# COVID-19

## THERAPEUTIC OPTIONS FOR EACH STAGE OF THE DISEASE

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In the following chapters, we take you through the medical phenomenon that is COVID-19 and its therapies, as seen and experienced in a clinical environment by a number of friends – doctors from Romania and from abroad, and as proven by clinical and published studies from the months that have passed since the beginning of the pandemic.

We hope that this material will prove helpful to those who, although medically trained, have not had the time to study this disease, and to all those who want to learn more about it.

We believe that being informed is the first step in fighting this extremely intelligent disease. Since, in all likelihood, very few people will be able to escape becoming infected by it during the coming months, then perhaps waiting for the consequences to emerge and being paralysed by fear in the meantime is not the best of options. The future belongs to people who acquire the knowledge to fight the disease not by running away from it, but by choosing the most appropriate methods of strengthening their immune system. Unfortunately, the media has ceased to be a means of informing the masses and has rather become a source of scaremongering, terror and misinformation.

If we exercise our capacity of discernment to find correct sources of information and employ our own personal critical interpretation in the process, the internet can still be relied on to provide a very good share of data. We have to trust the real science, and not that which is popularized, or the emotionally charged narratives that exercise mind control over the masses. Leaning towards truly authentic sources, whilst keeping our faith in God unshattered can prove vital for us during the pandemic and post-pandemic times that lie ahead.

Consequently, this material constitutes both a plea for reason and a critique of the folklore and the ideologized narratives that the media has made us feed our imagination with, as we await helplessly the implacable ending they threateningly propose. Those who delve deep into this material will understand that this disease is the greatest challenge that man has ever been faced with in modern times, i.e. the challenge to revert to a healthy lifestyle

or else assume the risk of suffering premature death due to one of the many pandemics that are yet to come. As always, the choices are ours more than we can grasp.

We hereby give thanks to all of our friends – doctors who fight against this merciless disease, with all that their knowledge and experience allow, in order to save the lives of patients. We fully believe that it is only through the cumulation of all these resources that we can finally reach our goal. If we were to find a positive effect to this pandemic, it would be none other than this tremendous international solidarity of doctors and scientists from all over the world, who put forward their knowledge and throw all their energy and even lives in the fight against the killer virus. We do not think there has ever been a time in the history of science when medicine took such a big leap towards understanding the immune system, the inflammatory processes and the modus operandi of viruses in the human body. All that remains is that these studies be integrated into clinical practice as soon as possible. We designed this material as a first step in that direction. Each person must do everything that depends on him/her, so that the lives of many more people might be saved.

# Why people die of COVID-19

SARS-CoV-2 is a highly versatile and dangerous virus, especially with patients that suffer from a combination of certain risk factors, and when the infection is not treated from its first phase of viral multiplication. In order to counteract its attack and neutralize the virus, one must have knowledge of the nature of the disease, the risk factors and the symptoms. At the same time, it is very important for the patient to be psychologically open to accept the disease without panic, and thus have it treated from its very first signs.

For instance, it is useful to know that this disease presupposes three big phases: the viral replication or symptomatic phase, the early (precocious or inflammatory) pulmonary phase and the late (tardive or hyperinflammatory) pulmonary phase.

These phases are preceded by a silent period, which corresponds to the incubation of the virus. For the sake of simplicity, we will not count this period among the phases of the disease, because it is asymptomatic and can be identified only retrospectively, by calculating the time passed between the patient's contact with a known or supposed COVID-19 infected person.

Furthermore, the three phases of the disease are followed by a post-COVID-19 phase, which, for some people, is marked by pulmonary, cardiovascular and metabolic complications, chronic fatigue, neurological and psycho-affective disorders, and also by possible long-term disorders of the immune system.

If we have not been infected by it yet, it is time we prepared ourselves for it. We need to study the risk factors, so as to see whether we fit in the category of those who could contract a severe form of COVID-19.

The risk factors that are outside our radius of influence (e.g.: age, gender, the pre-existence of comorbidities) can be counterbalanced by corrective actions applied to the other factors, such as: increasing vitamin D3 levels through supplementation, exchanging fast-food type eating habits with a healthy diet rich in fresh fruit and vegetables, finding ways to lower stress levels in our day-to-day lives, giving up smoking, taking up sports and exercising to fight a sedentary lifestyle etc. We have to do whatever is in our power to avert a severe form of COVID-19 (see Annex 7). However, the

most important thing is, perhaps, to detect the disease in time and start treatment on the first or second day.

During this pandemic, it would be safer to err on the side of caution and consider each episode of "cold" or "flu" we go through as COVID-19. Even the burn-out and headaches that come out of nowhere, the unexplainable muscle pains or other apparently ordinary symptoms should be regarded as a COVID-19 debut and treated as such, i.e. through a complex program of nutritional and antiviral supplements that are meant to stop a possible multiplication of the virus. We would rather administer "in vain" these treatments that are without any notable adverse effects, than lose the first and maybe most important moment in the fight against this disease. (These supplements are actually beneficial in any type of infection, be it viral or bacterial.)

Due to excessive, even obsessive fear, some people refuse to believe that they have COVID-19. The days pass and they only take Paracetamol against high fever, and if they have no fever, then they wait for the headache or other symptoms to subside. The problem is, if the disease is not treated during its viral replication phase, which is more often than not a silent period of the disease or some sort of mild respiratory virosis, the patient enters the inflammatory phase unprepared, and then his life is already in danger.

**ATTENTION!**

- In some cases, the symptomatic phase up to the 8th day can be so harmless, that many people completely ignore it, either by believing they are not infected, or by thinking it is not a very dangerous disease. This happens especially because, at a certain point in the evolution of the disease, during the symptomatic phase, the fever drops and the symptoms diminish very much, only to have them worsen two or three days later, when additional symptoms such as shortness of breath, tightness in the chest etc. surface.
- We insisted upon this aspect because we ourselves have had many friends or acquaintances whom we tried unsuccessfully to convince that their symptoms were typical of an infection with SARS-CoV-2 or that they were likely to have been infected, since some members of their family had it. Less than a week later, they were admitted to the emergency room with a sudden drop in oxygen levels, which had prompted their frightened fa-

mily to call an ambulance. How many people have lost their lives unnecessarily until now, just because they disregarded the symptoms and the disease itself?!

- Depending on the risk factors or the measures taken during the viral replication phase, the disease can either acquire a more severe character or it can go away easily, even more so than a common respiratory infection, but it will take it a longer time to heal, about two-three weeks. Therefore, it is essential to initiate the therapy at the first signs of disease. Even when there is no certainty that COVID-19 is the culprit, it is better to initiate the therapy preventively and have the patient cross the bridge between the viral replication phase and the inflammatory phase without the potentially fatal cytokine storm occurring.
- We have known many persons who took no treatment measures whatsoever up until the 8th or 9th day, only to wake up suddenly, in the space of a few hours (12-24 hours) with an unexpected drop in their oxygen levels to 94%-90% and even less. In these cases, the treatment at home becomes much more difficult to manage, but it is not impossible. Obviously, the first thing to be done in this situation is to increase the oxygen intake by means of an oxygen concentrator. The oxygen saturation must be monitored with a pulse-oximeter constantly and often enough, so as to be able to identify in due time if the patient's state becomes worse. As a matter of fact, any house, wherein there is a COVID-19 patient with a risk of developing a severe form, should have a pulse-oximeter, at least for the duration of the disease.

## Conclusion

No one can be sure that they would be among the lucky ones who develop only mild forms, especially if they have some of the risk factors as well. This is why, as soon as the first characteristic symptoms appear, it is highly important to start the treatment that is specific to the phase of the disease in which the patient is. A few days onwards, and it will become much clearer if the diagnosis says COVID-19 or something completely different. If the diagnosis is true, though, we will have gained time, if not, nothing will have been lost. And this is because the recommended medicines have no major adverse effects, and the supplements are completely harmless – in the worst case, they might provoke mild digestive issues (nausea, diarrhoea).

# Supplementation in COVID-19

The following recommended supplements are listed in order of their importance and they can be taken during all stages of the disease and the recovery period. They have no adverse effects when taken in the prescribed doses; they are, in fact, well under the toxic dose established by the various safety studies done throughout the years. Most of these supplements are immunomodulators and anti-inflammatories.

We have observed that many people are reticent to follow a treatment with supplements due to the large number of pills they have to take. This is mainly a case of psychological block. If we realize that these are not medicines, but merely more condensed foods, sourced mostly from plants, we will also realize that the entire issue of administering them relies with the act of swallowing them. In this context, it is good to remember that the doses that are too small will not have the expected effect, especially in a disease like COVID-19.

## Highly essential supplements

1. Vitamin D3 (60,000-100,000 IU in the first day, then 20,000 IU per each subsequent day during the course of the disease, i.e. for 10-14 days, and 5,000 IU/day for at least one month after healing);
2. Vitamin C (minimum 1,000 mg x 4/day) – preferably more (in powder form, up to 15-20 grams can be taken per day, dissolved in water and mixed with sodium bicarbonate in a ratio of 2:1 – 3:1, to diminish its acidity);
3. Zinc (50 mg x 2/day);
4. Magnesium chloride (200-300 ml/day from a 2.5% solution);
5. Omega 3 (2-4 g/day);
6. Selenium (200 mcg x2/day);
7. Melatonin (12 mg/day before bed);
8. Quercetin (1,000-2,000 mg/day);
9. Curcumin (1,000-4,000 mg/day).

## Optional supplements

10. Artemisinin (200-500 mg/day) – the active compound found in Asian plant Artemisia annua (sweet wormwood). However, Artesunate is more efficient, because it is a more readily absorbable formula;
11. N-acetylcysteine (600mg x 1-3/day or more, orally or as an injection);
12. Berberine (500-1,500 mg/day) as an extract from plants such as Berberis vulgaris, Oregon grape;
13. Green tea (1-3 cups a day) or a standardized extract (500-1,500 mg/day) containing Epigallocatechin gallate (EGCG) in a dose of 100-400 mg/day;
14. Astragalus, root extract (500-1,500 g/day);
15. Boswellia serrata, extract 65% (500 mg x 1-2/day);
16. Liquorice root (500 mg x 3/day) – with care, it can increase blood pressure!;
17. Ashwagandha, standardized extract (300-900 mg/day);
18. Feverfew plant capsules (400-1,200 mg/day);
19. Olive leaves – standardized extract containing Oleuropein 6% (500-1,500 mg/day);
20. Vitamin B complex with minimal doses of 5-10 mg of the main B vitamins (B1, B2, B3, B6), 1-3 capsules/day; (Vitamin B6 is extremely important in triggering the cellular immune response – patients in a severe condition require a minimum of 50-100 mg/day.);
21. Vitamin E (400-1,200 IU/day);
22. Vitamin A (25,000 IU/day) (as retinol) +/- carotenoids with antioxidant properties (natural beta-carotene 10,000-25,000 IU/day, astaxanthin 4-12 mg/day, lutein 10-20 mg/day);
23. Proteolytic and fibrinolytic enzymes such as Wobenzym (3 tablets x 3/day), Serratiopeptidase (20,000-40,000 IU x 3/day), Nattokinase (2,000 IU x 2/day) – for an anti-inflammatory effect they need to be taken on an empty stomach, 30 minutes before or 2-3 hours after meals. (They have a mild anticoagulant effect, another beneficial effect in COVID-19. They can be administered alone or together, always taking in consideration the fact that they potentate lightly the synthetic anticoagulants.);

24. Silymarin, standardized extract (750-1,000 mg/day), as hepatic support;
25. Alfa-Lipoic acid (300mg x2/day), as antioxidant and hepatic support;
26. Ginkgo biloba, standardized extract (120-360 mg/day) – improves blood circulation and has a mild anticoagulant effect.

## COVID prophylaxis

Even those who do not have any symptom of disease, or any known contact with a COVID-19 infected person, should prepare for many months, before they actually contract the disease, by taking the following supplements:

1. Vitamin D3 (5,000 IU/day) – with a minimum of 2 litres of liquids per day;
2. Vitamin C (1-3 g/day or more);
3. Zinc (25-50 mg/day);
4. Selenium (200 mcg/day);
5. Melatonin (3-12 mg/evening, before bed);
6. Magnesium (200-400 mg/day) – as magnesium citrate or chloride 2.5%, 100 ml/day;
7. Quercetin (500 mg/day);
8. Curcumin (500 mg/day).
9. Omega 3 (1,000 mg/day);

These reserves of vitamins, minerals and antioxidants will prepare the body fight the disease when the time comes, and even if that time never comes, they will still bring benefits, especially by maintaining the immune and cardiovascular systems in a better working order than before supplementation.

# Medicines with an antiviral or immune modulator effect

## Recommended medicines for the symptomatic phase

1. **Ivermectin** (200-400 μg/kg of body weight/day for 4 consecutive days) – an anti-parasitic agent with a very powerful antiviral effect. At an average body weight of 70 kg, the dose is between 14-28 mg/day, for 4 days. A dose of 25 mg/day taken for 4 days could be the standard treatment for adults. In the studies, the dose varies, so we have to tailor the dosage according to the number or severity of the risk factors. Thus, when the sum of the risk factors is high, the dose should be 400 μg/kg of body weight, for 4 consecutive days. This is a dose without any known toxicity, but sometimes it can prompt transitory headaches and dizziness. The Ivermectin solutions have a concentration of 1%: 1 ml contains 10 mg, so 2.5 ml of solution contain 25 mg, the daily recommended dose for an adult.
2. **Doxycycline** (100 mg x 2/day on the first day, then 100 mg/day) – for 5-10 days has proved useful in the prevention and treatment of severe cases, especially when combined with Ivermectin. In the more severe cases, the dose can be maintained at 200 mg/day for 5-10 days.
3. **Umifenovir** (trademarked as Arbidol in Russia, Arpetol in Belarus and Arbivir, Arbimaks, Arpeflu, Imustat in Ukraine; the same medicines are found in the Republic of Moldova, as well) – to be taken especially during the symptomatic period, because it is specialized on the very inhibition of viral replication (200 mg every 6-8 hours for 5 days). It can also be taken preventively, in case you have been or are in contact with a COVID-19 patient. In this situation, a dose of 200 mg/day is recommended. Its adverse effects are negligible.
4. **Plaquenil** (hydroxychloroquine) –200 mg/day can be taken for the entire duration of the disease, always associated with zinc 50 mg x 2/day. It prolongs the QT interval, which is quite a significant effect when taken in high doses (600 mg/day), which we do not recommend

unless it is done under medical supervision and after getting an electrocardiogram!

5. **Methylene blue** (5-7.5 ml in 200 ml water x 3/ day) – this can be used as an alternative to Plaquenil or in combination with it, but always associated with zinc.
6. **Dipyridamole**[1,2]. (50 mg x 3/day);
7. Ursodeoxycholic acid or Ursofalk (10 mg/kg of body weight/day: 500-1,000 mg once a day for 10-30 days).
8. **Colchicine** (0,5 mg x 2/day for 10-30 days) – it may cause diarrhoea.
9. **Aspenter** (75-150 mg/day) – low dose aspirin, antiplatelet.
10. **Famotidine** (40 mg/day for 10 days) – for its antiviral effect.
11. **Metformin** (250 mg x 2/day) as immunomodulator and blood sugar regulator; it can be given even to non-diabetic patients that are predisposed to developing diabetes, especially when they start receiving the steroidal anti-inflammatory medicine that leads to an increase in blood sugar. The quantity can be doubled if the blood sugar remains high.

## OBSERVATIONS

In theory, during the symptomatic – viral replication phase, the majority of patients do not need steroidal anticoagulants and anti-inflammatories. It is expected that too early an introduction of corticosteroids in the treatment will hinder the neutralisation of the virus by the immune system. However, in persons that are at risk of developing thrombosis, the anticoagulant agent can be introduced even at this phase, in a prophylactic dose: Clexane (Fraxiparin), or another fractionated heparin, 0.4 ml=4,000 U once a day to persons of average weight, or another fractionated heparin in equivalent dosage.

What happens, though, with the patients who exhibit signs of very acute inflammation even at this phase, with high fever and sometimes desaturation? If a mild desaturation is detected, then an prophylactic anticoagulant treatment will be started (which seems to be essential for the increase in saturation, because the main mechanism that leads to pulmonary degradation is the formation of microthrombi in the pulmonary capillaries)[3].

To this, an immune-modulator treatment is added, in order to diminish the inflammation without diminishing the immunity, and thus prevent the cytokine storm that might occur. Some of the above mentioned substances act as immune-modulators:

- Ivermectin;
- Doxycycline;

- Dipyridamole;
- Ursodeoxycholic acid (Ursofalk);
- Quercetin;
- Curcumin;
- Parthenolide (from Feverfew or Tanacetum parthenium);
- Ulinastatin (a glycoprotein and enzyme inhibitor for intravenous administration; this is not available on our pharmaceutical market yet).

This list could include many other natural or synthetic substances with an immune-modulator role. If the fever continues to rise day by day, that signals the patient is entering the inflammatory phase of the disease, and it is very likely that we may witness the start of the dreaded cytokine storm, which must be kept under control with corticosteroids and antibiotics.

## Discussion

Since there is no certainty of a bacterial infection in patients suffering from excessive inflammation, as it was not possible to identify specific bacteria in cultures of biological products in more than a small percentage of the patients, the present official treatment protocols do not prescribe wide-spectrum antibiotics to patients other than those who have increased procalcitonin seric levels.

In effect though, many doctors prefer to give antibiotics to patients with persistent high fever, even from the viral multiplication phase (immediately after the onset of the disease), especially when these belong to risk categories. This is due to the fact that the majority of doctors equate a high fever with a strong bacterial infection, but sometimes they do it out of prudence, as it is risky for them to administer an immunosuppressive (corticosteroidian) treatment to lower the inflammation in a patient that runs a high fever and is often subjected to invasive manoeuvres, without a minimal antibiotic coverage.

It has not yet been proved beyond any doubt that the practice of prescribing antibiotics in COVID-19 cases is beneficial. However, the clinical observations recorded to date show that the patients who were given combinations of wide-spectrum antibiotics, that also covered atypical and anaerobic bacteria, during the cytokine storm phase, had a better evolution than those who were given no antibiotics at all.

Although the excessive inflammatory response in COVID-19 seems to be based on an immune mechanism, there is a possibility that some bacteria (probably atypical), that have developed in the context of the suppression of interferon prompted by the virus in its viral multiplication phase, might also be involved.

The atypical bacteria do not bring a significant increase in seric procalcitonin, and the bacterial infections with atypical bacteria cannot be clearly differentiated from the viral infections on the basis of procalcitonin levels[4,5]. Regarding the most adequate antibiotic for this COVID-19 phase, it is safe to say that, up until recently, everyone's attention was drawn to Azithromycin (active on atypical bacteria as well), but it seems that this is beneficial only when associated with Plaquenil, as it potentates its antiviral effect.

However, since there is the possibility of cardiovascular complications (cardiac rhythm disorders due to an excessively prolonged QT interval) to appear because of this association, which is often corroborated with the effect of other QT increasing medicines that are taken at the same time, the latest recommendations exclude Plaquenil from the treatment scheme, thus making the use of Azithromycin almost futile.

