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Pain in COVID-19: Quis est culpa?

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ABSTRACT

Background: At present, during the coronavirus disease (COVID-19) pandemic, chronic pain is becoming more prominent, and it is also associated with the post-COVID-19 syndrome. Thanks to quick decisions on the therapy and as part of COVID-19 prevention, we have succeeded in stabilising the situation all over the world. On the other hand, 'quick decisions' have contributed to other significant issues which we are beginning to deal with now: in the effort to defeat the virus, many experts regarded the adverse effects of the medications used to be of secondary importance.

Purpose: The article aims to demonstrate the side effects of treatment with various drugs (and their combinations) that are used to treat COVID-19 disease.

Method: From the beginning of January until mid-May, the COVID-19 department of the 2nd Surgical Clinic of the Faculty of Medicine of the Comenius University in Bratislava (University Hospital Bratislava, Hospital of Saints Cyril and Methodius) treated 221 patients with moderate and severe course of COVID-19 (2nd wave of the pandemic). We saw some adverse effects and lack of effect of certain drugs for COVID-19.

Results: The benefits of preventive measures compared to treatment are enormous. For example, corticoids can impair metabolism, cause diabetes, or suppress immunity. Antibiotics may cause colitis and blood pressure medications may negatively impact blood circulation.

Conclusion: Preventive measures such as vaccination and activation of intrinsic antiviral immune systems are based on an incomparable benefit. Important in the process of the activation of antiviral immunity (linked to interferon synthesis) in the prevention of COVID-19 is the improvement of vitamin D deficit and the use of other micronutrients.

Practical value: The results of the study will be valuable in the field of medicine, for virologists, pharmacologists, pharmacists, and medical professionals.

Keywords: adverse drug reaction, co-morbidity, iatrogenic conditions, chronic pain, post-COVID-19 syndrome, side effects of treatment

INTRODUCTION

Coronavirus disease (COVID-19) was officially registered by the World Health Organization (WHO) on 31 December 2019, when the Ministry of Health of the People's Republic of China reported 44 cases of a severe acute respiratory syndrome (SARS) in the city of Wuhan in the Hubei Province. It was discovered that COVID-19 is caused by the new coronavirus SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2). On 11 March 2020, the WHO declared the spread of COVID-19 a pandemic [1-3]. The danger of COVID-19 infection lies in its higher transmission rate (several times higher than in the case of flu) and long incubation period (up to 14 days), which is further complicated by the fact that asymptomatic patients may also spread the infection. COVID-19 can have a severe course, particularly in patients with underlying chronic illness [3].

These characteristics of COVID-19 place increased demands on the organisation of the healthcare system. An especially high transmission rate is currently the reason why so many people worldwide contract COVID-19. This has led to an excess burden on healthcare systems in many countries. A severe course of infection (with affected lungs) in patients with chronic pathology very often requires the use of mechanical lung ventilation (MLV) and is associated with a high mortality rate [2, 3].

It is assumed that the ability to slow down the spread of the coronavirus infection is currently the most important preventive measure, which would result in decreased hospital admissions and a reduced burden on healthcare facilities. However, the attempts to fight the coronavirus infection

