Order no. 1.418
of 7 August 2020

on amendment of the Annex to Order of the Minister of Health no. 487/2020 on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus

Published in: the Official Gazette of Romania no. 719 of 10 August 2020

On seeing the Approval report of the General Directorate for Medical Assistance and Public Health Programmes of the Ministry of Health no. NT 6.722 of 7.08.2020,

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

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

the minister of health hereby issues the following Order:

Art. I – The Annex to Order of the Minister of Health no. 487/2020 on approval of the protocol for treatment of the infection with the SARS-Cov-2 virus, published in the Official Gazette of Romania, Part I, no. 242 of 24 March 2020, as further amended, is amended and replaced with the Annex which is integral part of this order.

Art. II - This Order shall be published in the Official Gazette of Romania, Part I

p.p. the Minister of Health,
Romică-Andrei Baciu,
Secretary of State

Annex
(Annex to Order no. 487/2020)

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

Taking into account the increase in the number of COVID-19 cases in Romania, including severe forms of the disease, and the accumulation of new clinical data, The Infectious Diseases Commission of the Ministry of Health proposes a revised treatment protocol; the first variant was based on a draft of infectious disease specialists from Cluj. 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, USA (1 – 6) 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.

This therapeutic protocol includes principles grouped in the following sections:

1. Antiviral medication
2. Immunomodulatory medication, including convalescent plasma
3. Anticoagulant medicines
4. Antibiotics and other antiinfective medicinal products (apart from COVID-19 medicinal products)
5. Support of vital functions
6. Other therapeutic measures

1. 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 excessive inflammation, 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 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:

• (hydroxy)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 to medicinal product interactions; in addition, it has been widely used in long-term treatments in rheumatology, in even larger doses than those frequently used in the treatment of COVID-19 (600 mg/day compared to 400 mg/day), without generating significant side effects. (Hydroxy)chloroquine alters 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. Gautret C. et al. have evaluated 42 patients; a faster virus clearance in patients with COVID-19 who have received hydroxychloroquine has been observed (8). 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, also leading to an interim authorisation for use in the USA (9). Contradictory data on the clinical efficacy of hydroxychloroquine have subsequently emerged:

- inefficiency and adverse reactions: a randomized study of 150 patients showed no significant decrease in duration of SARS-CoV-2 negation and increased adverse reactions in patients treated with hydroxychloroquine (10), other studies showed that it did not reduce lethality, nor the need for intensive care (11, 12);

- Efficacy: A study of 2.541 patients in the United States showed a 66% reduction in the risk of COVID-19 death in patients with severe disease with hydroxychloroquine compared to the standard treatment: 13.5% versus 26.4% (13).

Three decisions had an important impact on the perception of the efficacy of hydroxychloroquine, namely:

- discontinuation of patient enrolment in the UK RECOVERY study in the hydroxychloroquine recipient group due to lack of efficacy in reducing mortality from COVID-19 (4 June 2020);

- suspension on 15 June 2020 of the provisional authorisation granted by the FDA for the use of hydroxychloroquine in the treatment of COVID-19;

- discontinuation of patients in the SOLIDARITY trial organised by the WHO, in the group of those receiving hydroxychloroquine, due to lack of efficacy in reducing mortality associated with COVID-19 (17 June 2020).

In Romania, hydroxychloroquine has been widely used for therapeutic purposes and sometimes in order to prevent the occurrence of severe forms of COVID-19; negative data and adverse effects have limited its prescription. However, given the existing favourable data, this medicinal product remains an alternative in the absence of more effective medicinal products.

A particularly debated issue is the association of hydroxychloroquine with azithromycin. Initial data suggested a significant enhancement of the clinical efficacy; subsequently, the published results did not find such a benefit. Co-administration of two medicinal products which can prolong QT pleads against this combination; two studies found a significant elongation of QT in more than 10% of patients treated with this combination (14, 15).

The situation of bacterial resistance in Romania is an additional counterargument to the use of azithromycin. The American Society of Infectious Diseases recommends the prudent use of (hydroxy)chloroquine and avoidance of the association between hydroxychloroquine and azithromycin (6).

• Protease inhibitors

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, SARS-CoV-2 included. The clinical data published to this date 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 (17 - 19), 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 (20). 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 (21). 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 (22). Adverse reactions in patients in the study by Cao B. et al were discontinued in 14% of cases (21).

