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THE BULGARIAN EXPERIENCE IN THE THERAPEUTIC STRATEGY IN COMPLICATED CORONA VIRUS INFECTION

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ABSTRACT: Complicated coronavirus infection occurs as a systemic disease. Although the target organs of this new pathogen for the human population are the lungs and the heart. This virus does not leave an organ or system of the human body intact. Apart from the respiratory and cardiovascular systems, which plays a leading role in the development of the pathological process, the hepatobiliary, urinary, nervous, endocrine, gastrointestinal systems, including the skin and its appendages are most often affected by this disease. Even the musculoskeletal system is not left untouched. All affected organs and systems are the root of complications occurring in the convalescent period for patients which sometimes exceed six months. This is the main argument for conducting consistent, targeted monitoring of the so-called Post-Covid period. The aim is to prevent the chronicity of the pathology that forms a true Post-Covid syndrome and the subsequent disability of patients with a complicated coronavirus infection. The correct therapeutic approach in all patients with a complicated coronavirus infection is extremely important for shortening the Post-Covid convalescence period and reducing the consequences of Post-Covid syndrome. In this article we comment on the main strategic approaches in the treatment of complicated coronavirus infection with the belief that are the key to success in the treatment of the acute stage of the disease and minimizing complications in the convalescent period.

Keywords: COVID 19, Etiology, Oxygen saturation, Psychotherapeutic approach, inflammation,Drugs and Food supplements.

INTRODUCTION

In a pandemic setting, conducting clinical trials is a difficult task arising from the occurring epidemic environment. COVID 19 has created morbidity not only in human but also took its toll on economy around the world **[1, 2]**. The pharmaceutical solution to the most current problem COVID 19 is related to the search for the use of familiar drugs with known antiviral effect, and need of the development for

new ones. In order to legitimize their use, clinical trials must be undertaken, and this is a difficult task that requires compliance with additional rules and measures in addition to the known ones **[3, 4]**. A large number of antiviral drugs at various stages of development or use are currently being studied by innovative pharmaceutical companies to determine whether they are effective in treating patients with COVID 19 **[5, 6]**. Companies share compounds and information from their databases of joint experience to accelerate the development of therapeutic tools and diagnostics to deal with current and future coronavirus outbreaks **[7, 8]**.

MATERIALS AND METHODS

In this article we present the main strategic approaches in the treatment of complicated coronavirus infection applied in Bulgaria. Based on the etiology and pathogenesis of the specific disease process, our experience shows that this approach ensures optimal success in terms of good outcome, including optimal control of hospital mortality in the target group of patients and complete recovery of patients within one year period. The same conclusion is convincing in relation to the late complications associated with the leading pathological process (viral pneumonia), namely residual (possibly disabling) pulmonary fibrosis **[9, 12]**.

Results and Discussion

Therapeutic strategic approaches include:

1. Evaluation of hemodynamics and relevant treatment measures with adrenomimetics Cardiac, Diuretics, Vasoprotectants and Vasotonizing.
2. Assessment of respiratory activity gas exchange and relevant treatment measures O_2 starts in doses from 2 lit/min to ≥14 lit/ min at saturation ≤90% (for pulse oximetric monitoring). The target set is saturation ≥93%. In case of desaturation (against the background of maximum flow rate of oxygen therapy)of the order of ≤80% (in case of pulse oximetry) and tachypnea over 25 lit/min, high flow oxygen therapy 39 li/min high flow oxygenation device.

In case of desaturation (against the background of high flow oxygen therapy) of the order of ≤80% (in case of arterial CGA) and tachypnea over 30 lit/min, mechanical ventilation is discussed. Bronchodilators in indications (dynamic auscultatory evaluation).

Expectorants are used if necessary and in the appropriate period (not applied in the first 7 15 days in patients with involvement of more than 50% of lung volume and in periods of desaturation), as well as antitussives if necessary the above clarification applies.

Essential oils with selective excretion through the upper and lower respiratory tract. Only oral drugs (eg Tavipek/Tavipek Forte and Gelomirtol/Gelomirtol Forte) and topical preparations (eg sublingual tablets containing Menthol and Eucalyptol) are used. Strict adherence to the indications contraindications for initiating the above therapeutic actions is appropriate**[13, 14]**.

