Review the Use of Antivirus for COVID-19 Treatment

Lukman Prayitno¹, Julien Rosye Mawuntu², Herna³ and Tri Juni Angkasawati¹

Abstract
On 31 January 2020, World announced COVID-19 as an Emergency Public Health of International Concern. The number of patients in Indonesia continues to grow. Anti-viral in the COVID-19 Drug Information Laboratory in Indonesia are Lopinavir/Ritonavir, Favipiravir, Remdesivir, Oseltamivir, Chloroquine Phosphate and Hydroxychloroquine Phosphate. Therefore, it is necessary to know the basis and management of its use. An online systematic search was performed on articles published until 30 March 2020. We use search keywords that are tailored to the purpose of writing. All six antivirals were used for the treatment of RNA virus. Chloroquine, Hydroxychloroquine and Remdesivir effectively control the SARS-CoV2 virus invitro. Lopinavir/Ritonavir, Hydroxychloroquine and Oseltamivir have been used clinically for the treatment of SARS-CoV2 virus. In 2020, there are 42 clinical trials of six antivirals. Guidance of the antivirus are from China, Belgium and Indonesia. Its differences are based on the patient’s condition. There is a lack of evidence of six antiviral effectiveness against the SARS-CoV2 virus. It has been used for other RNA viruses. It is supported by a safety profile. In a pandemic situation and the absence of a specific antivirus, the use of the six antiviruses can be done and be useful.

Keywords
Antivirus, COVID-19, infection treatment, SARS-CoV2

Introduction
In December 2019, cases of pneumonia were discovered in Wuhan, China caused by a novel betacoronavirus. The overall case fatality rate is around 2.3%. This fatality increased to 8.0% in patients

¹ Centre for Research and Development in Humanities and Health Management, Ministry of Health, Jakarta, Indonesia.
² Amurang Regional General Hospital, Kotamobagu, Indonesia.
³ Centre for Research and Development in Biomedical and Basic Health Technology, Ministry of Health, Jakarta, Indonesia.

Corresponding Author:
Lukman Prayitno, Centre for Research and Development in Humanities and Health Management, Ministry of Health, Jakarta, Indonesia.
E-mail: yohaneslukman@gmail.com
aged 70–79 years and to 14.8% in those aged >80 years (Wu & McGoogan, 2020). The average time from
the first symptom appearing to becoming acute respiratory distress syndrome (ARDS) was 8 days (Wang
et al., 2020a). This transition occurs in many severe cases of COVID-19. This state is due to the
occurrence of cytokine release syndrome, or ‘cytokine storm’, overproduction of immune cells and
cytokines that lead to failure of multi-organ systems (lungs, kidneys and heart) which is fast (Shimabukuro-
Vornhagen et al., 2018). As of 31 January 2020, the World Health Organization (WHO) announced that
COVID-19 is registered as an Emergency Public Health Emergency of International Concern (PHEIC),
which means that it can pose risks to many countries and requires coordinated international responses.
As of 31 January 2020, the WHO announced that COVID-19 is registered as an Emergency PHEIC,
which means that it can pose risks to many countries and requires coordinated international responses.

The number of COVID-19 patients in Indonesia has also grown. Therefore, immediate efforts are
needed to provide effective treatment and to reduce the risk of transmission. Indonesian Drug and Food
Control Agency (BPOM) has issued Drug Information Laboratory for COVID-19. There are six antivirals
listed, namely Lopinavir/Ritonavir, Favipiravir (FPV), Remdesivir, Oseltamivir, Chloroquine
Phosphate and Hydroxychloroquine Phosphate. Because of the pandemic, it needs to study the articles
that aimed at finding out the results of the six antivirus tests on virus infections other than SARS-CoV2
virus, knowing the results of the six antivirus tests due to SARS-CoV2 virus, knowing the six clinical
trial plan of antivirus due to SARS-CoV2 in 2020 and knowing the guidance for using antivirus to treat
SARS-CoV2 virus.

Methods

Online systematic searches were carried out in studies published until 30 March 2020. According to
indexes from various databases, we used search terms with keywords: antiviral for SARS CoV2, antiviral
for COVID-19, COVID-19 treatment, clinical for COVID-19 patients and its co-morbid. Antiviruses
here include Chloroquine, Hydroxychloroquine, Lopinavir-Ritonavir, FPV, Remdesivir and Oseltamivir.
We have checked the reference list for each selected article using the snowball method applied to the
reference articles taken. This aims to broaden the references obtained. We also searched the Clinical Trial
Registry for the Antivirus. It means to identify ongoing trials. We do not register as a systematic review
protocol because of the limited available evidence and the urgency of this problem.