These outcomes 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 (4,5); the darunavir / cobicistat manufacturer claims that this product is in vitro ineffective against SARS-CoV2 and discourages its use in patients with COVID-19 (23), therefore its use is no longer justified. Ritonavir in combination with darunavir has also been used as an alternative in patients not tolerating lopinavir / ritonavir, however, the experience is limited.

• Remdesivir

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 (25, 26). 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 (27). Beigel J. et al., in another study involving 1063 severely ill patients treated with remdesivir versus placebo, there was a discrete benefit in terms of mortality: 8% versus 11.9% ($p = 0.06$) and duration until improvement: 11 days compared to 15 days, $p = 0.01$ (28). Goldman J.D. et al. showed a similar efficacy for the 5-day and 10-day treatment durations, namely (29).

It is currently used in clinical trials and can only be obtained for individual compassionate use for pregnant women or children over 12 years old with severe forms of COVID-19 (30); there is an "early access" programme in several countries of the European Unit, through which the national authority manages the use of remdesivir, based on a provisional registration of the product in Europe (31).

The current indication is harmonised with the general principle of the use of antivirals, as early as possible after the onset of symptoms, being more effective in patients with hypoxia who have not yet required mechanical ventilation or extracorporeal membrane oxygenation (6); the duration of administration became more flexible, 5 - 10 days (maximum duration for intubated patients), depending on the clinical evolution and the negation of SARS-CoV-2 PCR tests. The recommended doses are 200 mg on the first day (100 mg every 12 hours) and 100 mg in the following days, by intravenous infusion, after dilution in physiological serum; the duration of administration should be at least 30 minutes (31).

• 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. One

of its advantages consists of reduced adverse reactions. 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 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 (32). 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.

Given the favourable results reported and the low rate of adverse effects associated with its administration, umifenovir represents a solution; it should be used instead of 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; (33, 34); the doses used were 1,600 mg every 12 hours on the first day, then 600 mg every 12 hours for 7-14 days. It is not indicated in children and has been used in China in patients of childbearing potential only if they had a negative pregnancy test and always associated with contraceptive medication during treatment and at least seven days after stopping it; men were advised to use a condom for at least one week after hospital 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.

Table 1 - Antiviral medication proposed for the treatment of COVID-19

Medicinal product	Doses	Standard duration	Frequent adverse reactions
*Hydroxychloroquine**)	2 x 400 mg/day on the first day (2 x 2 tbsp/day), then 2 x 200 mg/day (2 x 1 tbsp/day) Children: 5 mg/kgc/day in 2 doses	5 - 7 days	Rhythm / driving disorders

Lopinavir/Ritonavir**) ***)	2 x 400/ 100 mg/day Children: 2 x 300/75 mg/m2/day	7 - 14 days	Diarrhoea (40.9%), nausea (40.9%), stomatitis (18,2%), anaemia (45,0%), leukopenia (40.0%)
Umifenovir	3 x 200 (400) mg/day	10 days	
Favipiravir	1,600 mg every 12 hours on the first day, then 600 mg every 12 hours 1,800 mg every 12 hours on the first day, then 800 mg every 12 hours****)	10 days	Teratogenic#), hyperuricemia (5%)##), diarrhoea (4.8%)##)
Remdesivir	200 mg/ day on day 1 then 100 mg/day Children weighing less than 40 kg: 5 mg/kgc/day on day 1, then 2.5 mg/kgc/day	5 - 10 days	hepatic cytolysis, phlebitis, constipation, nausea

*) It is recommended to perform daily EKG for QT evaluation; Contraindications: QT> 500 msec; benefit-risk analysis for pregnant women.

**) No combination of lopinavir / ritonavir with hydroxychloroquine and / or azithromycin is used in patients with cardiac problems at risk for QT prolongation arrhythmias.

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

****) For these doses, the toxicity of favipiravir is not sufficiently studied.

#) To be used only with contraception in fertile patients and in patients of childbearing potential.

##) The rate of side effects comes from studies performed at lower doses than proposed.

To conclude, the antiviral treatment should be started as soon as possible after the onset of symptoms; Moderate-severe / critical forms will include two antivirals whenever possible, as there are no definite data on the high efficacy of any of the usable ones. The choice of antivirals will depend on the potential adverse reactions, the patient's pathologies, as well as the availability of one or another of the antivirals at a given time. The route of administration also influences the choice of antivirals - preferably remdesivir iv and / or lopinavir / ritonavir syrup for orotracheally intubated patients.