Doxycycline, an antibiotic active on multiple bacteria, including those atypical (without a cell wall), was administered successfully in all phases of the disease, but its highest success rate was achieved when it was introduced from the viral multiplication phase. It becomes even more efficient when combined with Ivermectin.

Other antibiotics may be introduced later to patients entering the hyperinflammatory phase, who display signs of a severe COVID-19 infection.

**OBSERVATION**

Tamiflu (oseltamivir) is an antiviral medicine that blocks a viral enzyme called neuraminidase. Since the SARS-CoV-2 virus does not have this enzyme, the administration of Tamiflu is completely inefficient in COVID-19. It may prove somehow useful at the onset of the disease, when it is not possible to differentiate between flu or Influenza and COVID-19, but if the patient tests positive for COVID-19, to continue prescribing Tamiflu would be unjustified.

# Nebulization, gargles and medicine application

## How to block the viral replication, or the fight against the virus that has already invaded the mucous membrane of the respiratory tract

It seems that the viral reserve of an infected body is its nasal, oral and pharyngeal mucosa. In the viral replication phase, it is essential for the patient to use nebulization and gargles, in order to flush all viruses from these mucous membranes, at the very least from the throat and nose area, and if possible, from deeper down the lower respiratory tract. The studies show that, when applied regularly, these decontamination procedures can prevent viral transmission in a large measure[6]. What can we use?

1. Nebulization with **Methylene blue 0.1% (2-5 ml x 2/day)**
   With the aid of the mouth piece attached to the nebulizer, the patient can do inhalations with methylene blue 0.1%. This is the same external use methylene blue 1% that can be found in pharmacies, only diluted in physiological serum in a 1:10 ratio.

   We can do this dilution in two ways:
   (a) Either we take away 25 ml from a 250 ml bottle of physiological serum and replace them with methylene blue, which we insert into the bottle with a syringe. This bottle must then be wrapped in aluminium foil, because methylene blue is photosensitive – it loses some properties when exposed to light.
   (b) Or, we can combine 1 ml of methylene blue 1% with 9 ml of physiological serum in a 10 ml syringe (this is more practical, it allows one to prepare a smaller quantity that can be used up in 1-2 days).

The patient will then nebulize at least twice a day with 2-5 ml of this solution, until the disease goes away. Methylene blue is essential in the fight against

COVID-19. It can be taken internally, through the mouth, as a preventive[7] or therapeutic measure, as well as through nebulization.

Doctor Deepak Golwalkar recommends the additional sublingual administration of the methylene blue 0.1% solution, 2-3 ml twice a day.

It is recommended that this treatment be administered during the recovery period as well, as it cleanses the lungs and helps tremendously in their recuperation, by eliminating the risk of fibrosis. (Oral administration of methylene blue: a dose of 1 mg/kg body weight or 1 ml of the 1% solution for each 10 kg of body weight, i.e. for a 70 kg person, 7 ml in a 200 ml glass of water 1-3 times a day[8,9,10,11,12,13]).

2. Other solutions to be used in a nebulizer are **colloidal silver 10 ppm** or oxygenated water 1.5% for external use (combine oxygenated water 3% in a 1:1 ratio with physiological serum or distilled water). The oxygenated water 0.5-1.5% can also be used as a gargle and nasal wash agent, its effect is the decrease of the viral titre[14,15,16].

3. Another aid in the fight against COVID-19 are the **essential oils** of: thyme, oregano[17] (carvacrol), rosemary (ursolic acid)[18], eucalyptus, peppermint, clove, cinnamon and lavender. By their anti-inflammatory, immunomodulator, bronchodilator and antiviral action, these essential oils prove to be a very reliable support in the COVID-19 therapy[19].

4. **Betadine** can also be used for gargles and nasal applications[20,21,22,23,24,25]. For the gargle, betadine 10% solution for external use is diluted down to 0.15% as follows: 3-4 drops of betadine 10% are added to 20 ml of water and then the solution is used for gargles and mouth rinses for about 2 minutes, just like a regular mouthwash.

5. For nasal applications the **betadine 10%** for external use can be used directly and applied very gently with a cotton swab inside both nostrils (without exercising too much pressure). If the nose becomes irritated due to repeated administration, the procedure will be paused, but beware, these irritations are generally a result of the unnecessary act of applying exaggerated pressure with the cotton swab on the nasal mucosa.

6. **40º alcohol** has proved useful in destroying the viral coating: it can be poured on a bandage and then the patient will inhale the vapours for 5 minutes several times a day. It can also be used as mouthwash, 5-10 ml of plum brandy or bitters, several times a day. It can also be swallowed in a small dose, 5-10 ml x 3-5/day of home-made plum brandy, bitters or a medicinal tincture (thyme, basil etc.), preferably undiluted in water[26,27,28].

**ATTENTION!**

- Methylene blue is NOT to be administered to pregnant women, to people allergic to this substance, to people with Glucose-6-phosphate dehydrogenase deficiency and to people with severe liver or kidney disease[29].

# Precautions associated with the symptomatic treatment of fever and pain

The current recommendation is to use Paracetamol for the treatment of pain and fever episodes in COVID, because the other nonsteroidal anti-inflammatories, due to their stimulation of protein ACE2 overexpression and their inhibiting of the COX enzyme, have been suspected of increasing the risk of pulmonary bacterial complications, thrombosis, severe respiratory distress syndrome and acute kidney failure[30]. (Paracetamol is a special case of NSAID that has no anti-inflammatory and platelet antiaggregant action.)

However, it is important to note that Paracetamol is not an inoffensive medicine. With large and prolonged doses, it can induce irreversible lesions in the liver and kidneys, through cellular glutathione depletion. 2,000 mg/day (4 tablets) is already a large dose that produces visible metabolic changes, especially in those who have low glutathione levels prior to the treatment. 97% of the cases with medicine-induced acute liver failure are caused by Paracetamol.

Since many people consider Paracetamol as a useful medicine in alleviating the disease, the patients take it conscientiously every time their fever spikes, and even when they have no fever, they take it for symptoms like headaches, muscle pain etc., and they are convinced it helps "heal them faster". This is not exactly all that it does. Even though some authors have reckoned that using Paracetamol in COVID is safer than other NSAIDs would be, it is possible that this very excessive use of Paracetamol during the viral replication phase, in the absence of factors that regenerate the glutathione (N-acetylcysteine, Selenium), might become one of the most important risk factors in the severe forms of COVID-19[31].

At the same time, the absence of antiplatelet and anti-inflammatory effects is, in fact, a disadvantage in COVID, and recent studies have shown that, in spite of their theoretical negative effects, NSAIDs do not increase mortality rates, but rather slightly lower them[32].

It is true, however, that high doses of NSAIDs taken regularly cause a high rate of digestive complications (gastritis, ulcer). All this evidence lead us to the conclusion that, for the regular treatment of fever, pain and inflammation, the natural anti-inflammatories are the safest!

Many of the supplements recommended in the viral multiplication phase have a remarkable anti-inflammatory effect, especially at high doses, and sometimes, they are even more efficient than synthetic anti-inflammatories. These are: Curcumin, Boswellia, Quercetin, Liquorice, Feverfew, green tea extract, olive leaves extract, fibrinolytic enzymes, vitamin D3, melatonin in high doses etc.

Furthermore, when administered sustainedly, antiviral medicines like: vitamin C, magnesium chloride, zinc, Ivermectin, Arbidol, Plaquenil and, again, melatonin, vitamin D3 etc., prevent fever from rising by blocking the viral multiplication.

Therefore, we recommend avoiding a routine administration of Paracetamol and NSAIDs in COVID while there are natural substances that are safer and more efficient than synthetic medicines, as far as adverse reactions are concerned.

Certainly, there is no problem if someone takes one tablet of Paracetamol once every 2-3 days, or when the first symptoms appear, or in a moment when the disease worsens and the headaches and fever become unsupportable. However, it is better to avoid taking them regularly, and instead, to replace them with more natural substances, which do not merely suppress symptoms in an artificial manner, but help the body truly heal. The unpleasant symptoms are alarm signals that make us aware either that our body is very toxic, or that we are on the brink of a severe form of disease that would require a more complex treatment, with steroidal anti-inflammatories, anticoagulants and antibiotics (which will be detailed in the following pages).

An efficient treatment, be it natural or allopathic, with corticosteroids introduced at the right time, will lead to a rapid alleviation of the fever and improvement in the overall health of the patient, without the need for intensive use of symptomatic medication.

The goal of the therapeutic effort is to find ourselves in the lowest part of this diagram, i.e. in the area of a mild respiratory disease. If the treatment is started on the first days of the symptomatic phase, we will very likely be successful. However, delaying the introduction of antivirals and other supportive remedies can throw us into the second stage of the disease, the pulmonary phase, or even in a severe pneumonia and acute respiratory distress syndrome (ARDS).

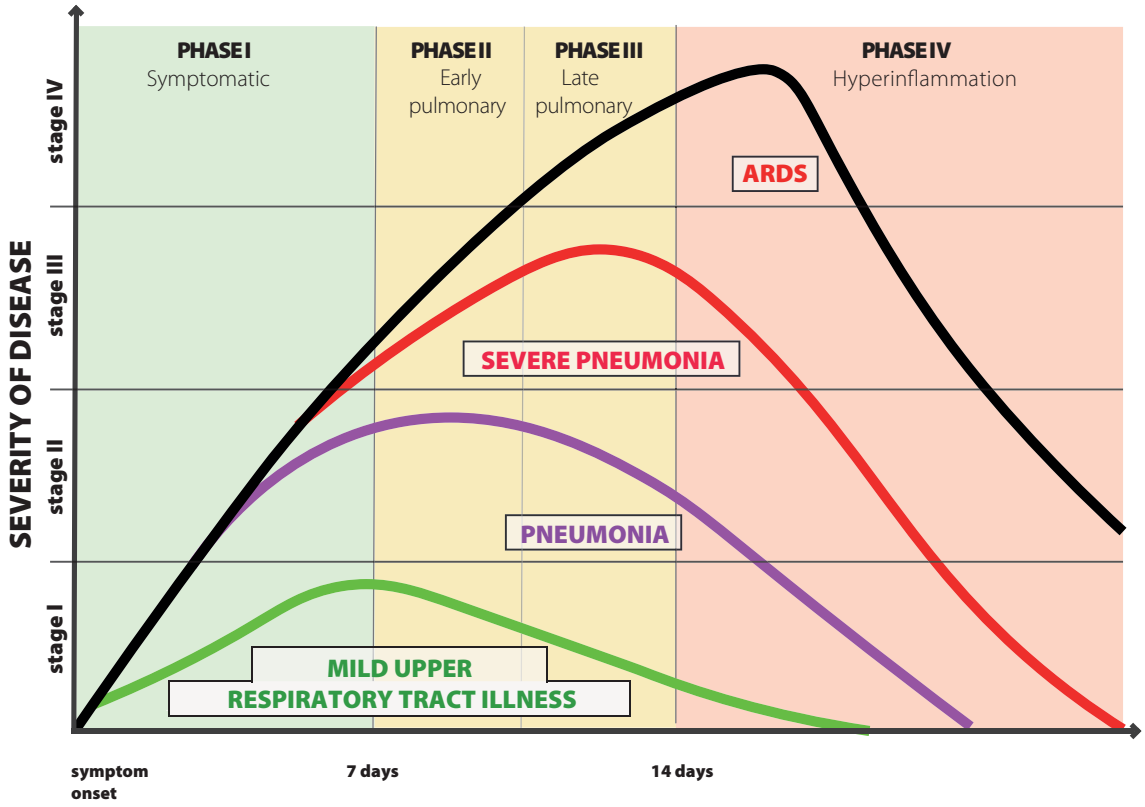



**Figure 1. The stages according to the phases of disease in order of occurrence**

# Medication for the early pulmonary or inflammatory phase

It is very important that the introduction of anticoagulants, anti-inflammatories and antibiotics be done only when the symptomatic phase is over, around the 7th day after the onset of COVID-19 specific symptoms. Undoubtedly, in the case of patients who develop a very severe, explosive form of disease from the very first days of the symptomatic phase, the moment of introducing these three classes of medicines may be brought forward a few days. At a prophylactic dose (4,000 U, respectively 2.5 mg/day), Clexane or Eliquis can be introduced without problems on the 3rd or 4th day from the debut of the first symptoms.

Furthermore, the antibiotic can be introduced empirically during this period, since the COVID-19 inflammation mechanisms may involve a yet unidentified bacterial infection.

In the early pulmonary phase, a mild desaturation (92-95%) can also take place. More often than not, this is rapidly reversible with the introduction of the anticoagulant and anti-inflammatory treatment, and does not need oxygen supplementation. At saturation values lower than 90% that do not increase significantly with treatment, it is necessary to use an oxygen concentrator that produces 2-10 litres/minute. With the concentrator, the lowest flow setting will be used, which will increase the saturation to over 95%. These important desaturations appear usually in the 3rd phase of the disease, the late pulmonary or hyperinflammatory phase.

## A. ANTITHROMBOTICS, ANTICOAGULANTS

a. *Fraxiparin (Clexane)* protects against the potentially fatal thrombosis[33]. COVID leads to the formation of microthrombi, which can affect the smaller blood veins of the lungs, kidneys and heart. The signs are: shortness of breath, tightness in the chest and back, dizziness, severe headaches that do not respond to medicines, even cognitive problems, sharp kidney pains etc. The saturation level dropping under 95% is yet

another alarm sign that might suggest the need to introduce anticoagulants and anti-inflammatories in the treatment[34,35,36,37,38].

At the same time, COVID has a rather high rate of large vein thrombotic complications (pulmonary thromboembolism, ischemic stroke, myocardial infarction), and the anticoagulant treatment is crucial for their prophylaxis.

## ADMINISTRATION

- 0.8 ml subcutaneously once a day, for persons weighing 80-100 kg;
- 0.6 ml subcutaneously once a day, for persons weighing 60-80 kg;
- 0.4 ml subcutaneously once a day, for persons weighing 50-60 kg.

### ATTENTION!

- In severe cases, characterized by an intense sensation of suffocation and a saturation under 92-93%, the same dose can be administered twice a day: 0.4-0.8 ml in the morning and 0.4-0.8 ml in the evening (0.4 ml=4,000 U).
- The doses recommended initially are lower than the therapeutic ones, namely 100 U/kg of body weight x 2/day, but when the values of D-dimers and coagulation times are unknown, these are sufficient. In any case, the evaluation of D-dimers remains essential in the decision to recommend anticoagulants. However, when this evaluation is not possible due to emergency quarantine or other measures, the anticoagulants should be introduced in this pulmonary phase as a replacement to aspirin, as they can save the life of the patient. Yet, this must be done after the exclusion of bleeding risk factors, such as digestive ulcerations, recent traumatisms etc., which either contraindicate the use of anticoagulants or recommend caution in their administration (small doses, monitoring haemoglobin levels and signs of digestive haemorrhage etc.).

b. *Eliquis* (*apixaban*) can be administered instead of Clexane if the latter is unavailable or its usage is impractical (patients that are alone and afraid to self-administer subcutaneous injections). Eliquis is administered in a dose of 2.5 mg twice a day, in the morning and evening; in severe cases, the dose is 5 mg x 2/day.

**ATTENTION!**

- With the **therapeutic dose** of Clexane or Eliquis, it is best to avoid any intramuscular injections, lest haematomas might form.
- In case the patient is already under anticoagulant treatment (e.g. Acenocoumarol, Warfarin), the above mentioned anticoagulants are not to be taken; the best course of treatment would probably be to increase the anticoagulant dose after testing the coagulation times and the D-dimers, according to the attending physician's advice.
- How long should anticoagulants be taken? At the beginning, they were used only until the saturation came back to normal values, i.e. until the patient came out of the late pulmonary phase, in about 2-3 weeks. At present, though, due to many records of post-COVID thrombotic phenomena (myocardial infarction, pulmonary thromboembolism, ischemic stroke etc.), many doctors recommend its use in patients that have been through severe forms of COVID for a minimum of 4-6 weeks, with a gradual reduction in dosage and, at the end of the anticoagulant treatment, with a requisite 3-month long administration of platelet antiaggregants Aspirin, Clopidogrel, Dipyridamole, either individually or in combinations of 2.

## B. STEROIDAL ANTI-INFLAMMATORIES (corticosteroidal hormones)

The steroidal anti-inflammatories are essential when the patient enters the pulmonary or inflammatory phase, around the 7th day from the onset of symptomatology. According to the latest studies, it seems that the most efficient steroidal anti-inflammatory is Methylprednisolone[39,40,41,42,43,44] (Medrol), followed by Dexamethasone[45].

## a. Medrol (Methylprednisolone)

**ATTENTION!**

- In most of the cases, the initiation of corticotherapy during the second (early pulmonary) phase of the disease, prevents the cytokine storm from the third phase.
- In phases I and II of the disease, it is necessary to start the treatment with a minimal dose of steroids and increase it only when need arises, as high doses given too early lead to immunosuppression and facilitate viral long-term

multiplication accompanied by virus excretion[46,47], which means an extension in disease duration. This was the reason why the use of glucocorticoids in the therapy against COVID-19 was avoided at first.

- Later studies have shown that the cautionary use of smaller doses of steroids srtarting from the pulmonary phase is very efficient – it speeds up the healing process and reduces mortality rates[48,49]. A safe dose would be under 0.5 mg Medrol/kg of body weight per day[50], i.e. maximum 40 mg for a person weighing 80 kg. It is the high doses, not the low ones, that are conducive to stimulating the viral replication and prolonged virus excretion out of the body[51].

**SIGNALS THAT SUGGEST THE NEED TO INITIATE CORTICOTHERAPY:**

- saturation levels dropping under 95%;
- tightness or pains in the chest and back;
- high fever (re)occurrence, accompanied by shaking chills and sweats;
- a state of general weakness and persistent malaise.

**DOSAGE:**

- Mild cases: 16 mg in the morning;
- Moderate cases: 16-24 mg x 2/day (at a saturation level of about 93%, an average of 0.5 mg/kg of body weight per day has shown positive effects on the subsequent evolution of the disease[52]);
- Severe cases: 32-48 mg x 2/day (if the disease is visibly getting worse – with a gradual drop in saturation under 90% and shortness of breath sensations);
- If need arises, the dose may be increased to 64 mg every 12 hours, or even 80 mg every 12 hours, according to East Virginia Medical School recommendations[53]. At any rate, this can occur only 14 days after the onset of symptoms, when the patient enters the hyperinflammatory phase. This concerns mostly persons at risk.

## b. Dexamethasone

It is a good alternative for Medrol (8 mg Dexamethasone equates 42 mg Methylprednisolone). The preferred method of administration is via intravenous injection (intramuscular injections should be used only occasionally, if the patient is not taking anticoagulants in therapeutic dose). Upon

necessity, the vials may be administered orally, in the same doses, as they have a good digestive absorption.

**DOSAGE:**

- Mild cases: 4-6 mg in the morning (intravenously, in 20 ml physiological serum);
- Moderate cases: 4-8 mg x 2/day;
- Severe cases: 8-16 mg x 2/day.