Result

Based on Table 1, the six antiviruses have mode of action and mechanism against viruses. Chloroquine
and Hydroxychloroquine have the same mode of action and effective virus mechanism because
hydroxychloroquine is a derivative of chloroquine. Hydroxychloroquine is synthesised by inserting
hydroxyl groups into chloroquine. Other antiviruses have different mechanisms. Dengue virus, SARS-
CoV1, HIV, MERS, Ebola and Influenza A (H1N1) viruses are kind of RNA viruses. The SARS-CoV2
virus is also an RNA virus. Therefore, these antiviruses are also expected to be used for the SARS-
CoV2 virus.
| Status                          | Drugs                  | Types                        | Anti-infective Mechanism                                                                 | Target Diseases                | Ref.                                                                 |
|--------------------------------|------------------------|------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|----------------------------------------------------------------------|
| Approved, investigational, vet approved | Chloroquine            | 9-Aminoquinolin              | Increasing endosomal pH, immunomodulating, autophagy inhibitors                         | Malaria, autoimmune disease, SARS, MERS | Wang et al., 2020b; Savarino et al., 2006; Vincent et al., 2005; Golden et al., 2015; Keyaerts et al., 2004; de Wilde et al., 2014; Barnard et al., 2006 |
| Approved, investigational, vet approved | Hydroxychloroquine     | 9-aminoquinolin              | Increasing endosomal pH, immunomodulating, autophagy inhibitors                         | Malaria, autoimmune disease, SARS | Biot et al., 2006; Ruiz-Irastorza et al., 2010; Lotteau et al., 1990; Kuznik et al., 2011 |
| Approved                        | Lopinavir/Ritonavir     | Protease inhibitors          | Inhibiting HIV-1 protease for protein cleavage, resulting in non-infectious, immature viral particles | HIV/AIDS, SARS, MERS          | Cvetkovic & Goa, 2003; Arabi et al., 2020; Chu et al., 2004          |
| Experimental                    | Remdesivir (GS-5734)    | Nucleotide analogue prodrug  | Interfering with virus post-entry                                                       | Ebola, SARS, MERS(A wide array of RNA viruses) | Wang et al., 2020b; Zumla et al., 2016; Colson et al., 2020         |
| Approved                        | Oseltamivir             | Neuraminidase inhibitor      | Inhibiting the activity of the viral neuraminidase enzyme, preventing budding from the host cell, viral replication, and infectivity | Influenza viruses A(H1N1) | Lo et al., 2019; Agostini et al., 2018; Tchesnokov et al., 2019; McQuade & Blair, 2015 |
| Investigational                 | Favipiravir (T-705)     | Nucleoside analogue: Viral RNA polymerase inhibitor | Acting on viral genetic copying to prevent its reproduction, without affecting host cellular RNA or DNA synthesis | Ebola, influenza A(H1N1) | Furuta et al., 2013; Goldhill et al., 2018; Cardile et al., 2017 |

**Source:** The authors. The information in the table cite from Tchesnokov et al. (2019)

**Note:** AIDS, Acquired immune deficiency syndrome; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MERS, Middle-East respiratory syndrome; SARS, severe acute respiratory syndrome; VZV, Varicella-zoster virus.
Based on Table 2, there are currently three invitro tests—Chloroquine, Hydroxychloroquine and Remdesivir. The results can be effective for controlling SARS-CoV2 virus. Based on Table 1, three antiviruses have been used for patient with SARS-CoV2 virus infection. These are Lopinavir/Ritonavir, Hydroxychloroquine and Oseltamivir. The use of Lopinavir/Ritonavir for severe patients was no different compared to standard care patients. Another study said the use of Lopinavir/Ritonavir combined with Arbidol and traditional Chinese medicine (Shufeng Jiedu Capsule) had a significant effect on patients with pneumonia. Studies show that the use of Hydroxychloroquine also had a significant influence to the improvement in patients. The addition of Azithromycin had a positive influence to the improvement in patients. The combination of Oseltamivir with antibacterial affects the transmission in hospitals. It is suspected to occur in 41% of patients, 26% of patients receiving ICU care, with 4.3% mortality.

| Study Design | N/Description | Results |
|--------------|---------------|---------|
| A randomised, controlled, open-label trial involving hospitalised adult patients with confirmed SARS-CoV-2 infection and severe condition (Cao et al., 2020). | A total of 199 patients; 99 were assigned to the Lopinavir-Ritonavir group, and 100 to the standard-care group. | In hospitalised adult patients with severe COVID-19, no benefit was observed with Lopinavir–Ritonavir treatment beyond standard care. |
| A non-randomised open label trial. Hospitalised patients with confirmed COVID-19 and fulfil the criteria (Gautret et al., 2020). | A total of 42 patients; 20 were received Hydroxychloroquine, 6 to the Hydroxychloroquine + Azithromycin and 16 to the control patients. | Hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin. |
| Retrospective study, single-centre case series (Wang et al., 2020a). | Four patients were recruited from 21 January 2020 to 24 January 24 2020. | After treatment (Lopinavir/Ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine), three patients gained significant improvement in pneumonia associated symptoms. The remaining patient with severe pneumonia had shown signs of improvement by the cut-off date for data collection. |
| Retrospective, single-centre case series (Wang et al., 2020a). | 138 consecutive hospitalised patients with confirmed novel coronavirus (2019-nCoV)-infected pneumonia (NCIP) | After treatment Oseltamivir to 89.9% patients and antibacterial therapy, this trial presumed hospital-related transmission of 2019-nCoV was suspected in 41% of patients, 26% of patients received ICU care, and mortality was 4.3%. |
| Evaluated cytotoxicity of HCQ and CQ in African green monkey kidney.Vero E6 cells evaluated the antiviral effect of HCQ and CQ against SARS-CoV-2 infection Invitro (Liu et al., 2020). | The dose–response of HCQ and CQ against SARS-CoV-2 were determined at four different multiplicities of infection (MOIs). All MOIs are 0.01, 0.02, 0.2, and 0.8. | The data suggest that the anti-SARS-CoV-2 activity of HCQ seems to be less potent compared to CQ, at least at certain multiplicities of infection (MOIs). |
Assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoVs (Wang et al., 2020b). The dose–response of compounds against SARS-CoV-2 were determined MOIs. MOIs is 0.05. Remdesivir and Chloroquine are highly effective in the control of 2019-nCoV infection in vitro.

The infected Vero cells were treated with medium containing either Chloroquine or Hydroxychloroquine at 0.032, 0.16, 0.80, 4, 20, 100 μM for 24 or 48 hours. Hydroxychloroquine exhibited better in vitro anti-SARS-CoV-2 activity than Chloroquine. The EC50 values for Hydroxychloroquine is always smaller than Chloroquine. It indicated that Hydroxychloroquine has a more potent antiviral activity.

Based on Table 3, five clinical trials of Remdesivir are present against SARS-CoV2. Ten clinical trials of Lopinavir/Ritonavir present against SARS-CoV2 virus. Four FPV clinical trials against SARS-CoV2 virus. Two clinical trials of Oseltamivir against SARS-CoV2 virus. Sixteen Chloroquine clinical trials against SARS-CoV2 virus. It has various purposes, for example, length of stay in hospital and so on.

