Review article:

CURRENT CORONAVIRUS (SARS-COV-2) EPIDEMIOLOGICAL, DIAGNOSTIC AND THERAPEUTIC APPROACHES: AN UPDATED REVIEW UNTIL JUNE 2020

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ABSTRACT

Coronaviruses are a group of enveloped viruses with non-segmented, single-stranded, and positive-sense RNA genomes. In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan City, China. The World Health Organization (WHO) declared the coronavirus outbreak as a global pandemic in March 2020. Fever, dry cough and fatigue are found in the vast majority of all COVID-19 cases. Early diagnosis, treatment and future prevention are keys to COVID-19 management. Currently, the unmet need to develop cost-effective point-of-contact test kits and efficient laboratory techniques for confirmation of COVID-19 infection has powered a new frontier of diagnostic innovation. No proven effective therapies or vaccines for SARS-CoV-2 currently exist. The rapidly increasing
research regarding COVID-19 virology provides a significant number of potential drug targets. Remdesivir may be the most promising therapy up till now. On May 1, 2020, Gilead Sciences, announced that the U.S. Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for the investigational Remdesivir as a potential antiviral for COVID-19 treatment. On May 7, 2020, Gilead Sciences, announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has granted regulatory approval of Veklury® (Remdesivir) as a treatment for SARS-CoV-2 infection, the virus that causes COVID-19 acute respiratory syndrome, under an exceptional approval pathway. Also, Corticosteroids are recommended for severe cases only to suppress the immune response and reduce symptoms, but not for mild and moderate patients where they are associated with a high-risk side effect. Based on the currently published evidence, we tried to highlight different diagnostic approaches, side effects and therapeutic agents that could help physicians in the frontlines.

**Keywords:** COVID-19, SARS-CoV-2, Remdesivir, Diagnosis, Epidemiology, Therapy

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**INTRODUCTION**

In December 2019, a novel coronavirus, SARS-CoV-2, was identified as the pathogen causing coronavirus disease (COVID-19) in Wuhan, China. On March 11, 2020, the World Health Organization declared COVID-19 as a global pandemic (Whitworth, 2020).

COVID-19 is an enveloped, positivesense, single-stranded RNA virus that belongs to the beta-CoV genus, which also includes SARS-CoV and MERS-CoV. It shares 89 % nucleotide identity with bat SARS-like CoVZXC21 and 82 % identity with human SARS-CoV (Chan et al., 2020a).

COVID-19 is transmitted by inhalation or contact with infected droplets. The incubation period for COVID-19 is on average, 5–6 days, but can be up to 14 days. During this period, also known as the “presymptomatic” period, some infected persons can be contagious, from 1–3 days before symptom onset (Wei et al., 2020). The clinical manifestations of COVID-19 varied from asymptomatic carrier status, acute respiratory disease (ARD) and pneumonia. The prevalence of asymptomatic cases is significant (20–86 % of all infections) and is defined as individuals with positive viral nucleic acid tests but without any COVID-19 symptoms. Most people with COVID-19 develop only mild (40 %) or moderate (40 %) disease, approximately 15 % develop a severe disease that requires hospitalization and oxygen support, and 5 % have a critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury (CDC, 2020b) Older age, co-morbidities such as diabetes, hypertension, cardiac disease, chronic lung disease, cancer and BMI > 40 kg/m² have been reported as risk factors for severe disease and death (CDC, 2020a).

**COMMON SIGNS AND SYMPTOMS**

Wang and colleagues (2020a) reported that there are 6 common signs and symptoms that 30 % of the patients have felt including fever (98.5 %), fatigue (69.9 %), dry cough (59.4 %), anorexia (39.8 %), myalgia (34.8 %), dyspnea (31.1 %) and for the most common comorbidities are hypertension (31.1 %) and cardiovascular disease (14.5 %). Symptoms may develop 2 days to 2 weeks following exposure to the virus (CDC, 2020b). According to Wu and McGoogan (2020), among 72,314 SARS-CoV-2 cases reported to the Chinese Center for Disease Control and Prevention (CCDC), 81 % were mild (mild or absent pneumonia), 14 % were severe (dyspnea, hypoxia, > 50 % lung involvement within 1-2 days), 5 % were critical (respiratory failure, shock, multiorgan dysfunction), and 2.3 % were fatal. Symptoms in children with infection appear to be uncommon, although some children with severe COVID-19 have been reported (CDC, 2020a). Based on currently available information and clinical expertise, risk factors for severe COVID-19 include older adults ≥ 65 years as well as people of all ages with severe chronic medical conditions.
ages with chronic lung disease or moderate to severe asthma, serious heart conditions, diabetes, severe obesity, chronic kidney disease, liver disease and immunocompromised people (CDC, 2020a).

SUGGESTED INFECTION MECHANISM

Upon infection with COVID-19, it binds to the host cell's angiotensin-converting enzyme 2 (ACE2) receptors which commonly expressed on the epithelial cells of alveoli, trachea, bronchi, and bronchial serous glands of the respiratory tract. Then the virus enters and replicates in these cells (Liu et al., 2011). The newly developed virions are then released and infect new target cells. Unfortunately, there is no specific antiviral treatment or vaccine recommended for COVID-19 that is currently available.

