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Emergency COVID-19: A Surprising Pandemic

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Abstract*. Coronaviruses are ARN viruses with high variability, widespread in nature in many animal species and in humans, which can cause diseases with varying degrees of severity, from mild forms to severe forms, with high mortality. The COVID-19 emergency evolves into a pandemic, being the main public health concern worldwide. The main manifestations are respiratory, pneumonic, but extrarespiratory symptoms may be present. Hygiene measures are the only ways to prevent now, because there is no a vaccine or antiviral treatment approved for use in patients with COVID-19. Several therapeutic strategies are under study for the new SARS-CoV-2.*

Keywords*: Coronavirus, SARS-CoV-2, antiviral*

1.Introduction

Coronaviruses were discovered early 1930s, when it has been shown that avian infectious bronchitis of chickens was caused by a virus now known as avian infectious bronchitis virus. The first human coronaviruses were discovered in the 1960s by researchers in the UK, being attributed to the etiology of common colds, along with rhinoviruses [1].

Coronaviruses are widespread throughout the world, being found in numerous animal species, such as birds, rabbits, reptiles, dogs, cats, pigs, mammals, bats.

These viruses can cause respiratory, digestive, liver and neurological diseases, with varying severity, sometimes with human mortality [2- 4].

Nowadays, over 2500 coronaviruses are known, belonging to the Coronaviridae family, which comprises two subfamilies, 5 genres, 27 subgenres and 39 species [5].

Severe acute respiratory syndrome associated with coronavirus was first identified in humans in 2003, transmitted from animals in open markets in China [6].

Subsequently, the improvement of genetic sequencing technologies allowed the discovery of thousands of viral variants in wild animals from the whole world, most of them not met in humans. They are classified into four subgroups: alpha, beta, gamma and delta. Viruses such as betacoronavirus, which are also part of viruses with human pathogenicity, have genetic similarities.

Seven human pathogenic coronaviruses are known: *229E, NL63, OC43, HKU1, MERS-CoV, SARS-CoV and SARS-CoV-2* [7].

Epidemiology COVID-19

Currently, the entire world is experiencing a pandemic associated with coronavirus infections.

The new coronavirus, re-called *SARS-CoV-2,* which causes infection called COVID-19 was first identified in month December 2019 in Wuhan province in China, it is associated with exposure to markets which were sold seafood.

Initially, it was thought that the snakes sold in these markets are *SARS-CoV-2* sources.
Surprisingly, the genetic analysis of the new virus revealed 85% similarity to a bat-derived coronavirus, suggesting that transmission to humans was carried out by an intermediate host, which

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could be the anteater (pangolin), a mammal species that it feeds on insects and which is protected by law [5].

SARS-CoV-2 transmission can be performed directly, from one person to another, through pflugge drops from respiratory secretions of symptomatic cases with rhinorrhea or cough, but also through contaminated surfaces.

Rarely, transmission can also be done by asymptomatic persons, in whom the infection is in the incubation state.

Given that COVID-19 is a new disease, epidemiological studies on the transmission of the virus are ongoing.

The transmissibility rate of COVID-19 is much higher compared to previous epidemics: over 100,000 *SARS-CoV-2 cases* up to March 9, 2020, compared to 8098 cases for *SARS-CoV* in 2003 and 2498 cases of *MERS-CoV* in 2012.

However, the apparent fatality rate is much lower, 3.5% for *SARS-CoV-2*, compared to 9.6% for *SARS-CoV* and 34.4% for *MERS-CoV* [8].

The average incubation duration of COVID-19 is 5 days, similar to SARS [9].

Clinical aspects of COVID-19

Coronaviruses are spherical particles, with ARV core, consisting of at least four structural proteins: surface protein S (spike), shell protein (E), membrane protein (M) and nucleocapside (N). Protein formations (S), called peplomeres, project to the outside, appearing on the electron microscope with the appearance of a solar crown , which explains the name of coronaviruses.

The role of these proteins is to initiate binding of the virus to the host cell and to fusion with the cell membrane [14].

Binding of surface glycoproteins of the virus to host cell receptors is accomplished through a region called "receptor binding domain" (RBD), which has at least two functional variants [15,16]. These functional variants may be compatible with an unknown receptor of human cells with which they interact, contributing to cell entry and overcoming species barriers [17].

After attachment and recognition of the receptors, cleavage of the viral glycoprotein takes place, releasing the fusion peptide, which allows intracellular virus entry. The host receptors for coronaviruses are the angiotensin converting enzyme 2 (ACE2) and dipeptidyl peptidase-4 [18, 19]. Although the structure of S proteins has over 75% homology between *SARS-CoV* and *SARS-CoV-2*, *the* affinity for ACE2 receptors is much higher in the case of the new coronavirus [20].

