Order no. 487
of 23 March 2020

on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus

On seeing the Approval report of the General Directorate for Medical Assistance and Public Health of the Ministry of Health no. VSC 3.987 of 23.03.2020,

taking into account provisions of Article 16 (1) g) of Law 95/2006 on healthcare reform, republished, as amended,

provisions of Decree no. 195/2020 on establishment of the state of emergency in Romania,

pursuant to Article 7 (4) of Government Decision No. 144/2010 on organisation and operation of the Ministry of Health, as amended,

the minister of health hereby issues the following Order**:**

Article 1 – The protocol for treatment of the infection with the SARS-Cov 2 virus is hereby approved, as provided in the Annex.

Article 2 – The special directorates of the Ministry of Health, public and private health units, as well as the medical staff involved in providing medical services related to the involved areas will lead to the implementation of this Order's provisions.

Article 3 - The Annex is integral part of this Order.

Article 4 - This Order shall be published in the Official Gazette of Romania, Part I

p.p. the Minister of Health,
Horaţiu Moldovan,
Secretary of State

Annex

TREATMENT PROTOCOL
for the SARS-CoV-2 infection

Taking into account the appearance of the SARS-CoV-2 epidemic at the end of 2019 in China and its pandemic expansion, as well as the increase in the number of COVID-19 cases in Romania, including severe forms of the disease, it is necessary to develop a protocol treatment that takes into account the data accumulated so far. This protocol addresses the general situation of patients with COVID-19, without addressing particular situations in detail. In order to carry out this protocol, the provisions of the documents issued by the World Health Organisation (WHO) and the European Centre for Disease Prevention and Control (ECDC), of the therapeutic guidelines elaborated in China, Italy, Belgium and other materials published since setup of the previous version were analysed.

Through the recommendations on the care of patients with SARS-CoV-2 infection, this protocol represents a support for the decisions of the medicinal product policy commissions within health units regarding the "off-label" use of some potentially active medicinal products, in accordance with Article 27 of Decree no. 195/2020 on establishment of the state of emergency in Romania.

This therapeutic protocol includes principles grouped in the following sections:

I. Antiviral medication
II. Immunomodulatory medication, including convalescent plasma
III. Management of coagulation disorders in patients with COVID-19
IV. Antibiotics and other antiinfective medicinal products
V. Support of vital functions
VI. Other therapeutic measures

I. Antiviral medication

The evolution of COVID-19 has an initial phase dominated by viral replication, with a variable duration; during this time, the patient goes through a presymptomatic period in order to become symptomatic. Antiviral medication should be administered as soon as possible after diagnosis (preferably from the beginning of the symptomatic period), aiming at:

- limiting the risk of the patient's transition to the phase dominated by inflammatory manifestations, in which severe manifestations of disease occur more frequently;

- reducing the duration of the disease, shortening the patient's hospitalisation, which increases patient safety, thus reducing the impact on consumption of hospital care resources per patient.

People infected with SARS-CoV-2 who remain asymptomatic throughout the course of the infection do not receive treatment, as it has not been shown that this would reduce the duration of excretion of the virus.

Potentially active antivirals against SARS-CoV-2

- (hydroxyl)chloroquine

Hydroxychloroquine has demonstrated in vitro activity against SARS-CoV-2, as well as some positive results in the treatment of patients with COVID-19. Yao X and colleagues have discovered that, compared to chloroquine, hydroxychloroquine inhibits SARS-CoV-2 7.6 times more effectively in vitro. Hydroxychloroquine is better tolerated than chloroquine and has fewer medicinal product-medicinal product interactions; in addition, it has been widely used

in long-term treatments in rheumatology, without generating significant side effects. The molecular mechanisms of action of chloroquine and hydroxychloroquine have not been fully elucidated. First, the two medicinal products can alter the pH of the cell membrane surface and thus inhibit the fusion of the virus to the cell membrane. Moreover, they can inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, and virus release from the infected cell. Data published on 17 March 2020 by the group coordinated by Gautret C. which evaluated 42 patients indicate a faster virus clearance in patients with COVID-19 who have received hydroxychloroquine.

The balance of possible benefits / risks (in vitro efficacy, possible clinical efficacy and reduced risk of adverse effects) has placed hydroxychloroquine as an antiviral therapeutic alternative at this stage of the COVID-19 pandemic, which led to an interim authorisation for use in the USA.

