Symptoms and Treatments of COVID-19

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the Coronavirus disease 2019 (COVID-19), is a member of the Coronaviridae family, with a 29 kb single-stranded RNA genome. It employs its structural spike (S) glycoprotein to attach to the ACE-2 (angiotensin-converting enzyme 2) receptor protein on the surface of the host cell. The S protein is composed of two subunits, S1 and S2. The S1 subunit is responsible for interaction with ACE-2, while the S2 subunit is involved in fusion with the cell. The very high affinity of protein S for ACE-2 is largely responsible for the increased infectivity of SARS-CoV-2 compared to other related viruses, such as SARS-CoV. This entry offers a general overview of the symptoms and treatments of COVID-19.

COVID-19 SARS-CoV-2 incubation period headache rhinosinusitis monoclonal antibodies antivirals viral vector

1. Symptoms of COVID-19

The incubation period of SARS-CoV-2 varies depending on the strain. Following 142 studies where 8112 patients were included, the mean incubation period for all strains was ~7 days—going as low as 3.4 for the Omicron variant. In people over 65 years old, the mean incubation period was ~7 days, as opposed to ~9 for children; severe illnesses led to a reduction of ~0.7 days in these values [1].

COVID-19 symptoms can vary from very severe to asymptomatic (none at all). Statistically, in 80% of people, the virus causes mild symptoms, but this largely depends on the type of SARS-CoV-2 strain, as well as on age; specifically, symptoms have been estimated to be observable in only 50% of the cases in children. Mild symptoms include fever, headache, sore throat, cough, diarrhea, vomiting, loss of taste and smell, and muscle pain. More severe symptoms are seen in some patients—dyspnea, shortness of breath, or abnormal chest imaging. In some patients, the lower respiratory tract is affected moderately, with oxygen saturation (SpO2) ≥94%. Patients with SpO2 < 94 and respiratory rates > 30 breaths/min or lung infiltrates > 50% represent the 4th category. Critical illness is the most serious category and entails septic shock, respiratory failure, and/or multiple organ dysfunction [2][3][4].

SARS-CoV-2 is mainly transmitted via respiratory droplets. It can also be transmitted through contaminated surfaces when a person touches the eyes, the nose, or the mouth with contaminated hands [5]. Asymptomatic and presymptomatic people are infectious. One to three days before the appearance of symptoms, people infected with

SARS-CoV-2 can transmit the virus; they are responsible for the transmission of the virus in a proportion of 40–50% [3].

More severe symptoms appear especially in the case of older patients or those with other medical conditions such as the following: diabetes, cancer, obesity, HIV infection, chronic kidney disease, pulmonary hypertension, cerebrovascular disease, chronic liver diseases (alcoholic liver disease, cirrhosis, autoimmune hepatitis, and non-alcoholic fatty liver disease), chronic lung diseases (chronic obstructive pulmonary disease, bronchiectasis, pulmonary embolism, and interstitial lung disease), disabilities (ADHD, Down syndrome, spinal cord injuries, cerebral palsy, and congenital disabilities), cystic fibrosis, heart conditions (heart failure, coronary artery disease, cardiomyopathies, etc.), transplants, mental health disorders (mood disorders, schizophrenia spectrum disorders, and depression), primary immunodeficiency diseases, pregnancy, tuberculosis, smoking, receiving corticosteroids or other immunosuppressive medication [2].

A study was carried out in which post-COVID-19 symptoms were listed at 1–180 and 90–180 days after the acute phase of the disease: anxiety/depression (22.82% proportion of symptoms—1–180 days after the acute phase, and 15.49%–90–180 days after the acute phase); abdominal symptoms (15.58% proportion of symptoms—1–180 days after the acute phase, and 8.29%—90–180 days after the acute phase); abnormal breathing (18.71% proportion of symptoms—1–180 days after the acute phase, and 7.94%—90–180 days after the acute phase); fatigue/malaise (12.82% proportion of symptoms—1–180 days after the acute phase, and 5.87%—90–180 days after the acute phase); chest/throat pain (12.60% proportion of symptoms—1–180 days after the acute phase, and 5.71%—90–180 days after the acute phase); headache (8.67% proportion of symptoms—1–180 days after the acute phase, and 4.63%—90–180 days after the acute phase); cognitive symptoms (7.88% proportion of symptoms—1–180 days after the acute phase, and 3.95%—90–180 days after the acute phase); myalgia (3.24% proportion of symptoms—1–180 days after the acute phase, and 1.54%—90–180 days after the acute phase) [5].

Regarding the neurological symptoms, there are three possible hypotheses: the direct involvement of the nervous system, a secondary mechanism to systemic diseases and lung damage, or the appearance of symptoms as a result of immune-mediated post-inflammatory complications [5].