2. Immunomodulatory medication, including convalescent plasma

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 (excessive cytokine release), with the help of the C-reactive protein, blood count, blood test (lymphocytes, platelets), increased ferritin, increasing IL-6, increase in the fibrinogen and D-dimers level, increased LDH.

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 a too intense immunosuppression, with delayed eradication of the SARS-CoV2 infection and possible reactivation of chronic infections: tuberculosis, pneumocystosis, chronic viral hepatitis.

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

- Systemic corticosteroids

Corticosteroids are the main treatment for 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. An important argument in favour of their use was the preliminary data from the RECOVERY study; the 2,104 patients who received 6 mg of dexamethasone daily (until discharge or up to 10 days) had a significantly lower lethality rate: 22.9% compared to 25.7% among the other 4,321 patients; the benefit was found for various categories of hypoxic patients, but not for those who did not require additional oxygen (36).

Therefore, the specific indication is in cases of COVID-19 with excess inflammation (increased / increasing values of the monitored inflammation parameters, see above) and possibly with evolving pneumonia (polypnea, decrease of SpO2 below 93% and blood pressure of oxygen), when administration should be initiated as soon as possible: dexamethasone, iv, 8 - 24 mg / day, for 7 - 10 days, possibly methylprednisolone. The duration and dose are decided according to the patient's progress. Corticosteroids are not indicated in patients who maintain satisfactory respiratory function without additional oxygen supply,

for whom the benefit is not obvious, but adverse reactions are as common as in other groups of patients (6).

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

- in cases with other indication for use, 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).

Immunomodulators

• 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"). 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 (37). There is data reported by Xu X et al. on efficacy of tocilizumab in a number of 21 Chinese patients; following administration of 1-2 doses of tocilizumab, afebrility, decreased oxygen demand and partial correction of lymphopenia were obtained in all patients (38). In an observational study of 154 patients with COVID-19 requiring mechanical ventilation, Somers E.C. and collaborators showed a 45% decrease in lethality, despite doubling of the risk of bacterial superinfection (54% vs. 26%) (39). Rojas-Marte G. and colleagues conducted a case-control study that included 193 patients with severe forms of COVID-19; a slightly lower lethality was observed in patients receiving tocilizumab (52% vs 62%), and the difference was significant in patients who did not receive mechanical ventilation, 6% vs 27% (40).

In the clinical experience of the authors, the results obtained with tocilizumab were favourable, following administration of 8 mg / kilogram body weight doses, repeated at 8 - 12 hours, up to a maximum of 3 administrations.

• 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 more frequent 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 first published data are favourable. Navarro-Millan I. and colleagues evaluated 11 patients who received anakinra in a New York hospital; the seven in whom treatment was initiated within the first 36 hours of respiratory failure did not reach mechanical ventilation, and of the other four

patients, in whom the first dose was administered after more than four days of hypoxia, three survived (41). In another study in France, 25% of 52 patients treated with anakinra required intensive care, compared to 73% in a control group of 44 previously treated patients in the same hospital (42).

In the case of COVID-19, subcutaneous or intravenous use of 200-400 mg / day, in daily decreasing doses, was used for 7-10 days.

There were not sufficient results published for other immunomodulators: siltuximab (a series of 30 cases treated in Italy, with a better outcome than patients with standard treatment), baricitinib (a series of 12 patients with COVID-19 pneumonia, with clinical improvements in all patients), sarilumab (study discontinued prematurely due to lack of efficacy), rituximab.

Convalescent plasma

Convalescent plasma administration assumes that the former immunocompetent patient after the SARS-CoV-2 infection will have sufficient levels of protective antibodies to be used to limit viral replication and mitigate the excessive inflammatory response in a patient with COVID-19. Duan K. et al reported that clinical and biological improvement was observed in a series of 10 patients with COVID-19 with respiratory impairment who required additional oxygen and received convalescent plasma along with standard therapy at that hospital (43). Li L. et al conducted a randomized study of 103 patients that showed both a reduction in lethality and a higher rate of clinical improvement at 28 days, without reaching statistically significant differences compared to patients who did not received convalescent plasma (44).