**Table 3.** Ongoing Antivirus Test to SARS CoV2 Virus (WHO’s list of studies for the treatment of COVID-19, 2020).

| No | Antivirus                                      | Study Identifier                                                                 |
|----|-----------------------------------------------|----------------------------------------------------------------------------------|
| 1  | Remdesivir                                    | NCT04252664; NCT04257656; NCT04280705; NCT04292730; NCT04292899                 |
| 2  | Lopinavir + Ritonavir (Kaletra)               | NCT04255017; ChiMCTR2000002940; NCT04252885; NCT04276688; NCT04261907 (ChiCTR2000029603); NCT04291729 (ChiCTR2000030472); ChiCTR2000029387; ChiCTR2000029539; ChiCTR2000030187; NCT04307693 |
| 3  | Favipiravir                                    | ChiCTR2000029548; ChiCTR2000029544; ChiCTR2000029600; ChiCTR2000030113           |
| 4  | Oseltamivir                                    | NCT04261270                                                                     |
| 5  | Oseltamivir, Lopinavir, Ritonavir, Favipiravir, Darunavir, Chloroquine | NCT04303299                                                                     |
| 6  | Chloroquine                                    | NCT04261517; ChiCTR2000029542; ChiCTR2000029559; ChiCTR2000029609; ChiCTR2000029741; ChiCTR2000029740; ChiCTR2000029826; ChiCTR2000029868; ChiCTR2000029837; ChiCTR2000029939; ChiCTR2000029935; ChiCTR2000029988; ChiCTR2000029975; ChiCTR2000030031; ChiCTR2000029803; ChiCTR2000030417 |
| 7  | Hydroxychloroquine                             | ChiCTR2000029899; ChiCTR2000029898; ChiCTR2000029992; ChiCTR2000030054; 2020-000890-25. |

Source: The authors.
| Disease Category | Tingbo, et al. (2020) | Van Ierssel, et al. (2020) | Burhan, et al. (2020) |
|------------------|------------------------|-----------------------------|----------------------|
| Mild Risk Group  | 200 mg po tid Arbidol (Umifenovir) tablets | 400 mg at suspicion/diagnosis; | Chloroquine phosphate 500 mg po bid (for 5 days) OR |
|                  | 2 tablets po q12h Lopinavir/Ritonavir | 400 mg 12 h later | Hydroxychloroquine (200 mg available) 400 mg/24 hours po (for 5 days) if needed Antivirus can be given: |
|                  | Interferon spray 1 spray pr. tid | Followed by 200 mg BID up to day 5 NB: stop Hydroxychloroquine if follow-up at home if no Hydroxychloroquine available, consider Chloroquine base 600 mg (10 mg/kg) at diagnosis and 300 mg (5 mg/kg) 12 hours later, followed by 300 mg (5 mg/kg) BID up to day 5 or Chloroquine Phosphate 1,000 mg at diagnosis and 500 mg 12 h later, followed by 300 mg BID up to day | Oseltamivir 75 mg po bid or |
|                  | | | Favipiravir (Avigan) 600 mg po bid (for 5 days) |
| Moderate Risk Group | | | Chloroquine phosphate 500 mg po bid (for 5–7 days) OR |
|                   | | | Hydroxychloroquine (200 mg available) first day 400 mg po bid, then 400 mg po qd (for 5–7 days) |
|                   | | | Antivirus: Oseltamivir 75 mg po bid OR |
|                   | | | Favipiravir (Avigan dosage 200 mg) loading dose 1600 mg po bid day 1 and then 600 mg po bid (days 2–5) |
| Severe Disease | 200 mg tid Arbidol tablets | Start Hydroxychloroquine (Plaquinil®) IF NO CONTRA-INDICATION | Chloroquine phosphate, 500 mg po bid (days 1–3) followed by 250 mg po bid (days 4–10) OR |
|                  | 2 tablets po q12h Lopinavir/Ritonavir | 400 mg at diagnosis; | Hydroxychloroquine dose of 400 mg po qd (for 5 days), (every 3 days ECG control) |
|                  | Interferon spray 1 spray pr.nar tid | 400 mg 12 hours later | Antivirus: Oseltamivir 75 mg po bid Or |
|                  | Immunoglobulin 20 g ivgtt qd | Followed by 200 mg BID up to day 5 NB: If no Hydroxychloroquine available, consider Chloroquine base 600 mg (10 mg/kg) at diagnosis and 300 mg (5 mg/kg) 12 hours later, followed by 300 mg (5 mg/kg) BID up to Day 5 OR Chloroquine Phosphate 1,000 mg at diagnosis and 500 mg 12 h later, followed by 300 mg BID up to day 5 Consider Lopinavir/Ritonavir 400/100 mg (= 2 tablets of 200/50 mg) BID for 14 days) as second choice ONLY if Hydroxychloroquine/Chloroquine contra-indicated and provided it can be administered within 10 days after symptoms onset (check also drug interaction!); or in children <10 kg (after IDS advice) | Favipiravir (Avigan dosage 200 mg) loading dose 1,600 mg po bid day 1 and then 600 mg po bid (days 2–5) |

(Table 4 Continued)
(Table 4 Continued)

| Disease Category | Tingbo, et al. (2020) | Van Ierssel, et al. (2020) | Burhan, et al. (2020) |
|------------------|-----------------------|----------------------------|----------------------|
| Critical Disease | • Arbidol tablets 200 mg po. tid  
• Lopinavir/Ritonavir 2 tablets q12h (or darunavir 1 tablet qd)  
• Immunoglobulin 20 g ivgtt qd  
• Thymic peptides 1.6 mg ih biw | Remdesivir (compassionate use)  
• 200 mg loading dose (IV, within 30 min)  
• 100 mg OD for 2 to 10 days If remdesivir unavailable: Consider (hydroxy)chloroquine, crushed in nasogastric tube, at the same dosage and monitoring as above; replace with remdesivir if it becomes available  
However, since the clinical efficacy of (hydroxy)chloroquine is not demonstrated, caution is required in case of kidney/liver/cardiac failure, and abstention in such situations is preferred | In severe and critical conditions the patient can experience cardiac arrest so that basic life support is needed. |

Source: The authors and Burhan et al. (2020).