**ADVERSE EFFECTS OF CORTICOSTEROIDS (THEY MUST ALWAYS BE TAKEN INTO ACCOUNT, ESPECIALLY DURING A HIGH DOSE TREATMENT):**

- Increased blood sugar;
- Water and salt retention;
- Increased blood pressure;
- Decreased immune response and secondary (bacterial, fungal) infections facilitated;
- Inflamed mucosal lining of the digestive tract;
- Induced states of restlessness and anxiety;
- Elevated risk of osteoporosis and cataract (more so in the prolonged high dose treatments that are not generally used in COVID cases).

## C. ANTIBIOTICS

It seems that, in order to prevent the cytokine storm from escalating in high risk patients who display signs of systemic inflammation from the second week of the disease, antibiotic combinations can be extremely efficient, either by their antibacterial mechanism, or by other, still unclear means.

a. **Augmentin** can be administered orally, 1 g every 8-12 hours, or injectable, 1 g every 8-12 hours, for 7-10 days, associated with Metronidazole.
b. **Metronidazole** is administered orally 250-500 mg every 8 hours, or intravenously, 500 mg every 8-12 hours, together with Augmentin.
c. **Doxycycline**. If it was not previously introduced, during the viral multiplication phase, it can be introduced later on, as a second antibiotic, instead

of Metronidazole, in combination with Augmentin. Although their combination would, in theory, lead to a mutual negativation of effects through the antagonism between a bactericidal antibiotic (Amoxicillin) and a bacteriostatic antibiotic (Doxycycline), in practice, there are several reported benefits of such association. In small doses (20-25 mg/day), Doxycycline can be used long-term (4-8 weeks) for its pulmonary antifibrotic effect, during the convalescence period as well.

d. **Clarithromycin, Azithromycin, Josamycin** are alternatives to Augmentin for patients allergic to penicillins, or they can be combined even with Augmentin instead of Metronidazole or Doxycycline. Exercise caution with their interactions with other medication, as they prolong the QT interval (an EKG should preferably be done before and after the first 2-3 days of treatment).

**ATTENTION!**

- The antibiotics are to be taken after a meal; also, probiotics should be consumed during and 10 days after antibiotic administration, preferably 2-3 hours after each dose of antibiotic. Antifungal medicines will also be prescribed: Fluconazole or Itraconazole, preferably in a discontinuous manner, every three days of antibiotic treatment.
- There are other possible combinations of antibiotics, especially with the intravenous ones, but they will be reserved for severe cases that have entered the 3rd phase of cytokinic hyperinflammation.
- The use of fluoroquinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin etc.), although efficient at times, involves rather great risks of developing irreversible neurological and metabolic adverse reactions. In the past few years, there have been issued a few official warnings that discourage their use when there are other treatment alternatives available. They are to be administered with great caution, only as and when indicated and supervised by a doctor that is aware of their possibly serious adverse reactions, that go so far as to cause permanent neurological disabilities!

**OBSERVATION**

- Initially, Azithromycin was favoured as the antibiotic of choice to be used in the beginning of antibiotic therapy. In time, though, it was found not to be as efficient as it was claimed. Thus, at present, it has been removed from almost all the official protocols. However, the reason behind its inefficacy might be another. The studies show that it has a significant antiviral effect if it is admi-

nistered together with hydroxychloroquine (Plaquenil)[54]. Since hydroxychloroquine was eliminated from many official protocols, it stands to reason that the Azithromycin's effect has also completely disappeared.

- Consequently, it can be administered from the second half of the symptomatic phase, but only in association with hydroxychloroquine, which potentates its antiviral effect, and with zinc[55,56]. In this context, it is used more for its antiviral effect.
- Azithromycin is administered for a minimum of 3 days and a maximum of 6 days. For optimum absorption, it must be taken 1 hour before a meal. The problem posed by Azithromycin, as well as by hydroxychloroquine, is that they cause an increase in the QT interval on the EKG, which makes their combined administration a risky endeavour, especially with patients under medication for chronic conditions, as there is a significant number of other medicines on the market that prolong the QT interval and thus induce life-threatening cardiac arrhythmias
- To avoid the risk of fibrillation and heart attack during the treatment, it is important to perform an electrocardiogram that would indicate the length of the QTc (corrected QT) interval. If this is under 450-500 milliseconds, then Plaquenil and Azithromycin can be administered together, preferably from the viral multiplication phase, otherwise, Azithromycin would never have to be recommended to anyone, except maybe to patients that are allergic to penicillins.
- If the high fever and pneumonia symptomatology (back pains, tightness in the chest, shortness of breath, decreasing saturation and excessive sweating) persist, the combined antibiotherapy described earlier (Augmentin, Metronidazole, and/or Doxycycline) will have to be initiated immediately.

## D. HYPOGLYCAEMIC AGENTS – METMORFIN

a. **Corticosteroids** produce a significant increase in the blood sugar of diabetic patients. This must be monitored, and the antidiabetic medication must be supplemented accordingly. The treatment with corticosteroids increases the blood sugar levels in all patients, even non-diabetic ones. This is a risk we knowingly take on the short term, for a maximum of 2-3 weeks, as the benefits the anti-inflammatory therapy brings to this disease are important. However, blood sugar levels must be kept under control through medication or natural supplementation (hypoglycaemiant teas, blueberries etc.). 250-500 mg of Metformin in the morning and evening, becomes necessary in the case of elevated blood sugar levels, unless there are contraindications present (heightened risk of lactic acidosis: severe

heart, liver, kidney failure). Although its use with COVID-19 patients was cautioned against at first, due to the theoretical high risk of lactic acidosis (the risk is not significant in patients with average forms of organ failure), the studies have proved that it has a multitude of benefits and a positive effect on survival rates in COVID-19.

b. In the case of diabetic patients whose blood sugar levels cannot be efficiently controlled via Metformin, insulin will be introduced in small doses or, if the patient is already on insulin, the existent doses of insulin will be adequately increased.

## E. ANTIHYPERTENSIVES

a. In hypertensive and previously normotensive patients, it is very likely that their blood pressure will rise; because of that, it is necessary to monitor their blood pressure and prescribe or upgrade their antihypertensive therapy.

b. **Diuretics:** Furosemide (20-40 mg/day) – because cortisol facilitates water and salt retention, especially when the patient consumes salty foods or is administered elevated quantities of saline solutions intravenously – in association with Spironolactone (25-100 mg per day) has added antifibrotic and antiandrogenic effects in COVID-19, by lowering the risk of a cytokine storm.

**c. Conversion enzyme inhibitors.** In spite of some cardiologists' recommendation to avoid angiotensin conversion enzyme inhibitors and sartans, due to the stimulation of the number of viral receptors (represented by the ACE2 enzyme from the surface of cells), it seems that these very categories of medicines play an essential role in stabilizing hypertension in COVID-19. Therefore, the patients already under chronic treatment with Perindopril[57], Ramipril[58], Accupro, Valsartan[59], Candesartan[60,61] etc., do not have to interrupt their treatment, but rather to adjust their doses, according to the cardiologist's advice.

d. **Vasodilators:** Physiotens (moxonidine), 0.2-0.4 mg when needed (maximum of 0,8 mg/day), Doxazosin (1-2 mg x 2-3/day), if there are no contraindications.

e. **Magnesium sulfate injection:** 5-10 ml of an intravenous solution with a concentration of 25% (1,250 mg magnesium sulfate/5 ml vial – 5 ml=250 mg elemental Mg) when needed, 1-3 times a day, via slow IV drip.

**ATTENTION!**

- In COVID-19, the records show cases of severe sinus bradycardia caused by the disease itself, which can be substantially worsened by the treatment with beta blockers. If beta blockers were used prior to the disease, then their dosage will be reduced or gradually stopped, and then they will be replaced by antihypertensives belonging to other classes, if severe sinus bradycardia (under 50 beats per minute) occurs. In this situation, the patient needs to be referred to a cardiologist for proper monitoring and treatment. It seems that an important role in the onset of bradycardia is played by the metabolic intoxication with substances such as bacterial endotoxins and the like. When they are partially neutralised by sodium bicarbonate and when their elimination is eased by liver and gut detoxification cleanses, the bradycardia is alleviated as well. A combined treatment with high doses of intestinal absorbents (activated charcoal, clays, zeolite) will be established, to be taken 2-3 hours apart from other medication and supplements, twice a day.

## F. GASTRIC ANTACIDS:

a. the treatment will either continue with the **Famotidine** recommended in the viral multiplication phase;
b. or more powerful antacids such as **Controloc** or **Nexium** will be introduced, especially during corticotherapy, 1 tablet of 20 or 40 mg per day, with no food ingestion for 30 minutes afterwards. If needs be, they can be administered via injection.

## G. ANXIOLYTICS

For some persons, Dexamethasone or Medrol can cause insomnia and agitation, especially when taken right before bed time. COVID-19 *per se* is a disease that generates anxious-depressive feelings, both through the direct action of its viral load, and through the media-induced panic. These low feelings and states can

be overcome without medication, but in the more severe cases, especially when the person is more emotionally sensitive, the following medicines are useful:

a. Anxiar (Lorazepam) 0.25-1 mg/day – according to Ministry of Health indications, this is the most adequate medicine for the treatment of severe anxiety.
b. Ashwagandha, rhodiola, passiflora, common hawthorn flowers, valerian, melissa etc. are very suitable aids in the control of negative states and anxiety. Naturally, the recommendations for a restful sleep also include high doses of melatonin, which plays an added essential role of immunomodulator and anti-inflammatory agent.

## H. ANTIEMETICS

a. Metoclopramide or Haloperidol are efficient against the COVID-19 symptom of severe hiccup episodes that last for hours or days.
b. Nausea can be addressed successfully with the aid of Ondansetron (4-16 mg/day) or Metoclopramide (maximum 10 mg x 2/day). When the patient vomits about everything they ingest, it is recommended that a 4-8 mg vial of Osetron be injected intravenously or intramuscularly every 12 hours. Be cautioned, this medicine also prolongs the QT interval, so combining it with Plaquenil and Azithromycin is not indicated!

## I. IMMUNE MODULATORS SUCH AS:

a. **Colchicine** – an old medicine used in gout attacks that has proved efficient in blocking the COVID-19 cytokinic inflammation62.

### ADMINISTRATION

- It may be started at the same time with the steroids Medrol or Dexamethasone, or it may be started one or two days earlier. The recommended dose is 0.5 mg every 12 hours, for 10-14 days. The adverse effects are rare, but in some cases, diarrhoea may occur, which will not cease unless the patient stops taking Colchicine.

- The treatment with Colchicine can be continued for up to 30 days even after the corticosteroids are stopped, if the inflammatory processes (sore throat, fever etc.) persist.

**BE CAUTIOUS OF OVERTREATING MILD CASES!**

- This complex treatment employing anticoagulants, corticosteroids and antibiotics is necessary only in moderate and severe COVID-19 cases, which are characterised, first and foremost, by high fever and a decreasing saturation. They should not be administered *a priori* to everybody, starting with day 7 or 8 of disease, when the transition between the viral phase and the inflammatory phase happens!
- Young patients with no risk factors, who do not suffer from persistent fever or desaturation, but who have only vague, unspecific symptoms, will be treated intensively with the vitamins, antioxidants and immunomodulators that were detailed in the "Supplements" chapter.
- A diet as close to nature as possible, as well as gut detoxification procedures (enemas, intestinal absorbents) and liver cleanses (teas, Epsom salt and olive oil flushes) help tremendously with the recovery from disease-induced fatigue, weakness and even depression.
- We have dwelt a lot on the danger of neglecting the disease in its initial stages, which leads to a fast decline in the predisposed patients. There is yet another danger to heed, that of overtreating it, particularly with antibiotics, non-steroidal anti-inflammatories and Paracetamol (taken usually for fever and pains) and even cortisone that is introduced too early and unnecessarily in the treatment scheme.
- It is important that each patient be evaluated by a doctor or nurse, or by a person somewhat experienced in mild and severe COVID-19 cases, or by an impartial observer, other than the patient himself (who is prone to overestimating symptoms and overtreating the disease). This must be done in order to see whether we are confronted with a potentially severe case or merely with a patient who finds it difficult to cope with a mild case of disease (especially due to anxiety).
- If you are unsure of the state or phase of your own condition, until you are able to get a solid opinion, please "abuse" vitamin C, magnesium chloride, teas and natural anti-inflammatories (curcumin, quercetin), apply betadine inside your nostrils regularly, inhale alcohol etc., rather than start one or more courses of antibiotics, thinking they might save you.
- However, if you experience severe symptoms in the inflammatory phase of the disease, it is essential that you start the combined treatment above as soon as possible.

# The treatment of severe COVID-19 forms, characterised by the cytokine storm

(in the late pulmonary or hyperinflammatory phase)

## The transition into the 3rd (hyperinflammatory) phase

Most of the patients that arrive at this stage are those who, having taken no treatment at all during the first two phases of the disease, realise that something wrong is going on with them and/or go to the hospital only after the persistent high fever and respiratory failure has already set in.

There are other, not so many persons who, due to predisposing factors, do not respond well to antivirals, immunomodulators or corticotherapy in small doses. In these, the saturation continues to drop, at an alarming rate, with every high fever episode, which means the patient is deep in the hyperinflammatory – cytokine storm phase, and the case is very grave. In this situation, it is necessary to start a complex treatment based mainly on high doses of corticosteroids, plus a combined antibiotherapy (with a wide spectrum that covers gram-negative as well as anaerobic bacteria).

For these often desperate cases, we recommend high doses of vitamin C (25-50 grams intravenously twice a day) via an IV line, to which they should add vitamin B1, vitamin B6 and magnesium sulfate[63,64.]

Studies show that there is a synergistic connection between the administration of corticosteroids, vitamin C and vitamin B1 (thiamine) in sepsis[65,66,67]. A meta-analysis has recently observed that the intravenous administration of high doses of vitamin C leads to a decrease in mortality rates in critically ill patients[68].

Moreover, studies show that taking daily intramuscular or oral vitamin D doses of 100,000 IU for 5-7 days, considerably increases the chances of survival, most likely due to the anti-inflammatory and immunomodulator effect of high dose vitamin D[69].

As an alternative to pulse therapy with Solu-Medrol, we have Tocilizumab, an inhibitor of IL6 interleukin, which must be administered before irreversible

respiratory failure sets in. It seems, however, that it is less efficient than the pulse therapy with Solu-Medrol administered at the opportune moment.

In addition, natural treatments with a strong antibiotic and anti-inflammatory effect, like Artesunate, Quercetin and Curcumin injections, could be employed as alternatives, but knowledge of their use is restricted to a few researchers that are experienced in utilising them in various pathologies, while their benefits are still very much unknown within the larger medical environment. We hope that this situation will soon change, but until it does, the most efficient and accessible therapy that can stop the cytokine storm is the pulse therapy with Solu-Medrol.

## Pulse therapy with Solu-Medrol

Although the majority of patients can be stabilized with small and moderate doses of corticosteroids, there is a significant percentage of patients that, in the absence of a precocious antiviral treatment and of immunomodulator interventions timely and sustainedly administered, suffer an implacable progress towards the cytokine storm: an exaggerated and uncontrolled inflammation that leads to the rapid destruction of lungs (by compromising their oxygenation) and of other vital organs (heart, liver, kidneys, brain).

In order to recognise the debut of the cytokine storm, it is absolutely vital to monitor constantly the patient's temperature, saturation, pulse, respiratory rate and respiratory effort, as well as analyse other parameters that mirror the patient's overall health state: a sudden lack of appetite, constant nausea, generalized weakness, loss of interest for people and the world around etc. These can be spotted at the beginning of the disease as well, during the viral multiplication phase, but when the 3rd – hyperinflammatory phase of the disease sets in, these symptoms will be extremely brutal and, in the absence of treatment, they will eventually lead to a progressive deterioration in the condition of the patient.

In such cases, it would be very useful to run some lab tests that could confirm the presence of the cytokine storm (a marked increase in CRP, D-dimers, ferritin, LDH, AST and ALT levels, GGT, a decrease in serum albumin, changes in the hemogram: lymphopenia, high total neutrophils

and increased percentage of unsegmented immature neutrophils, the pulmonary CT scan showing extended bilateral infiltrates).

If the clinical signs are suggestive, if the lab tests confirm the systemic inflammatory syndrome, and if the parameters of breathing and oxygenation are declining rapidly, then the best solution is the administration of high doses of corticosteroids via intravenous pulse therapy with Solu-Medrol: 250-500 mg once a day for 3-5 consecutive days.

This intervention can save the lives of patients that are susceptible of emergency admission into the intensive care unit, and even help them avoid long-term mechanical ventilation or dependence on supplemental oxygen[70]. Even so, the pulse therapy must be administered early on, before irreversible pulmonary tissular changes and multiple organ failures set in, which happen during the final phase of COVID-19, right before death occurs.

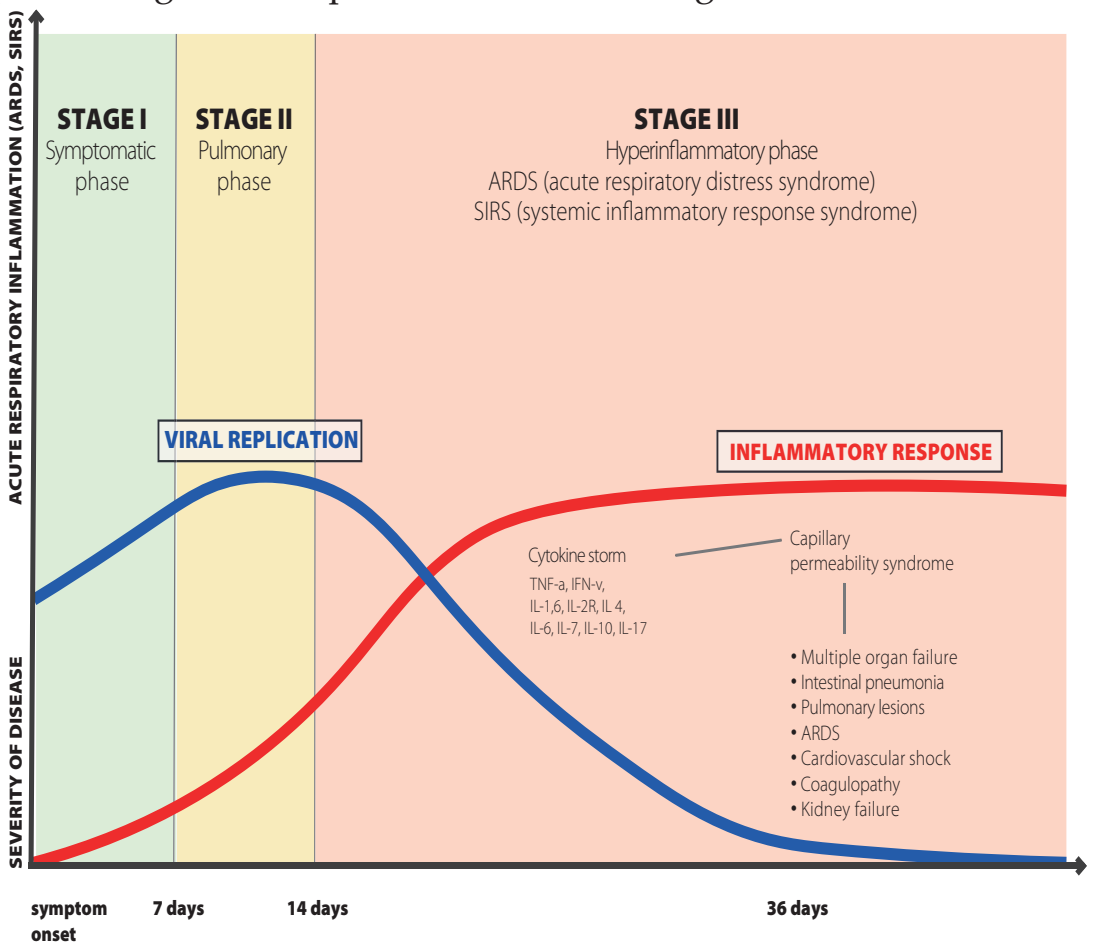



**Figure 2: The inflammatory response in patients that reach the 3rd phase of the disease**

It can be easily noticed that those who reach the hyperinflammatory stage of the disease risk an inflammatory response that can lead to death, even when

their viral load tends to zero. Now is the moment to apply pulse therapy with Solu-Medrol and administer high doses of injectable vitamin C and vitamin B1 and, if available and possible, curcumin and glutathione in IV form, without giving up on the other inflammatory-phase specific medication presented earlier.