In order to use convalescent plasma you need:

- to obtain the donor's consent after confirmation of his healing;

- the presence of sufficient anti-SARS-CoV-2 antibodies; the FDA recommends a neutralizing antibody titer of at least 1/160; since the determination of neutralizing antibodies is often not available, the IgG antibody titer is determined by ELISA; a titer of more than 1/1350 correlates in more than 80% of situations with a sufficient titer of neutralizing antibodies (45);

- donor testing to meet blood donation criteria: the absence of blood-borne infections and the absence of anti-HLA antibodies which increase the risk of TRALI (transfusion related acute lung injury).

The occurrence of TRALI in a patient with severe COVID-19 may significantly worsen the respiratory dysfunction of a patient who already has severe respiratory impairment; volume overloads have also been reported following plasma transfusion in patients with COVID-19. In a database of 5,000 patients who received convalescent plasma, 4 deaths and 21 other major accidents related to the administration were recorded in the first hours: TRALI, post-transfusion overload and allergic reactions (46).

As regards the use of convalescent plasma there are uncertainties related to:

- optimal timing of harvesting - given the limited data on antibody dynamics, including the rapid decrease in the anti-SARS-CoV-2 IgG titer, during the first 2-3 months after healing (47, 48);

- the quality of antibody detection tests;

- effective plasma dose; doses of 200-400 ml were used.

This therapeutic method should be used as early as possible in patients with potentially severe forms of COVID-19; As the availability of effective convalescent plasma is currently limited, we believe that this therapeutic method should be used primarily in patients with a deficient inflammatory-immune response profile, in whom immunosuppression is contraindicated. Currently, the administration of convalescent plasma is done in Romania in line with 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 cured donor of COVID-19 from intensive care units (ICUs) and the monitored use for critical patients with COVID-19 from the ICUs, as further amended and supplemented.

Table 2 - Immunomodulatory medication proposed for the treatment of COVID-19

Medicinal product	Doses	Standard duration	Frequent adverse reactions
Dexamethasone (backup alternative - methylprednisolone)	8 - 16 mg iv/day (24 mg/day in obese patients)	7 - 10 days	Irritation of the digestive mucosa, diabetes imbalance
Tocilizumab	8 mg/ kg (maximum 800 mg per administration)	1 - 3 administrations every 8 - 12 hours	Reactivation of some infections: tuberculosis, chronic hepatitis (HBV), herpes infections, impaired liver function to hepatic impairment, intestinal perforation, hypercholesterolemia
Anakinra		7 - 10 days	Liver damage
Convalescent plasma	200 - 400 ml	Single administration	acute respiratory distress (TRALI), post-transfusion overload, allergic reactions
Undergoing assessment: siltuximab, baricitinib, rituximab			

In conclusion, immunomodulatory treatment is indicated for a subset of patients with potentially severe development and should be initiated as soon as

possible after onset of the inflammatory phase, based on benefit/risk criteria depending on cytokine release, risk of infection and other associated adverse reactions. A rational therapeutic approach would include two steps: a) corticosteroids and/or immunomodulators for oral/subcutaneous administration and b) immunomodulators administered in intravenous bolus (such as tocilizumab) associated with corticosteroids. The treatment with convalescent plasma is currently recommended as a priority in patients with severe forms, possibly associated with COVID-19 infections and reduced inflammatory response, to compensate for the immune response deficiency. The choice of immunosuppressants will depend on the possible side effects and pathologies of the patient, as well as on the availability of one or another of the immunomodulators at a given time.

3. Anticoagulant medication

The administration of anticoagulants to the patient with COVID-19 has:

- a prophylactic purpose, to prevent the occurrence of major thrombotic events and microthrombosis, especially in the pulmonary circulation;
- a therapeutic purpose, in case of major thrombotic events.

The accumulated data show that in COVID-19 there is an obvious procoagulant condition, which can aggravate the patient's progression by exacerbating the respiratory dysfunction, both by microscopic lesions, "pulmonary intravascular coagulation" and by major pulmonary thromboembolism. Deep venous thrombosis, repeated thrombosis of vascular access lines, etc. have also been described. Cui S. et al. identified deep vein thrombosis in 20 of the 81 patients with severe pneumonia admitted to ICUs, and in 17 of them the level of D-dimers was more than three times the normal value. Of the 20 patients, eight died (49). Conversely, therapeutic administration of fractionated heparins resulted in reduced lethality in a group of 449 patients with severe forms of COVID-19 and / or elevated D-dimers (50). Limiting patient mobilization during hospitalization and altered water balance may increase this risk of thromboembolic events.