One of the most common symptoms of SARS-CoV-2 infection is headache. Regarding the pathogenesis of this symptom in the case of COVID-19, quite a few things are known. According to ICDH-3 (third edition of the International Classification of Headache), an explanation that could be a first hypothesis is that the headache is attributed to a systemic viral infection with symptoms like fever, cough, malaise, diarrhea, dyspnea, and taste and smell impairment. The second hypothesis would be that this headache could be attributed to viral encephalitis or meningitis. However, it remains uncertain whether the headache from COVID-19 is related to direct viral damage to the peripheral or central nervous systems. Also, the number of patients with encephalitis, meningitis, or encephalopathy infected with SARS-CoV-2 kept increasing [6].

There is also a link between headache and rhinosinusitis in the case of COVID-19. In approximately half of the patients infected with SARS-CoV-2, rhinosinusitis appears as a symptom. Thus, in most cases, the headaches in

these patients are closely related to acute rhinosinusitis (ARS). In some situations, the headache occurs without acute ARS; thus, rhinosinusitis can be encountered in the case of SARS-CoV-2 infection, but it does not appear in a certain way [6].

Globally, as of 12:15 pm CEST, 21 June 2023, there have been 768,187,096 confirmed cases of COVID-19 (211,331 new cases in the last 7 days) and 6,945,714 cumulative deaths reported to WHO. Until 21 June 2023, reported to the WHO were 276,545,765 confirmed cases in Europe, 204,478,043 confirmed cases in the Western Pacific, 193,056,651 confirmed cases in the Americas, 61,185,070 confirmed cases in South East Asia, 23,382,124 confirmed cases in the eastern Mediterranean, and 9,538,679 confirmed cases in Africa. As of 19 June 2023, a total of 13,461,344,203 vaccine doses had been administered． With the appearance of variants such as Omicron, the cases of COVID-19 increased exponentially, resulting in thousands of deaths [7].

2. Treatments for COVID-19

Treatments for COVID-19 include antivirals (e.g., molnupiravir, remdesivir, Paxlovid), anti-inflammatory drugs (e.g., dexamethasone), immune modulators (e.g., tocilizumab, baricitinib), and anti-SARS-CoV-2 monoclonal antibodies (e.g., casirivimab/imdevimab, bamlanivimab/etesevimab) [8][9].

Regarding antiviral treatments, Remdesivir is the one recognized by the FDA for the treatment of patients infected with SARS-CoV-2. Other antivirals, such as lopinavir and ritonavir (used to treat HIV infection), have been used as therapeutic agents against COVID-19. However, according to some reports, no significant improvements have been observed in patients infected with this virus. Chloroquine is another drug whose sulfate and phosphate salts (used in malaria) have been touted against SARS-CoV-2, but eventually not found to be effective. Molnupiravir is another antiviral drug that was recently approved by the FDA against infection with the SARS-CoV-2 virus [10].

Two monoclonal antibodies, Tocilizumab and Sarilumab (used in rheumatoid arthritis), were recommended for patients in the ICU by the NHS [11].

Casirivimab, together with Imdevimab, form another monoclonal antibody complex called REGEN-COVT, which has been reported to reduce hospitalization and death in COVID-19. This treatment is approved by the FDA for patients with mild and moderate symptoms, as well as for patients (both children and adults) with severe symptoms [12].

The most successful approach against COVID-19 has been vaccination, which has been available to the public since late 2020 with BNT162, developed by Pfizer and BioNTech and first rolled out in the UK. Various other variants are approved, as illustrated below [13].

The mRNA (messenger RNA)-based vaccines are composed of chains of messenger ribonucleic acid (mRNA) encapsulated in lipid nanoparticles. The first mRNA vaccines to receive emergency use authorization were

BioNTech/Pfizer and Moderna. The effectiveness of those developed by Moderna and BioNTech/Pfizer is almost 95%. They encode the viral glycoprotein S (spike) of the SARS-CoV-2 virus [13].

Viral vector-based vaccines use viruses to carry genes that encode vaccine antigens into host cells. The vector is a virus other than the one targeted by the vaccine (e.g., an adenovirus). The genes of a pathogen are first put into the genome of a viral vector [14].

Vaccines with viral vectors can be classified into two types: replicable and non-replicable. Vaccines based on viral vectors that can replicate infected cells not only lead to the production of antigens but also to the reproduction of the viral vector (and hence, subsequently, the amplification of the immune response). Several COVID-19 vaccines are based on this technology: Oxford-AstraZeneca, Johnson & Johnson, and Sputnik [14]. The Johnson & Johnson vaccine (JNJ-78436725) uses a human adenovirus, Ad26, as a viral vector encoding a variant of the SARS-CoV-2 protein S [15].

Sinovac or CoronoVac (produced in China and Brazil) is a classical vaccine in the sense that it uses the inactivated virus as an antigen. Its efficacy against mild or moderate forms of COVID-19 has been reported to be distinctly lower than that of the mRNA or of the viral vector vaccines [15].

A fourth approach has been taken by the NVX-CoV2373 vaccine (made in the USA), using only protein subunits of the virus—but still with lower efficacy than the mRNA and viral vector versions [16].