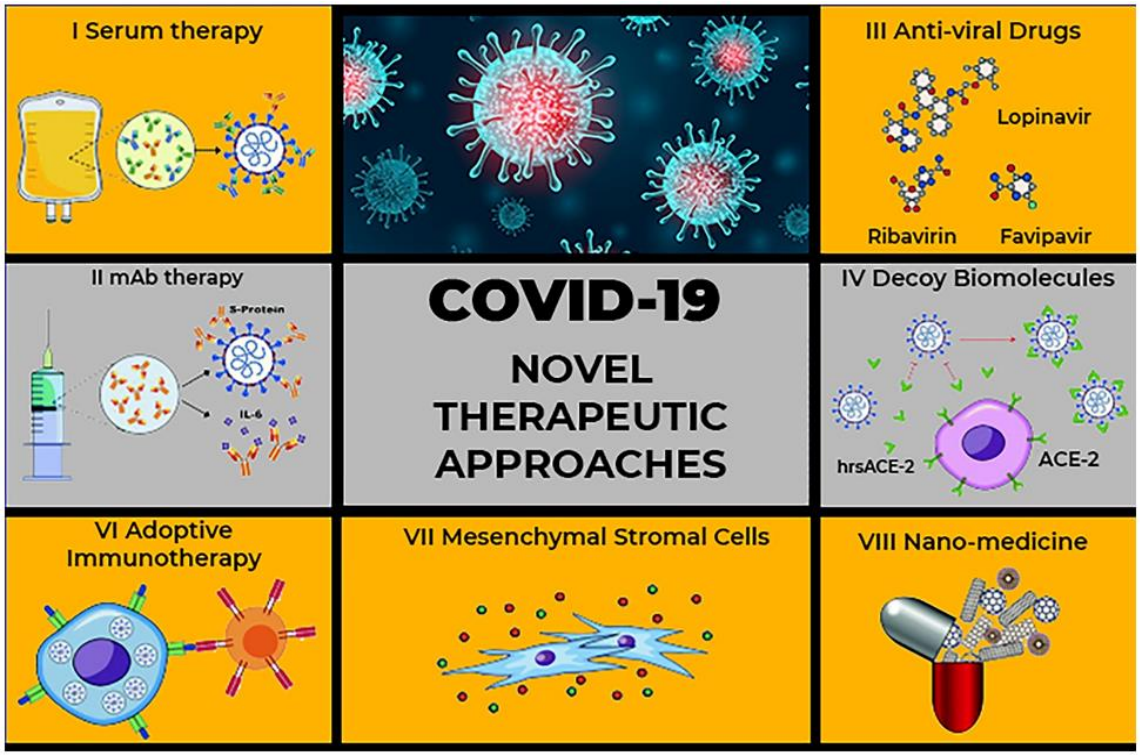

Figure 1. New treatment options for COVID-19 (adapted by the authors according to various sources of literature [5, 6])

merely using quarantine measures (wearing masks, gloves, hand sanitation and washing, restriction of social contacts, isolation, etc.) have nothing do to with the most important source of prevention: the activation of intrinsic antiviral immune systems [3]. Important in the process of the activation of antiviral immunity (linked to interferon synthesis) in the prevention of COVID-19 is the improvement of vitamin D deficit and the use of other micronutrients. Vaccination is also extremely important in COVID-19 prevention. Vaccination aims to achieve collective immunity which will result in the gradual elimination of the virus from the worldwide population [4, 5].

In efforts to help patients suffering from COVID-19, many new treatment protocols have been prepared and various antiviral drugs and other potentially useful medicament have been used. The purpose of the article is to demonstrate the side effects of treatment with various drugs (and their combinations) that are used to treat COVID-19 disease. We also focus on the benefits and relative safety of vaccination.

CURRENT STRATEGY OF COVID-19 TREATMENT

When COVID-19 (with affected lungs in particular) is treated with medications, it is very important to prevent the development of 'the cytokine storm': an avalanche-like increase in the concentration of proinflammatory cytokines resulting in lung damage and hypoxia [6, 7]. This condition requires oxygen therapy (treatment using oxygen or mechanical lung ventilation). By affecting 'the cytokine storm', it is possible to reduce the mortality of COVID-19 patients [3]. The presence of another disease (atherosclerosis, obesity, diabetes mellitus, bronchial asthma, arterial hypertension, etc.) in these patients supports and accelerates the synthesis of proinflammatory cytokines, including interleukin-1, chemokine CCL2, interleukin-6 and interferon-gamma. Interleukins increase the activation of leukocytes and the breakdown of mast cell granules [3, 5].