3. Etiological treatment Hyper immune serum is used (this would be a standardized drug preferably recombinant monoclonal antibodies) there are currently no such for mass use. Regeneron is used to a limited extent

with the clarification that it is still a cocktail of two monoclonal antibodies: Casirivimab (REGN10933) and Imdevimab (REGN10987). That is, the preparation itself can be called "polyclonal REGN COV2".

Heterogeneous IgG concentrate is administered from recovered and followed (nomenclature) donors. Given the information currently available (we have over two years of experience worldwide) on the peak values of both total anti SARS CoV_2 AB and anti SARS CoV_2 IgG AB, a donation campaign should be organized for anti SARS CoV_2 hyperimmune plasma (non convalescent) from which to float a heterogeneous IgG concentrate by the type of preparations such as Privigen, Octagam, Gamavenin, Imunovenin and others. **[15, 19]**.

Convalescent plasma can be used given all the indications and contraindications for the use of blood components. The use of such a blood component, floated by a convalescent donor, within the modern medical philosophy, is an absolutely unprofessional act.

Regarding the use of aminoquinolines, it is generally believed that drugs of this group are ineffective in the treatment of coronavirus infection. The only benefit of the recipient is the accumulation of side effects. There are no statistically significant results from the use of Ivermectin, confirming the claims of efficacy of the drug in the treatment of coronavirus infection. The only benefit of the recipient is the accumulation of side effects and a significant delay in adequate treatment. Patients take the magic pill and are under the psychogenic influence of being treated in the safest way until the surprising moment of sharp deterioration it usually occurs 5-7 days after taking the first Ivermectin tablet **[20, 21]**.

Nucleoside RNA dependent RNA polymerase inhibitors (essentially nucleotide analogues) are used. Remdesivir, is a nucleoside inhibitor essentially a purine analogue. The likelihood of these drugs intercalating into DNA should not be underestimated. The decision to apply them is very difficult. In the first place it is almost impossible to capture the moment to start therapy. The window for application is very narrow. In fact, this is the period in which the virus multiplies there is no statistically significant difference in survival, severity of complications and length of hospital stay compared to patients who did not receive treatment with Remdesivir. Favipiravir (essentially a pyrimidine analogue). The arguments set out above apply. There is still insufficient experience with the drug in the treatment of complicated coronavirus infection. Hasty conclusions and necessarily imposing it in medical practice can lead to undesirable results.

Global "etiological response" vaccine. We now have several real and ready to use dosage forms. There are a number of concerns about the safety of the RNA vaccine it is appropriate to focus on late complications. Genetic engineering is the future of humanity but we are still beginning in this reality. There is more confidence with conventional vaccines epitope based. Vector vaccines inspire even more confidence, even though they are essentially genetically engineered and always have concerns about isoimmunization against the vector.

4. Medicinal treatment to control inflammation we use the application of Antipyretics and Analgesics according to indications, that is if necessary, can also be a regular appointment for a dynamically monitored period especially for persistent headacheand for long (over 6 hours) febrile periods. Nonsteroidal anti-inflammatory drugs conventional/according to indications or as a regular appointment in generally accepted doses (propionates & allyl carboxylates etc.). COX2 inhibitors (selective NPS) for example Nimesulide 0.1mg daily in one dose.

Glucocorticoids according to the severityof the inflammatory process takes into account the volume of the lung parenchyma involved in the presence of a proinflammatory constellation in the leukogram and the presence of comorbidity favorable to the escalation of pneumonia/ usually from 0.04mg to 0.4mg. According to vital indications, 0.25-0.5mg up to 1.0mg can be applied daily. Doses of Methyl prednisolone equivalent exceeding 0.75mg/kg in 24 hours is not recommended, except for vital indications for a courselasting no more than 5 7 days. We prefer glucocorticoids with a medium duration of action (biological half-life 12-36 hours) have the most powerful modulating effect on inflammation and do not suppress the pituitary adrenal axis as strongly and lasts for a long time as compared to Dexamethasone. It has good anti-edematous effect, but not a better modulator of inflammation. We apply it only for specific indications it shows an especially good effect for persistent headaches We get out of the glucocorticoid either abruptly (usually not well tolerated), or alternately the better option, but not applicable to every patient. The aim for glucocorticoid treatment to last no more than 7-10 days.