Note: 1 Risk group: age >65 years AND/OR underlying end organ dysfunction (lung, heart, liver, etc.), diabetes, coronapathy, chronic obstructive pulmonary disease and arterial hypertension

2 Clinical classification
   a. Mild/uncomplicated
      Uncomplicated patients with viral respiratory infections have non-specific symptoms such as fever, weakness, cough (with or without sputum production), anorexia, malaise, muscle aches, sore throat, mild tightness, nasal congestion and headaches. Although rare, patients can complain of diarrhoea, nausea or vomiting. Elderly and immunocompromised patients with atypical symptoms.

   b. Moderate
      Adolescent or adult patients with pneumonia but no sign of severe pneumonia and no need for oxygen supplementation. or children with non-severe pneumonia with coughing or breathing difficulties accompanied by rapid breathing.

   c. Severe/Severe pneumonia
      Adolescent or adult patients with fever or under inspection of airway infection/pneumonia, plus one of: breath frequency >30×/min, severe respiratory distress, or oxygen saturation (SpO2) <93% in room air or PaO2/FIO2 ratio <300. Or paediatric patients with coughing or breathing difficulties, plus at least one of the following:
      • Central cyanosis or SpO2 <90%;
      • Severe respiratory distress (such as snoring, heavy chest wall pull);
      • Signs of severe pneumonia: inability to breastfeed or drink, lethargy or loss of consciousness or seizures.
      • Other signs of pneumonia are: chest wall traction, tachypnoea: <2 months, ≥60×/minute; 2–11 months, ≥50×/minutes; 1–5 years, ≥40×/minutes; >5 years, ≥30×/minutes.

   d. Critical
      Patients with respiratory failure, ARDS, septic shock and/or multiple organ failure.
Table 4 contains three existing antiviral management for COVID-19. The first treatment is based on clinical experience of the first hospital affiliated with the medical school of Zhejiang University in China. They use Arbidol (Umifenovir) tablets, Lopinavir/Ritonavir tablets, interferon spray, immunoglobulin IV and thymic peptides inhalation. The second management treatment is an interim guideline in Belgium. They use Hydroxychloroquine tablet, Chloroquine tablet, Lopinavir/Ritonavir tablet and Remdesivir tablet. The third management treatment is based on compilation protocol that was made by representatives of the five Indonesian Doctors Associations. They use Chloroquine Phosphate tablet, Hydroxychloroquine tablet, Oseltamivir tablet and FPV tablet. There are differences in the use of antivirus. Differences in the clinical severity of patients cause differences in the use of antivirals and additional necessary support medications. The use of antivirus is also influenced by adverse effects and availability in hospitals.

There are differences in the use of antivirus. Differences in the clinical severity of patients cause differences in the use of antivirals and additional necessary support medications. The use of antivirus is also influenced by adverse effects and availability in hospitals.

Discussion

Coronavirus is a RNA blanket virus from the genus Betacoronavirus. It can be found in birds, humans and other mammals. Six coronavirus species cause infections in humans, four of which (229E, OC43, NL63 and HKU1) cause flu symptoms. However, some authors claim that SARS-CoV2 is associated with SARS-CoV and MERS-CoV, which have zoonotic origins associated with significantly severe disease and higher mortality (Zhu et al., 2020).

Wang and Cheng’s (2020) report results research that SARS-CoV and MERS-CoV use ACE2 cell surface receptors in lung, heart, kidney and intestinal tissue. This process can accelerate the virus replication and spread. This binding triggers conformational changes in glycoprotein S that allows division by the transmembrane protease serine protease type-II (TMPRSS2) of the S protein and the release of S fragments into the cellular supernatant which inhibits the virus neutralisation by antibodies (Glowacka et al., 2011).

Coronavirus therapy can be divided into several specific pathways: some work on important enzymes or functional proteins viruses, prevent the synthesis and replication of viral RNA; some act on the structural protein of the virus, blocking the virus from binding to human cell receptors, or inhibiting the virus’s own assembly process; several virulence-producing factors to restore the innate host immunity; some act on host-specific receptors or enzymes, preventing the virus from entering the host cell (Wu et al., 2020).

Based on previous experiences in combating the SARS-CoV and MERS-CoV epidemics, we can learn several lessons for treatment strategies for coronavirus (Zumla et al., 2016). An efficient approach to drug discovery is testing whether existing antiviral drugs are effective in treating related viral infections (Wang et al., 2020b).

Chloroquine

An expert consensus was published on 20 February. It was based on in vitro evidence and clinical experience that has not yet been published. Chloroquine phosphate tablets at a dose of 500 mg twice daily for 10 days can be used for mild, moderate and severe pneumonia SARS-CoV2 without
contraindications to the drug (Multicentre collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for Chloroquine in the treatment of novel coronavirus pneumonia, 2020). According to the US CDC and US FDA, the optimal dose and duration of therapy are unknown (Coronavirus Disease—2019, 2020; US FDA, 2020). In the use of Chloroquine for malaria therapy, there is a small risk of macular retinopathy, which depends on cumulative dose (Bernstein, 1991), and the presence of several reports of cardiomyopathy as a severe side effect (ITS, 2020). Other side effects of Chloroquine Phosphate are dizziness, headaches, nausea, vomiting, diarrhoea and various types of skin rashes. The most severe adverse reaction is a heart attack. An electrocardiogram needs to be checked before taking medication. Medication must be prohibited for arrhythmia patients (e.g., conduction blocks), retinal disease, or hearing loss (ITS, 2020).