CURRENT EPIDEMIOLOGICAL SITUATION

According to the European Centre for Disease Prevention and Control (ECDC), since 31 December 2019 and as of 14 June 2020, 7,759,691 cases of COVID-19 have been reported including, most cases in America (n = 3788548) were reported from the United States (2,074,526), Brazil (850,514) and Peru (225,132), followed by Europe (n = 2,170,600): most cases were reported in Russia (520,129), United Kingdom (294,375) and Spain (243,605), Asia (n = 1557541): most cases were in India (320,922), Iran (184,955) and Turkey (176,677), Africa (n = 233528): most cases were in South Africa (65,736), Egypt (42,980), Nigeria (15,682), Oceania (n = 8766): most cases were in Australia (7,290), New Zealand (1,154) and Guam (185) (Figure 1), including 430,127 deaths, most deaths in America (n = 201,874) were reported from the United States (115,436), Brazil (42,720) and Mexico (16,872), followed by Europe (n = 182674): most deaths were in United Kingdom (41,662), Italy (34,301) and France (29,398), Asia (n = 39147): most deaths were in India (9,195), Iran (8,730) and Turkey (4,792), Africa (n = 6294): most deaths were in Egypt (1,484), South Africa (1,423) and Algeria (760), Oceania (n = 131): most deaths were in Australia (102), New Zealand (22) and Guam (5) (ECDC, 2020).

Figure 1: Novel coronavirus COVID-19 geographical distribution over the world 2020-05-09 (ECDC, 2020)
The countries that beat COVID-19 were divided into three groups as follows: countries beating COVID-19: green plots (Figure 2), countries that are nearly there: yellow plots (Figure 3) and countries that need to take action: red plots (Figure 4). These plots adjusted for each country to better show the data. The vertical axis is plotted in arbitrary units, to easily compare the shapes of the curves (EndCoronavirus, 2020).

SARS-COV-2 DIAGNOSIS

The diagnosis of COVID-19 mainly depends on the demonstration of the virus in respiratory secretions by special molecular tests. Common laboratory findings include normal/low white cell counts with elevated C-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease (Singhal, 2020). In addition to laboratory testing capacity and reagent shortages, the rapidly growing SARS CoV 2 pandemic has encouraged many diagnostic manufacturers to develop and sell fast and easy-to-use equipment to facilitate testing outside the laboratory (WHO, 2020a).

Figure 2: Countries beating COVID-19 in alphabetical order (EndCoronavirus, 2020)
Figure 2 (cont.): Countries beating COVID-19 in alphabetical order (EndCoronavirus, 2020)
Currently, there are two main categories commercially available for COVID-19 tests. The first category includes molecular assays for detection of SARS-CoV-2 viral RNA using polymerase chain reaction (PCR)-based methods. The second category includes serological and immunological assays that largely depend on detecting antibodies produced by individuals as a result of exposure to the virus or on the detection of antigenic proteins in infected individuals. It is necessary to ensure that these two categories of tests serve overlapping purposes in the management of the SARS-CoV-2 pandemic (Carter et al., 2020). Current COVID-19 diagnostic tools and techniques are shown in Table 1 and a diagnostic model for COVID-19 in Figure 5.
Figure 3: Countries that are nearly there (EndCoronavirus, 2020)
Figure 4: Countries that need to do an action (EndCoronavirus, 2020)
Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)
Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)
Figure 4 (cont.): Countries that need to do an action (EndCoronavirus, 2020)
Figure 4 (cont.): Countries that need to do action (EndCoronavirus, 2020)
Figure 5: The Diagnostic Model for COVID-19
| Category | Test | Principle | Sample | Advantages | Disadvantages | Reference |
|----------|------|-----------|--------|------------|---------------|-----------|
| 1- Molecular Detection of COVID-19 Nucleic Acids | a- Reverse Transcription-Polymerase Chain Reaction (RT-PCR) (gold standard test) | This assay based on the conversion of a short sequence of COVID-19 genomic RNA to complementary DNA copy (cDNA) using specific RNA-dependent DNA polymerase. This process is known as reverse transcription followed by real-time RT-PCR, amplification and detection of DNA. | Upper respiratory system samples especially nasopharyngeal swab | Sensitive, gold standard test | Time-consuming, expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment | Chan et al., 2020b |
| b- Microarray Nucleic Acid Hybridization | | The process starts with reverse transcription followed by cDNA loading into specific wells containing Covid-19 specific oligonucleotides fixed on their surfaces. After washing the viral DNA remains hybridized, emitting signals that indicate a positive result. | Upper respiratory system samples especially nasopharyngeal swab | Sensitive, requires a short time | Expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment | Chen et al., 2010 |
| 2- Serological and Immunological Assays | a- Enzyme-Linked Immunosorbent Assay (ELISA) | COVID-19 ELISA plate wells are coated with a COVID-19 antigen. This process starts with adding of patient sample to the coated well if the sample contains anti-COVID-19 antibody, so it will bind specifically, forming an antigen-antibody complex that can be detected by another labeled secondary antibody that produces a color or fluorescence. | Blood serum or plasma | Requires a short time, not very expensive | Variable sensitivity, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment | Carter et al., 2020 |
| b- Lateral Flow Immunoassay | A rapid diagnostic test, patient samples are applied to a nitrocellulose membrane that contains immobilized COVID-19 antigen and allows the flowing of the sample. If the sample contains anti-CoV-19 antibodies, it will be trapped with a specific antigen causing the color band visualization. | Blood serum or plasma | Rapid test about 10 minutes, cheap, can be used in a non-laboratory environment, very simple and easy to be used | Insensitive | Wang et al., 2005 |
**Table 1 (cont.):** Current SARS-CoV-2 diagnostic tools and techniques