- <u>Protease inhibitors</u>

Lopinavir is a protease inhibitor used to treat the HIV infection in combination with ritonavir in order to increase its availability. Lopinavir has some degree of activity against in vitro coronaviruses, including SARS-CoV-2. The clinical data published so far are inconsistent. Three observational studies failed to identify a reduction in the duration of virus excretion in patients treated with lopinavir / ritonavir compared to favipiravir or placebo, while the use of lopinavir / ritonavir resulted in faster elimination of the virus during the Wuhan epidemic, in the case of early administration, in the initial viral phase (the first 10 days after the onset of symptoms). In a randomized clinical trial on 200 patients with moderate to severe disease, Cao and colleagues have showed that lopinavir / ritonavir caused a faster regression of symptoms and reduced the death rate, with no difference in statistical significance; it should be noted that initiation of the viral treatment was relatively late in this study. In another single-blind trial (ELACOI Trial) performed on 44 patients with mild to moderate disease, lopinavir / ritonavir had more side effects and did not reduce the duration of viral excretion compared to umifenovir or placebo. These outcomes, although an insufficient number of patients may be reported for a disease with low mortality, have led to a decline in the use of lopinavir / ritonavir for the treatment of COVID-19. However, considering the existing favourable data, this medicinal product remains an alternative, in the absence of more effective products. An additional benefit is the liquid form of administration - usable in patients who received orotracheal intubation and in newborns.

Darunavir / Cobicistat and atazanavir / ritonavir have been used as alternatives for patients intolerant to lopinavir / ritonavir, but experience with these substances is much more limited; the darunavir / cobicistat manufacturer claims that this product is in vitro ineffective against SARS-CoV2 and discourages its use in patients with COVID-19, therefore its use should be avoided.

- <u>Remdesivir</u>

Remdesivir is another potentially useful antiviral for the treatment of COVID-19, which inhibits RNA-dependent RNA polymerase, prematurely blocking RNA transcription. It has in vitro activity against coronaviruses, including SARS-CoV-2. The medicinal product has completed a phase III clinical trial for the treatment of Ebola infection and there is relatively detailed pharmacokinetic data for the human body. Data obtained in clinical trials in treatment of COVID-19 was contradictory; Wang et al. included 237 patients in a comparative study on remdesivir versus placebo, which was prematurely discontinued due to lack of efficacy and an increased rate of side effects: 12% versus 5% placebo. In another study involving 1063 severely ill patients treated with remdesivir versus placebo, there was a discrete benefit in terms of mortality: 8% versus 11.8% ($p = 0.06$) and duration until improvement: 11 days compared to 15 days, $p = 0.01$. An advantage for use in severe forms is its parenteral administration. It is currently used in clinical trials and can only be obtained for individual compassionate use for

pregnant women or children with severe forms of COVID-19. An "early access" programme is also being developed in several countries of the European Unit, through which the national authority manages the use of remdesivir, based on a scientific recommendation developed by the EMA.

- Other potentially active antivirals

Umifenovir works against influenza viruses and is used in this indication in Russia and China; its antiviral action is based on blocking the penetration of the virus into the cells (fusion inhibitor) and on the immunomodulatory effect. Its advantage consists of reduced side effects. In the SARS-CoV-2 epidemics in China, umifenovir was used in combination with other antiviral medicinal products; Deng L. et al. found that, in patients with uncomplicated pneumonia in COVID-19, the association of umifenovir (200 mg every 8 hours) with lopinavir / ritonavir allowed faster nasopharyngeal clearance and a faster regression of pulmonary imaging changes compared to the regression in patients receiving lopinavir / ritonavir monotherapy. There are currently two ongoing clinical trials evaluating the effect of umifenovir compared to the effect of lopinavir / ritonavir, namely to the standard antiviral-free treatment. Umifenovir can also be used in children over 12 years of age for SARS-CoV-2 infection; for other viral infections, it can be used from the age of 2 years (25% of adult doses for children aged 2 to 7 years and 50% of adult doses for children aged 7 to 12 years).

Given the favourable results reported and the low rate of adverse effects associated with its administration, umifenovir represents a solution; it should be used in association with another antiviral that is more difficult to tolerate (lopinavir / ritonavir, remdesivir or hydroxychloroquine).

Favipiravir is an RNA polymerase inhibitor that has been used for influenza and the Ebola infection. It was originally manufactured in Japan, but used more frequently in China; due to its teratogenic effects, its use is only allowed for special situations such as epidemics or emerging infections with influenza viruses, in Japan. As regards the SARS-CoV-2 infection, favipiravir was more efficient in terms of viral eradication and regression of lung imaging than both lopinavir / ritonavir and umifenovir; the doses used were 1,600 mg every 12 hours on the first day, then 600 mg every 12 hours for 7-14 days. The medicinal product cannot be administered to children, men in the period of maximum fertility (it accumulates in semen) and pregnant women (teratogenic risk); it was used in China in female patients of childbearing age only if their pregnancy test result was negative and always in association with contraceptive medication during treatment and at least 7 days after ending the treatment; men were advised to use a condom for at least one week after discharge.