**Hydroxychloroquine**

Based on the Physiologically Based Pharmacokinetic Models (PBPK), a loading dose of 400 mg twice daily Hydroxychloroquine Sulphate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV2 infection. It reaches three times potency of Chloroquine Phosphate 500 mg twice for 5 days (Yao et al., 2020). According to US CDC and US FDA, the optimal dose and duration of therapy are unknown (Coronavirus Disease-2019, 2020). Hydroxychloroquine is an analogue of chloroquine which has less concern about drug interactions (Biot et al., 2006). Hydroxychloroquine side effects are GI intolerance, cytopenia, QT prolongation, headache, dizziness (Multicentre collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia, 2020). Hydroxychloroquine is preferred over Chloroquine due to its lower ocular toxicity (Lim et al., 2009).

**Lopinavir/Ritonavir**

The use of Lopinavir (400 mg)/Ritonavir (100 mg) is two tabs orally q12h. Based on reports, it can be used up to 14 days. Most patients showed side effect symptoms that require early withdrawal (Tian et al., 2020; Young et al., 2020). Lopinavir/Ritonavir is metabolised through the CYP3A enzyme in the liver. It needs to monitor potential drug interactions. This has been proven by 51.9% incidence of abnormal liver function which has received combination of Arbidol and Lopinavir/Ritonavir. Therefore, unnecessary drug combinations must be reduced. Side effects of Lopinavir/Ritonavir and Darunavir/Cobicistat are diarrhoea, nausea, vomiting, increased serum aminotransferase, jaundice, dyslipidaemia and increased lactic acid. These symptoms will recover after stopping the drug. This medicine may be used for pregnant women (ITS, 2020).

**Oseltamivir**

Chen et al. (2020b) reported that the dosage of Oseltamivir in the case series of 99 patients was 75 mg orally every 12 hours. Oseltamivir is contraindicated for children and adolescents, 10–19 years, in principle since March 2007, due to concerns that it may cause abnormal behaviours (Maxwell, 2007). Nausea and vomiting were demonstrated as adverse reactions to Oseltamivir in treatment trials
involving both adults and children and are the established adverse reactions to Oseltamivir. Dose-dependent increase of headache was demonstrated only in prophylaxis trials because common symptoms of influenza including headache were not considered adverse event in the treatment trials (Jefferson et al., 2014).

**Remdesivir**

Until now, the optimum dose and duration of remdesivir therapy are unknown. Based on phase 3 clinical trial protocols in severe COVID-19 patients, remdesivir is used: 200 mg IV on day 1, then 100 mg IV daily on days 2–5 (arm 1) or 200 mg IV on day 1, then 100 mg IV daily on days 2–10 (arm 2) (Clinical Trials, 2020); 200 mg IV on day 1, then 100 mg IV daily on days 2–10 (Clinical Trials, 2020). Based on the compassionate use access protocol, remdesivir was used: 200 mg IV on day 1, then 100 mg IV on days 2–10 (Grein et al., 2020). Transaminase increases are presently the only adverse effect that appears clearly linked to remdesivir’s use. They need special attention to elevations of transaminases, hypersensitivity reactions, renal events, pregnancy and unexpected adverse reactions in the periodic safety reports and the expedited summary safety reports (European Medicines, 2020). Another article states that no adverse events were observed (Holshue et al., 2020).

**Favipiravir**

Chen et al. (2020a) state that a FPV dosage of 1,600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 days was used in one open-label COVID-19 study. Another guideline states that FPV’s starting dose was of 1,600 mg followed by 600 mg three times a day (tid) (ITS, 2020). In a study conducted by Cai et al. (2020), the total number of adverse reactions in the FPV study group was four (11.43%), which was significantly less than 25 adverse reactions (55.56%) in the control group (P <.001). Two patients had diarrhoea, one had a liver injury, and one had a poor diet in the FPV group. Meanwhile, there were five patients with diarrhoea, five with vomiting, six with nausea, four with rashes, three with liver injuries and two with chest tightness and palpitations in the control group. FPV is prohibited for use in pregnant women (ITS, 2020).

The success of COVID-19 therapy is also influenced by the patient’s condition and disease severity. Older patients and those who have comorbidities, such as cardiovascular disease and diabetes mellitus, have an increased risk of severe illness and death. They may present with mild symptoms but have a high risk of damage and must be admitted to an appropriate unit for close monitoring (WHO, 2020). A median number of days from the first symptom to death is shorter among people aged 65 years or older (Wang et al., 2020c; Yang et al., 2020). Similar to H7N9 (Gao et al., 2013), elderly male patients with comorbidities and ARDS show a higher risk of death.

The success of therapy is also influenced by complications experienced by patients. Wang et al. (2020a) report that among 138 hospitalised patients with COVID-19, 7.2% had an acute heart injury and 16.7% had arrhythmias. In a smaller group of 41 patients, 12.1% had an acute heart injury (Huang et al., 2020). In a cohort study of more than 416 patients, cardiac injuries occurred in 19.7% of patients during treatment in hospital (Grein et al., 2020). In another cohort of 191 patients with COVID-19, 17.2% of patients had a heart injury (Zhou et al., 2020). A meta-analysis of six studies published from China, including 1,527 patients with COVID-19, reported that 8% of patients had a heart injury (Li et al., 2020).

COVID-19 is a viral infection, therefore antibiotics are not recommended to prevent bacterial infections in mild or ordinary patients; it must be used with caution in severe patients based on their
condition. Some COVID-19 patients have risk of secondary fungal infections because of weakened cellular immunity due to viral infections, use of glucocorticoids and/or broad-spectrum antibiotics. It is necessary to carry out microbiological detection of respiratory secretions such as smear and cultivation for critically ill patients; and provide D-Glucose (G-test) and galactomannan (GM-test) blood or bronchoalveolar lavage fluid for suspected patients (ITS, 2020).