Evaluation of the level of D-dimers, fibrinogen, platelets is mandatory and can provide a benchmark for the evolution of the case and the duration of administration. The results of Thachil J. et al. are usually consistent: elevated levels of D-dimers and fibrinogenemia and thrombocytopenia correlated with the severity of the case; a level of D-dimers at the initial assessment, of more than four times the normal level, is considered a criterion of disease severity, regardless of the degree of respiratory dysfunction (51). Prolongation of PT, APTT, increase in D-dimers, decrease in fibrinogen and platelets indicate progression to disseminated intravascular coagulation (DIC).

Recommendations are:

- no anticoagulants are indicated for asymptomatic SARS-CoV-2 infections;

- continuation of anticoagulant treatment by patients who have previously initiated treatment for other conditions; if there are drug interactions with the COVID-19 treatment, switch to therapeutic administration of low molecular weight heparin;

- prophylaxis of deep vein thrombosis for all symptomatic hospitalized patients with standard doses of fractionated heparin (most data being related to the benefit of enoxaparin, 40 mg / day in adults with normal body weight, adjusted for obese and patients with renal impairment); in case of contraindications for them (platelets below 25,000 / mmc, active haemorrhage) fondaparinux will be used - ISTH (International Society on Thrombosis and Haemostasis) recommendation – or, if unavailable, mechanical prophylaxis of deep vein thrombosis will be used (51)

- prophylaxis with high doses of heparin (fractionated or not), administered every 12 hours ("intermediate" doses), is preferred in several clinics in some patients with risk factors for deep thrombosis and more severe forms of COVID-19, e.g. for patients in intensive care or after discharge from intensive care (52), in those with the cytokine storm syndrome and significant increase in D-dimers and / or fibrinogen; unpublished data from China indicate a definite benefit if D-dimer values are more than six times the normal level (53);

- anticoagulant treatment for patients with deep vein thrombosis, repeated thrombosis of the vascular approach lines or pulmonary thromboembolism, with unfractionated or fractionated heparin;

- anticoagulant prophylaxis after discharge will be administered selectively to patients recovering from a severe form of COVID-19, especially in those over 40 years, immobilized, with a personal history of higher than normal levels of thrombotic pathology or D-dimer; the recommended duration is 7 to 14 days for enoxaparin and six weeks for rivaroxaban or betrixaban after discharge (54).

In addition, we believe that patients with worsening respiratory dysfunction should receive a therapeutic dose of anticoagulant until a computed tomography scan is performed to rule out pulmonary thromboembolic lesions; if this scan is not possible, the patient will be left with therapeutic doses of anticoagulant for the time necessary to correct the respiratory problem and normalize the D-dimers level.

The classification of patients in one or another of these indications is re-evaluated according to the clinical evolution and laboratory data.

Rescue therapy in case of failure of heparin administration in pulmonary thromboembolism exceeds the scope of this protocol.

In conclusion, prophylactic administration of anticoagulant or continuation of pre-existing anticoagulant therapy is indicated for all symptomatic patients with COVID-19 unless they have an absolute contraindication. The administration of high doses of anticoagulant (intermediate or even therapeutic)

is done for standard indications, but also for patients with COVID-19 with worsening respiratory distress and / or with marked inflammatory syndrome ("cytokine storm").

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

The administration of antibiotics and anti-infectives in patients with COVID19 aims to:

- treat initial COVID-19 associated infections (such as bacterial pneumoniae);

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

- a special situation of infections is the reactivation of infections in patients receiving immunosuppressive treatment (tuberculosis, herpes infections, pneumocystosis etc.).

During the first period of evolution of the disease, the patient with COVID-19 may have concomitant bacterial infections, usually respiratory, increased or increasing serum procalcitonin, leucocytosis with neutrophilia, radiological appearance of alveolar lung opacity, D-dimers > 1 μg/ml (55). 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 (56). Fluoroquinolone and macrolides (azithromycin included) should be avoided in patients with rhythm or conduction disorders due to the risk of triggering such manifestations by lengthening the QT interval. Although some studies report the efficacy of azithromycin in combination with hydroxychloroquine, there is contrary data as well, thus the inclusion of this antibiotic in the standard treatment of COVID-19 and / or bacterial infections in conditions of frequent resistance of pneumococci and probably of Mycoplasma pneumoniae to macrolides cannot be supported in Romania (8, 57).