| Category | Test | Principle | Sample | Advantages | Disadvantages | Reference |
|----------|------|-----------|--------|------------|---------------|-----------|
| c- Neutralization Assay | The patient sample is added to COVID-19 infected cell culture. If the patient sample contains anti-CoV-19 antibodies, it inhibits viral replication in COVID-19 infected cell cultures. | Whole blood, serum, or plasma | Sensitive | Time-consuming, expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment. | Whiteman et al., 2018 |
| d- Chemiluminescent Immunoassay | An automated serological diagnostic test, patient samples are added to specific reagents, contain antibody specific for anti-COVID-19 labeled by chemiluminescent substance followed by chemiluminescent substance excitation and after returning to its stable state, it will emit photons that can be detected by chemiluminescent signal instrument. | Blood serum or plasma | Ultra-sensitive, rapid | Expensive, requires high laboratory infrastructure, well-trained staff and cannot be used in a non-laboratory environment. | Cai et al., 2020 |
| e- Surface Plasmon Resonance (SPR) gold nanoparticle-based biosensor | Depending on using a coronaviral surface antigen decorated by gold offering a stable, specific sensitive platform for COVID-19 antibody detection | Blood serum or plasma | High sensitivity, selectivity, rapid, cheap, reliability, portability, can be used in non-laboratory environment, easily to be manufactured | This method is an indirect method, where it detects antibody, so developing of SPR biosensor to detect COVID-19 itself still is a great challenge. | Park et al., 2009 |
| f- COVID-19 Antigen Assays | Based on the detection of COVID-19 antigen using its specific antibody, depending on ELISA, lateral flow and chemiluminescent assays | Blood serum or plasma | Rapid | Variable sensitivity, variable costs | Carter et al., 2020 |
SARS-COV-2 DIFFERENT THERAPEUTIC APPROACHES

Symptomatic treatment and oxygen therapies represent the major treatment interventions for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock (Cascella et al., 2020).

To the best of our knowledge, different therapeutic approaches have been evaluated against COVID-19 in vivo, vitro and in clinical trials. Many of these therapies had a great impact on clinical recovery. Current COVID-19 therapies are shown in Table 2.

Table 2: Different SARS-CoV-2 therapeutic approaches and mechanisms

| Treatment                                | Mechanism of action                                                                 | Reference                                      |
|------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------|
| 1 Chloroquine and Chloroquine phosphate  | Well known anti-malarial agents beside their efficacious as anti-inflammatory agents with autoimmune cases including rheumatoid arthritis and Lupus erythematosus. Chloroquine and Chloroquine phosphate have slightly alkaline pH, so both can increase the endosomal pH of the host cells, and suppress virus/cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV and finally causing a significant inhibitory effect on viral infections. So, anti-viral and anti-inflammatory activities of Chloroquine and Chloroquine phosphate may account for their potent efficacy in treating patients with COVID-19 pneumonia. | Gao et al., 2020 |
| 2 Lopinavir/Ritonavir (LPV/r) Combined Therapy | Both Lopinavir and Ritonavir are protease inhibitors, this combination can block viral replication. Lopinavir is considered actually to be the agent that acts on the virus. Ritonavir is a CYP3A inhibitor that reduces Lopinavir metabolism, thereby boosting Lopinavir levels. | Lim et al., 2020; Cao et al., 2020 |
| 3 Teicoplanin                             | Teicoplanin acts on the early step of the viral life cycle by inhibiting the low pH cleavage of the viral spike protein by cathepsin L in the late endosomes thereby preventing the release of genomic viral RNA and the continuation of the virus replication cycle. | Baron et al., 2020 |
| 4 Remdesivir                              | Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in premature termination. May 1, 2020, Gilead Sciences, announced that the U.S. Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for the investigational Remdesivir as a potential antiviral for COVID-19 treatment. May 7, 2020, Gilead Sciences, announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has granted regulatory approval of Veklury® (Remdesivir) as a treatment for SARS-CoV-2 infection, the virus that causes COVID-19 acute respiratory syndrome, under an exceptional approval pathway. | Wang et al., 2020b; Devaux et al., 2020 |
| 5 Arbidol and Arbidol mesylate            | Arbidol and Arbidol mesylate were shown to have a direct antiviral effect in early viral replication in vitro for SARS-CoV. | Deng et al., 2020a |
### Table 2 (cont.): Different SARS-CoV-2 therapeutic approaches and mechanisms