Given the selective inclusion criteria, the need to inform patients, the need for additional testing and the administration of contraceptives which may have significant interactions with other medicinal products, favipiravir remains a therapeutic alternative when other antivirals are not available and all conditions mentioned for safe administration are met - for example, in menopausal patients.

- Neuraminidase inhibitors

The administration of oseltamivir, peramivir or zanamivir is not justified in the treatment of COVID-19, as this virus does not have neuraminidases; it is recommended to combine the anti-influenza medication (oseltamivir is available in Romania) in patients with COVID-19 until the diagnosis of influenza is excluded by gene amplification test or as long as necessary for treatment of a concomitant infection with an influenza virus.

To conclude, antiviral treatment should be started as soon as possible after the onset of symptoms and will include two antivirals, as there is no certain data on the high efficacy of any of the usable ones, and their choice will depend on possible side effects and pathologies of the patient, as well as on the accessibility of one or the other antivirals at a given time. The route

of administration also influences the choice of antivirals - preferably i.v. remdesivir and / or lopinavir / ritonavir syrup for patients with severe (intubated) forms.

II. Immunomodulatory medication

In some patients, the initial infectious phase is followed by a second stage, in which the inflammatory-immune response is exacerbated; clinically, this phase is associated with recrudescence / worsening of symptoms, particularly pulmonary ones; a significant proportion of the cases with unfavourable evolution is represented by patients with an excessive inflammatory response ("cytokine storm"), who are often adults without known previous pathologies. At the same time, another subgroup of patients may have a deficiency in immunity which prevents the control of the SARS-CoV-2 infection and predisposes to superinfections (patients in the classic risk groups are more common here).

Extensive biological monitoring is important in order to seize the moment of the inflammatory reaction, with the help of the C-reactive protein, LDH, blood test (lymphocytes, platelets), ferritin, IL-6, fibrinogen, D-dimers.

The administration of immunomodulatory medication seeks to reduce the risk of unfavourable evolution, including death, in these categories of patients. The expected beneficial effects can be counterbalanced by intense immunosuppression, with delayed eradication of the SARS-CoV2 infection and possible reactivation of chronic infections: tuberculosis, pneumocystosis, HSV, chronic viral hepatitis.

The main therapeutic essays for this purpose were based on: systemic corticosteroids, immunosuppressive medicinal products / modulators, convalescent plasma.

<u>Systemic corticosteroids</u>

Results in patients with SARS-CoV-1 infection were analysed in several studies: 25 studies did not provide conclusive results, and a worsening of the disease was found in 4 other studies.

Alternatively, corticosteroids are the main treatment in the control of the excessive cytokine release syndrome. Used in patients with acute respiratory distress in COVID-19, corticosteroids significantly reduced lethality to 46% versus 62% in those who did not receive corticosteroids. The specific indication applies to cases of COVID-19 with excess inflammation and possibly developing pneumonia, when the administration should be initiated as early as possible: methylprednisolone (1-2 mg / kilogram body weight / day) or dexamethasone, 16-20 mg / day, for 5-7 days.

The administration of corticosteroids is also justified in patients with COVID-19:

- in cases with other indication for use (for corticosteroids), such as asthma attack, exacerbated COPD or adrenal insufficiency;

- in cases of septic shock unresponsive to vasopressor amines (HHC, usually 50 mg every 6 hours).

<u>Immunomodulators</u>

- Tocilizumab

This IL-6 receptor antagonist has been used in a subgroup of patients with severe forms of COVID-19 with excessive inflammation activation ("cytokine storm"). The identification of patients who would benefit from tocilizumab can be based on parameters such as increased ferritin levels, decreased lymphocyte and platelet counts, increased C-reactive protein, fibrinogen, and D-dimer levels. There is data reported by Xu et al. on efficacy of tocilizumab in a number of 21 Chinese patients; following administration of 1-2 doses of tocilizumab,

afebrility was obtained in all patients, as well as decreased oxygen demand, and partial correction of lymphopenia. In the clinical experience of the authors, the results obtained with tocilizumab in association with corticosteroids were favourable, following administration of 8 mg / kilogram body weight doses, repeated at 8 - 12 hours, up to a maximum of 3 administrations.