Antihistamines (deliberately included in this group) aimed at modulating histamine liberation processes that are "synergistic" of inflammation). We prefer first generation preparations, for example chloropyramine 0.05mg. The central mechanism of action is clearly useful especially in agitated patients.

We do not recommend the use of colchicine or the use of Anti IL MAB. Our experience shows that the results are unsatisfactory, moreover in conditions of high risk of side effects, including clinically significant and prolonged depression of immunity **[13, 14]**. If the dynamic balance of the inflammatory process is disturbed in favor of mediation, the patient necessarily ends with intubation – mortality tends to 100%.

5. Blood Rheology is monitored by using fractionated heparins in therapeutic doses and antiplatelets in therapeutic doses as anticoagulants.

If at the time of hospitalization, the patient is on anticoagulant/antiplatelet therapy due to comorbidity, it is not replaced (i.e. anticoagulant therapy is continued at the time of hospitalization) except in special indications.

6. Prevention of microbial superinfection with dynamic microbiological control by applying Tetracyclines, Macrolides and Lincosamines: not preferred asmonotherapy or first line drugs in atypical pathogens to be used with caution in combination with aminoglycosides their use in the specific situation is extremely limited, both due to

their absence on the free pharmaceutical market and due to the strict indications for use as anti-TB drugs.

Quinolones (IV generation) in general accepted doses(for a course of up to 15 20 days) in combinations, if there are no contraindications (with caution in myasthenic) significantly increase myasthenic complaints, but are not as dramatic as lincosamines.

Aminoglycosides (not preferred as monotherapy, especially in atypical bacterial flora such as Myco-plasmataceae for example pathogens without a typical cell wall not recommended in combination with glycopeptides, with caution in combinationwith lincosamines)

–Glycopeptides not preferred as monotherapy, especially in atypical bacterial flora. Not recommended in combination with aminoglycosides.

All antimicrobials are administered intravenously. We are not impressed by the use of cephalosporins (inhibit bacterial cell wall synthesis) except in cases with specific microbiological indications always in combination with a preparation acting at the "submembrane" (bacterial cell membrane) level and with high intracellular (macro-organic cells) exposure. It is appropriate in such a combination to comply always with the rule of combining a bactericidal with a bacteriostatic antimicrobial preparation (usually antagonism). As an example, an exception to this rule is the combination of tetracycline/macrolide with aminoglycoside they empirically have a synergistic effect in atypical flora. This effect is understandably due to the mechanism of action of the respective bactericidal antimicrobial preparation in the specific example, aminoglycoside inhibits protein synthesis in the bacterial cell. It must be from a group different from the group of antimicrobial agents that inhibit the synthesis of the bacterial cell wall. When there are absolute microbiological indications for the use of beta lactam antibiotics, it is preferable to use them as monotherapy with acceptable clinical parameters to combine with bactericidal antimicrobial agents acting at the "submembrane" level (quinolones, nitroimidazoles, sulfamethoxazole & trimethoprim. The same applies to ureidopenicillins, carbapenems and monobactams. When choosing a specific antimicrobial preparation alone or combination, always take into account renal function.

Dynamic monitoring for fungal superinfection is a key point in antimicrobial prophylaxis. We use Miconazole as oral gel prophylaxisstarts on the 5^{th} 7^{th} day of the antimicrobial bacchanalia and almost always saves the use of antifungal in higher dose associated hepatotoxicity. It is appropriate to recall that almost all patients have impaired liver markers at hospitalization.

Antibiotic (antimicrobial) combinations do not change in fever persisting after 72 hours. Febrile/subfebrile periods may persist between 15-25 days. It should always be born in mind that between the 7 and 15 day there is a recurrent febrile intoxication period. This is the time for a thorough microbiological diagnosis blood cultures, urine cultures, sputum for MBD & wound secretions.

7. The assessment of the immune status should not be missed. In case of indications obligatory precise assessment

of humoral immunity/ passive immunization with conventional (possibly recombinant) immunoglobulins of IgG class have a very good effect.

In indications mandatory precise assessment of cellular immunity or granulocyte colony stimulating factor is applied to a very good effect in doses of 30-120 IU as a weekly dose divided into 30-60 IU daily, with strict monitoring of leukocyte count in the peripheral hemogram.