## Other adjuvant interventions in the cytokine storm (these can be done only in specialized hospitals or clinics)

## OZONE THERAPY

Both autohemotherapy and intrarectal ozone have proved extremely efficient in reducing the inflammation in COVID and in modulating the immune response. Recommended as major autohemotherapy that offers minimal doses of 8-10 mg of ozone/session. With multiple blood ozonizations, the saturation will rapidly increase.

## INTRAVENOUS LASER THERAPY

This therapy presupposes the irradiation of blood with a laser and a special IV cannula. These are frequencies specific for the destruction of pathogens, the improvement of immune response and blood circulation. Blood irradiation with ultraviolet light from the UVB, UVA and UVC spectrum is just as efficient. There are also the so-called UV-boxes that irradiate blood flowing through a quartz tube, with the help of UV lamps. The procedure is usually combined with major ozone autohemotherapy, which leads to an important increase in blood oxygenation and enhancement in the immune response[71].

## PLASMAPHERESIS

Plasmapheresis is beneficial in reducing the level of proinflammatory mediators, as well as in the absorption of bacterial endotoxins, with the aid of haemofiltration systems equipped with special endotoxin filters[72,73,74].

# The post-COVID syndrome

One of the least tackled issues that severe COVID patients are faced with, is the persistence of certain symptoms for three to six months after the disease, with some cases reporting even the development of chronic conditions such as: pulmonary fibrosis, kidney failure, cardiac arrhythmias and neurological disorders. More often than not, patients leave the hospital with no clear recommendations as to what medication to take during convalescence, with no long-term follow-up plan that could identify certain late complications, much less with any recovery plan feasible with the aid of procedures offered by balneary resorts, for example.

From a study performed on 287 COVID survivors, only 10.8% have suffered no post-disease complications. Among those, 80.2% had had a mild form, 14.9% a moderate form, and 4.9% a severe form. The most frequent post-COVID lingering symptom is fatigue (72.8%), followed by anxiety (38%), joint pain (31.4%), headaches (28.9%), chest pains (28.9%), dementia (28.6%), depression (28.6%), dyspnea (28.2%), cloudy vision (17.1%), tinnitus (16.7%), intermittent fever (11.1%), obsessive-compulsive disorder (4.9%), pulmonary fibrosis (4.9%), diabetes (4.8%), migraines (2.8%), infarction (2.8%), kidney failure (1.4%), myocarditis (1.4%)[75].

Another study performed on a group of 538 patients (61.3% moderately ill), recorded 49 types of lingering symptoms, such as: fatigue (59.1%), fever-like sensation (46.5%), anorexia (24.3%) and diarrhoea (24.3%), loss of taste and smell (22.3%), headaches (21.4%), coughing (20.8), dyspnea (21%)[76].

The very low percentage of persons suffering from pulmonary fibrosis in the two studies is mostly due to the very small number of severe cases considered. In another study that focused more on severe cases, more than a third of the patients that left the hospital presented pulmonary fibrotic anomalies upon discharge[77,78]. Also, 47% had their lung capacity to diffuse carbon monoxide altered, and 25% had a reduced total lung capacity[79]. Why some patients recover from fibrosis and others don't, is yet to be determined[80]. At any rate, there is a tight connection between the anomalies registered through medical imaging and the alteration of pulmonary function[81].

The post-COVID neurological syndrome[82] describes the multitude of neurological and neuropsychological diseases that follow COVID. This is about depression and anxiety, sleep disorders, post-traumatic shock[83] and even worse, about the onset of some neurodegenerative and neuroinflammatory processes[84] and some neuropsychiatric diseases[85], that originate both from the virus-induced inflammation, and from the micro and macrovascular thromboses[86,87]. The neuropsychological post-COVID changes become easier to explain as medical imaging has proved that, three months after the recovery from COVID-19, all 60 of the monitored persons presented significant structural changes in various areas of their cerebral cortex[88]. Of the 60 persons, 78.33% had had a mild form, 20% a severe form, and only 1.67% had reached a critical state. This shows that cerebral structural changes are a constant in COVID-19, and their main risk factor is the very immune dysregulation, whose effects may include long-term inflammation, with all the consequences already mentioned, as well as many others.

In view of all these, COVID-19 therapy does not have to end at the moment when the virus can no longer be detected in the body, but much later, when the immune processes will have regained their balance, the inflammation will have disappeared and the processes of cellular regeneration and neurogenesis will have played their part in the complete post-disease recovery.

For that to happen, the patient's biological parameters involved in immune processes, inflammation and coagulopathy have to be followed at least for a while after hospital discharge or after overcoming the disease at home. If the D-dimers are still elevated (at least two times the normal value) and the C-reactive protein is significantly higher, if the person has been immobilized during the disease and displays a sum of risk factors, it is advisable to follow doctor Marik's[89] protocol and continue the anticoagulant[90,91] and anti-inflammatory treatment.

Likewise, continuing to administer small doses of the afore mentioned supplements plays yet another important part in the post-COVID recovery, as most of them act as antioxidants, anti-inflammatories, antifibrotics and steroidal immunomodulators.

For instance, the polyphenols and high doses of vitamin D, vitamin C and antioxidants like N-acetylcysteine, play an essential role both in preventing pulmonary fibrosis and in regulating the immune processes.

There are a few mechanisms of post-COVID fibrosis occurrence, and they are mostly connected to the activation of the transforming growth factor beta (TGF-β) and of protein kinase mTor signalling pathway[92,93]. Honokiol[94], Vitamin D[95], Resveratrol[96], Quercetin[97], Epigallocatechin-3-gallate (EGCG)[98,99] and Luteolin[100] are important inhibitors of the signalling of this growth factor. N-acetylcysteine blocks the transformation of epithelial tissue into mesenchymal tissue, which follows the activation of the transforming growth factor beta (TGF-β) and thus prevents fibrosis[101]. Most of these polyphenols are remarkably active in blocking the mTor signal and inhibit the fibrotic process accordingly. The best known are: Resveratrol[102,103,104], Quercetin[105], Curcumin[106,107], Epigallocatechin-3-gallate (EGCG)[108], Genistein[109]. Caffein[110] is also recommended in this process. In therapeutic doses, Omega 3 is another important anti-inflammatory agent that should not miss from the post-COVID-19 therapy.

Needless to say, hyperbaric oxygen[111,112], ozone therapy[113,114,115] and other detoxification methods are recommended both in the treatment of COVID, and in the post-COVID recovery. These have a key role in cellular oxygenation and in angiogenesis and immunoregulation processes.

## Interrupting the corticotherapy in COVID-19

The duration of corticotherapy in moderate COVID-19 cases should not exceed 10-14 days, but in severe and critical cases, it can be extended up to 3 weeks or even more, with a gradual reduction in dosage.

There are two major roles of corticotherapy in COVID-19: saving the life of the patient and reducing pulmonary fibrosis and other complications triggered by systemic inflammation.

The application of high and very high doses (pulse therapy) for a few days during the cytokine storm will be life saving for the patient. The prolonged application of small doses, progressively decreased (e.g. 16 mg – 8 mg – 4 mg Medrol per day), have the role of preventing residual pulmonary fibrosis and myocardial, renal and cerebral lesions.

The graph below shows that the interruption of steroid (anti-inflammatories like Medrol and Dexamethasone) and vitamin C treatment increases

the risk of reinflammation which, unfortunately, occurs in many patients who, after hospital discharge, do not continue the anti-inflammatory treatment until full recovery, which can take one or two weeks or more, depending on the severity of the disease.


**Figure 3: Relapse of disease if treatment with steroids (Medrol) and vitamin C is interrupted**

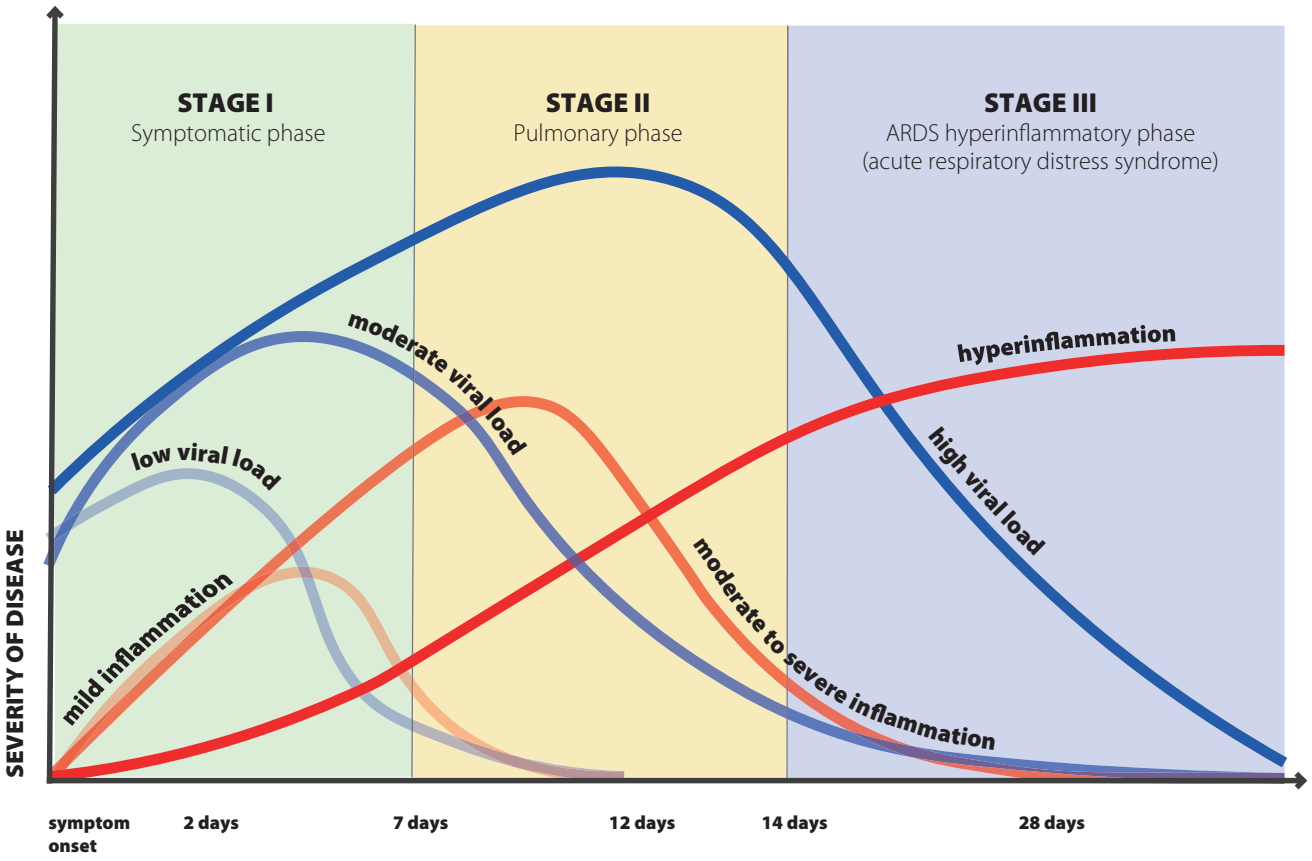
Marik, Paul. "EVMS critical care COVID-19 management protocol." Norfolk, VA: Eastern Virginia Medical School (2020).

At the beginning of the recovery period post-hospital discharge, the patients should typically continue, on the basis of their lab test results, with the anticoagulant and the steroidal anti-inflammatory medicines, with methylene blue inhalations, with Doxycycline 25 mg and with the recommended supplements. This is valid when the D-dimers and the other coagulation and inflammation factors are still considerably elevated, but also when some post COVID-19 pulmonary sequelae exist. The treatment averts fibrosis and even a certain return of the disease inflammation-wise. Many a time, the patients, when discharged from the hospital with no much needed medical treatment, have had a severe relapse, have been readmitted into the hospital and, in some cases, died.

However, the graphs cannot capture on a real scale the difference in viral load between mild and severe forms. In severe forms, viral load levels can be found - viruses per milliliter - with orders of magnitude up to 4-5 times higher than in mild forms. This explains why some people do not transmit the virus to family members, and others transmit it to most people they come in contact with.

Viral levels 10,000 or 100,000 times higher in a person hospitalized in the same ward with other COVID patients can slow the healing of others by the high amount of viruses present in the aerosols of that salon. Considering that with time the viral load decreases, the last hospitalized patients are the most strongly contagious, thus being able to bring back to the aerosols of the salons higher viral levels.

In this context, air filtration equipment, at least in the larger hospital wards, would be essential for healing patients, but also for protecting doctors from the danger of contamination.




| | STAGE I<br>Symptomatic phase | STAGE II<br>Pulmonary phase | STAGE III<br>Hyperinflammatory phase |
|---|---|---|---|
| CLINICAL SIGNS | normal saturation 98%-99%, mild cough, body temperature 37°-37.5° C, headache, asthenia, myalgia, loss of taste and smell, nausea, diarrhoea, aches, sharp pains in affected organ or area | saturation decreased under 93%, body temperature ~ 38° C, dyspnea, hypoxia, aches, tightness in chest and back, adenopathies, paresthesia, dysphagia, cognitive problems, depression, insomnia | saturation decreased to 70%-89%, body temperature 38°-39.5° C, interstitial pneumonia, pulmonary lesions, ARDS, cardiovascular shock, coagulopathy, renal and hepatic failure |
| MEDICATION | Ivermectin, Umifenovir, Plaquenil, Methylene blue, Dypiridamole, Aspenter, Famotidine, Paracetamol, Doxycycline, Metformin | Clexane (or Eliquis), Medrol (or Dexamethasone), Colchicine, Ivermectin, Umifenovir (if it was not administered during the symptomatic phase), Plaquenil, Methylene blue, Dypiridamole, Famotidine, Metformin, Spironolactone antibiotics if high fever, Augmentin (Cefort or Meropenem), Doxycycline, Metronidazole, | Clexane (or Eliquis), Solu-Medrol therapy, injectable Vitamin C and B1, antibiotics if high fever, Augmentin (Cefort or Meropenem), Doxycycline, Metronidazole, Metformin, Dypiridamole |
| SUPPLEMENTS | **Essential throughout the entire disease**<br>Vitamin D3, Vitamin C, Zinc, Magnesium Chloride, Omega 3, Selenium, Melatonin, Quercetin, Curcumin | **Optional throughout the entire disease**<br>Artemisinin, N-acetylcysteine, Berberine, Epigallocathechin gallate (EGCG), Astragalus, Ashwagandha, Feverfew, Oleuropein, Vitamin B Complex, Vitamin E, Vitamin A, Proteolytic enzymes such as Wobenzym, Silymarin, Alpha-Lipoic Acid | |

**Figure 4: A representation of the three phases of disease, with stage specific treatment, tailored according to viral load and inflammatory response**[116,117]

ANNEX 1

# COVID-19 symptoms

In truth, the man becomes aware of the disease when the symptomatic phase starts. Due to the reasons described at the beginning of this material, most of the patients struggle to identify this symptomatic phase debut, which is a crucial moment in the disease management protocol that comprises phase-specific therapy recommendations.

## Symptoms more frequently found in the first days of disease

1. throat irritation, congestion and itchiness that causes mild cough, the feeling that something discomforting is stuck in the throat, or even mild to moderate throat pain;
2. mild throat soreness;
3. dry or mildly productive cough;
4. acute headache, much more severe than usually;
5. dizziness;
6. a slight rise in temperature – around 37.5°C, that can revert to normal values during the day, and then go up again in the evening and in the morning.
7. shaking chills;
8. intense pain throughout the body;
9. muscle pain (myalgia);
10. back pain;
11. joint pain (arthralgia);
12. bone pain;
13. intense fatigue (asthenia), the need to lie down and sleep anywhere, a sort of burn-out state at its lowest limit;
14. loss of taste and smell;
15. pain in sinuses or in the throat ganglia that can get inflamed;

16. intense, sharp pains in the area of certain organs – bile-liver or kidneys, or in any area where an organ has been ailing for several years;
17. lack of appetite;
18. nausea;
19. vomiting;
20. diarrhoea;

## Problems associated with a decline in the disease, the last part of the symptomatic phase and the first part of the inflammatory phase

21. tightness in the chest and back, with the slight sensation of discomfort when breathing, a symptom that occurs later, usually in the second part of the symptomatic phase, around day 5-7;
22. insomnia, depressions, anxiety, panic attacks, cognitive issues, brain fog, hallucinations, loss of consciousness, convulsions;
23. excessive sweating, especially at night;
24. dysphagia, or difficulty in swallowing – the difficult passage of food through the upper digestive tract, from the pharynx, to the oesophagus, to the stomach;
25. adenopathies (enlargement of lymphatic ganglia with painful manifestations);
26. hiccup episodes that last for hours or days;
27. urticaria, eczemas, or other forms of skin rashes;
28. disturbances of eyesight: cloudy vision, double vision;
29. numbing of hands, arms, legs, feet, face (paresthesias);
30. sharp kidney pains (in the back, under the rib cage);
31. decreased urine output;
32. loss of sphincter control;
33. oedemas (in the lower limbs, the face – especially swollen eyelids);
34. bruising or other changes of extremities (fingers, toes).

Upon entering the inflammatory phase, there is a rapid decrease in the saturation, which must be monitored throughout the disease, with the aid

of a pulse-oximeter. That being said, it is imperative to have a pulse-oximeter at hand.

**ATTENTION!**

- COVID-19 can cause the so-called *silent hypoxia,* wherein the saturation may decrease to critical values, without the patient displaying signs of suffocation or other symptoms that would betray the critical state he is in. Therefore, it is possible for a person to reach an oxygen saturation of 80% without realizing it, and when the condition worsens, to be compelled to have an emergency admission into the hospital, or else be in danger of losing his life. This is why many were admitted to the Intensive Care Unit and later intubated. Consequently, absolutely every patient must have their arterial oxygen saturation monitored after the second half of the symptomatic phase.