Stabilisation of accompanying chronic co-morbidities is very important for the treatment strategy and prevention of COVID-19, since the presence of complications like cardiomyopathy, thrombotic embolism, obesity, arterial hypertension, coronary artery disease and diabetes mellitus in patients is associated with a risk of more severe course of the disease [3, 5, 6]. Treatment protocols for this new disease are constantly changing and new options for treatment and prevention are emerging (**Figure 1**) [5, 6]. **Figure 1** shows new possibilities for the treatment of COVID-19 disease (such as serum therapy, monoclonal antibody therapy (mAb), adoptive immunotherapy, mesenchymal stromal cells, anti-viral drugs, decoy biomolecules, nano-medicine, etc.). From the beginning of January until mid-May, the COVID-19 department of the 2nd Surgical Clinic of the Faculty of Medicine of the Comenius University in Bratislava (University Hospital Bratislava, Hospital of Saints Cyril and Methodius) treated 221 patients with moderate and severe course of COVID-19 (2nd wave of the pandemic).

In February 2021, the mortality rate at our department reached 33%, with a third of patients requiring high-flow oxygen therapy. During this period, Slovakia became the worst in the world in terms of the number of deaths and hospitalised cases per capita. Treatment was often complicated by co-morbidities, which worsened the disease course. We also saw some adverse effects and lack of effect of certain drugs for COVID-19. Certain drugs could not be used due to various contraindications and interactions with other drugs (chronic treatment), etc. We also had 5.8% of bleeding cases associated with the use of anticoagulant therapy (as part of antiviral therapy), in combination with preparations from the group of janus kinase inhibitors.

DRUG THERAPY OF COVID-19, ADVERSE EFFECTS OF DRUGS

The worldwide opinions on the treatment and prevention of the disease differ. An increasing number of sites prefer therapy recommended by Front Line COVID-19 Critical Care Alliance under the leadership of the world-renowned expert on intensive care medicine, Dr. Paul Marik from the USA, who counts among the world's most published scientists. Together with his team, they created a so-called 'MATH+' protocol for the treatment of hospitalised patients and an 'I-MASK+' protocol for prevention and early treatment in the home environment [8, 9]. Protocols are constantly updated as new knowledge emerges. Treatment success also depends on good timing, since the lungs are affected starting from the 5th day of non-improving condition and it is inevitable to initiate complex anti-inflammatory and anti-coagulant therapy according to the hospital protocol as early as possible. Otherwise, the lungs become even more affected, complications develop, and it may be too late.

In any event, COVID-19 treatment is complicated and includes 'a cocktail of medications' which are not always helpful and even have the potential to harm patients [10]. By the adverse effect of a drug, we mean any harmful and undesired reaction which occurs with common therapeutic or preventive doses of the drug. It is usually mild in nature and disappears after withdrawal from the drug. It does not necessarily occur in every patient. Patients can find information on adverse effects in the patient information leaflet. We distinguish between serious (life-threatening, hospitalisation) and less serious adverse effects of drugs (conditions that can be managed at home).

In terms of risk (frequency), the adverse effects are divided into very common, common, uncommon, rare, and very rare. If an adverse effect is very common, it means that more than 100 patients in 1,000 may develop it. A common adverse effect is developed by 10-100 patients out of 1,000 and uncommon in 1-10 people out of 1,000. If an adverse effect occurs in less than 1 person in 1,000, we speak of a rare effect. If it occurs even more rarely, it is a very rare side effect [11]. Below are some of the most used drugs for COVID-19 and their most significant adverse effects.