**Conclusion**

Six antivirals have been used in the treatment of infections caused by RNA viruses. They are also potent for the treatment of COVID-19 disease caused by the SARS-CoV2 virus which is also an RNA virus. They also have safety profile. Because of pandemic situation and no specific antivirus found, the six antiviruses can be of use. There are differences in the use of antivirals cause by patient severity. The difference in severity also causes additional necessary support medications. The use of antivirus is influenced by its availability in hospitals and its presence or absence of adverse effects.

**Suggestion**

The use of six antiviruses must be supported by comprehensive observation of the effectiveness of therapy, side effects, drug interactions and others. Therefore, it needs collaboration between doctor, pharmacist and nurse to obtain the optimum effect.

**Acknowledgement**

We thank Mr Hendrianto Trisnowibowo, Ms Yuslely Usman, Ms Yuyun Yuniar and Mr Herianto Lahing who have been a discussion partner.

**Authors’ Contribution**

Lukman Prayitno is the main contributor in making this article. Other authors help to prepare data. They are member contributors.

**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Funding**

The authors received no financial support for the research, authorship and/or publication of this article.

**References**

Agostini, M. L., Andres, E. L., Sims, A. C., Graham, R. L., Sheahan, T. P., Lu, X., Smith, E. C., Case, J. B., Feng, J. Y., Jordan, R., Ray, A. S., Cihlar, T., Siegel, D., Mackman, R. L., Clarke, M. O., Baric, R. S., Mark, R., & Denison, M. R. (2018). Coronavirus susceptibility to the antiviral remdesivir (gs-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio, 9(2), e00221–00318. https://doi.org/10.1128/mBio.00221-18
Arabi, Y. M., Asiri, A. Y., Assiri, A. M., Jokhdar, H. A. A, Alothman, A., Balkhy, H. H., AlJohani, S., Harbi, S. A., Kojan, S., Jeraisy, M. A., Deeb, A. M., Memish, Z. A., Ghazal, S., Faraj, S. A., Hameed, F. A, Saedi, A. A., Mandourah, Y., Mekhlafi, G. A. A., Sherbeeni, N. M., … (2020). Treatment of Middle East respiratory syndrome with a combination of Lopinavir/Ritonavir and interferon-β1b (MIRACLE trial): Statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. Trials, 21(1), 8. https://doi.org/10.1186/s13063-019-3846-x

Barnard, D. L., Day, C. W., Bailey, K., Heiner, M., Montgomery, R., Lauridsen, L., Chan, P. K. S., & Sidwell, R. W. (2006). Evaluation of immunomodulators, interferons and known in vitro SARS-CoV inhibitors for inhibition of SARS-Cov replication in BALB/c Mice. Antiviral Chemistry and Chemotherapy, 17(5), 275–284. https://doi.org/10.1177/095632020601700505

Bernstein, H. N. (1991). Ocular safety of hydroxychloroquine. Annals of Ophthalmology, 23(8), 292–296.

Biot, C., Daher, W., Chavain, N., Fandeur, T., Khalife, J., Dive, D., & Erik De Clercq, E. D. (2006). Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. Journal of Medicinal Chemistry, 49(9), 2845–2849. https://doi.org/10.1021/jm0601856

Burhan, E., Susanto, A. D., Nasution, S. A., Ginanjar, E., Pitoyo, C. W., Susilo, A., Firdaus, I., Santoso, A., Juzar, D. A., Arif, S. K., Wulung, N. G. H. L., Damayanti, T., Wiyono, W. H., Prasenohadi, Afiatin, Wahyudi, E. R., Tarigan, T. J. E., Hidayat, R., Muchtar, F., & Tim COVID-19 IDAI. (2020). Protokol Tatalaksana COVID-19, Jakarta; 1st ed. Cite at April 20, 2020. http://www.inaheart.org/perki/upload/files/Protokol%20Tatalaksana%20COVID-19%205OP%20FINAL(4).pdf

Cai, Q., Yang, M., Liu, M., Chen, J., Shu, D., Xia, J., Liao, X., Gu, Y., Cai, Q., Yang, Y., Shen, C., Li, X., Peng, L., Huang, D., Zhang, J., Zhang, S., Wang, F., Liu, J., Chen, L., … (2020). Experimental treatment with Favipiravir for COVID-19: An open-label control study. Engineering. https://doi.org/10.1007/j.engleng.2020.03.007

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., … (2020). A trial of Lopinavir-Ritonavir in adults hospitalized with severe covid-19. NEJM, 382, 1–13. https://doi.org/10.1056/NEJMoa2001282

Cardile, A. P., Warren, T. K., Martins, K. A., Reisler, R. B., & Bavari, S. (2017). Will there be a cure for Ebola? Annual Review of Pharmacology and Toxicology, 57, 329–348. https://doi.org/10.1146/annurev-pharm-tox-010716-105055

Chen, C., Zhang, Y., Huang, J., Yin, P., Cheng, Z., Wu, J., Chen, S., Zhang, Y., Chen, B., Li, M., Luo, Y., Ju, L., Zhang, J., & Wang, X. (2020a). Favipiravir versus arbidol for COVID-19: A randomized clinical trial. medRxiv. https://doi.org/10.1101/2020.03.17.20037432

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020b). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet, 395, 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chu, C. M., Cheng, V. C., Hung, I. F., Wong, M. M., Chan, K. H., Chan, K. S., Kao, R. Y. T., Poon, L. L. M., Wong, C. L. P., Guan, Y., Peiris, J. S. M., Yuen, K. Y., & HKU/UCH SARS Study Group. (2004). Role of Lopinavir/Ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax, 59(3), 252–256. https://doi.org/10.1136/thorax.2003.012658