There are risks related to reactivation of tuberculosis, hepatic cytolysis, hypercholesterolemia.

- Baricitinib

Baricitinib is a JAK (Janus kinase) inhibitor used in treatment of moderate to high forms of rheumatoid arthritis (oral administration) at a standard dose of 4 mg / day with a low rate of infectious reactivation. Cantini F. et al. used baricitinib for 14 days in association with lopinavir / ritonavir for treatment of 12 patients with moderate pneumonia and COVID-19. Clinical improvements were obtained in all patients; in only one case, treatment was discontinued on day 10 due to hepatic cytolysis, more likely caused by lopinavir / ritonavir.

- Anakinra

Anakinra is an IL-1 receptor antagonist currently used in the treatment of rheumatoid arthritis and Still's disease; it is administered by subcutaneous route, 100 mg / day, but up to 400 mg / day can be administered in severe forms of inflammatory diseases. Off-label doses of up to 3,600 mg / day were used in the treatment of severe sepsis as a continuous infusion over several days without excessive side effects compared to the standard doses. In the case of COVID-19, subcutaneous or intravenous use of 200-400 mg / day has been proposed for several days (up to 10 days).

- The convalescent plasma will be used in accordance with the provisions of Order of the Minister of Health no. 654/2020 on approval of the Methodology for the collection, testing, processing, storage and distribution of plasma from the donor cured by COVID-19 and the monitored use for critically ill patients with COVID-19 in intensive care units.

III. Management of coagulation disorders in patients with COVID-19

Venous thromboembolism - VTE (deep vein thrombosis - DVT and pulmonary embolism - PE) is a common complication in acute infectious diseases; the risk of VTE is 2 - 32 times higher in such diseases.

The incidence of VTE in patients with COVID-19 has not yet been established. There are arguments demonstrating the association of a hypercoagulable state in patients with COVID-19. Hypercoagulability is related to the systemic inflammatory syndrome, endothelial dysfunction, an elevated factor VIII and von Willebrand factor. Given this hypercoagulable state, the risk of thrombosis increases by association of additional risk factors: pregnancy, prolonged immobilisation, dehydration, age, contraceptive use, obesity, associated diseases, cytostatics, surgical interventions, steroid therapy, etc.

The risk of VTE is significantly increased in patients admitted to intensive care - Klok demonstrates in a study on 184 patients admitted to intensive care in March-April 2020 an increased incidence of thrombosis complications (31%) in all age groups.

The aim of this document is to provide the clinician, who treats COVID-19 patients, with a set of general and specific recommendations on coagulation abnormalities and anticoagulant therapy:

A. General recommendations

1. Asymptomatic COVID-19 patients do not require routine anticoagulation. Exceptions are chronically anticoagulated patients (in whom the current therapy will be continued, making sure that it is administered in optimal doses and monitoring its efficacy where required) and patients with a high thromboembolic risk caused by other medical conditions.

2. All symptomatic COVID-19 patients have an indication for routine anticoagulation. The therapeutic regimen (prophylactic or curative) will be selected individually, depending on the thromboembolic risk class, considering the individual features and the bleeding risk.

3. The established scores for patients hospitalised with medical conditions, such as the PADUA score (table 1), can be used to calculate the thromboembolic risk; however, specific risk factors for COVID-19 patients should also be considered in the individual assessment: symptoms of respiratory failure, respiratory rate > 24 breaths / minute, SaO2 <90%, elevated CRP and fibrinogen levels, increasing D-dimer values - their presence placing patients at high risk.

4. Patients with high thromboembolic risk and low bleeding risk have an indication for curative anticoagulation. For patients admitted to ATI - it is preferable to choose unfractionated heparin (UFH) with a target activated partial thromboplastin time (APTT) of 60 - 85 sec. or alternatively enoxaparin 1 mg / kilogram body weight x 2 / day. For other patients hospitalised in infectious disease departments or other medical departments, enoxaparin 1 mg / kilogram body weight x 2 / day (or other low-molecular-weight heparin (LMWH) in equivalent dose) or Unfractionated Heparin (UFH) with target activated partial thromboplastin time (APTT)of 60 - 85 sec is preferred.

5. The risk class is periodically re-evaluated, the modification of the clinical, biological or imaging picture requiring adjustment of the therapeutic decisions.

6. Patients with an indication for chronic oral anticoagulation require evaluation of medicinal product interactions, in which case switching to injectable anticoagulant (UFH or LMWH) is recommended at a therapeutic dose. In patients with metal valve prostheses, vascular prostheses or implantable cardiac devices, the choice of anticoagulant treatment will be decided after a cardiology consultation.