Corticosteroid drug has been a subject of various studies, including Recovery which validated its efficacy and brought excellent news [12]. Dexamethasone cannot treat COVID-19, but as has been mentioned, it effectively reduces the massive inflammation that develops in this disease and causes many deaths [13, 14]. WHO issues guidelines on the treatment of various diseases. Dexamethasone has been included in the guideline for the treatment of COVID-19. It is cheap, available, effective and can save many lives. Guidelines recommend using intravenous or tablet form of the corticosteroid therapy with Dexamethasone in patients with a severe course of the disease [13, 14]. Prevention of complications is always better than their later management. When immunity is suppressed with corticosteroids, no cytokine storm occurs, but our body is weakened in the fight against the virus itself. For this reason, the therapy should only be administered to patients with severe course of the disease, since in the case of a milder course corticosteroids would do more harm than good. No improvements have been seen in patients with a milder course of the disease. The following adverse effects of corticosteroids may develop, depending on the dosage and duration of the treatment, which means that the frequency of their occurrence cannot be established (**Table 1**) [13, 15, 16].

Antiviral agents (remdesivir, lopinavir-ritonavir, hydroxychloroquine, tocilizumab) were also tested in the previous months (originally against ebola, malaria and AIDS [acquired immunodeficiency syndrome]) with high expectations of scientists. Unfortunately, it turned out that they have no impact on the mortality of COVID-19-positive patients. The WHO study also did not demonstrate their effect on the shortening of hospitalisation or mechanical lung ventilation therapy [17-19]. The side effects of antivirotic drugs are listed in **Table 2** [17-19].

Plasma is a pale-yellow fluid that represents the liquid part of the blood and helps 'distribute' blood cells in the body. It consists mainly of water (90-92%), the rest of its volume consists of proteins (8%) and inorganic substances (1%) [20, 21]. When a person encounters some foreign substance (virus, bacterium, etc.), the human body produces antibodies against the substance and saves them 'for bad times.' It means when it encounters the foreign substance again, it will be ready for it. Basically, antibodies are a type of protein contained in the plasma, which is why scientists came up with the idea of plasma therapy. A patient with COVID-19 is given the plasma of another patient who has overcome the coronavirus infection and recovered, i.e., his/her plasma contains antibodies which may help the patient in the early stages of therapy. The solution is almost painless and has no side effects.

The risk of plasma administration, adverse effects [20, 21]:

- volume overload in the case of fast infusion rate and high plasma volume (TACO–transfusion associated circulatory overload), in patients with cardiac risk factors, risk of heart failure and lung oedema,
- citrate intoxication in the case of fast infusion rate and high plasma volume, in the case of liver failure, shock, acidosis and hypothermia,
- allergic reactions, in rare cases anaphylactic shock,
- the risk of transfusion-transmitted infections: bacteria, viruses (HIV–human immunodeficiency virus, HCV–hepatitis C virus, HBV–hepatitis B virus, CMV–cytomegalovirus, and others), and
- acute lung injury associated with transfusion (TRALI–transfusion associated lung injury).

Per the hospital treatment protocol, low molecular weight heparin (LMWH) is often used since COVID-19 causes a hypercoagulable state [19]. As of 6 November 2020, aspirin became subject to the largest clinical study examining treatment options for patients hospitalised with COVID-19 [12]. This widely available and well-known drug has its place in the first aid kit in almost every household.

Aspirin has antipyretic (reducing fever), analgetic (reducing pain), antiphlogistic (suppressing inflammation) and anticoagulation (against blood coagulation) effects. All of them could be helpful in the treatment of COVID-19, but the research is currently focusing on the last one, i.e., the anticoagulation effect [5, 12, 19]. Life-threatening complications that COVID-19 can cause include blood clots (thrombi). It is due to blood platelets responsible for coagulation (clotting) of blood, which are hyperactive in this disease. Adverse effects of anticoagulation therapy: bleeding in case of overdose, allergic reaction, thrombocytopenia, potential osteoporosis, bruising.