## Medical devices necessary in COVID-19

In order to have a correct reading of the saturation, one must first check the accuracy of the pulse-oximeter on healthy people. Many of the devices on the market have high error rates. The errors appear mainly because of the low sensitivity of the device, so it is necessary to:

- have the finger used for measuring warm or warmed;
- have the fingernail clean, without varnish or polish;
- wait for at least 20-30 seconds until the value stabilizes;
- change the finger (use preferably the index or middle finger) if the value is too low, because there is a possibility that the chosen finger might be poorly irrigated with blood.

A blood pressure monitor will also be needed in any house where there is a COVID-19 patient, especially when the patient has a sum of risk factors as well. In the case of pre-diabetic or diabetic patients, the glucometer should not be missing from the kit, and the blood sugar must be monitored daily, at least during the treatment with steroidal anti-inflammatories.

Obviously, when the saturation goes below 93%, the oxygen must be supplemented with the aid of an oxygen concentrator.

**ATTENTION!**

- The symptomatic phase may debut with one or more of the above mentioned symptoms. When a combination of two of these symptoms appears, or when excessive burnout is associated with one of them, for example with discomfort in the throat area, itchiness and mild cough or fever, it is very likely that COVID-19 is the culprit. If loss of taste and/or smell appears, then it is certainly COVID-19, but that does not make it a compulsory symptom, as many people seem to believe. The origin of symptoms having been labelled, it is high time the treatment were started.
- We recommend you to have on hand at least the supplements needed in the therapy, if not some medication like the antivirals Arbidol, Ivermectin or Plaquenil and zinc, which can also be taken prophylactically, in small doses.

ANNEX 2

# The immune processes in the symptomatic phase

There are mainly four stages of the disease produced by the SARS-CoV-2 coronavirus. However, to avoid any misunderstanding, we will exclude the incubation phase from the diagrams, since it does not display any symptom, and therefore we cannot identify and treat the infection during it. The incubation period lasts an average of 5 days. Therefore, the phases of the disease that correspond to the different stages in its evolution are:

1. **The symptomatic phase, c**haracterized by viral replication, which lasts about 7 days;
2. **The early pulmonary phase;**
3. **The late pulmonary phase,** also known as the hyperinflammatory phase, characterized by the cytokine storm.

Both the early and the late pulmonary phases belong to the inflammatory response of the body stage. This means that the virus is not the problem during these two phases, but the inflammation generated as a response to its attack is. We are confronted with an exaggerated immune response now. Depending on the improvement or decline of the disease, these two phases last a minimum of one week and a maximum of three weeks, or end in death.

Not all people go through all three phases of the disease. Some that develop the mildest forms may stop at the first phase (see the graph in Figure 4). Those who develop more severe forms reach the early pneumonia stage (see the graph in Figure 6), but overcome it easily, and some who develop the most severe forms, marked by the cytokine storm, reach the hyperinflammatory stage or phase, where their lives are in danger (see the graph in Figure 7). The goal of the therapies is to block the evolution of the disease in as early a phase as possible, by inhibiting viral replication and the pathologic inflammatory response.

The symptomatic phase is extremely deceptive, and most people treat it too leniently for the following reasons:

## Cognitive and psychological causes:

- Some people are truly unaware that they have COVID-19, because they do not know what it entails. The media focuses more on frightening the masses, rather than informing them.
- Other people, in spite of having all the symptoms, do not want to believe they have COVID-19, although they might suspect or guess it is thus. Here we have two different typologies:
  1. those who, psychologically speaking, cannot accept their "condemnation", as they are constantly terrorized by messages in the media, who think that having COVID means the end of their lives;
  2. and those who do not believe COVID exists, or that it is nothing more than an ordinary respiratory virosis, which requires no attention at all.

## Causes dependent upon the characteristics of the disease:

- Undoubtedly, during this symptomatic phase, COVID-19 is not a very convincingly terrifying disease. That is because its characteristic symptoms, that last, as previously mentioned, between 6-8 days, are in most cases weaker than those of an ordinary respiratory virosis that we have gotten used to in the past years.
- In the majority of respiratory viroses, the severity of symptoms follows closely the viral replication, and thus the disease ends up identifying with the viral replication, which prompts the patients to take curative measures and start a treatment course. In COVID-19, there is a delay in the maximum level of severity of the disease, so many people do not realise that this virosis may endanger their lives.
- Everybody expects a virosis to pass after 7-8 days; however, COVID-19 raises its ugly head only after this interval.

In the case of COVID, the maximum level of viral replication is reached quite a few days before the maximum level of the worst disease manifestation, and so, even when the disease seems to be gone, the patients find they cannot breath anymore and their state is deteriorating rapidly.

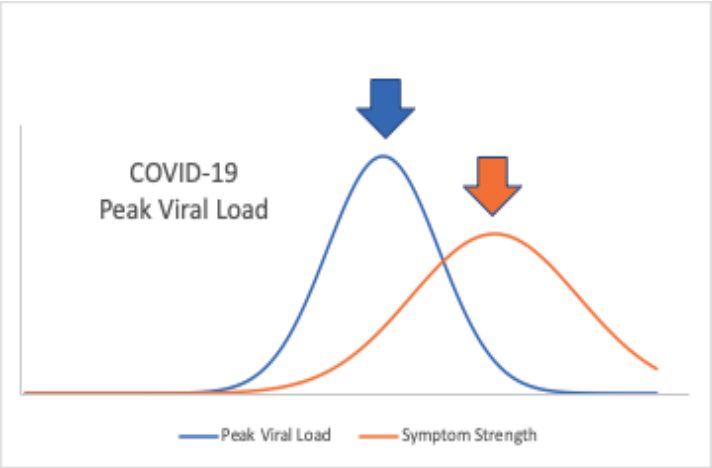



**Figure 5: The maximum level of the severity of symptoms is delayed a few days compared to that of the viral replication**

- An additional argument is signalled by the fact that a lot of people, family members included, have not developed too severe a form of COVID-19, especially the young, or the normoweight or the ones without comorbidities. So, when they see family members or friends going through a mild form of disease, they are convinced or, at the very least, they would like to believe the same will happen to them, too. Very few realise that the risk factors are the most important in this disease, and the conditions you suffer from – your comorbidities, are but one of them.

Thus, keeping in mind at least the reasons given above, most of the people make the great mistake of not getting the proper treatment during this phase of the disease.

If they were to take action now, at this stage, they would make firm decisions and protect themselves against the factors that could aggravate their disease, and only a handful of them would then reach the point of extremely dangerous desaturation, intubation and death. This is due to the fact that, at this phase, the viral replication could be considerably reduced, enough so as to avoid the cytokine storm, that "tsunami" that puts man's life in danger.

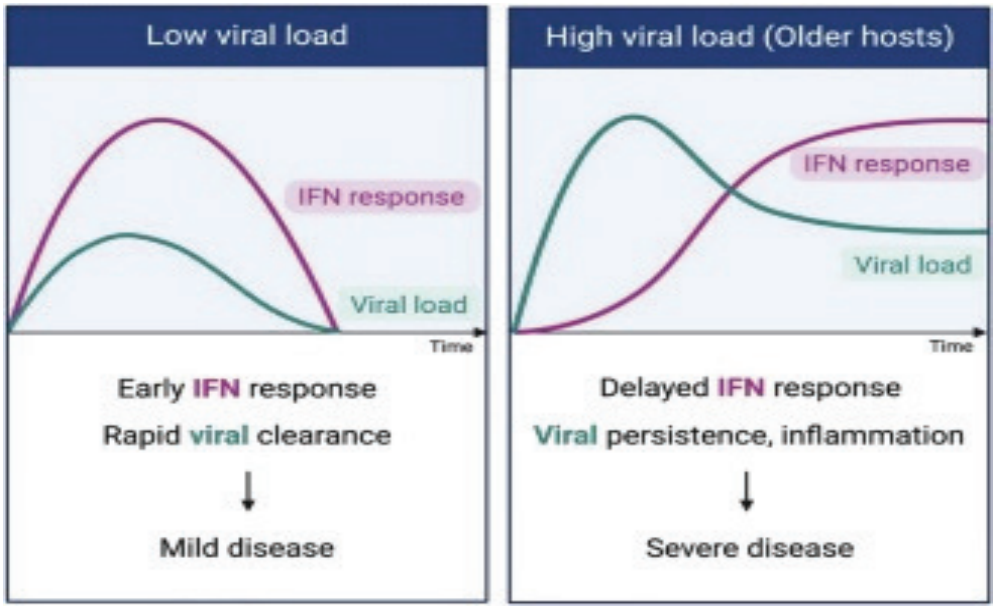
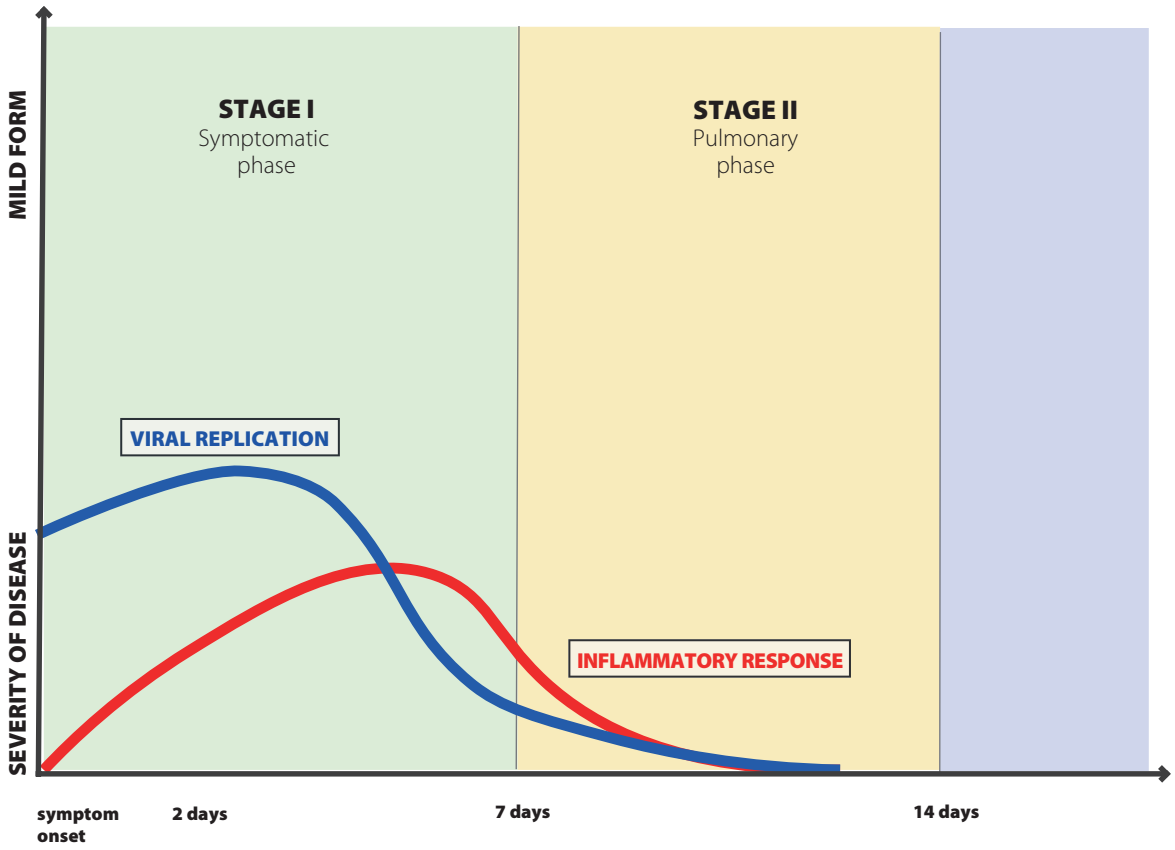



**Figure 6: Interferon response to the presence of the virus in the body**

See: Park, Annsea, and Akiko Iwasaki. "Type I and Type III Interferons–Induction, Signalling, Evasion, and Application to Combat COVID-19." Cell Host & Microbe (2020).

In the first image, we have a low level of viral load and an early increase in interferon, which will contribute to a quick elimination of the virus, so the disease will have a mild form. In the second image, we have a high level of viral load and a delayed interferon response, which causes a long-term persistence of the virus and an exaggerated inflammation, so the disease will become more severe.

Figure 2 shows that an adequate treatment of the viral replication during the symptomatic phase will cause the inflammatory response to become sufficiently weak, so as to make the disease seem and feel like a mild virosis. This involves the use of the entire antiviral, immunomodulator, and antioxidant strategy that contributes to the impairment of viral replication.




**CLINICAL SIGNS**

**STAGE I**
Symptomatic phase
– days 1-7 from the onset of symptoms –

**Normal oxygen saturation**
Body temperature 37°-37.5° C, even higher in some cases. Fever subsides to paracetamol. A mild cough, headache, asthenia, myalgia, loss of taste and smell, nausea, diarrhoea, aches, sharp pains in affected organ or area.

**TESTS**

During the mild phase, the medical test results are normal, but in the moderate phase, there are changes in: Lymphocytes ↓, Albumin ↑, PCR ↑, LDH ↑.

**MEDICATION**

Ivermectin, Umifenovir, Plaquenil, Methylene blue, Dypiridamole, Aspenter, Famotidine, Paracetamol, Doxycycline, Metformin, Spironolactone (for men)

The antivirals not taken during the symptomatic phase (you may not have them at hand) can be administered during the next 7 days as well.

**SUPPLEMENTS**

**Essential throughout the entire disease**
Vitamin D3, Vitamin C, Zinc, Magnesium Chloride, Omega 3, Selenium, Melatonin, Quercetin, Curcumin

**Optional throughout the entire disease**
Artemisinin, N-acetylcysteine, Berberine, Epigallocathechin gallate (EGCG), Astragalus, Ashwagandha, Feverfew, Oleuropein, Vitamin B Complex, Vitamin E, Vitamin A, Proteolytic enzymes such as Wobenzym, Silymarin, Alpha-Lipoic Acid

**Figure 7: COVID-19 during the symptomatic phase in mild cases**

**ATTENTION!**

- In order to follow the therapy in COVID-19, it is vital to determine as accurately as possible the day in which the symptoms started. That is the precise moment from which the disease time/duration is measured.
- The treatment must be taken regardless of pre-existing risk factors and the gravity of symptoms. The graph shows a mild case, however, the protocol must be followed, irrespective of the severity of the form. A mild case means either that there are no risk factors involved, or that the antiviral treatment has blocked the viral replication from the start, and so the virus could not replicate sufficiently enough, so as to generate an elevated immune response.
- Some of the risk factors might be unknown. For instance, intestinal dysbiosis, a condition that would presumably aggravate the disease, that would most likely have marginally intense symptoms throughout the symptomatic phase, may trigger an overwhelming inflammatory response in the 7th-8th day.
- In the first 7 days of disease, it is recommended to take steroidal anti-inflammatories. In order to reduce inflammation, the steroids (Medrol and Dexamethasone) inhibit the immune response that facilitates viral replication, i.e. a high viral load and a long-term virus excretion interval. That is to say, a more severe form of COVID-19. The steroidal anti-inflammatories should be administered after about 7 days from the onset of symptoms, preferably at the first signs of severe inflammation, which can be detected in the substantial drop in oxygen saturation, under 93%, for example.
- The moment the steroidal anti-inflammatories are introduced and their dosage established is perhaps the most important action against this viral disease. If it is done earlier than it should, then it may make the disease worse. If it is done too late, it may enhance the risk of the saturation dropping and the inflammation getting out of control.

ANNEX 3

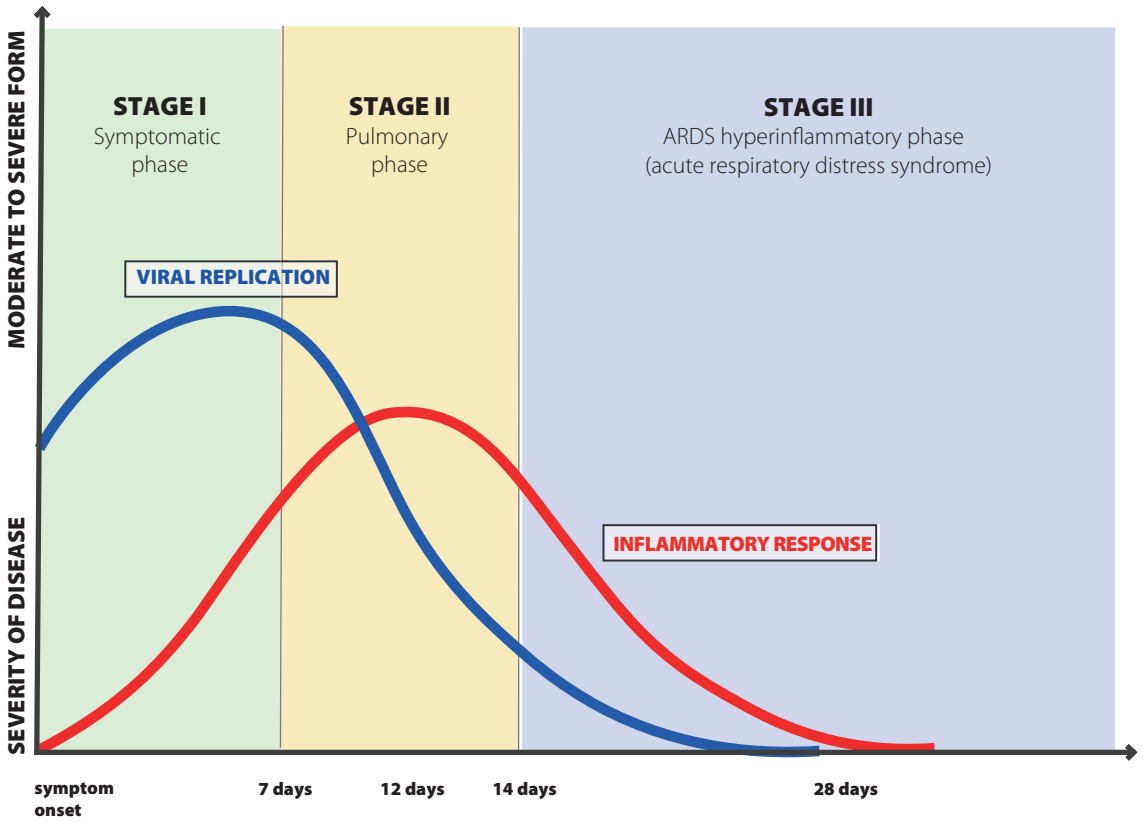
# The early pulmonary (inflammatory) and the late pulmonary (hyperinflammatory) phase

The greatest issue raised by the SARS-CoV-2 virus is none other than the deregulation of the immune system. For instance, it blocks the early response of innate immunity, and the response of type I and III interferon (IFN-I and IFN-III), both of which could have inhibited the viral replication, and triggers a powerful response in proinflammatory cytokines, IL-1B, IL-6, TNF-$\alpha$ etc., thus throwing the ratio between Th1 and Th2 off balance[118.]