| Treatment | Mechanism of action | Reference |
|-----------|---------------------|-----------|
| 6 Inhibitors of Renin-Angiotensin System (RAS) | Both SARS and SARS-CoV-2 invade the cell through the ACE2 receptor. SARS-CoV reduces ACE2 expression, causing an imbalance between the ACE/Ang II/AT1R axis and the ACE2/Ang (1–7)/Mas receptor axis. A novel therapeutic strategy for hypertension targets the ACE/Ang II/AT1R axis. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and agents acting on the renin-angiotensin system (ARAS) inhibit the ACE/Ang II/AT1R pathway in addition to modulation of the ACE2/Ang (1–7)/Mas receptor pathway. COVID-19 patients observed to have a dysfunction in the renin-angiotensin system (RAS). It was also noticed that ACEI/angiotensin-receptor blockers (ARB) had the potential to decrease the viral load, regulate immune function and inhibit inflammatory responses. | Sun et al., 2020a; Meng et al., 2020 |
| 7 Protease Inhibitors | SARS-coronaviruses enter the host cells by activation their envelope glycoproteins using the host cell proteases. SARS-coronaviruses use cell surface serine proteases for their activation. So, cysteine protease inhibitors interfere with viral cell invasion and effectively prevent viral spread. | Zhou et al., 2015 |
| 8 Mesenchymal Stem Cells (MSCs) | MSCs transplantation improved the outcome of COVID-19 patients. These findings may be due to regulating inflammatory response and promoting tissue repair and regeneration, where mesenchymal stem cells are blank cells that can differentiate into most cellular types in addition to their paracrine fashion of cytokines and growth factors that dampen inflammation and cell death. | Leng et al., 2020 |
| 9 Tocilizumab | Well-known recombinant humanized anti-human interleukin-6 receptor monoclonal antibody that is mainly used for rheumatoid arthritis patients. In COVID-19 infection, a massive number of T-lymphocytes and mononuclear macrophages are activated, emitting different cytokines such as interleukin-6 (IL-6), which binds to the IL-6 receptor on its target cells, causing the cytokine storm and severe inflammatory responses in most organs including lungs, liver, kidney and other tissues and organs. Tocilizumab can specifically bind soluble interleukin-6 receptor (sIL-6R) and membrane-bound interleukin-6 receptor (mIL-6R) and inhibits their signal transduction. | Xu et al., 2020a |
| 10 Human monoclonal antibody | Coronavirus neutralizing antibodies target the viral trimeric spike (S) glycoproteins that exist on the viral surface and mediate viral entry into the host cells. | Li et al., 2020 |
| 11 Baricitinib | Most viruses invade cells through receptor-mediated endocytosis. ACE2 is the receptor that COVID-19 uses to infect lung cells. ACE2 is a cell surface protein that distributed many cells including kidney, blood vessels, heart, and, especially, lung AT2 alveolar epithelial cells. AT2 cells are mainly prone to viral infection. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. Baricitinib with therapeutic dosage (2 mg or 4 mg once daily) is sufficient to inhibit AAK1. | Richardson et al., 2020 |
| 12 COVID-19 recovered patients’ convalescent plasma | COVID-19 recovered patients’ convalescent plasma contains a huge quantity of COVID-19 monoclonal antibodies. So, direct administration of COVID-19 recovered patients’ convalescent plasma might suppress viremia. Several studies showed a shorter hospital stay and lower mortality rate in convalescent plasma-treated patients than those who were not treated with it. | Chen et al., 2020 |
Table 2 (cont.): Different SARS-CoV-2 therapeutic approaches and mechanisms