Clinical Trials. (2020). Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with severe coronavirus disease (COVID-19). https://www.clinicaltrials.gov/ct2/show/NCT04292899

Colson, P., Rolain, J. M., Lagier, J. C., Brouqui, P., & Raoult, D. (2020). Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. International of Journal Antimicrobial Agents, 55(4), 105932. https://doi.org/10.1016/j.ijantimicag.2020.105932

Coronavirus Disease-2019 (COVID-19). (2020). Information for clinicians on therapeutic options for COVID-19 patients. US CDC and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html

Cvetkovic, R. S., & Goa, K. L. (2003). Lopinavir/Ritonavir: A review of its use in the management of HIV infection. Drugs, 63(8), 769–802. https://doi.org/10.2165/00003495-200363080-00004
de Wilde, A. H., Jochmans, D., Posthuma, C. C., Zevenhoven-Dobbe, J. C., Nieuwkoop, S. V., Bestebroer, T. M., van den Hoogen, B. G., Neyts, J., & Snijder, E. J. (2014). Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrobial Agents and Chemotherapy, 58(8), 4875–4884. https://doi.org/10.1128/AAC.03011-14

European Medicines. (2020). Summary on compassionate use. Remdesivir Gilead. Procedure No. EMEA/H/K/5622/CU. European Medicines Agency, EMA/178637/2020, Human Medicines Division. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf

Furuta, Y., Gowen, B. B., Takahashi, K., Shiraki, K., Smeke, D. F., & Barnard, D. L. (2013). Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivirus Research, 100(2), 446–454. https://doi.org/10.1016/j.antiviral.2013.09.015

Gao, H. N., Lu, H. Z., Cao, B., Du, B., Shang, H., Gan, J. H., Lu, S. H., Yang, Y. D., Fang, Q., Shen, Y. Z., Xi, X. M., Gu, Q., Zhou, X. M., Qu, H. P., Yan, Z., Li, F. M., Zhao, W., Gao, Z. C., Wang, G. F., … (2013). Clinical findings in 111 cases of influenza a (H7N9) virus infection. The New England Journal of Medicine, 368(24), 2277–2285. https://doi.org/10.1056/NEJMoal1305584

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honoré, S., Colson, P., Chabrière, E., Scola, B. L., Rolain, J. M., Brouqui, P., & Raoul, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open label non-randomized clinical trial. International Journal of Antimicrobial Agents, 56(1), 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949

Glowacka, I., Bertram, S., Müller, M. A., Allen, P., Soilleux, E., Pfefferle, S., Steffen, I., Tsegaye, T. S., He, Y., Gniirss, K., Niemeyer, D., Schneider, H., Drosten, C., & Pöhlmann, S. (2011). Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. Journal of Virology, 85(9), 4122–4134. https://doi.org/10.1128/JVI.02232-10

Golden, E. B., Cho, H. Y., Hofman, F. M., Louie, S. G., Schonthal, A. H., & Chen, T. C. (2015). Quinoline-based antimalarial drugs: A novel class of autophagy inhibitors. Neurosurgical Focus, 38(3), E12. https://doi.org/10.3171/2014.12.FOCUS14748

Goldhill, D. H., te Velthuis, A. J. W., Fletcher, R. A., Langat, P., Zambon, M., Lackenby, A., & Barclay, W. S. (2018). The mechanism of resistance to Favipiravir in influenza. Proceedings of the National Academy of Sciences of the United States of America, 115(45), 11613–11618. https://doi.org/10.1073/pnas.1811345115

Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F. X., Nicastri, E., Oda, R., Yo, K., Roldan, E. Q., Studemeister, A., Redinski, J., Ahmed, S., Bernet, J., Chelliah, D., … (2020). Compassionate use of remdesivir for patients with severe Covid-19. The New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2007016

Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., Spitters, C., Ericson, K., Wilkerson, S., Tural, A., Diaz, G., Cohn, A., Fox, L. A., Patel, A., Gerber, S. I., Kim, L., Tong, S., Lu, X., Lindstrom, S., … (2020). First case of 2019 novel coronavirus in the United States. The New England Journal of Medicine, 382, 929–936. https://doi.org/10.1056/NEJMoa2001191

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, Li., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Jefferison, T., Jones, M. A., Doshi, P., Del Mar, C. B., Hama, R., Thompson, M. J., Spencer, E. A., Onakpoya, I., Mahtani, K. R., Nunan, D., Howick, J., & Heneghan, C. J. (2014). Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database of Systematic Reviews, 2014(4), CD008965. https://doi.org/10.1002/14651858.CD008965.pub4

Keyaerts, E., Vijgen, L., Maes, P., Neyts, J., & Van Ranst, M. (2004). In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochemical and Biophysical Research and Communications, 323(1), 264–268. https://doi.org/10.1016/j.bbrc.2004.08.085
Kuznik, A., Bencina, M., Svajger, U., Jeras, M., Rozman, B., & Jerala, R. (2011). Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. The Journal of Immunology, 186(8), 4794–4804. https://doi.org/10.4049/jimmunol.1000702

Li, B., Yang, J., Zhao, F., Zhi, L., Wang, X., Liu, L., Bi, Z., & Zhao, Y. (2020). Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical Research Cardiology, 109(5), 531–538. https://doi.org/10.1007/s00392-020-01626-9

Lim, H. S., Im, J. S., Cho, J. Y., Bae, K. S., Klein, T. A., Yeom, J. S., Kim, T. S., Choi, J. S., Jang, I. J., & Park, J. W. (2009). Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by Plasmodium vivax. Antimicrobial Agents and Chemotherapy, 53(4), 1468–1475. https://doi.org/10.1128/AAC.00339-08

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery, 6(16), 1–4. https://doi.org/10.1038/s41421-020-0156-0