Table 1. Adverse effects of corticosteroids

Infections & infestations	Masking of infections, signs & exacerbations of viral, fungal, bacterial, parasitic & opportunistic infections, & activation of strongyloidiasis
Blood & lymphatic system disorders	Moderate leukocytosis, lymphocytopenia, eosinopenia, & polycythaemia
Immune system disorders	Hypersensitivity reactions (e.g., rash after medication), moderate anaphylactic reactions, such as arrhythmia, bronchospasm, hypotension or hypertension, circulatory system failure, cardiac arrest, & weakening of immune system
Endocrine disorders	Adrenal gland suppression & development of cushing syndrome (typical signs: moon face, abdominal obesity, & plethora)
Metabolism & nutrition disorders	Sodium retention with oedema, increased elimination of potassium (risk of arrhythmia), body weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolemia & hypertriglyceridemia, increased appetite
Psychiatric disorders	Depression, irritability, euphoria, increased activity, psychoses, mania, hallucinations, emotional lability, anxiety, sleep disorders, suicidal tendencies
Nervous system disorders	Pseudotumor cerebri, manifestation of latent epilepsy, increased number of seizures in obvious epilepsy
Eye disorders	Cataract, with posterior subcapsular opacification, glaucoma, worsened symptoms of corneal ulcers, increased incidence of viral & fungal eye disorders, worsened bacterial inflammation of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy, & blurred vision
Vascular disorders	Hypertension, increased risk of atherosclerosis & risk of thrombosis, vasculitis (also as a symptom of withdrawal in case of long-term treatment), increased capillary fragility
Gastrointestinal disorders	Gastrointestinal ulcers, gastrointestinal bleeding, pancreatitis, stomach pain, urination
Skin & subcutaneous tissue disorders	Striae, atrophy, telangiectasia, petechiae, ecchymosis, hypertrichosis, steroid acne, perioral dermatitis, & pigment disorders
Musculoskeletal & connective tissue disorders	Myopathy, muscular atrophy & weakness, osteoporosis (dose-dependent, also possible in the case of short-term treatment), aseptic bone necrosis, tendon disorders, tendinitis, tendon rupture, epidural lipomatosis, & growth inhibition in children
Reproductive system & breast disorders	Impaired elimination of sex hormones (with subsequent irregular periods to amenorrhea, hirsutism, impotence)
General disorders & administration site conditions	Prolonged wound healing

Note. Adapted by the authors according to various sources [13, 15, 16]

Table 2. Adverse effects of many antiviral agents

Frequency	**Adverse reaction**
Immune system disorders	
Rare	Hypersensitivity
Unknown	Anaphylactic reaction
Nervous system disorders	
Common	Headache
Cardiac disorders	
Unknown	Sinus bradycardia
Gastrointestinal disorders	
Common	Nausea
Hepatobiliary disorders	
Very common	Increased transaminase levels
Skin and subcutaneous tissue disorders	
Common	Rash
Laboratory and additional examinations	
Very common	Prolonged prothrombin time
Injuries, poisonings, & procedural complications	
Rare	Infusion-related reaction

Note. Adapted by the authors according to various sources [17-19]

Vitamin D, present in three forms in the body, also helps to regulate the cytokine storm in a natural way. One of those forms is calcifediol (25-hydroxyvitamin D3), the concentration of which is also determined when testing for vitamin D in the blood. When calcifediol is supplemented, the body can absorb it easily and its concentration in the blood increases rapidly [22]. These characteristics were one of the reasons why Spanish scientists have chosen this form of vitamin for their pilot clinical study.

The research included 76 patients with COVID-19, all receiving the best available treatment. In addition, 50 patients received calcifediol. As a result, only one person required intensive care and none of the patients died. Of the remaining 26 patients (control) who did not receive calcifediol, as many as 13 (50%) ended up in the ICU (intensive care unit) and two patients died [12]. The results are significant and indicate that the administration of vitamin D in this form can alleviate the course of the disease and significantly reduce the number of patients requiring intensive care. However, they need to be explored further (with a larger, better comparable sample), since the study did not include patient risk factors, such as obesity, high blood pressure or diabetes that complicate the course of COVID-19 [3, 12, 22]. In any case, vitamin D plays a significant role in the proper functioning of our immune system and its sufficient blood concentrations influence the course of COVID-19. Adverse effects: hypercalcemia and hypercalciuria, pruritus, rash and urticaria (uncommon) [23-25].