| Treatment                                        | Mechanism of action                                                                                                                       | Reference                                      |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| 13 Indinavir/Remdesivir combined therapy          | Docking studies proved that both Indinavir/Remdesivir have low docking scores and docking sites which overlap with the protein pockets effectively. So, it is expected that this combined therapy can block the replication of COVID-19 RNA. These 2 drugs have limited cytotoxicity, so they are highly recommended for COVID-19 treatment. | Chang et al., 2020                            |
| 14 Nelfinavir                                    | Nelfinavir was recommended to be used as a potential therapy for COVID-19 through inhibition of its main protease using an integrative approach combining molecular docking, homology modeling and binding free energy calculation. | Xu et al., 2020b                              |
| 15 Regulation of interferon production           | The DNA sensor cyclic GMP–AMP synthase (cGAS), anaplastic lymphoma kinase (ALK) and stimulator of interferon genes (STING) were suggested to be potential therapeutic effective targets preventing the cytokine storm during COVID-19 infection. | Deng et al., 2020b                            |
| 16 Direct Acting Antivirals (DAAs)               | Currently, FDA approved drugs that target specific viral nonstructural proteins and lead to disruption of viral replication and infection include Sofosbuvir, Ribavirin, and Remdesivir. There are 4 classes of DAAs, which are classified by their mechanism of action and their targets. Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs) and NS5A inhibitors. These drugs were recently used for HCV treatment in Egypt (recovery rate about 99%). DAAs are suggested to be possible inhibitors for COVID-19 by binding COVID-19 RNA dependent RNA polymerase (RdRp). DAAs can be used against the novel strain of coronavirus with promising results. | Elfiky, 2020                                   |
| 17 Human umbilical cord mesenchymal stem cells (HUCMSCs) | HUCMSCs have shown significant tissue repair and immunomodulation with a low immunogenic effect that makes these cells very ideal candidates for the allogenic adoptive transfer therapy. HUCMSCs were also suggested to be a potential treatment for H5N1 infection-induced acute lung injury. COVID-19 showed a similar inflammatory cytokine profile to that of H5N1. | Liang et al., 2020                             |
| 18 CD-sACE2 Inclusion Compounds                  | The main receptors for SARS-CoV and SARS-CoV-2 are ACE2 Soluble (sACE2) retaining ACE2 enzyme activity in addition to binding SARS-CoV S-protein. So sACE2 can inhibit SARS-CoV infected cells. Since SARS-CoV and SARS-CoV-2 infection mechanisms are the same, sACE2 can inhibit the infection of SARS-CoV-2. To improve the water solubility of sACE2, the formation of a complex between CD and sACE2 would be effective and enables it to meet drug atomization inhalation requirements. | Sun et al., 2020b                              |
| 19 Favipiravir (Avigan®)                         | Favipiravir is a Pyrazine carboxamide broad-spectrum antiviral drug that has been approved in Japan for influenza treatment. It is a prodrug that is phosphorylated and ribosylated intracellularly to form its active metabolite (Favipiravir ibofuranosyl -5′-triphosphate) that acts as a competitive inhibitor for viral purine nucleosides in addition to inhibition of RNA-dependent RNA polymerase (RdRp) of RNA viruses. Finally, it interferes with viral replication. | Du and Chen, 2020                             |
| 20 Ivermectin                                    | FDA-approved for parasitic infections treatment. Caly et al. reported that Ivermectin has the potential to inhibit COVID-19 in vitro by interfering with the nuclear import of host and viral proteins, where its single treatment was able to cause ~5000-fold reduction in COVID-19 virus after 48 h in cell culture model. | Caly et al., 2020                             |
Despite the approved beneficial effects of these therapeutic approaches, recent studies concluded that most of these candidate’s administration has a toxic effect in overdoses, causing common and severe adverse effects including nausea, pruritus, arrhythmias, hypoglycemia, anemia, jaundice, hyperlipidemia, electrolyte abnormalities, acute renal injury, hematological disorders, hyperuricemia, neuropsychiatric effects and various drug-drug interactions.

Chloroquine (CQ) interferes with ventricular repolarization that increases the risk of torsades de pointes (TdP) and may cause sudden cardiac death (Ursing et al., 2020), also it causes neuropsychiatric manifestations in-
cluding confusion agitation, psychosis, mania, hallucinations, paranoia, suicidal ideation, depression, insomnia and catatonia (Aneja et al., 2019) as well as severe hypoglycemia (El-Solia et al., 2018). Moreover, CQ has severe immunological mediated adverse effects including drug reaction with eosinophilia and systemic symptoms (DRESS) (Girijala et al., 2019), Stevens-Johnson syndrome (Leckie and Rees, 2002) and toxic epidermal necrolysis (Cameron et al., 2014).

Lopinavir/Ritonavir (LPV/r) combination has been reported to have gastrointestinal disorders, so in some SARS-CoV-2 patients, the treatment was stopped due to these severe side events (Owa and Owa, 2020). Notwithstanding the minimal side effects of Teicoplanin, it may cause thrombocytopenia in some treated cases (Terol et al., 1993).

A recent clinical trial regarding Remdesivir with severe COVID-19 patients concluded that adverse events including hypokalemia, constipation, hyperaluminemia, anemia, jaundice, hyperlipidemia, liver enzyme elevation and thrombocytopenia were reported (Wang et al., 2020c).

An exploratory randomized controlled trial assessing the efficacy and safety of Arbidol in COVID-19 patients reported that patients had adverse events including diarrhea, nausea and loss of appetite (Eikenberry et al., 2020), also hypotension, acute renal injury, teratogenicity, hypersensitivity, electrolyte abnormalities, fatigue, diarrhea, weakness, anemia and chest pain are the most common risk factors during treatment of COVID-19 patients using inhibitors of the renin-angiotensin system (Ingraham et al., 2020).

Zhang and colleagues (2020) reported that intravenous transplantation of Wharton’s jelly derived mesenchymal stem cells (hWJCs) was safe and effective especially, in COVID-19 critical severe cases. Regarding Tocilizumab that was used as a treatment for severe COVID-19 cases, it may cause serious adverse reactions, like intestinal perforation, candidiasis and lipid metabolism abnormalities (Tao et al., 2020).

FDA has approved convalescent plasma therapy in COVID-19 critical patients, but up till now, only three studies with small sample size reported effectiveness and safety so more clinical trials are needed to ensure both safety and efficacy (Bloch et al., 2020).