According to the COVID-19 Treatment Guide Panel, regarding the treatment of COVID-19 until June 2023, here are the following conclusions:

- Remdesivir is the only antiviral drug approved by the FDA for patients infected with SARS-CoV-2 who are older than 28 days and weighing more than 3 kg. No clinical drug–drug interaction studies of RDV have been performed. In the case of patients infected with SARS-CoV-2 with an eGFR < 30 mL/min, the FDA does not recommend the use of RDV.

- Ritonavir-Boosted Nirmatrelvir (Paxlovid) was authorized under an FDA EUA in COVID-19 for mild-to-moderate symptoms in high-risk patients over 12 years of age who weighed over 40 kg. Regarding drug–drug interactions in the case of nirmatrelvir stimulated with RTV, they are very important. It is recommended to carefully check the drugs that are still being administered to the patient, including herbal supplements, OTC drugs, or even recreational drugs.

- Molnupiravir has been authorized under the FDA EUA for COVID-19 in patients with mild to moderate symptoms in high-risk patients over 18 years. In the case of MOV, no clinical studies have been conducted for the drug–drug interaction.

- High-Titer COVID-19 Convalescent Plasma was authorized under the FDA EUA in COVID-19 in the case of immunocompromised patients or for patients under immunosuppressive treatment. It is not recommended to

add it to the intravenous infusion. It is also recommended to decrease the CCP volume or the transfusion rate in patients with heart failure or cardiac dysfunction.

- IFN Beta was not approved by the FDA as it is still in clinical trials.
- PEG-IFN Lambda Beta was not approved by the FDA as it is still in clinical trials [17].

The COVID-19 vaccines have been approved by the Food and Drug Administration (FDA), meeting the standards required by them regarding the effectiveness and safety of the patients to whom they are administered [18].

According to the indications given by the CDC, for children between the ages of 6 months and 5 years, it is recommended to receive several doses of the vaccine, according to certain criteria: the number of doses previously administered, age, etc. For those aged between 5 months and 4 years, the administration of three doses of the Pfizer-BioNTech COVID-19 vaccine with at least one updated dose is recommended, and for those aged over 5 years, at least one updated dose of the vaccine is recommended. In the case of the Moderna vaccine, it is recommended to take the two doses, with at least one updated dose. For children over 6 years of age, the updated Pfizer-BioNTech or Moderna vaccine is recommended. The elderly, over 65, are recommended to take the second dose of Pfizer-BioNTech or Moderna. Those who are immunocompromised are advised to take additional doses of the updated Pfizer-BioNTech or Moderna vaccine. For patients who choose not to receive an mRNA-based vaccine, depending on age and dose recommendations, Novavax or Johnson & Johnson/Janssen vaccines with an updated dose are available [18].

In the case of COVID-19, as far as allergies are concerned, there are few situations, many of which are only immunogenic reactions not mediated by IgE. However, there are situations in which it is recommended to avoid them in order to avoid side effects that could sometimes be dangerous, or even fatal. Two important potential allergens in the case of COVID-19 vaccines are PS80 and PEG. PS80 (polysorbate 80) is a polymer derived from polyethoxylated sorbitan and oleic acid and is a potential allergen in Janssen/Johnson & Johnson and Astra Zeneca vaccines. It is used in many other vaccines and medicines as an excipient and is also a food additive. PEG is a polymer of ethylene oxide. It is found as an excipient in the Pfizer/BioNTech and Moderna vaccines and is not indicated for patients with PEG allergies [19][20].

The two excipients have a similar chemical structure, both being polymers derived from ethylene oxide, hence the possibility of cross-reactivity between PS80 and PEG. To date, there are no COVID-19 vaccines that do not contain PS80 or PEG. To avoid anaphylaxis in the event of the administration of one or more doses of the COVID-19 vaccine, an algorithm has been created. Thus, the first dose can be administered in the case of patients who have no history of anaphylaxis to PEG or other drugs. In the situation where the patient, due to anaphylaxis, did not tolerate PEG, it is recommended to avoid the administration of vaccines containing PEG, the most suitable option being those containing polysorbate. In the case of the second dose, if after the administration of the first dose containing PEG no side effects appeared, the second dose can be administered. If after the first dose there was a slight urticaria or a delayed systemic reaction located at the injection site and the reactions could be easily resolved with antihistamines, the second dose can be administered after the overdose with cetirizine 20 mg. It is

recommended to monitor the post-vaccination symptoms for a longer period; in case they become more severe, further investigations are necessary. If the reactions in the first 2 h after the administration of the first dose containing PEG were severe (severe systemic allergies, anaphylaxis), the COVID-19 vaccine is not administered. Skin tests will be performed for the available vaccines for PEG and other allergens, and then, under longer and more careful supervision, the administration of a COVID-19 vaccine that matches according to the skin tests can be taken into account [20].

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