The mildest cases, asymptomatics included, have a good response of Th1 (T helper 1) cells, which means an improved control over the immune response and a better activity of cytotoxic T cells. Conversely, in severe COVID-19 cases, the Th1 lymphocytes are inhibited and reduced to a very small number, just like in the case of AIDS. Children, adolescents and healthy people under and around 40 years of age, have a good response to COVID-19, due both to the increase in type I and III interferon, and to a good response of Th1 lymphocytes. This explains the milder forms they develop: in their case, the viral replication is very much inhibited, the virus is limited from spreading throughout the body, the immune response is balanced, and the proinflammatory cytokine storm is avoided.

In the representation below, we have a severe case of COVID-19, characterised by a high viral load and a rather long-term virus elimination period, which can vary between 15-30 days[119], case that was triggered by an inflammatory response, elevated in reaction to a high level of viral replication.

The cause of this severe form can be blamed on the risk factors, but in many cases, it may be attributed to utter neglect of the disease during the symptomatic phase. Even those who do acknowledge the disease, are convinced that taking Azithromycin and Paracetamol, or Sinupret and Tamiflu is quite enough, and that the virus is thus defeated. In the meanwhile, the virus multiplies unhindered by anything, and gets ready to show its major virulence only during the early and late pulmonary phase.




**CLINICAL SIGNS**

**STAGE II**
Pulmonary phase
– days 7-14 from the onset of symptoms –

**Oxygen saturation decreased under 93%, respiratory rate 30/minute**
Body temperature ~ 38° C – in mild forms it may stay around 37.5° C and in severe forms around 38.5° C -39° C – dyspnea, hypoxia, aches, tightness in chest and back, adenopathies, paresthesia, dysphagia, cognitive problems, depression, insomnia

**TESTS**

Lymphocytes ↓↓, Neutrophils ↑↑, Thrombocytes ↓↓, Albumin ↓, PCR ↑↑, LDH ↑↑, D-dimers ↑↑, Fibrinogen ↑, Ferritin ↑↑↑, Prothrombin ↑, Troponin ↑, Procalcitonin ↑, IL-6 ↑↑

**MEDICATION**

**At this stage, anticoagulant and anti-inflammatory medication is introduced, and antivirals are eliminated, if they have already been administered.**
Clexane (or Eliquis), Medrol (or Dexamethasone), Colchicine,
Antivirals: Ivermectin, Umifenovir, Plaquenil (if it was not administered during the symptomatic phase)

Antibiotics (when high temperature does not subside to paracetamol):
Augmentin, Doxycycline, Metronidazole, (or Cefort or Meropenem), Dypiridamole, Methylene blue, Famotidine, Metformin, Spironolactone

**SUPPLEMENTS**

**Essential throughout the entire disease**
Vitamin D3, Vitamin C, Zinc, Magnesium Chloride, Omega 3, Selenium, Melatonin, Quercetin, Curcumin

**Optional throughout the entire disease**
Artemisinin, N-acetylcysteine, Berberine, Epigallocathechin gallate (EGCG), Astragalus, Ashwagandha, Feverfew, Oleuropein, Vitamin B Complex, Vitamin E, Vitamin A, Proteolytic enzymes such as Wobenzym, Silymarin, Alpha-Lipoic Acid

**Figure 8: COVID-19 therapy during the pulmonary phase**[120,121]

ANNEX 4

# Medical tests in COVID-19

Medical tests are extremely suggestive for the evolution of disease in SARS-CoV-2[122,123,124,125]. Among the first to suffer significant changes, is the number of lymphocytes[126,127,128]. The connection between the severity of the lymphopenia and that of the disease is so strong, that it made possible the development of a predictive model. Therefore, Li Tan et al.[129] have found that the relative lymphopenia (lymphocytes percentage) thresholds of 5% and 20% are highly relevant when medical tests are checked in two moments of the disease, namely on days 10-12 and on days 17-19 from the onset of symptoms. Thus, those who will have the lymphocyte values over 20% during the first 12 days, are certainly curable. Those whose values upon the second check-up were under 5% were definite candidates to the intensive care unit.

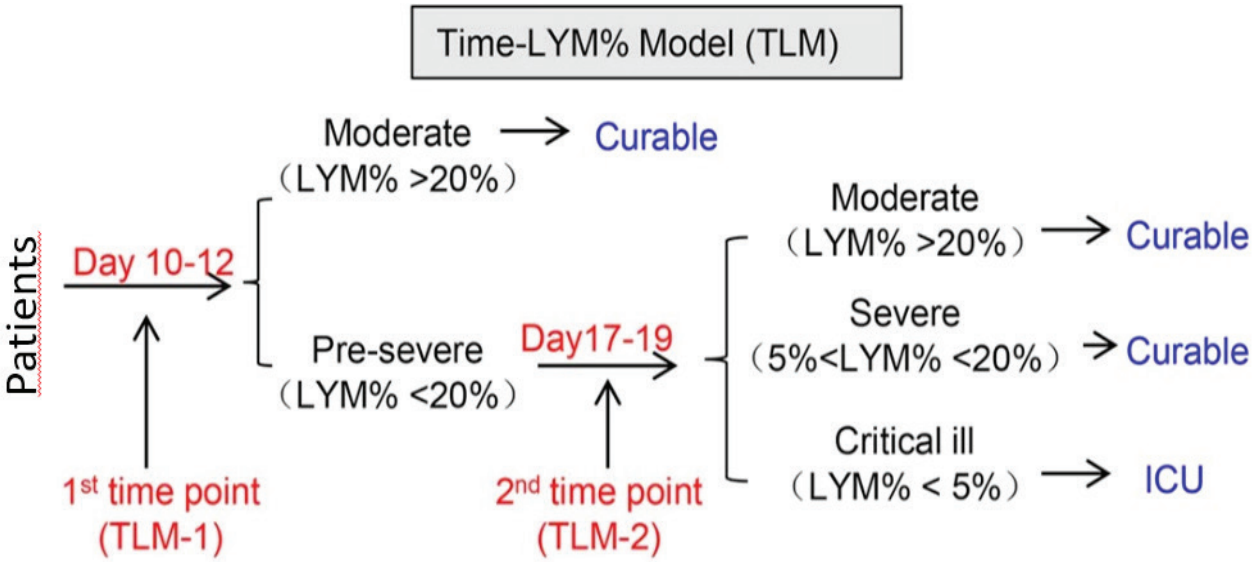



**Figure 9: Predictive model of disease gravity based on lymphopenia observed in two 7-day apart moments**

See: Tan, Li, et al. "Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study." *Signal transduction and targeted therapy* **5.**1 (2020): 1-3.

Another predictive marker in COVID-19 is the C-reactive protein (CRP). It seems that an early rise in CRP during the first few days after symptom onset represents an increased risk for a severe form of COVID and a high negative score for the CT[130,131]. The same thing can be said about interleukin-6 (IL6)[132], which increases to up to 10,000 times its normal values in severe cases[133].

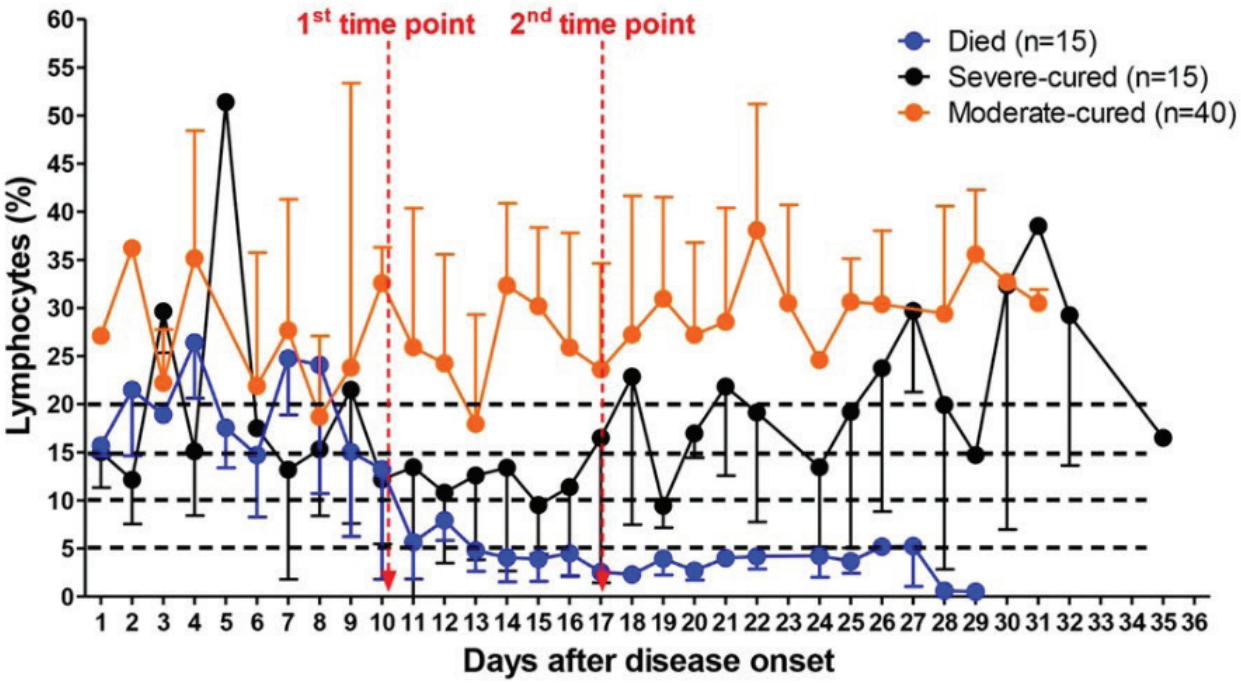



**Figure 10: Variations of lymphocyte values in terms of time and COVID disease severity – moderate, severe, fatal**

See: Tan, Li, et al. "Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study." *Signal transduction and targeted therapy* **5.**1 (2020): 1-3.

The marked increase in ferritin can also be considered a negative prognostic marker in severe cases[134] and of mortality[135].

Other COVID specific increased values are in:

- Lactate Dehydrogenase[136] (LDH) > 245 U/L;
- ALT > 40 U/L;
- AST > 35 U/L;
- D-dimers > 0.55 mg/l[137,138,139];
- Fibrinogen > 4 g/L[140,141];

- Prothrombin time > 15 seconds[142,143];
- Troponin I > 28 ng/L in severe cases (high sensitive cardiac Troponin I)[144,145,146,147];
- IL-6 > 20 pg/ml in severe forms, > 55 pg/ml in critical forms, with high risk of mortality;

Also, decreasing in COVID-19 are the values of:

- Albumin < 35 g/L[148,149] (the most probable mechanism is not the hepatocellular injury, but the diffusion of albumin in the extracellular space via an increased capillary permeability);
- Thrombocytes[150,151,152], a mild thrombocytopenia appears: 100-150 x 109 thrombocytes/L.

One of the best analysis of the most important markers associated with the cytokine storm and with a poor prognostic in COVID-19, is found in Zhang et al.[153]

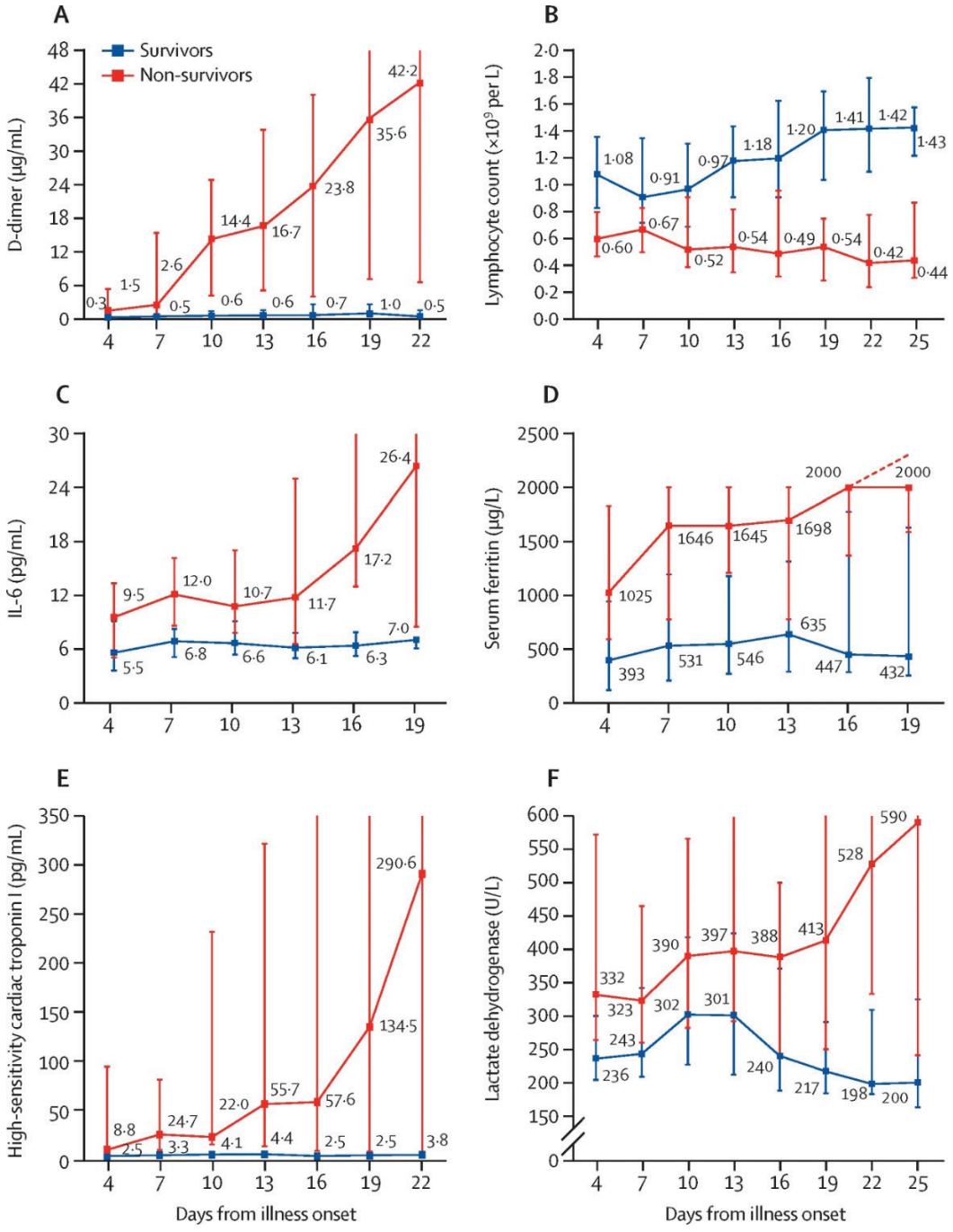



**Figure 11: Variations in the most important markers of cytokine storm in COVID-19 survivors and non-survivors**

See: Zhou, Fei, et al. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." The Lancet (2020).

| | | Zhongliang Wang et. all[154] | |
|---|---|---|---|
| | Interval of normality | $SpO_2$≥90%(n=36) | $pO_2$<90%(n=7) |
| Lymphocytes | (1.1-3.2) | 1.19(0.95-1.46) | 0.61(0.37-1.00) |
| Neutrophils × $10^9$/L | (1.8-6.3) | 2.16(1.6-2.70) | 5.24(2.90-6.44) |
| Thrombocytes | (125-350) | 72.00(138-206) | 167.00(144-215) |
| Albumin g/L | (40-55) | | |
| Alanine Aminotransferase, U/L | (10-40) | 24.00(16.00-40) | 31.50(23.00-52.00) |
| Aspartate Aminotransferase, U/L | (8 – 33) | 26.00(21.00-39) | 40.50(24.00-62) |
| C-Reactive Protein mg/L | (0-10) | 11.30(6.53-26) | 81.55(48.85-105) |
| D-dimer mg/L | (0-0.55) | | |
| LDH U/L | (140 –280) | 207.00(181.00-274.00) | 517.50(267.00-549 |
| Procalcitonin ng/L | <0.05 | 0.13(0.13-0.15) | 0.13 (0.13-0.15) |
| Creatinine µmol/L | (57-97) | 65.30(58.00-78.50) | 71.50(52.50-80.40) |
| IL6, pg/ml | <0.71 | 6.69(4.44-12.43) | 51.69(34.31-161.65 |
| IL10, pg/ml | <2,130 | 4.18(3.31-5.275) | 6.92(4.21-11.53) |
| TNF$\alpha$, pg/ml | <1,323 | 2.08(1.93-2.35) | 2.14(1.90-2.34) |

| | Luo, et al.[155] | | |
|---|---|---|---|
| | Deceased (n=100) | Recovering (n=303) | Severe or critical (n=205) |
| | 0.73 (0.46-0.92) | 1.18 (0.90-1.62) | 0.90 (0.54-1.24) |
| | 7.09 (4.00-11.00) | 3.10 (2.39-4.43) | 4.62 (2.97-7.97) |
| | 169 (121-219) | 205 (153-264) | 179 (136-245) |
| | 33.2 (31.2-36.5) | 38.5 (35.4-41.7) | 34.7 (32.3-37.9) |
| | | | |
| | | | |
| | 95.0 (58.9-178.7) | 23.8 (5.0-49.9) | 59.7 (20.7-103.5) |
| | 5.38 (1.21-17.78) | 0.50 (0.27-1.07) | 1.22 (0.52-7.46) |
| .00) | | | |
| 0.78 | 0.199 (0.116-0.949) | 0.044 (0.026-0.070) | |
| | 82.0 (62.8-104.8) | 68.0 (59.3-82.0) | 71.0 (61.0-88.0) |
| 5) | | | |
| | | | |
| | | | |

## The immunological window in weeks 2 and 3 of the disease and the importance of imagistic diagnosis (computerized-tomography)

A crucial theme is counting among the COVID-19 diagnosed patients those who have symptomatology highly suggestive of this disease, but whose PCR tests for SARS-CoV2 (from nasal or nasopharyngeal swabs), and blood tests for specific IgM and IgG antibodies are negative.

An explanation would be that the majority of people produce detectable antibodies only after 2-3 weeks of disease and, at the same time, many cease to have detectable levels of viral load in the nose and throat 1-2 weeks from the onset of symptoms.

Consequently, starting from the second and up to the end of the third week, exactly during the time that some patients reach respiratory failure, they risk being diagnosed with other diseases and not receive proper care, if insufficient attention is paid to the succession of symptoms, if they are not seen by experienced clinicians and lab tests and CT scans are not performed so as to raise the COVID-19 alarm.

In this phase of the disease, it is vital to have a native pulmonary CT scan. COVID-19 is known to produce very suggestive lesions, bilateral interstitial infiltrates that look like ground glass, with a tendency towards organisation ("organising pneumonia").

