like- abnormal chest imaging consistent with COVID-19, rapidly worsening gas exchange/respiratory status over 24-48 hours and requiring >6 L/min O2 or on mechanical ventilation, absence of systemic bacterial, fungal or parasitic co-infection with high clinical suspicion for cytokine release syndrome and clinically deterioration of the patient[11]. Maximum 2 doses (8 mg/kg/dose) are recommended.

Combination Drugs

Bamlanivimab plus etesevimab and casirivimab plus imdevimab are two anti-SARS-CoV-2 combination monoclonal antibodies that have got emergency use authorization for mild to moderate

non-hospitalized patients who are at high risk of disease progression[53]. Neither of these two drug combinations is available in Bangladesh.

Corticosteroids: Corticosteroids are used to treat various diseases exploiting its anti-inflammatory and immunosuppressive effect. As viral infections can lead to a hyper-inflammatory state, they are often used as an adjunct treatment for viral pneumonia[54]. As the pathogenesis of COVID-19 revealed association with cytokine storm, corticosteroids are thought to control such cytokine storm and its consequences, like- acute respiratory distress syndrome, disseminated intravascular coagulation and shock owing to their anti-inflammatory effects. But at the same time, by its immunosuppressant effect, corticosteroids can aggravate the viral load with prolongation of viral excretion time[14]. There is also chance of secondary infection and long-term serious complications. So the risks and benefits of corticosteroid therapy for COVID-19 are inconclusive[55]. The use of corticosteroids was found to cause increased mortality and length of ICU stay in pneumonia caused by influenza virus. It was also associated with systemic complications[56,57]. During SARS-CoV-1 outbreaks, ribavirin and hydrocortisone therapy were compared with placebo in a study and suggested delayed viral clearance in the group treated with the combination therapy in comparison to placebo group[58]. Similarly, MERS-CoV patients treated with steroids also experienced worse outcomes in terms of viral replication, need for mechanical ventilation and renal replacement therapy as well as mortality rate[35,59,60]. Similar negative results were demonstrated in patients with COVID-19. In a single-center retrospective study involving 102 severe and critically ill COVID-19 patients, the mortality was found higher in the methylprednisolone-treated group[55,61]. But there are some evidences in favor of the corticosteroid use against SARS-CoV-2 infection. A single-center retrospective cohort study evaluated the effect of corticosteroids in COVID-19 hospitalized patients complicated by acute hypoxemic respiratory failure (AHRF) in a non-intensive care unit setting. Corticosteroid was found to lower the incidence of ICU transfer, intubation and in-hospital[62]. An open-labelled randomized controlled trial exploring the efficacy of dexamethasone in COVID-19 patients showed reduction in mortality of about 36% in patients on mechanical ventilation and of about 18% in patients on supplemental oxygen therapy[63,82]. But no benefit was observed in mild cases of COVID-19. Another study found beneficial effect of corticosteroid in a specified subgroups of patients requiring oxygen 3 L/min or C-reactive

protein level 100 mg/L in terms of reduced risk of intubation or death by day 28[64]. But corticosteroid was associated with hyperglycemia in increased number of patients compared to control group. So in a nut-shell, it can be said that corticosteroids may reduce mortality or lower the need for supplemented oxygen or intubation in severe or critical patients with COVID-19. But must be discouraged in patients with mild symptoms [65,66,67,68]. World Health Organization recommended the use of corticosteroid for strictly specific condition[69].

The principal corticosteroids used in most of these studies and other ongoing trials have been methylprednisolone and dexamethasone because of their high bioavailability. In Bangladesh, moderate cases of hospitalized COVID-19 who did not response with the treatment or deteriorated, oral dexamethasone (6 mg/day in single or two divided dose for 10 days) or methylprednisolone (60-80 daily in single or two divided doses for 7 days) are recommended[11]. In treating hospitalized severe COVID-19 cases, Injection dexamethasone 6 mg daily for 10 days or Injection methylprednisolone 250 mg daily for 5 days have been recommended.

Anti-Thrombotic Agents: Microorganism induces inflammatory reactions as a part of for host defense resulting increased generation of pro-inflammatory cytokines which subsequently activates coagulation. It may lead to consumptive coagulopathy if not checked at early stage. SARS-CoV-2 by inducing cytokine storm can cause systemic thrombosis. Moreover, it can directly injure vascular endothelial cells resulting thrombus generation[70,71]. Several studies reported elevated level of biomarkers of inflammation, like- erythrocyte sedimentation rate, C-reactive protein, neutrophilia and lymphopenia in complete blood count, interleukin-6 as well as elevated level of biomarkers reflecting coagulopathy, like- D-dimer, activated partial thromboplastin time (aPTT), prothrombin (PT), lactate dehydrogenase (LDH), fibrin degeneration products and fibrinogen, serum ferritin in patients with SARS-CoV infection[56,72,73]. Among these biomarkers, D-dimer is considered to be the most important as it is used not only to predict thrombosis but also to assess risk as a prognostic tool[74]. Higher D-dimer level was found to be associated with increased need of ICU admission, mechanical ventilation and mortality[71,73,75]. And use of low molecular weight heparin (LMWH) as an anti-coagulant demonstrated a reduction in the death rate in a study population with higher D-dimer level [76]. As thrombocytopenia and bleeding may be a consequence of anti-coagulant therapy, it

should be monitored cautiously and in such case protocol for managing bleeding should be adopted [9,70,74].