Table 1 – The Padua prediction score

Increased risk for venous thromboembolism ≥ 4

Clinical features	*Score*
Active cancer)*	*3*
History of pulmonary embolism / deep vein thrombosis	*3*
*Reduced mobility **)*	*3*
*Diagnosed thrombophilia ***)*	*3*
Trauma / Recent Surgery (≤ 1 month)	*2*
Age > 70 years	*1*
Heart/respiratory failure	*1*
Myocardial infarction / Ischemic stroke	*1*
Acute infection and / or rheumatic diseases	*1*
Obesity (BMI ≥ 30)	*1*
Hormone treatment	*1*

**) Patients with metastases and / or who have had chemotherapy or radiation therapy in the past 6 months.*

***) Immobilisation in bed (with the possibility of moving to the bathroom) either due to patient limitations or on medical recommendation, for at least 3 days.*

****) Antithrombin deficiency, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome*

B. Specific recommendations

1. Coagulation tests upon hospital admission:

D-dimers, prothrombin time, platelets - these parameters are used to classify patients with COVID-19 on risk groups. The clinician should be aware that there are many tools for determining D-dimers and great diversity in terms of the reference range, namely the units of measurement for the D-dimers level.

The D-dimers level indicating a negative prognosis is variable, depending on the study, the instrument used, the units of measurement.

In general, a 3-4-fold increase in D-dimer values is a negative prognosis (according to the ISTH guideline).

Other coagulation tests required: APTT, fibrinogen, INR, thrombin time, PDF.

The patient's history is very important, because the presence of diseases can be an explanation for certain coagulation-related abnormalities: haemophilia, thrombophilia, immune thrombocytopenic purpura, liver cirrhosis, history of thrombosis, anticoagulant / antiplatelet therapy, diabetes, collagenosis, vasculitis.

2. Monitored coagulation tests

Regular repetition of the following tests is required: platelet count, prothrombin / PA / INR time, D-dimers, APTT, fibrinogen, antithrombin level (if possible).

The prolongation of PT, APTT, increase in D-dimers, decrease in fibrinogen and platelets indicate progression to disseminated intravascular coagulation (DIC). For the diagnosis of DIC, the ISTH (International Society of Thrombosis and Haemostasis) score is recommended - table 2.

Table 2

Parameters to be monitored	*Score*
Platelet count	
> 100 x 10^9/L	*0*
50 - 100 x 10^9/L	*1*
< 50 x 10^9/L	*2*
D-dimers:	
- regular	*0*
- moderate increase (1 - 10 times the upper limit of normal)	*2*

- strong increase (> 10 times the upper limit of normal)	*3*
Fibrinogen *> 1.0 g/L* *≤ 1.0 g/L*	 *0* *1*
Prothrombin time extended with: *< 3 seconds* *3 - 6 seconds* *> 6 seconds*	 *0* *1* *2*
True diagnosis of DIC	*Minimum 5 points*

The evolution towards DIC is a negative prognostic factor. According to the Tang study, 71.4% of deceased patients had DIC on day 4 and only 0.6% of survivors had this complication. Moreover, the authors observed a negative prognosis in patients who showed a significant increase in the level of D-dimers, prolongation of the TP and decrease in fibrinogen on day 10 and day 14, respectively.

If DIC is suspected, a peripheral blood smear (for schizocytes) and reticulocyte count are also required to demonstrate microangiopathic haemolytic anaemia.

3. Prophylactic anticoagulation in symptomatic patients hospitalised with COVID-19

The American Society of Haematology and the International Society of Haemostasis and Thrombosis recommend low-molecular-weight heparin (LMWH) prophylactic anticoagulation in all patients hospitalised for COVID-19, unless there are major contraindications (active bleeding). Prolongation of PT / INR or APTT is not a contraindication for anticoagulation, but it will stop if the platelet count falls below 25 x 10^9 / L (25,000 / cubic millimeter) and / or the fibrinogen level drops below 0.5 g / L (47).

Equivalent (subcutaneous) dose of LMWH for thromboprophylaxis of low- or intermediate-risk patients (at the discretion of the attending physician):

- enoxaparin (clexane) - for patients with creatinine clearance (ClCr)> 30 mL / min, a single dose of 40 mg / day; for ClCr 15 at 30 mL / min - a single dose of 30 mg / day;

- dalteparin (fragmin) - a dose of 5,000 units / day;

- nadroparin (fraxiparin) - for patients with G ≤ 70 kg, a single dose of 3,800 or 4,000 anti-factor Xa units / day; for patients with G> 70 kg, a single dose of 5,700 units / day;

- tinzaparin (innohep) - a single dose of 4,500 anti-Xa units / day.