Several relevant clinical investigations have shown that vitamin C effectively shortens the period of viral infections. Since COVID-19 is one of the viral diseases, professionals assume that is desirable to apply vitamin C at the time of active coronavirus disease [26]. It is estimated that infectious disease is shortened by up to 8% in adults and 14% in children [12, 26]. Even though the benefits of vitamin C for the body are widely known, since the coronavirus infection is new, there are not enough relevant scientific studies to confirm the effect of taking vitamin C-containing products during COVID-19. There are even cases of acute renal insufficiency caused by high doses of vitamin C [27, 28]. Antibiotic treatment is very common and effective, however only in the case of bacterial infections. Since COVID-19 is caused by a virus, antibiotics are not effective against it. In the case of COVID-19, antibiotics are administered only when there is a risk that the patient (due to the weakening of the organism) will develop complications in the form of accompanying bacterial infection. This is most common in hospitalised patients with a more severe form of the disease [29,30]. Some side effects of antibiotic drugs are listed in **Table 3** [29-32].

Table 3. Adverse effects of antibiotics (most common/general)

Adverse effects of antibiotics (most common/general)
Allergic manifestations
Biological effects (wide spectrum antibiotics)
They affect the microbiome→dysmicrobia
Gut dysmicrobia–vitamin K deficit, diarrhoea, Cl difficile infections
Vaginal dysmicrobia, vaginosis, & candidal vaginitis
Soor
Bacterial superinfection with resistant stems
Toxic effects: Often dose-dependent
Cumulative, e.g., nephrotoxicity, neurotoxicity, hepatotoxicity, phototoxicity, & damage to growth cartilage

Note. Adapted by the authors according to various sources [29-32]

Table 4. Adverse effects of the vaccine vs. consequences of COVID-19

Long-term (side) effects	
Vaccine	**COVID-19**
All adverse effects specified in the patient information leaflet are short-term in nature.	Some people have long-term symptoms even after recovery.
Long-term side effects of vaccines are rare.	76% of patients (Lancet) had persisting signs even 6 months after recovery
None of the vaccines registered in the EU later had their registration withdrawn due to side effects that develop later.	56% of patients (Australian study) had damaged lungs even three months after dismissal from hospital.
Various vaccines are tested on volunteers for the last 3 years, with no known case of long-term side effects.	For the time being it is not completely clear how long the consequences of COVID-19 might persist and whether they will not be permanent in some cases.

Note. Adapted by the authors according to various sources [37-40]

Fluoroquinolone antibiotics are often used to treat secondary infections during COVID-19 and may result in severe chronic complications [33]. They are antibacterial drugs that came into use around 1987. At first, they were reserved for the treatment of the most severe infections, but soon became effective safe, cheap, and therefore commonly used antibiotics. It took more than 20 years to discover that their safety is not as ideal as it seemed. Besides skin manifestations, headaches and dizziness, fluoroquinolones may rarely cause severe damage to the nervous system. There is also the possibility of damage to the musculoskeletal system–tendon damage, even rupture of the achilles tendon (mostly in the elderly) occurs with higher total doses [34, 35].

Due to a certain degree of teratogenicity and adverse effect on the development of joint cartilage, its administration is usually not recommended to pregnant and breastfeeding women and children, except for severe, otherwise untreatable infections. In addition to various non-significant and transient health issues, fluoroquinolones may also cause heart rhythm disorders that in unique cases might be life-threatening. On 12 May 2016, the European Medicines Agency (EMA) finally published the opinion that due to the risk of potentially permanent damage to health, patients with uncomplicated infectious diseases should not be treated with this group of antibiotics if there are other treatment options available. This is true in the case of patients with non-significant respiratory and urinary infections as has already been mentioned [36].