Lo, M. K., Feldmann, F., Gary, J. M., Jordan, R., Bannister, R., Cronin, J., Patel, N. R., Klena, J. D., Nichol, S. T., Cihlar, T., Zaki, S. R., Feldmann, H., Spiropoulou, C. F., & de Wit, E. (2019). Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Science Translational Medicine, 11(494), eaau9242. https://doi.org/10.1126/scitranslmed.aau9242

Lotteau, V., Teyton, L., Peleriaux, A., Nilsson, T., Karlsson, L., Schmid, S. L., Quaranta, V., & Peterson, P. A. (1990). Intracellular transport of class II MHC molecules directed by invariant chain. Nature, 348, 600–605. https://doi.org/10.1038/348600a0

Maxwell, S. R. (2007). Tamiflu and neuropsychiatric disturbance in adolescents. BMJ, 334(7606), 1232–1233. https://doi.org/10.1136/bmj.39240.497025.80

McQuade, B., & Blair, M. (2015). Influenza treatment with Oseltamivir outside of labeled recommendations. American Journal of Health System Pharmacy, 72(2), 112–116. https://doi.org/10.2146/ajhp140390

Multicentre collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. (2020). Expert consensus on Chloroquine Phosphate for the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi, 43(3), 185–188. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.009

Ruiz-Irastorza, G., Ramos-Casals, M., Brito-Zeron, P., & Khamashta, M. A. (2010). Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: A systematic review. Annals of Rheumatic Diseases, 69(1), 20–28. https://doi.org/10.1136/ard.2008.101766

Savarino, A., Di Trani, L., Donatelli, I., Cauda, R., & Cassone, A. (2006). New insights into the antiviral effects of chloroquine. Lancet Infectious Diseases, 6(2), 67–69. https://doi.org/10.1016/S1473-3099(06)70361-9

Shimabukuro-Vornhagen, A., Godel, P., Subklewe, M., Stemmler, H. J., Schlößer, H. A., Schlaak, M., Kochanek, M., Böll, B., & von Bergwelt-Baildon, M. S. (2018). Cytokine release syndrome. Journal of Immunotherapy of Cancer, 6(1), 56–69. https://doi.org/10.1186/s40425-018-0343-9

Tchesnokov, E. P., Feng, J. Y., Porter, D. P., & Gotte, M. (2019). Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. Viruses, 11(4), E326. https://doi.org/10.3390/v11040326

Tian, Y. T., Dan, Q. J., Yan, Z. W., Wang, Y., & Qiang, W. G. (2020). A systematic review of Lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. Journal of Medical Virology. https://doi.org/10.1002/jmv.25729

US FDA. (2020). Fact sheet for health care providers emergency use authorization (EUA) of Chloroquine Phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. https://www.fda.gov/media/136535/download

Van Ierssel, S., Dauby, N., & Bottieau, E. (2020). Interim clinical guidelines for patients suspected of/confirmed with COVID-19 infection. Belgium : 2020. Cite at March 19, 2020. http://www.biotech.ca/wp-content/uploads/2020/03/COVID-19_InterimGuidelines_Treatment_ENG.pdf.
Vincent, M. J., Bergeron, E., Benjannet, S., Erickson, B. R., Rollin, P. E., Ksiazek, T. G., Seidah, N. G., & Nichol, S. T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology Journal, 2, 69. https://doi.org/10.1186/1743-422X-2-69

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020a). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, 323(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020b). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research, 30, 269–271. https://doi.org/10.1038/s41422-020-0282-0

Wang, P. H., & Cheng, Y. (2020). Increasing host cellular receptor—angiotensin-converting enzyme 2 (ACE2) expression by coronavirus may facilitate 2019-nCoV infection. bioRxiv. https://doi.org/10.1101/2020.02.24.963348

Wang, W., Tang, J., & Wei, F. (2020c). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal of Medical Virology, 92(4), 441–447. https://doi.org/10.1002/jmv.25689

WHO. (2020). Clinical Management of Severe Acute Respiratory Infection (SARI) when COVID-19 disease is suspected, Version 1.2, WHO, 2020, Ref No: WHO/2019-nCoV/clinical/2020 . https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

WHO’s list of studies for the treatment of COVID-19. (2020). Overview of planned or ongoing studies of drugs for the treatment of COVID-19, Version of 17.03.2020. https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19//-/media/5B83D25935DF43A38FF823E24604AC36.ashx

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., & Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B. https://doi.org/10.1016/j.apsb.2020.02.008

Wu, Z., & McGoogan, J. M. (2020). 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, 323(13), 1239–1242. https://doi.org/10.1001/jama.2020.2648

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. The Lancet Respiratory Medicine, 8, 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., & Liu, D. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Infectious Diseases. https://doi.org/10.1093/cid/ciaa237

Young, B. E., Ong, S. W. X., Kalimuddin, S., Low, J. G., Tan, S. Y., Loh, J., Oon-Tek Ng, Marimuthu, K., Ang, L. W., Mak, T. M., Lau, S. K., Anderson, D. E., Chan, K. S., Tan, T. Y., Ng, T. Y., Cui, L., Said, Z., Kurupatham, L., I-Cheng Chen, M., … (2020). Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA, 323(15), 1488–1494. https://doi.org/10.1001/jama.2020.3204

Zhou, F., Yu, T., Du, R., Fan, G., Li, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet, 395(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., Tan, W., & The China Novel Coronavirus Investigating and Research Team. (2020). A novel coronavirus from patients with pneumonia in China, 2019. The New England Journal of Medicine, 382, 727–733. https://doi.org/10.1056/NEJMoa2001017

Zumla, A., Chan, J. F., Azhar, E. I., Hui, D. S., & Yuen, K. Y. (2016). Coronaviruses - drug discovery and therapeutic options. Nature Reviews Drug Discovery, 15(5), 327–347. https://doi.org/10.1038/ndd.2015.37