It is recommended to adjust the doses of LMWH according to certain particular clinical situations (associated diseases such as kidney disease, obesity).

Unfractionated heparin is recommended for patients with ClCr below 15 mL / min or on dialysis.

In patients with significant obesity or in other particular clinical and biological circumstances (at the discretion of the attending physician) the LMWH dose may be increased - enoxaparin 40 mg subcutaneously, twice daily.

If the patient's health deteriorates under anticoagulant therapy with prophylactic doses (significant increase in the level of D-dimers, tendency to thrombocytopenia), the suspicion of

DVT, PE or DIC arises. In this situation, the decision to anticoagulate at therapeutic doses or the change to unfractionated heparin into therapeutic doses will be discussed, in consultation with colleagues from intensive care units (ICU), haematology and cardiology units.

In patients with a history of heparin-induced thrombocytopenia, fondaparinux (arixtra) - 2.5 mg once a day, subcutaneously, is recommended.

Mechanical thromboprophylaxis is recommended in patients with anticoagulation issues.

The use of oral anticoagulants (particularly DOAC - direct oral anticoagulants) is not recommended due to possible interactions with other medicinal products administered to the patient with COVID-19, their presence in the current treatment of COVID-19 patients requiring switching to a curative dose for parenteral anticoagulation (LMWH or UFH).

4. Prophylactic anticoagulation in outpatients

It is recommended to continue prophylactic anticoagulation in all patients with COVID-19 and increased risk of VTE: discharge from intensive care, limited mobilization, history of VTE, active cancer, obesity, thrombophilia, elevated D-dimers.

LMWH or rivaroxaban 10 mg may be administered per os (p.o.) daily for 39 to 45 days. In all cases, the risk of bleeding will be considered.

5. DIC/PE/TVP management

The treatment of these complications will be performed in collaboration with specialists from the cardiology and intensive care units.

An interesting feature of the DIC, which complicates the course of patients with COVID-19, is that bleeding occurs rarely, although coagulation disorders are severe. In order to avoid thrombotic complications (which are much more common), it is recommended that replacement therapy (ME, PPC, platelet preparations) be thoroughly individualised. This substitution therapy should not be given according to coagulation test results alone, but only to patients with active bleeding, an increased risk of bleeding or to those who are going to undergo procedures involving the risk of bleeding.

The role of the tranexamic acid is unknown and its use is not recommended.

We must keep in mind that there are no randomized studies that provide highly recommended information and that our COVID-19 knowledge and management are rapidly evolving.

IV. Antibiotics and other anti-infectives (except for those specific to COVID-19)

The administration of antibiotics and, more broadly, anti-infectives in patients with COVID-19 aims to:

- treat initial COVID-19 associated infections;

- treat infections associated with medical care, more frequently respiratory infections, and with other localisations as well: of soft parts, systemic infections, including cases of sepsis and septic shock;

- a special situation of infections associated with medical care is the reactivation of latent infections in patients receiving immunosuppressive treatment (tuberculosis, herpes infections, pneumocystosis).

During the first period of the disease, the patient with COVID-19 may have concomitant bacterial infections, usually respiratory, which may generate productive cough, increased or increasing serum procalcitonin, leukocytosis with neutrophilia, radiological appearance of alveolar lung opacity, D-dimers > 1 μg/ml. The risk of concomitant bacterial infections appears to be significantly lower than in patients with influenza. A bacteriological screening with testing for the presence in the urine of pneumococcal or Legionella antigens, serologies for atypical

bacteria, blood cultures is useful. The antibiotics recommended in early installed pneumonia are those recommended for community forms: amoxicillin clavulanate 1.2 g i.v. every 8 hours + doxycycline 100 mg every 12 hours or moxifloxacin 400 mg / day (for pregnant women: ceftriaxone + azithromycin); the duration of administration will not exceed 5-7 days. Doxycycline has been assigned an additional favourable role as a possible IL-6 inhibitor. Fluoroquinolone should be avoided in patients with rhythm or conduction disorders. Although Gautret reports the efficacy of azithromycin in combination with hydroxychloroquine, an analysis performed for only six cases cannot support the inclusion of this antibiotic in the standard treatment of COVID-19 and / or bacterial infections in conditions of frequent resistance of pneumococci to macrolides in Romania. A study by Gautret and colleagues in a group of 1,064 patients with hydroxychloroquine and azithromycin showed no side effects, favourable clinical outcome and viral clearance in 91% of cases in 10 days.