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 (58). 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 (59).

Following administration of immunosuppressants to control excessive inflammation, the patient should be monitored for the risk of bacterial superinfections and the reactivation of latent infections; in order to be able to assess 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.

In conclusion, the administration of anti-infective medication, other than that specific to COVID-19, should be done in a cautious and selective manner. The correct use of medical history, physical examination data, biological tests (procalcitonin and complete blood count), imaging examinations and microbiological tests (blood cultures, other examinations) may allow the identification of patients in need of antibiotics to resolve COVID-19-associated infectious problems. Given the relative rarity of infections associated with this syndrome, the current situation should have a favourable unintended consequence, namely limitation of the selection pressure of antibiotic-resistant microorganisms and restriction of the circulation of these microorganisms.

5. 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 following the onset of the pandemic, which may jeopardize the prognosis of the patient with COVID-19 (haemodynamic dysfunction, acute renal failure, severe bacterial superinfections), the severe respiratory impairment remains the main life-threatening condition and, therefore, special attention should be paid to the monitoring of respiratory function in the COVID-19 patient. The decrease in O2 saturation to 92% in the atmospheric air in patients at rest, with no 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.

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

- fighting fever (acetaminophen), myalgias
- fighting insomnia;
- limiting anxiety in order to improve general condition - lorazepam;
- combating nausea, vomiting - metoclopramide, ondasetron, possibly dexamethasone;
- in patients with viscous respiratory secretions - fluidification of secretions can be resorted to by nebulisations with acetylcysteine and beta-mimetics;
- eschar prophylaxis in the immobilized / severe patient requires a change of position every two hours;
- prophylaxis of stress ulcer by gastric antisecretory medicinal products and enteral nutrition;
- there is a risk of potentiation of activity between statins and ritonavir-associated protease inhibitors; therefore it is recommended 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;
- giving up on smoking.

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 was discussed, the European Society of Cardiology group 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 (60, 61).

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 be careful about side effects such as those related to kidneys or the digestive mucosa. Patients receiving NSAIDs for various conditions may continue the treatment if there are no major drug interactions with the COVID-19 medication, with monitoring for potential adverse reactions.

The following are considered unnecessary or even harmful: intravenous immunoglobulins, volume recovery with colloidal solutions (debatable for albumin) (58).

Table 3 - Proposed treatment depending on the severity of the COVID-19 case

Form of disease (severity)	Recommended treatment	Recommended duration
Asymptomatic	No	-
Mild - acute upper respiratory tract infections (RTIs)	An available antiviral Recommended anticoagulant prophylaxis (mandatory for inpatients) if they do not have anticoagulant therapy already underway for other indications	7 days
Average Pneumonia without severity criteria	Antivirals (preferably two) should be administered as early as possible Potential anticoagulants - prophylaxis, intermediate doses or therapy Dexamethasone (or methylprednisolone) 7 - 10 days +/- other immunomodulators	Depends on the patient's progress
Severe[a)]/ Critical[b)]	Antivirals (questionable clinical role beyond 12 to 14 days from the onset of symptoms; the epidemiological indication is maintained) + therapeutic anticoagulant + dexamethasone (corticosteroid), 7 - 10 days + tocilizumab (in patients with excessive inflammation) *), possibly other immunomodulators **) +/- Convalescent plasma +/- antibiotics	Depends on the patient's progress

a) Severe = at least one of the following: respiratory rate ≥ 30/min. (≥ 40/min. in preschoolers); SaO2 ≤ 93%; PaO2/ FiO2 < 300; pulmonary infiltrates that increase by more than 50% in 24 to 48 hours.

b) Critical = at least one of the following: acute respiratory distress; sepsis; alteration of consciousness; Multiple organ dysfunction syndrome (MODS).

*) For tocilizumab 1 - 3 doses of 8 mg / kg every 8 to 12 hours.

**) In case of unavailability of tocilizumab or earlier initiation in the patient with significant increasing inflammation.

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 case of 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.

This protocol is based on the following references: *)

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