Otherwise Direct-acting antivirals (DAAs) demonstrated, a safe therapeutic approach with common side effects including fatigue, headache, nausea and neuropsychiatric symptoms (Medeiros et al., 2017). Concerning using of Favipiravir (Avigan®) as a treatment for COVID-19 patients, it was reported that Favipiravir elevates plasma uric acid, so this finding should be considered in hyperuricemia, gout and kidney impairment patients (Mishima et al., 2020).

Despite the beneficial effect of Corticosteroids with COVID-19 patients, they are associated with a high risk of death, side effects like bacterial infections and hypokalemia so they are not recommended for mild and moderate COVID-19 patients, but they should be used in severe cases only to suppress the immune response and reduce symptoms (Yang et al., 2020).

**CHLOROQUINE TRIGGERS OXIDATION AND HEMOLYTIC ANEMIA IN G6PD DEFICIENT CASES & WORLD HEALTH ORGANIZATION DISCONTINUED ITS TREATMENT TRIALS**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common human enzymatic disorders affecting around 400 million people worldwide (Luzzatto and Arese, 2018). Decreased G6PD production results in low levels of NADPH and reduced glutathione stimulating hemolytic anemia which is characterized by oxidative stress and red blood cell lysis (Francis et al., 2013).

The risk of hemolytic anemia should be considered during Chloroquine/Hydroxy Chloroquine (CQ/HCQ) therapy of patients with G6PD deficiency (Mohammad et al., 2018).
Beauverd and colleagues (2020) reported that SARS-CoV-2 infection can enhance severe acute hemolysis in patients with G6PD deficiency, and CQ/HCQ can worsen this crisis. During the treatment of SARS-CoV-2, it is important to carefully monitor potential hemolytic effects of CQ/HCQ in G6PD deficiency cases. If a decline in hemoglobin levels during the first days of CQ/HCQ treatment is observed, the treatment should be stopped. Hemolysis usually is reversible after finishing therapy with CQ/HCQ (De Franceschi et al., 2020). Also, Kapoor and Kapoor (2020) warned of the use of CQ because of the risk of hematological disorders in patients with G6PD deficiency.

In contrast, both (Youngster et al. 2010; Beutler 1994) concluded that CQ or HCQ mono-therapies are safe also in G6PD deficient cases.

Afra and colleagues (2020) reported that infections might be the most common causes of hemolysis in G6PD deficient patients. Thus, SARS-CoV-2 patients may show significant hemolysis even before CQ or HCQ administration.

Finally, SARS-CoV-2 treatment using CQ or HCQ, especially in areas with high G6PD deficiency prevalence, should alert medical staff to this possible harmful effect. The US Food and Drug Administration warned of cardiotoxicity caused by hydroxychloroquine and mentioned G6PD as a baseline test before the onset of hydroxychloroquine treatment (FDA, 2020). Moreover, in July 2020 the WHO discontinued clinical trials with hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 (WHO, 2020b), where both therapies produced little and no reduction in the mortality of hospitalized SARS-CoV-2 cases when compared to standard of care.

CONCLUSION

Finally, COVID-19 pandemic is a highly infectious disease caused by the novel coronavirus SARS-CoV-2 that can be transmitted through droplets and close contact and represents a global public health crisis. Fever, fatigue and dry coughs are the most common signs and symptoms of COVID-19. Due to rapid transmission, countries around the world should increase attention to disease surveillance systems. SPR gold nanoparticle-based biosensors may be a promising diagnostic technique as it had high sensitivity, selectivity, reliability, portability, is rapid and cheap, but this method is an indirect method, where it detects antibody, so developing of SPR biosensor to detect COVID-19 itself still is a great challenge. No proven effective therapies or vaccines for SARS-CoV-2 currently exist. The most promising therapy up till now maybe Remdesivir, also we recommend Corticosteroids therapy for severe cases only to suppress the immune response and reduce symptoms, but not for mild and moderate patients where they are associated with high-risk side effects. G6PD should be considered as a baseline test for starting CQ or HCQ treatment protocol to avoid its possible hemolytic effect. We should further strive to develop specific medications, support the research and development of vaccines, and also decrease morbidity and death of SARS-CoV-2 to preserve the population.

Authors contribution

Ahmed Nabil: Resources, Conceptualization, Original draft writing, Supervision, Review & Editing. Koichiro Uto: Original draft writing, Review & Editing. Mohamed M. Elshemy: Original draft writing, Review, Editing & Resources. Reham Soliman: Writing, Review & Editing. Ayman A. Hassan: Writing & Editing. Mitsuhiro Ebara: Conceptualization, Resources, Original draft writing, Supervision, Review & Editing. Gamal Shiha: Conceptualization, Original draft writing, Review, Editing & Supervision.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**REFERENCES**

Afra TP, Vasudevan Nampoothiri R, Razmi TM. Doubtful precipitation of hemolysis by hydroxychloroquine in glucose-6-phosphate dehydrogenase-deficient patient with COVID-19 infection. Eur J Haematol. 2020; epub ahead of print.

Aneja J, Goya D, Choudhary B. Psychosis consequent to antimalarial drug use in a young child. Family Med Prim Care. 2019;8:1781-3.