All the patients with a saturation under 90%, that cannot be otherwise diagnosed, should do all they can to have an emergency pulmonary CT scan and some routine tests done, as these could point to a case of COVID-19 with all its complications:

1. The complete blood count (with special attention to leukocytes, lymphocytes, neutrophils, percentage of immature neutrophils, thrombocytes, haemoglobin).
2. ESR;
3. CRP;
4. Seric ferritin;
5. LDH;
6. ALT;

7. AST;
8. Creatinine;
9. Glycemia;
10. Albumin;
11. D-dimers.

In severe cases, the Interleukin-6 and high-sensitive troponin I can also be done (the latter, when there is a suspicion of cardiac complications).

**ATTENTION!**

- If done too early, in the viral replication phase, when some patients suffer a mild desaturation – down to 92-93%, the pulmonary CT scan will be negative, and the patients, and even their attending physicians might be deceived into thinking it is not COVID-19 and that they can rest easy. Under no circumstances is the antiviral and immunomodulator treatment to be stopped in the presence of a normal CT scan in the 5th-10th day of the disease. They should persevere in taking them and further monitor the saturation, temperature and all other parameters, for the danger is still there! They can, however, delay the introduction of corticosteroids and antibiotics if the temperature is also normal, or they can introduce corticosteroids in small doses. In minimal prophylactic doses, the anticoagulants should be administered to all patients with a saturation under 95%, even in the absence of fever.

ANNEX 5

# Information on the recommended medicines

## Antiviral medication

**Umifenovir** has proved to be the most efficient in suppressing viral replication; it is an anti-Coronavirus medicine produced in Russia under the trademark name of Arbidol, and in Belarus under the name of Arpetol. It is administered in doses of 200 mg every 6-8 hours in the first days from symptom onset, for 5-7 days. Beware that this medicine has only a mild anti-inflammatory effect. It fights against the virus by inhibiting viral replication.

**Ivermectin** seems to be the most promising antiviral medicine at present. Studies starting from May 2020 show that it reduces the viral DNA 5,000 times in 48 hours from the first dose[156]. Shortly after, though, it was shown that the dose recommended for anti-parasitic effect (200 μg/kg of body weight/day) should be higher in vivo[157]. In no time, there were clinical pilot studies that proved the efficacy of Ivermectin, even when administered in a unique dose of 200 μg/kg of body weight, in the first day of hospitalisation158. Afterwards, the dose was increased to 400 μg/kg body weight per week, with better efficacy[159]. Although the results were very good with that dosage, as it reduced the mortality by up to 50%[160], a study performed in Egypt discovered that the administration of a dose of 400 μg/kg body weight for four consecutive days shows an effectiveness of the treatment never seen before. By comparing its efficiency with that of Hydroxychloroquine, we note that a significant improvement in the health of phase I patients took place in 99% of cases, compared to 74% in the case of Hydroxychloroquine, and for phase III, the percentage was 94% compared to 50%. For stage III, the mortality rate in the case of Ivermectin use was 2%, while in the case of Hydroxychloroquine it was 20%. Therefore, we recommend the protocol used in the hospital from Egypt[161].

**Hydroxychloroquine (Plaquenil)**[162,163,164,165,166,167] has a very powerful action in COVID-19, especially when associated with zinc 100 mg/day[168,169,170].

*Administration*: It is safe to take one 200 mg tablet a day. The protocol approved by the Ministry of Health imposes 400 mg/day, but its effects can be noticed even at smaller doses, yet only when associated with zinc[171.]

In COVID, it is administered for two weeks, and in smaller doses, that many studies recommend – 200 mg/day has very little know toxicity[172]. Plaquenil will be taken during meals, just like zinc. It is very important!

**Famotidine** has proved to be an efficient antiviral – studies show it reduces hospitalisation time and mortality[173,174,175]. As an antihistamine[176] with gastric antacid effects (H2 histamine receptors antagonist) it is very useful in preventing or fighting the cutaneous manifestations of the disease, urticaria[177], eruptions, itchy skin[178]. In any event, histamine is a powerful mediator of inflammation[179].

**Doxycycline** has an antiviral[180] cardioprotective, immunomodulator, anti-inflammatory[181], and antifibrotic effect. It can be initiated with a dose of 100 mg every 12 hours for 5 days, continued with 100 mg/day for another 5 days, and then, in high fibrosis risk cases, with small doses of 20-50 mg/day for a few weeks.

**Spironolactone** (25-100 mg/day) has an added antifibrotic effect in COVID-19, hypotensive, anti-inflammatory, antiandrogenic[182] and antiviral[183]. Recommended for administration in particular to male patients, as it is an androgenic agent that can contribute to the decrease of viral replication in men.

## Anti-inflammatory medication

**Glucocorticoids** Medrol and Dexamethasone, and when the cytokine storm is impossible to control, pulse therapy with Solu-Medrol injection[184,185,186,187.]

**Colchicine** is another efficient anti-inflammatory in this disease[188]. It can be used even during the viral replication phase, as it has an anti-inflammatory

and antiviral effect[189]. It has proved efficient in preventing the cytokine storm as well[190,191,192,193]. An observational study done in three clinics in Colombia demonstrated Colchicine has a positive effect when administered in doses of 0.5 mg every 12 hours for 7-14 days, even during cortisone therapy[194]. Another observational study showed that the introduction of Colchicine in the therapy at the onset of the inflammatory phase leads to a major improvement in the health of the patients in only three days[195].

## Other medication

**Omalizumab,** a monoclonal antibody against the IgE, was found to be very useful in reducing urticaria or other allergic cutaneous manifestations in Covid-19[196.]

**Cetirizine** is a H1 histamine receptors blocker. Studies show it is useful in urticaria and other cutaneous manifestations, as a replacement for Omalizumab[197.]

ANNEX 6

# Supplements recommended in COVID-19

The following supplements can be also administered preventively, before the disease sets in. They have no adverse effects. On the contrary, they solve some problems within the body, which could otherwise cause the development of a very serious COVID-19 form.

High doses of **vitamin D3**. The first day will have to start with a high initial dose of 60,000-100,000 IU, followed by 20,000 IU/day for a few weeks after disease onset. It is associated with vitamin K2, 50 –100 μg per day.

**Zinc** (50 mg x 2/day); Highly important!

**Oral Vitamin C** – to the maximum intestinal tolerance. Minimum 4 g/day, ideally over 10 g/day.

**Melatonin** – anti-inflammatory, antioxidant, antiviral[198,199], a true weapon against the cytokine storm[200], recommended in the anti-COVID-19 treatment from multiple points of view[201,202,203], recommended in sepsis[204]. Administered 12-15 mg/day (some authors recommend up to 200 mg/day) during the virosis. In the beginning, the doses will be small, and then gradually increased, until the optimal dose is reached[205]. The powerful effects melatonin has in stopping the cytokine storm recommend its use against severe inflammation and very low saturation as well, in doses up to 500 mg/day. Safety studies prove that there are no adverse effects associated with these doses, especially when taken for short periods of time[206].

**Magnesium chloride** – anti-inflammatory and antifibrotic, combats the cough. In solution form with a concentration of 25 g per litre of water: drink up to 300-500 ml of this solution in portions of 100 ml. Attention, the daily recommended amount must be ingested in small quantities, to avoid

diarrhoea. If diarrhoea does occur, the doses will be reduced. Magnesium supplementation is essential in COVID-19[207,208], it protects against pulmonary fibrosis[209] and inflammation[210], and magnesium chloride plays a crucial role both in combating bacteria, and in eliminating the cough through the pulmonary support it provides.

**Curcumin –** anti-inflammatory[211], antioxidant[212], antiviral[213], anticoagulant[214], 3-4 g/day. It is important to know that it has a remarkably low absorption rate, as it has rather poor water solubility. It is recommended to use only high quality products, i.e. combined with piperine that increases its absorption, or in the form of phytosomes, liposomes, or any other delivery systems that increase absorption. Such a product would help immensely in COVID-19 and in all inflammatory diseases, for that matter, cancer included.

**Quercetin –** anti-inflammatory, antioxidant, antiviral[215,216]. Works in synergy with vitamin C[217] and zinc. And since it is an ionophore for zinc, it helps it enter the cell and block viral replication. From many points of view, Quercetin is a good replacement for Plaquenil[218]. There is even a formula that can be nebulized, which helps very much in lung recovery[219]. It is also possible to try replacing Dexamethasone with Quercetin, if patients do not respond to Dexamethasone treatment, i.e. their saturation does not increase as well as expected[220]. Safety studies specify doses up to 5 g/day[221], but for pulmonary diseases, 2 g/day are sufficient[222].

**Artesunate –** anti-inflammatory, antioxidant[223], antiviral[224,225,226,227]. Artesunate is an anti-malarial medicine just like Plaquenil; it can be used as a replacement for Plaquenil, now that Plaquenil has been ousted from the market precisely for its significant efficiency against the coronavirus.

**Omega3 –** essential anti-inflammatory[228,229], immunomodulator[230] and antiviral[231,232].

**Selenium –** Selenium deficiency is associated with an increase of mortality rates in COVID-19[233]. Antioxidant, reduces endothelial cell apoptosis and thrombocyte aggregation[234].

**Methylene blue** – strong antiviral, can also replace Plaquenil, as a zinc ionophore. The recommended dose is 50-75 mg x 3/day, which is 5-7.5 ml 1% solution in 200 ml water x 3/day.

**Butyric acid**[235,236] – contributes to maintaining the integrity of the intestinal mucosal barrier by blocking the primary chronic inflammation in the intestine, a condition that many people suffer from.

**Oleuroperin** – anti-inflammatory[237], antioxidant[238], antiviral[239].

**N-acetylcysteine** – anti-inflammatory and antioxidant[240.]

**Metformin**[241,242,243,244,245,246] – 250 mg in the morning, and for obese patients, another equal dose in the evening, in case they are not administered a higher dose for diabetes.

**Berberine** –anti-inflammatory, antioxidant, antiviral[247,248.]

**Epigallocathechin gallate** – anti-inflammatory[249], antioxidant.

**Ashwagandha** – anti-inflammatory, modulator of the mental state, sleep aid, adaptogenic, immunomodulator, antiviral[250,251.]

**Reishi (ganoderma)** – plays an important part in reducing the negative effects the virus has on haematological parameters[252.]

**B complex Vitamins** – act synergistically with one another. In sepsis, Vitamin B1 (thiamine) is very useful[253,254,255,256,257,258], and in the restoration of adrenal secretion blocked by corticoids, the pantothenic acid is recommended. Vitamin B6 has an important role in the activity of T-cells, as it regulates the cellular and humoural immune response (the production of antibodies)[259,260,261].

**Vitamin E (400-1,200 IU/day)** –important immunomodulator effect[262,263].

**Vitamin A** (25,000-50,000 IU/day, for 30 days) – with multiple positive effects in COVID-19[264,265.]

**Intravenous Vitamin C** 15-25 grams in 250 ml physiological serum once a day. It can be administered daily until inflammation occurs. It is, perhaps, the best protector against an inflammation spike.

When malaise worsens, the dose can be shifted from one Vitamin C intravenous infusion to two, and from 15-25 grams up to 50 grams. Following a strong inflammatory reaction with sensations of suffocation and a major drop in saturation (under 90%), the doses of IV vitamin C must be increased to more than 50 grams, 2 times a day. The benefits will very soon become visible.

I have personally known cases in which, even at saturations lower than 80%, the high doses of IV Vitamin C worked wonders by rapidly increasing the saturation. It is important to eliminate the excess of salt and water that accumulates in the body through high dose Vitamin C IV solutions. To this end, an injection of 1 vial of Furosemide (20 mg) will be administered once or twice a day. To avoid fluid accumulation in tissues, especially during a parallel treatment with steroids, it is recommended to replace with water the physiological serum used in the preparation of IV solutions containing more than 25 grams of Vitamin C.

For further information on Vitamin C, see *Annex 11.*

ANNEX 7

# Risk factors in developing a severe form of COVID-19

**Age** is one of the most important risk factors. For example, in children, the disease takes only very mild forms most of the times. The disease passes in 2-3 days, after a light fever, maybe diarrhoea and a headache. It is only in rare cases that a child will develop a severe form (although there were reports of immune post-COVID-19 complications, like the Kawasaki syndrome). The teenagers are likewise, not usually prone to suffering a severe form; their cases are slightly more serious than those of children, especially when they have some risk factors. People over the age of 25 may develop more severe forms, particularly if they are not treated at all. Nevertheless, the majority of cases do not require hospitalisation. The more serious problems occur in people over the age of 40, and especially in those over 50. Over 60 years of age, the incidence of severe cases amplify far more. Why are the elderly so susceptible to developing severe forms of the disease? It seems that the adaptive immune response mediated by T cells decreases with age, in favour of the production of inflammatory cytokines, i.e. exactly what puts the SARS-CoV-2 patient in danger[266] (aging brings about a shortage of naive T cells)[267]. Also, with age, the level of chronic inflammation increases and type I and III interferon response to the virus decreases.

**Obesity.** The overweight and obese will develop the most severe forms[268,269,270,271]. A meta-analysis published at the end of June, 2020, shows that the inefficacy of COVID-19 therapy increases directly proportional to the patient's body weight, and for a body mass index of 30-35 kg/m2, the severity of the case soars abruptly. There are 14 mechanisms through which the overweight and the obese patients risk developing graver forms of COVID-19 and of other conditions[272]. We must, therefore, make an effort to lose weight, because this pandemic, or other ones derived from it, threaten to be here for years to come.

**The male sex.** It was determined that men develop graver forms of COVID-19 than women[273,274]. It is all because of hormones. It seems that

elevated levels of androgens are a risk factor[275]. The mechanisms cannot yet be completely elucidated. Women with higher levels of testosterone (such as those who suffer from polycystic ovary syndrome) are also prone to developing more severe forms.

**Arterial hypertension and other cardiovascular diseases.** Apparently, people with high blood pressure also have an overexpressed ACE2 protein – a receptor used by the virus to gain entrance in the human cells, and that makes them more vulnerable in the face of a viral invasion.

**Diabetes.** Both the diabetics and the persons that ingest big quantities of carbohydrates are at great risk. Fast carbohydrates must be reduced, sugar, in particular, must be eliminated from the diet as much as possible, and the same goes for white flour products in excess. Hyperglycaemia is in itself a risk factor for a severe form of COVID-19[276], and for that reason it is best to avoid a hyperglycaemic diet and to have it treated by making smart dietary choices and even by taking Metformin or Berberine.

The metabolic syndrome, abdominal obesity together with hypertension, diabetes and dyslipidemias[277].

**Vitamin D3 deficiency** due mainly to the lack of sun exposure, is made worse by the quarantine regimen the population has been subjected to in the past year. If daily sun exposure is not possible, it is recommended to take high quantities of vitamin D3 for a long period of time. That would be 5,000-10,000 IU daily for a period of months, while monitoring vitamin D3 levels in the blood, namely 25 OH-vitamin D3 (in reserve form). The ideal value is 50-100 ng/ml.

**Sedentarism.** Constant physical effort plays an essential protective role through its multiple effects. To date, the persons who are highly active physically, especially in the open air, have had only mild forms of COVID-19, in most of the cases.

**Stress.** Stress must be fought against, especially when chronicized. Acute stress increases inflammation[278,279], and so does chronic stress, but the latter also blocks the suppression of inflammatory interleukins like IL6[280], which have a major contribution to the life-threatening cytokine storm. In other words, those suffering from chronic stress will have a much harder time controlling the inflammation and the COVID-19 induced cytokine storm, and thus the severity of disease will increase.

Furthermore, stress leads to intestinal permeability, a key factor in the processes of inflammation and amplification of the inflammatory effect of COVID-19[281]. Therefore, people should avoid exposure to messages from the media as much as possible, because they sustain a negative psychological state, the feeling of permanent threat and, especially, the obsessive fear of SARS-CoV-2, manifested through the suicide cases of those who found out they had COVID-19. Stress triggers and increases inflammation in the body and affects the lungs. It paves the way for a severe form of disease.

**Smoking**[282,283] enhances substantially the oxidative stress.

**A diet** rich in saturated fats, sweets and fast carbohydrates[284].

**A diet rich in animal proteins** – meat, milk, cheese, eggs – increases the inflammation, especially if the food is overprocessed, canned, smoked etc. In this context, it is very useful to diminish the intake of animal proteins and add more fruits and vegetables, preferably unprocessed, to the diet, so as to benefit from the vitamins and enzymes they contain. Intermittent fasting or water fasting, when done regularly, one or two days a week, will help prevent severe cases of COVID-19.

**Intestinal dysbiosis and permeability**[285]. Chronic inflammation of the intestine cause real holes to form in the mucosal lining, allowing endotoxins (lipopolysaccharide like substances) to enter the bloodstream and to associate with *spike* (S) SARS-CoV-2 proteins in amplifying the inflammation[286]. The moment the disease appears it is important both from a preventive and therapeutic standpoint, to administer Butyric acid (a short-chain saturated fatty acid), which restores or consolidates the intestinal mucosa, as well as other supplements that can regenerate the mucosa (liposoluble vitamins A, E, glutamine, blueberry extract, clay etc.).

**Hidden infections:** dental[287], in the tonsils, sinuses, colon (diverticulitis), ovaries, Fallopian tubes, kidneys etc. These chronic infectious hotbeds contain anaerobic bacteria, which produce proinflammatory toxins that act in synergy with the SARS-CoV-2 virus towards enhancing the inflammation.

**Heavy metal toxicity** predisposes the body to more severe forms of COVID-19. Heavy metals contribute to the formation of bacterial and fungal biofilms wherein microorganisms proliferate, and where neither the immune system, nor the antibiotics can reach and destroy them. In persons suffering from chronic infections and degenerative diseases, possible heavy

metal poisoning must be taken into account, and chelation therapy must be promptly done[288].

**Severe chronic respiratory diseases** (asthma, chronic obstructive pulmonary disease – COPD, pulmonary mycoses – aspergillosis, occupational pulmonary fibroses – asbestosis etc. or idiopathic) seem not to predispose by themselves to a severe form of COVID-19, but the persons that already suffer from chronic respiratory failure and develop an aggressive form of COVID-19, have less pulmonary compensatory mechanisms to help them survive.

**Cancer, autoimmune diseases, chronic kidney and liver diseases** point to an already vulnerable terrain, on which COVID-19 can easily take a turn for the worst.

**Chronic or acute inflammation of any type.** An inflammation preceding COVID constitutes one of the most important risk factors for this unmistakably inflammatory disease.