The occurrence of mechanical ventilation-associated pneumonia was rare in patients with COVID-19, even though the mean duration of ventilation was approximately 3 weeks; in an analysis of 150 cases treated in Wuhan, bacterial superinfection was recorded in 1% of those who survived and in 16% of those who died. In case of pneumonia associated with mechanical ventilation, a treatment scheme adapted to the microbial circulation from the respective intensive care unit will be used. In a meta-analysis, Lippi M. shows that serum procalcitonin levels above 0.5 ng/ml are correlated with an increased risk of adverse outcome.

Following administration of immunosuppressive medicinal products to control the cytokine release syndrome (CRS) (e.g. tocilizumab, baricitinib, anakinra), the patient should be monitored for the risk of breakthrough infections, reactivation of latent tuberculosis, reactivation of herpes infections, or pneumocystosis; in order to be able to evaluate these risks as accurately as possible, we recommend, along with the medical history, the collection and storage of a blood sample prior to the first administration of immunosuppressant, from which serological tests (HSV), Quantiferon TB-Gold and other tests can be performed.

To conclude, the administration of anti-infective medication, other than anti-COVID-19 medication, is indicated in restricted and well-defined categories of patients with this syndrome. The correct use of medical history, physical examination data, biological tests (primarily procalcitonin and complete blood count), imaging examinations and microbiological tests (blood cultures, other examinations) may allow the judicious use of antibiotics required in order to solve the infectious problems associated with COVID- 19. Given the relative rarity of infections associated with this syndrome, the current situation may have a favourable unintended consequence, namely limitation of the selection pressure of antibiotic-resistant microorganisms and restriction of the circulation of these microorganisms.

V. Support of vital functions

Care of patients with severe and critical forms of COVID-19 will be provided by intensive care physicians. Although several syndromes have been described in the months leading to the onset of the pandemic, which may jeopardize the prognosis of the patient with COVID-19 (haemodynamic dysfunction, acute renal failure, severe bacterial breakthrough infections), the main life-threatening condition is the severe respiratory distress and therefore, special attention should be paid to the monitoring of respiratory function in COVID-19 patients. The decrease in O2 saturation to 92% in the atmospheric air in patients at rest, without previous respiratory distress, requires rapid evaluation of arterial gasometry and the enrichment of inspired air with oxygen; additional measures to reduce hypoxemia are decided by the intensive care physician. The aim is to avoid aggravation of tissue hypoxia without resorting as much as possible to more invasive interventions such as mechanical ventilation with IoT or extracorporeal oxygenation. Among the possible methods of intervention, it should be noted

that the non-invasive ventilation is a procedure that involves a high risk of aerosolization of SARS-CoV-2, particularly in the mask ventilation variant.

The elements of detail in this regard go beyond the scope of this therapeutic protocol.

VI. Other therapeutic measures may be useful in most cases:

- fighting fever (acetaminophen), myalgias;

- fighting insomnia;

- limiting anxiety to improve the overall condition - lorazepam;

- combating nausea, vomiting - metoclopramide, ondasetron, dexamethasone;

- in patients with viscous respiratory secretions - in COVID-19 or a bacterial breakthrough infection - the fluidification of secretions can be resorted to by nebulisations with acetylcysteine and beta-mimetics or with hypertonic and beta-mimetic solution;

- the prophylaxis of bedsores in the immobilised / severe patient requires the change of position every two hours;

- prophylaxis of stress ulcer by gastric antisecretory medicinal products and rapid resumption of enteral nutrition;

- there is a risk of potentiation of activity between statins and ritonavir-associated protease inhibitors; therefore it is proposed to limit the dose of atorvastatin to 20 mg / day;

- *In forms with significant inflammation and / or hypoxemia in diabetic patients, the risk of ketoacidosis is higher and correction with fast-acting insulin is recommended.*

Controversial or seemingly unnecessary therapeutic interventions

• Although the need to replace ACE inhibitors and / or sartans in the treatment of patients diagnosed with COVID-19, if previously received, was discussed, the European Society of Cardiology group - the group for hypertension issued on 13 March 2020 a recommendation for these medicinal products to be maintained in treatment regimens; a similar recommendation was issued in the USA on 17 March 2020 by the American Cardiology Association.

• There is a reluctance to use NSAIDs in the treatment of COVID-19 that has been widely disseminated in France since March 2020, related to the inhibition of the beneficial effect of inflammation in cases of low-medium severity COVID-19. There is no clinical data to support this claim; however, it is reasonable to assume that the adverse effects of NSAIDs in COVID-19, such as renal or related to the digestive tract, are more common.