Baron SA, Devaux C, Colson P, Raoul D, Rolain JM. Teicoplanin: an alternative drug for the treatment of COVID-19? Int J Antimicrob Agents. 2020;55(4):105944.

Beauverd Y, Adam Y, Assouline B, Samii K. COVID-19 infection and treatment with hydroxychloroquine cause severe haemolysis crisis in a patient with glucose-6-phosphate dehydrogenase deficiency. Eur J Haematol. 2020;10.1111/ejh.13432. epub ahead of print.

Beutler E. G6PD deficiency. Blood. 1994;84:3613-36.

Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020;130:2757-65.

Cai X, Chen J, Hu J, Long Q, Deng H, Fan K, et al. A peptide-based magnetic chemiluminescence enzyme immunoassay for serological diagnosis of Coronavirus disease 2019 (COVID-19). J Infect Dis. 2020;222:189-93.

Cali L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787.

Cameron MC, Word AP, Dominguez A. Hydroxychloroquine-induced fatal toxic epidermal necrolysis complicated by angioinvasive rhizopus. Dermatol Online J. 2014;20(11):25419748.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382:1787-99.

Carter LJ, Garner LV, Smoot JW, Li Y, Zhou Q, Saver- son CJ, et al. Assay techniques and test development for COVID-19 diagnosis. ACS Cent Sci. 2020;6:591-605.

Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). StatPearls [internet]: StatPearls Publishing, 2020.

CDC. People who are at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html. Accessed 25 June 2020a.

CDC. Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?CDC_AA_refVal=https%3A__www.cdc.gov__%2Fcoronavirus%2F2019-ncov%2Fsymptoms.html. Accessed 25 June 2020a.

Chen Q, Li J, Deng Z, Xiong W, Wang Q, Hu Y-Q. Comprehensive detection and identification of seven animal coronaviruses and human respiratory coronavirus 229E with a microarray hybridization assay. Intervirology. 2010;53:95-104.

clinicaltrials.gov. Protective effect of aspirin on COVID-19 patients (PEAC). 2020;NCT04365309.
De Franceschi L, Costa E, Dima F, Morandi M, Olivieri O. Acute hemolysis by hydroxychloroquine was observed in G6PD-deficient patient with severe COVID-19 related lung injury. Eur J Intern Med. 2020;77:136-7.

Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020a;81:e1-e5.

Deng X, Yu X, Pei J. Regulation of interferon production as a potential strategy for COVID-19 treatment. arXiv. 2020b;2003.00751.

Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020;55:105938.

Du Y-X, Chen X-P. Favipiravir: Pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020;online ahead of print.

ECDC, European Centre for Disease Prevention and Control. COVID-19 situation update worldwide, as of 9 May 2020. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases. Accessed 9 May 2020.

Eikenberry SE, Mancuso M, Iboi E, Phan T, Eikenberry K, Kuang Y, et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infect Dis Model. 2020;5:293-308.

El-Solia A, Al-Otaibi K, Ai-Hwiesh AK. Hydroxychloroquine-induced hypoglycaemia in non-diabetic renal patient on peritoneal dialysis. BMJ Case Rep. 2018;2018:bcr2017223639.

Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020;248:117477.

EndCoronavirus. Which countries do best in beating COVID-19? https://www.endcoronavirus.org/countries. Accessed 31 May 2020.

Fintelman-Rodrigues N, Sacramento CQ, Lima CR, da Silva FS, Ferreira AC, Mattos M, et al. Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. bioRxiv. 2020:2020.04.04.020925.

Francis RO, Jhang JS, Pham HP, Hod EA, Zimring JC, Spitalnik SL. Glucose-6-phosphate dehydrogenase deficiency in transfusion medicine: the unknown risks. Vox Sang. 2013;105:271-82.

FDA. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting. Accessed 1 July 2020.

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72-3.

Girijala RL, Siddiqi I, Kwak Y, Wright D, Patel DB, Goldberg LH. Pustular DRESS syndrome secondary to hydroxychloroquine with EBV reactivation. J Drugs Dermatol. 2019;18:207-9.

Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. Rev Med Virol. 2006;16:37-48.

Hadadi A, Mortezaazadeh M, Kolahdouzan K, Alavian G. Does recombinant human erythropoietin administration in critically ill COVID-19 patients have miraculous therapeutic effects? J Med Virol. 2020;92:915-8.

Ingraham NE, Barakat AG, Reilkoff R, Bezdicek T, Schacker T, Chipman JG, et al. Understanding the renin-angiotensin-aldosterone-SARS-CoV-axis: A comprehensive review. Eur Respir J. 2020;2020;2000912.

Kapoor KM, Kapoor A. Role of chloroquine and hydroxychloroquine in the treatment of COVID-19 infection- A systematic literature review. medRxiv. 2020:2020.03.24.20042366.

Leckie MJ, Rees RG. Stevens–Johnson syndrome in association with hydroxychloroquine treatment for rheumatoid arthritis. Rheumatology. 2002;41:473-4.

Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis. 2020;11:216-28.