International Society on Thrombosis and Haemostasis and American Society of Hematology recommended prophylactic LMWH in all hospitalized COVID-19 patients including those who are not critical, unless there is any contraindication. With a history of heparin-induced thrombocytopenia, use of fondaparinux is recommended. Therapeutic dose of anti-coagulant should not be used even in seriously ill COVID-19 patients [74]. In Bangladesh, the guideline for COVID-19 management recommended thromboprophylaxis for mild COVID 19 cases with risk factors and patients with moderate severity. LMWH (Injection Enoxaparin) at a dose of 1mg/kg SC twice daily/ day has been suggested. The dose need to be adjusted when Creatinine Clearance is < 30ml/min. In that case, Unfractionated heparin (UFH) needs to be started. Thromboprophylaxis should continue until symptom resolved, followed by rivaroxaban 10 mg tablet once daily for 1 month[11].

Antibiotics: Antimicrobials are prescribed widely in patients with COVID-19. The reasons behind such prescription is treating associated secondary co-infection, hospital-acquired or ventilator-associated pneumonia. SARS-CoV-2 infection presents in a similar manner as atypical bacterial pneumonia, hospital-acquired or ventilator-associated pneumonia. So, prescribing broad-spectrum antimicrobials in hospitalized COVID-19 patients are given recommendation, where the duration of hospital stay is more than 6 days[9,30,77]. Macrolides, fluoroquinolones, tetracyclines, β-lactam antibiotics are used frequently to combat infections caused by *Klebsiella pneumoniae*, *Staphylococcus aureus* (methicillin-resistant), *Streptococcus pneumoniae* (multi-drug resistant), *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

There are studies where use of azithromycin, a macrolide with hydroxychloroquine in SARS-CoV-2 infection had been explored. A retrospective cohort study conducted in multiple centers revealed no benefits from these combination therapy, rather they caused synergistic QT prolongation with increased risk of cardiac arrest[12,78]. But another study found this combination therapy beneficial in reducing viral burden in a large number of patients[38]. Efficacy of doxycycline had also been explored in some studies conducted in Bangladesh but the results are contradictory[48,79]. Evidence of

efficacy and safety of antimicrobial agents used in COVId-19 is very limited.

Adjuvants: There are multiple agents that are used to be prescribed in COVID-19 patients along with anti-viral, anti-coagulant and immunomodulatory agents. These are nutritional supplements like-vitamin D, zinc, anti-inflammatory agent, like-montelukast. In addition, anti-tussive and anti-histamines are also prescribed to treat the patient symptomatically.

Vitamin D and Zinc: Involvement of the immune system in the pathogenesis of COVID- 19 has hypothesized the beneficial effects of nutritional supplements with antimicrobial and immunomodulatory activity. As there is evidence that people with vitamin D insufficiency or deficiency are more prone to develop respiratory infections, vitamin D had been used as an adjunct in the treatment of influenza and recurrent respiratory infection. A retrospective study on patients with respiratory failure suggested increased severity of COVID-19 in patients with vitamin D deficiency. Vitamin D by promoting differentiation and recruitment of cells involved in immune response, facilitates the elimination of microorganism. Not only that, it can reduce the producing and releasing defensins and cathelicidin and thus reinforcing the barrier function of different organs[80].Common cold caused by rhino virus is a very common illness which affects people of all ages. Treating common cold with zinc is well established as it had been found that the incidence is more among zinc-deficient population. Studies revealed that zinc can reduce the frequency and duration of the upper respiratory infection. Zinc exerts its anti-viral activity by interfering viral replication. In vitro studies proved its efficacy against influenza virus, respiratory syncytial virus, polio virus, several picornaviruses as well as coronavirus. Anti-viral activity of zinc needs its Intracellular mobilization and it is facilitated by hydroxychloroquine. So, the combination of hydroxychloroquine with zinc is more effective in interfering viral replication at various steps of the life cycle of SARS-CoV-2 [8,80]. In addition, having immunomodulatory properties, zinc helps fighting infection and healing wounds.

Montelukast: Montelukast having some experimentally proved properties either related to SARS-CoV-2 and/or related to the host and/or related to the serious COVID-19 outcomes, are used to prevent and treat SARS-CoV-2 infection. Montelukast is able to prevent endothelitis and of neurological disorders linked to SARS-CoV-2, improve atherogenic vascular inflammation and

limit ischemia/reperfusion phenomenon and to limit cytokine storm and mitigate acute respiratory distress syndrome. Based on such theoretical evidence, montelukast should be tested further for its use in COVID-19 cases[81].

Conclusion

Remedisivir is the only drug that has got FDA approval for the management of COVID-19. Some drugs have got emergency use authorization (EUA) considering risk-benefit ratio. There are different country-based guidelines for clinical management of COVID-19 which vary in some aspects from guideline of national institute of health (NIH) depending on the availability of drugs and results of trials conducted in that particular region. In Bangladesh, we have observed use of many other drugs which neither have FDA approval nor have been recommended in guideline. Rationalization and justification of use of such drugs need cautious supervision.

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