ADVERSE EFFECTS OF VACCINES

Vaccines for the prevention of COVID-19 are administered intramuscularly and may cause reactions within hours or even days after administration. Reported suspected adverse effects are usual and in accordance with the already known adverse effects listed in the medicinal product dossier (**Table 4**) [37-40]. The most often reported adverse reactions are short-term and non-serious [40]. They include, for example, injection site pain which may develop into the pain in the arm and extremity to which the vaccine was administered, increased temperature, chills, shivering, headache, muscle and joint pain, weakness, fatigue, nausea, and others. Such reactions are mild to moderate in intensity and resolve within a few days of vaccine administration. The safety profile of vaccines used for the prevention of COVID-19 is reviewed monthly at the local and the European Union level. At the European Union level, the safety profile of registered vaccines has been shown to be largely in accordance with the drug dossier and the benefits of the vaccine far outweigh any potential risks. In addition to symptomatic treatment, patients with a more severe course of the disease require hospitalisation, supportive oxygen therapy (administration of oxygen), and in cases that are even more severe than that must be put on MLV [41-43].

Adverse Effects of MLV

Ventilator pneumonia; nosocomial infections; patient airway damage due to long-term pressure by the tracheal cannula, insufficiently or excessively moisturised mixture of inhaled gases or excess oxygen concentration in the inhaled mixture; lung injury due to excess pressure; VILI (ventilator-induced lung injury) or lung injury associated with ventilation; pneumothorax; emphysema; lung oedema and others [43-45].

Adverse Effects of Oxygen Therapy

Lung injury (oxygen toxicity due to its high concentration→acute respiratory distress syndrome (ARDS), chronic lung fibrosis, emphysema); damage to the central nervous system (CNS) (rate of progression is directly proportional to the partial pressure)→impaired vision (tunnel vision), tinnitus, nausea, mimic muscle jerks, dizziness, confusion (the picture is variable)→tonic-clonic spasm, impaired consciousness; eyesight damage→hyperoxic myopia, retinopathy; damage to other organs→erythrocyte destruction, damage to the myocardium, endocrine glands (adrenal glands, gonads and thyroid gland) and kidneys [46-52].

CONCLUSIONS

Currently, all treatment protocols include corticoids, antiviral agents, vitamins, medications to stabilise underlying and accompanying co-morbidities and antibiotics. The benefits of preventive measures compared to this 'treatment cocktail' are enormous. For example, corticoids can impair metabolism, cause diabetes, or suppress immunity. Antibiotics, on the other hand, may cause colitis and blood pressure medications may negatively impact blood circulation. Moreover, we do not even know whether these drugs will help a patient recover from a severe condition in the case of a patient who avoided the vaccine (and other preventive measures) and later arrived at the intensive care unit in a severe condition. Therefore, preventive measures such as vaccination and activation of intrinsic antiviral immune systems are based on an incomparable benefit. And that is why one should not rely on treatment with an uncertain result.

Vaccination is an effective means of combatting the SARS-CoV-2 virus that has caused the pandemic and paralysed countries, families, communities, and individuals worldwide. Scientific authorities and historical facts clearly show that the most efficient way of defeating any virus is the use of a safe and effective vaccine. COVID-19 vaccination represents not only the protection of the individual being vaccinated but also the collective protection of the community and society. A vaccinated person is less likely to spread the infectious disease to other persons. It means that vaccination can help protect those who cannot receive the vaccine.

To ensure the so-called collective immunity on a national level, in the case of COVID-19, it is necessary to vaccinate more than 60-70% of the population. Vaccination is essential for saving lives, but it will not end the pandemic overnight. Therefore, we must use other forms of prevention. In the process of activating antiviral immunity (linked to the synthesis of interferon), supplementing vitamin D and other micronutrients is particularly important in the prevention of the 'cytokine storm' and in the compensation of chronic concomitant diseases.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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