Li M, Jin R, Peng Y, Wang C, Ren W, Lv F, et al. Generation of antibodies against COVID-19 virus for development of diagnostic tools. medRxiv. 2020;2020.02.20.20025999.

Liang B, Chen J, Li T, Wu H, Yang W, Li Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. chinaXiv. 2020;2:v1.
treatment of favism in G6PDH deficiency. N Engl J Med. 2018;378: 60-71.

Luzzatto L, Arese P. Favism and glucose-6-phosphate dehydrogenase deficiency. N Engl J Med. 2018;378:60-71.

Medeiros T, Salviato CdM, do Rosário NF, Sараіva GdN, Esberard EBC, Almeida JR, et al. Adverse effects of direct acting antiviral-based regimens in chronic hepatitis C patients: A Brazilian experience. Int J Clin Pharm. 2017;39:1304-11.

Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect. 2020;9:757-60.

Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by Favipiravir, an antiviral drug. Tohoku J Exp Med. 2020;251:87-90.

Mohammad S, Clowse MEB, Eudy AM, Criscione-Schreiber LG. Examination of hydroxychloroquine use and hemolytic anemia in G6PDH-deficient patients. Arthritis Care Res (Hoboken). 2018;70:481-5.

Owa AB, Owa OT. Lopinavir/ritonavir use in Covid-19 infection: Is it completely non-beneficial? J Microbiol Immunol Infect. 2020;epub ahead of print.

Park TJ, Hyun MS, Lee HJ, Lee SY, Ko S. A self-assembled fusion protein-based surface plasmon resonance biosensor for rapid diagnosis of severe acute respiratory syndrome. Talanta. 2009;79:295-301.

Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30-e1.

Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qinhai M, Yongxia S, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol Res. 2020;156:104761.

Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473-5.

Sanders JM, Monogue ML, Jodlowski TZ, Caturelli JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A Review. JAMA. 2020;epub ahead of print.

Sheahan TP, Sims AC, Zhou S, Graham RL, Paujissers AJ, Agostini ML, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020;12(541):eabb5883.

Singhal T. A review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87:281-6.

Sun ML, Yang JM, Sun YP, Su GH. [Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia]. Zhonghua jie he he hu xi zazhi = Chin J Tuberculosis Respir Dis. 2020a;43:219-22.

Sun P, Lu X, Xu C, Wang Y, Sun W, Xu J. CD-sACE2 inclusion compounds: An effective treatment for coronavirus disease 2019 (COVID-19). J Med Virol. 2020b;epub ahead of print.

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094-9.

Tao Y, Tang LV, Hu Y. Treatments in the COVID-19 pandemic: an update on clinical trials. Exp Opin Emerg Drugs. 2020;25(2):81-8.

Terol MJ, Sierra J, Gatell JM, Rozman C. Thrombocytopenia due to use of teicoplanin. Clin Infect Dis. 1993;17:927.

Ursing J, Rombo L, Eksborg S, Larson L, Bruvoll A, Tarning J, et al. High-dose chloroquine for uncomplicated Plasmodium falciparum malaria is well tolerated and causes similar QT interval prolongation as standard-dose chloroquine in children. Antimicrob Agents Chemother. 2020;64:e01846-19.

Wang B, Potter SJ, Lim Y, Cunningham AL, Dwyer DE, Su Y, et al. Rapid and sensitive detection of severe acute respiratory syndrome coronavirus by rolling circle amplification. J Clin Microbiol. 2005;43:2339-44.

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAM. 2020a;323:1061-9.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020b;30:269-71.
Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78.

Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJJM, et al. Presymptomatic transmission of SARS-CoV-2—Singapore, January 23–March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:411-5.

Whiteman MC, Bogardus L, Giacone DG, Rubinstein LJ, Antonello JM, Sun D, et al. Virus reduction neutralization test: A single-cell imaging high-throughput virus neutralization assay for dengue. Am J Trop Med Hyg. 2018;99:1430-9.

Whitworth J. COVID-19: a fast evolving pandemic. Trans R Soc Trop Med Hyg. 2020;114:241-8.

WHO, World Health Organization. Advice on the use of point-of-care immunodiagnostic tests for COVID-19: Scientific brief. https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19. Accessed 8 April 2020a.

WHO, World Health Organization. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19. Accessed 4 July 2020b.

Wu Z, McGooagan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239-42.

Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020a;117:10970-5.

Xu Z, Peng C, Shi Y, Zhu Z, Mu K, Wang X, et al. Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. bioRxiv. 2020b:2020.01.27.921627.

Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020;81(1):e13-e20.

Youngster I, Arcavi L, Schechmaster R, Akayzen Y, Popliski H, Shimonov J, et al. Medications and glucose-6-phosphate dehydrogenase deficiency. Drug Saf. 2010;33:713-26.

Zhang Y, Ding J, Ren S, Wang W, Yang Y, Li S, et al. Intravenous infusion of human umbilical cord Wharton’s jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. Stem Cell Res Ther. 2020;11(1):207.

Zhao Y, Vedantham P, Lu K, Agudelo J, Carrion R Jr, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. Antivir Res. 2015;116:76-84.