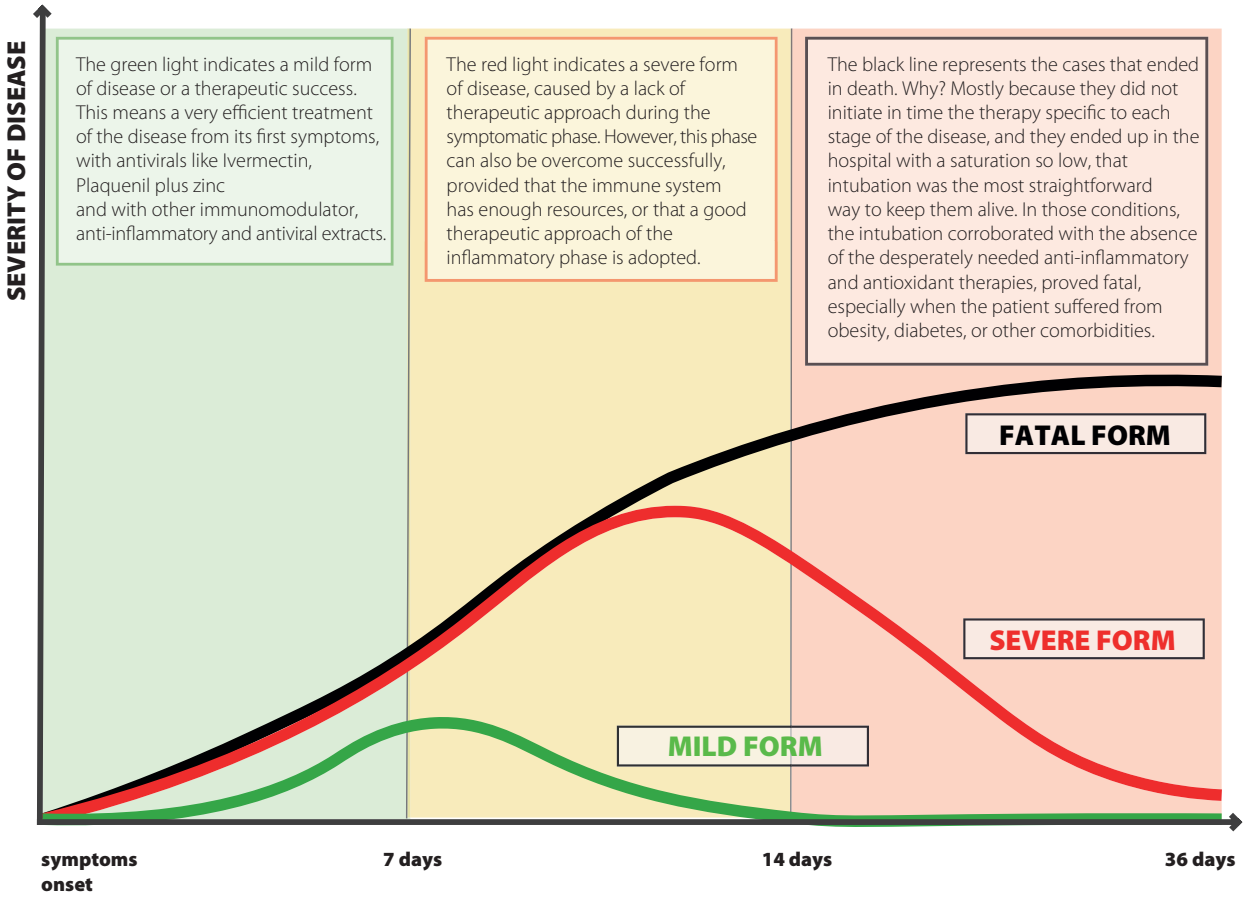



**Figure 12: Disease severity according to risk factors and therapeutic course of action**

ANNEX 8

# Recommended practices for people suffering from COVID-19

1. In general, **cold air and currents of air (drafts)** lead to a rapid escalation of symptoms. Once the first symptoms set in, it is best not to go outside. Stay away from any type of drafts. Air the room, because a lot of oxygen is needed, but move to another room while doing it. Also, you can air the kitchen or hall while your room door is open, but do not open the room's window at the same time. Do not cause any drafts! Cold air stimulates inflammation extremely quickly and strongly. I know persons who, upon feeling better, went outside in the cold air. Soon after, their symptoms became more severe, and they were unable to breath properly due to reinflammation. Cold air can reduce the saturation by a few percent in a very short amount of time.

Similarly, stay away from drafts or colder air after taking a bath or a shower, because, if you believe you have overcome the disease and think it is completely gone, you may yet start all over again. A close friend, a doctor, had to be admitted to the hospital after such an experience, where she could barely be saved with the aid of Tocilizumab, IV vitamin C and other medication.

The recommendation for persons who have had a moderate or severe form of COVID-19 is to avoid cold air and intense physical efforts for at least one or two weeks afterwards. In fact, this interval should be proportional to the severity of the disease. Otherwise, there is a risk of reactivating the inflammation.

2. **Overweight, obese or diabetic persons** must take extra precautions when dealing with this disease. If they follow the recommendations above, their case will be milder. Otherwise, they are at great risk.

3. During the disease, all **fast carbohydrates** (white bread, any flour product without bran, any type of pastry, sweets of any kind) have to be given up to. It must be clearly understood that, just like in cancer, the rapid viral replication, as well as the release of storm-producing cytokines, are based on

glycolysis (partial and inefficient breaking down of glucose until converted into pyruvate), and not on oxidative phosphorylation. Hence, the production of the same quantity of energy exclusively via glycolysis will require ten times the quantity of glucose that would have been needed if the path of mitochondrial oxidative phosphorylation were followed. Consequently, the elimination of fast carbohydrates and glucose from the diet is essential. Likewise, the use of Metformin or Berberine during the 2-3 weeks of COVID-19 help tremendously. In any case, the patients that enter the inflammatory state must start the treatment with Metformin or Berberine immediately. It seems that a diet low in sweets and fast carbohydrates, but rich in healthy fats is a means of limiting the cytokine storm[289].

4. During the same period of time, it is imperative to **consume liquids,** 2.5-3 l/day, depending on body weight. This will enhance kidney function and, at the same time, it will help the body to detoxify, because SARS-CoV-2 produces a lot of toxins that need to be eliminated rapidly, so as not to burden further the metabolic functions. It is recommended to administer high quantities of digestive absorbents such as medicinal charcoal (5-10 tablets), clay (1 teaspoon) and zeolite (1-3 capsules) with a big glass of water, at least 2 hours away from other supplements or medicines, 30 minutes before meals.

5. **Constipation** should be avoided during this period. It is necessary to clean the colon, because, in case of intestine permeability (either pre-existent or acquired during COVID-19), high amounts of toxins from stagnant faecal matter will enter the bloodstream and worsen the symptoms. The ingestion of foods rich in fiber, psyllium husks, a high quantity of Vitamin C and magnesium chloride, which have laxative effects, will most likely cure constipation. If, however, the constipation does not ease with any of the above, the patient is recommended to take a daily enema with chamomile or yarrow tea.

6. **Intense physical effort** should be avoided, as it could make the disease worse, since the body is very weak. However, light physical effort is good and even recommended, for at least 10-15 minutes per day.

7. It is advisable to avoid **contact with media,** because it maintains people in a state of permanent stress through its negative newscasts, which will intensify and maintain the inflammation, thus making the situation worse. During

quarantine, it would be better to find ways to boost our inner peace with the aid of prayer and by abandoning ourselves in God's hands.

8. With regards to **diet**, fruits, vegetables and unprocessed foods can be a great support in COVID-19, so it is best to avoid animal protein as much as possible. There are, though, some animal proteins that can be consumed during this disease: eggs, yoghurt, kefir (for its probiotic content), fish and pasture-raised chicken soup[290]. Moreover, the Mediterranean diet is said to be one of the most appropriate in this disease[291].

More and more studies link the microbiome (the sum of all populations of gut bacteria) to the overall health state. In this sense, it was found that intestinal dysbiosis can prove an important risk factor in COVID-19. Also, COVID itself can contribute to this dysbiosis and intestinal permeability, thus generating a vicious cycle. To help maintain a healthy microbiome, it is recommended to consume fermented foods: sauerkraut or pickled vegetables, home-made kombucha or kefir, probiotic rich foods and a raw vegetable salad (celeriac, parsley, carrot), apples, garlic, leeks and onions, foods rich in soluble fibers that act like probiotics and feed the intestinal bacteria. When probiotic supplementation is concerned, the most potent product known to us is  Pro EM San Pur by Tisso, but any other high quality probiotic will do just as well[292]. Therefore, the restoration of the microbiome must be one of the most important dietary goals during the prevention and treatment of the SARS-CoV-2 infection.

ANNEX 9

# In which therapeutic context is Azithromycin to be recommended?

Unfortunately, when confronted with fever during this disease, most patients rush to antibiotics. If Azithromycin has no effect, then they resort to other antibiotics, focusing thus on a false target. In fact, the first fever is viral, not bacterial. Therefore, at this stage, there is no point in using Azithromycin.

The most recent studies[293,294] show that Azithromycin has very little efficiency against COVID-19, even when there is a typical bacterial infection, which happens, as studies point out, in 9-11% of cases. Its efficiency is recognisable only when it is administered together with Hydroxychloroquine. Hundreds of studies demonstrate this[295,296,297,298].There are also subsequent reviews that contradict even this fact[299], but we cannot pretend not to see that their methodology is corrupted, precisely because they exclude or circumvent those studies that prove the efficiency of the synergistic treatment with Hydroxychloroquine and Azithromycin.

Still, from our point of view, when we take into account the honest research studies and the observations made by known doctors that have fought against COVID-19, the administration of Hydroxychloroquine (Plaquenil) together with Azithromycin has quite a significant antiviral character. Umifenovir (Arbidol or Arpetol) or Ivermectin though, seem to be much more efficient. They do not contradict one another, as any of these antivirals can be chosen separately or they can be combined in therapy, depending on their availability on the market, of course.

What we want to highlight here, is that the administration of Azithromycin alone during the viral phase is not a solution. Also, in the inflammatory phase, when the need for an antibiotic arises – body temperature of over 38-38,5 °C, with no reaction to anti-inflammatories – the better course of treatment would be Augmentin with Doxycycline or Metronidazole or other wide-spectrum injectable antibiotics (3rd or 4th generation Cephalosporins with Metronidazole or Amikacin, Meropenem with Metronidazole or Amikacin, Piperacillin/Tazobactam etc.).

ANNEX 10

# The role of Vitamin D3 in COVID-19

The most severe forms of COVID-19 are manifested in persons with low levels of vitamin D3[300,301]. "There is a strong correlation between prevalence of severe vitamin D deficiency and population mortality rate from COVID-19 in Europe"[302,303]. It seems that, indeed, the low levels of vitamin D3 represent one of the most powerful predictors of a severe form of COVID-19[304,305].

More recent studies insist on increasing Vitamin D3 doses to prevent infections and enhance the immune response to disease such as Influenza and COVID-19. Accordingly, they recommend doses of 10,000 IU daily for a period of a few weeks, until the level of 25-Hydroxy-Vitamin D3 (25-OH-D3) increases significantly, followed by a daily dose of 5,000 IU, which should suffice. The goal is to increase the level of 25-OH-D3 to 40-60 ng/mL[306]. This level can be increased up to 60-80 and even 100 ng/mL, without major health risks.

There are exceptions: a small number of patients suffering from known or latent sarcoidosis cannot be prescribed high doses of vitamin D3, as that could activate their disease. Patients suffering from nephrocalcinosis (abnormal sedimentation of calcium in the kidneys) or hypercalciuria are yet another exception.

Since the mortality risk through COVID-19 is much higher in patients belonging to vulnerable groups, a unique dose of 200,000 IU can be prescribed at the onset of disease, followed by a daily dose of 10,000 IU for a few weeks, decreased afterwards to 5,000 IU. (A study from 2017 found that a unique high dose of 200.000 IU vitamin D3 considerably reduced inflammation, without having any adverse effects[307].)

A study done on intubated patients from the intensive care unit, found that the time they spent in the ICU decreased proportionally with the size of vitamin D doses they were administered. With a dose of 100,000 IU administered daily for 5 days, i.e. a total of 500,000 IU, there was a reduction

by half in the number of days compared to the control group[308]. In another study, also on intubated patients from the intensive care unit, the dose of 500,000 IU lead to an increase in haemoglobin by approximately 10% per week[309]. The ratio of 11.30 g/dL compared to 8.19 g/dL in the control group, after only 3 weeks, is an impressive result for those who know how difficult it is to elevate haemoglobin in an intensive care environment. It is interesting that the effect was observed with a dose of 500,000 IU, and not with 250,000 IU. Once more, high doses prove to be much more efficient. According to these two studies, there are lots of reasons to administer high doses of 500,000 IU of vitamin D to intensive care intubated patients, and all the more so, since vitamin D is already a proven good remedy against the cytokine storm[310].

It is also important not to neglect drinking more liquids and supplement with magnesium during the days when high-dose vitamin D is administered, lest kidney stones might form. The supplementation with magnesium chloride or magnesium citrate in doses of 300 mg elemental Mg per day (100 ml magnesium chloride 2.5% or 3 tablets of magnesium citrate 100 mg/day) is extremely useful. Furthermore, if vitamin D3 is taken for a longer period of time, it is also beneficial to take vitamin K2 (50-100 μg daily), as it protects against calcium sedimentation in kidneys or in artery walls, just like liquid intake does.

There is a possibility to administer a unique intramuscular slow-release dose of 100,000 IU or 300,000 IU of vitamin D3, which leads to a quick recovery, as it was noted that the 25(OH)D increased much more rapidly with injections than with oral supplementation of vitamin D3.

**ATTENTION!**

- During the high-dose Vitamin D treatment, more liquids have to be consumed, and a big quantity of magnesium (300 mg/day) has to be taken.
- Vitamin D and the liposoluble vitamins in general are best taken after meals, preferably after a fatty meal, as fats facilitate their absorption.

ANNEX 11

# The role of Vitamin C in COVID-19

One of the achievements of the pandemic was the popularization of vitamin C benefits in COVID-19, which was done by Chinese doctors, via scientific articles and public statements. This was not their idea to begin with, but they were well advised by a few scientists and organizations, whose goal was to promote the benefits of vitamin C intake. The Chinese acted in all honesty and brought those benefits to the attention of others[311]. By contrast, the Western medical world allowed the same information on vitamin C benefits to be immediately discredited and ridiculed, out of sheer malevolence and without any scientific basis. There were even direct bans blocking information on vitamin C from showing on social networks and in electronic correspondence.

However, a handful of Western doctors and many lay people acting in good faith, who had not been previously informed, received the message and started using high-dose vitamin C therapy very successfully in COVID-19.

In severe forms of COVID-19, it is absolutely essential to administer high doses of vitamin C intravenously. At the same time, the oral alternative mode of administration should not be neglected, either, as it is easily accessible by everybody.

According to his own testimony, Professor Linus Pauling, hailed as the greatest scientist of the 20th century, the father of molecular biology, physicist, chemist and biologist, consumed 18 grams of vitamin C daily for the last decades of his life. In his studies, he cites the case of a cancer patient who ingested 100 grams of vitamin C daily, for many years.

Ergo, if you do not have access to Vitamin C in IV form, there is the possibility of taking hourly doses of a few grams of vitamin C orally. Mind that vitamin C halving time is as little as 20-30 minutes, which means that 2 hours after a dose, there is only a maximum of a 16th part of the given dose left in the bloodstream! Its administration in doses more than four hours apart is inefficient in severe cases.

And since the injectable administration, even when possible, cannot be done very frequently (unless continual IV drips of vitamin C are used in an

intensive care unit), it is recommended to have concurrent oral doses administered as often as possible.

It is preferable to take ascorbic acid in powder form, and not tablets, as the latter contain many excipients and are much more expensive, considering the quantities needed. In persons suffering from gastritis, ascorbic acid (vitamin C) will be replaced with sodium ascorbate (alkaline vitamin C), bought as such, or prepared by mixing ascorbic acid with sodium bicarbonate in a 2:1 ratio (2 parts of ascorbic acid and 1 part sodium bicarbonate).

When consumed in quantities bigger than the body's power of assimilation at one point, it may cause diarrhoea. This can be avoided by dividing the daily dose in small and frequent portions of maximum 3-4 grams at one time). Each person has their own capacity of intestinal absorption of vitamin C, and that can be increased in time by the constant practice of taking daily doses of grams. During severe illness, however, all the people have an absorption capacity of vitamin C greater than their normal, 'healthy' one.

Injectable vitamin C is much faster and efficient in its antiviral, immunomodulator and anti-inflammatory actions, as the seric levels that can be reached through vitamin C injections are much higher than those reached through its oral administration[312], but it is not widely available. And even when it is accessible, it is absolutely essential to have it administered in several doses multiple times a day – every maximum 6 hours in severe infections, for instance. When the patient is not in a coma, the administration through injection will always be completed by frequent oral doses of vitamin C, in order to ensure a constant seric level.

The immune cells (leukocytes), along with the adrenal gland cells, are the greatest vitamin C consumers in the body. Their functionality in the absence of vitamin C is inefficient and leads to the release of a high amount of free radicals that cannot be neutralized, and that causes extended tissular lesions to appear in the aftermath of the leukocytes' attempt to destroy viruses and other invaders[313].

Vitamin C plays a crucial role in COVID, as it protects the endothelium of blood vessels[314,315,316.]

Vitamin C in high doses destroys viruses directly through a pro-oxidative mechanism. In small, repeated doses that ensure a constant elevated seric level, it has anti-inflammatory and antioxidant effects on the body's own tissues.

It diminishes the C-reactive protein, which is exceedingly elevated in COVID-19, and which is one of the most important proinflammatory markers[317]. It also blocks COX 2[318] enzyme, which plays an important part in the inflammatory processes.

High intravenous doses of vitamin C reduce the cytokine storm amplitude, and that recommends it for administration to all patients in the hyperinflammatory phase[319].

Last but not least, vitamin C inhibits the proinflammatory effect of liposaccharides, which are involved in the formation of the cytokine storm in COVID-19[320].

Through these effects and many others unmentioned here, vitamin C reduces the risk of the cytokine storm that destroys the lungs and other organs.

**ATTENTION!**

- For high doses of intravenous vitamin C, the patient should be tested for the level of Glucose-6 Phosphate-Dehydrogenase (G6PD, an enzyme that metabolises vitamin C in erythrocytes). When this enzyme has a low level, genetically determined by certain mutations (very rare, more frequent in the Mediterranean area than in our parts, and more often occurring in men than women), there is the risk of adverse reactions when doses higher than 12-15 grams are administered intravenously: a more or less severe hemolysis of erythrocytes appears, depending on the severity of the enzymatic deficiency and the amount of vitamin C administered.
- When the amount of this enzyme is normal, then the patient can be given up to 50 grams twice a day without any risk. Safety studies prove that the administration of up to 1.5 gram/kilogram of body weight does not have major adverse effects[321.]
- If testing is not possible or available and the patient's life is in danger, vitamin C can be administered in doses starting from 12.5 grams, with a gradual daily increase up to 25 grams. This should be done only if the administration does not produce any discomfort, which would indicate the presence of hemolysis (red urine, jaundice-yellow skin and sclera).
- Most of the people that suffer from a G6PD deficit already know their diagnosis, as they have most likely already suffered haemolytic reactions to the administration of other medicines.

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This paper is not designed and does not provide professional diagnosis, opinion, treatment, or services to you or others. The information presented about COVID-19 therapy is for educational purposes only, so it does not replace medical or professional care and should not be used in place of a visit, consultation, or appeal for advice from your doctor or other health-care providers.

It represents the conclusions of a purely scientific approach based on a vast literature, especially research in the field of COVID-19 therapy in recent months, but also the observations reached by doctors who fought to save the lives of patients with COVID-19, and who drew their own conclusions that harmonize perfectly with the approach I brought to your attention.