ACE-2 receptors are expressed in the lung, but also in the esophagus, the epithelial cells and the enterocytes of the ileum and colon, explaining the association of digestive manifestations [21].

The decryption of the viral replication cycle allows the identification of potential therapeutic targets in order to achieve effective drugs.

To the present date, no treatment for *SARS-CoV-2* is available, but huge efforts are being made to find molecules to combat or prevent these infections.

Therapeutic strategies for COVID-19

The researches for the development of therapies for COVID-19 are concentrated in several strategies.

The first potential therapeutic direction is aimed at stimulating the host's immune response by using interferons.

The second direction addresses the virus, blocking receptor binding and viral replication. Blocking of the entry stage of the virus into the cell can be done by blocking the vaccine protein subunit for the viral spike, inhibiting the transmembrane protease, blocking the ACE-2 receptors or administering soluble ACE-2 receptors.

The antiviral medication itself is based on testing broad-spectrum antivirals (ribavirin, interferons, cyclophilina), testing existing molecules to track effects on *SARS- CoV- 19* (Lopinavir/ritonavir) or

discovering new proteins [20].

Anti-HIV drugs have been tried, especially in the class of protease inhibitors, especially Lopinavir/ritonavir in combination with ribavirin, but the results are not conclusive.

Several clinical trials are testing remdesivir, initially developed for the treatment of hemorrhagic fevers caused by Ebola and Marburg viruses, but which seems to have the greatest therapeutic potential (Figure 1). The study protocols that used it in combination with interferon B or chloroquine have led to encouraging clinical results [22].

Remdesivir is an adenosine analog prodrug that requires a phosphorylation activation step to inhibit RNA synthetase, replacing it as a false brick during RNA chain replication. However, opinions still lack Remdesivir safety and efficiency necessary uses area in medical practice.

Chloroquine is used for the treatment of malaria and autoimmune diseases, but it has recently been shown to have the potential of broad-spectrum antiviral drug (Figure 2). The mechanism of action is blocking the entry of the virus into the gas cell and also gives the immunomodulator [23].

The chloroquine alternative is hydroxychloroquine, which has demonstrated in vitro anti-viral efficacy on *SARS-CoV-2* (Figure 3). The pharmacological profile, with increased intracellular accumulation and half-life, as well as lower drug interactions than in the case of chloroquine, are arguments in favor of this option, which is still limited in clinical studies [24-27].

The World Health Organization estimates that in the next 18 months would be possible to see a vaccine available anti- *SARS-CoV-2* if it can provide financial support for this project [8].

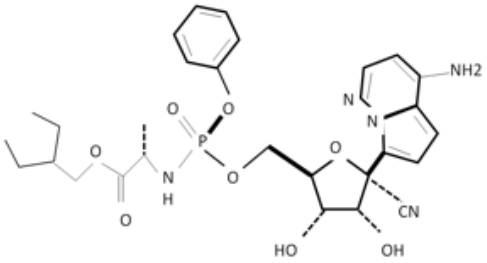

Figure 1. Chemical structure of Remdesivir: 2-ethylbutyl (2 *S*) -2 - [[[(2*R* , 3*S* , 4*R* , 5*R*) -5- (4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino] propanoate [28]

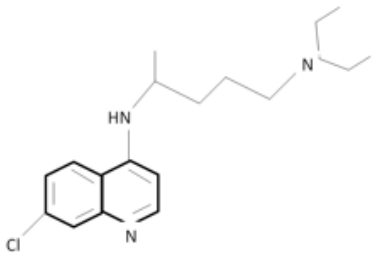

Figure 2. Chemical structure of Chloroquine: N4-(7-chloro-4-quinolinyl)-N1,N1 -diethyl-1,4-pentanediamines [29]

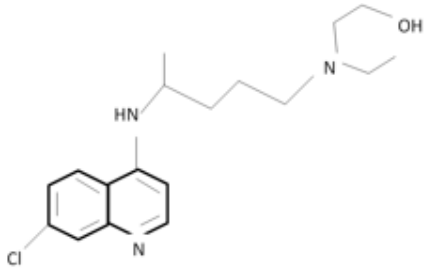

Figure 3. Chemical structure of Hydroxychloroquine: 2-[4 - [(7-chloroquinolin-4-yl) amino] pentyl-ethylamino] ethanol [30]

4. Conclusions

The infection with *SARS-CoV-2* is an emerging zoonosis, with a pandemic evolution, constituting a global challenge, involving the efforts of researchers, doctors, politicians, social and economic workers, but also of the general population.

The pathogenic and clinico-epidemiological aspects of *SARS-CoV-2* are insufficiently known.

There is no a vaccine approved for clinical use or treatment for *SARS-CoV-2,* but there are many trials in progress that justify the hopes of finding an effective drug.

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