• The following are considered unnecessary or even harmful: intravenous immunoglobulins, volume recovery with colloidal solutions (debatable for albumin).

Proposed treatment depending on the severity of the case and the risk factors for severe evolution

Form of disease (severity)	*Recommended treatment*	*Dose/day*	*Standard duration of treatment*	*Adverse reactions*
Asymptomatic	*No*			
Mild *- acute upper respiratory tract infections (RTIs)*	*hydroxychloroquine**	*2 x 400 mg/day on the first day (2 x 2 tb/day), then 2 x 200 mg/day (2 x 1 tb/day) Children 5 mg/kilogram body weight/day, split into two*	*5 - 7 days*	*Rhythm/driving disorders*
	Associated with lopinavir/ritonavir)*	*2 x 400/100 mg/day (2 x 2 tb/day) Children*	*7 - 10 days*	*diarrhoea (40.9%), nausea (40.9%),*
	or	*2 x 300/75 mg/m2/day*		*stomatitis (18.2%),*
	*Azithromycin **)*	*500 mg/day, day 1, then 250 mg/day, another 4 days*	*5 days*	*anaemia (45.0%),*
	Umifenovir	*3 x 200 mg/day*	*10 - 14 days*	*leukopenia (40.0%)*
Average *Pneumonia without severity criteria*	*hydroxychloroquine *)* *+*	*2 x 400 mg/day on the first day (2 x 2 tb/day), then 2 x 200 mg/day (2 x 1 tb/day) Children 5 mg/kilogram body weight/day split into two*	*5 - 7 days*	
	*Lopinavir/Ritonavir***) or*	*2 x 400/100 mg/day Children*	*10 - 14 days*	*Administered with food or with a mug of milk*
	*Azithromycin **)*	*2 x 300/75 mg/m2/day*	*5 days*	
	Umifenovir	*500 mg/day, on day 1, then 250 mg/day, another 4 days 3 x 200 mg/day*	*10 - 14 days*	

Severe[a]***/ Critical***[b]	*hydroxychloroquine *)*	*2 x 400 mg/day on the first day, then 2 x 200 mg/day Children 5 mg/kilogram body weight/day split into two*	*minimum 5 days*	*In accordance with the description concerning remdesivir mentioned above*
	+ remdesivir	*200 mg/day on day 1, then 100 mg/day Children sub 40 kg - 5 mg/kilogram body weight/day on day 1, 2.5 mg/kilogram body weight/day thereafter*	*10 days*	
	or Lopinavir/Ritonavir if remdesivir is not available (until it is procured)	*The dose is administered as syrup via nasogastric tube ****).*		
	+ immunomodulatory therapy:			
	*Tocilizumab (in patients with "cytokine storm" symptoms*****)*	*8 mg/kilogram body weight, maximum 800 mg slow endovenous infusion in adults (12 mg/kg in children under 30 kg)*	*1 - 3 doses with at least 8 hours between them*	
	Corticoids, convalescent plasma, other immunosuppressive medicinal products			

**) ECG to be performed daily for QT evaluation; contraindications: QT > 500 msec, myasthenia gravis, porphyria, retinal pathology, epilepsy; benefit-risk analysis for pregnant women; can be replaced with umifenovir, favipiravir, remdesivir (with the restrictions specified in the text).*

***) In patients with corrected QT <500 ms, with daily ECG and ionogram at 48 hours.*

****) Replace lopinavir / ritonavir with umifenovir in combination with hydroxychloroquine in patients with cardiac problems at risk for QT prolongation arrhythmias.*

*****) Lopinavir / ritonavir tablets lose about half of their effectiveness.*

******) Hemophagocytic lymphohistiocytosis. a. Severe = at least one of: respiratory rate ≥ 30 / min (≥ 40 / min in preschoolers); SaO2 ≤ 93%; PaO2 / FiO2 <300; pulmonary infiltrates that increase by more than 50% in 24-48 hours. b. Critical = at least one of: acute respiratory distress; sepsis; altered consciousness; multiple organ failure (MOF).*

The duration of treatment is indicative, it can be prolonged or shortened according to the patient's progress, but without being reduced to less than 5 days (provided that no severe side effects occur).

The patient is monitored clinically and biologically - biochemically daily, in patients with moderate-severe-critical forms; the repetition of imaging and biological tests is mandatory in an emergency in case of clinical aggravation.

Testing for viral RNA in faeces is not justified on the basis of existing data.

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