Immunomodulatory therapy is used in strict compliance with the indications and contraindications for the use of the drug. In addition to restoring immunoglobulin homeostasis, the administration of IgG, especially in moderately high and high doses, has a modulating effect on the inflammatory process, as well as on a number of auto aggressive manifestations in conditions of hyperreactivity.

An assessment of the hydro electrolyte energy balance and appropriate treatment measures, such as conventional parenteral substitution, as well as medication control of headache is performed. In case of non-responsiveness to the therapy specified in point 4. Strict control of major diseases is required.

It is necessary to apply general strengthening medication through the use of immune stimulating (meaning food supplements) and vitamins. Patients with COVID 19 should limit their motor regime according to the clinical course of the disease.

Physical capacity is assessed and modulated with timely start of rehabilitation (including passive kinesitherapy) in order for the patient to optimally move at the end of the hospitalization period.

Diet is controlled. After appetite is restored, and it recovers even before the changed taste disappears, it turns into ravenous appetite. We have registered an incident based on aspiration after overeating in a patient during a period of nasal high flow oxygen therapy

Viral infections are still a serious challenge for modern medicine, despite the constant development and improvement of the pharmaceutical industry. According to the WHO, in the last 20 years several viral epidemics have been caused by members of the genus Betacoronavirus: severe acute respiratory syndrome coronavirus (SARS CoV) in 2002-2003 and middle east respiratory syndrome coronavirus (MERS CoV), which leads to viral pneumonia and acute respiratory distress syndrome in some patients. This distress syndrome is a respiratory failure characterized by widespread inflammation in the lungs with symptoms including shortness of breath, rapid breathing, and bluish skin coloration **[22, 23]**.

In December 2019, a new infectious respiratory disease was registered in Wuhan City, Hubei Province, China, with etiology, associated with a new strain of virus belonging to the family *Corona viridae*. On February 11, 2020, the disease was named Covid 19. Due to the potential of this new virus to spread worldwide, on March 11, 2020, when the number of patients with Covid 19 outside China increased 13 times and the number of those affected countries tripled with the registration of the disease in more than 118000 patients in 114 countries and more than 4000 deaths, the WHO declared Covid 19 a pandemic. Till the end of August 2020,

the infected people in the world reached 25000000 - 800000 deaths were registered. The virus passes through the nasal and larynx mucous membranes, enters the lungs through the respiratory tract and the peripheral blood from the lungs, causing Viremia **[8]** and then attacks the targeting organs that express angiotensin converting enzyme 2 (ACE2) receptors, present in the lungs, heart, blood vessels, kidneys and gastrointestinal tract **[24-26]**. The etiological cause of coronavirus infection, which has captured the attention of almost the whole world at the moment, is SARS CoV2. This naming was recommended on February 11 by the World Health Organization and subsequently practically imposed worldwide **[27, 28]**.

SARS CoV 2 virus is a single stranded RNA virus with an affinity for epithelial cells and mainly affects the human respiratory system. Like other coronavirus infections such as SARS CoV and MERS CoV, which humanity encountered in 2003 and 2012, respectively, SARS CoV2 can lead to the development of severe life-threatening disease in some infected patients. Its rapid and widespread proliferation affecting much of the human population, along with the serious course of the disease, led WHOto declare a "World Pandemic". The epidemic has affected almost every country in less than 6 months, posing a number of challenges to health, the economy and society due to relatively high morbidity and uncontrollably increasing mortality **[9]**.

For COVID 19, stage I is for early infection and involves an incubation period associated with mild and often non specific symptoms: fever and a dry cough, with observed lymphopenia and neutrophilia without other significant abnormalities. During moderate stage II is developed a viral pneumonia, with cough, fever and without hypoxia (IIa) or with hypoxia (IIb) and with bilateral pulmonary infiltrates **[28, 29]**. In severe stage III an acute respiratory distress syndrome **[30]** and cytokine release syndrome are developed. Patients have severe disease if they have any of the following criteria: respiratory rate of at least 30 breaths per min, oxygen saturation of 93 % or lower in a resting state, ratio of arterial partial pressure of oxygen and oxygen concentration no greater than 300 mm Hg, or more than 50% lesion progression in lung imaging within 24–48 h **[11]**. Very often mechanical abdominal ventilation is applied in patients with Covid 19 with acute hypoxic respiratory insufficiency like after cardiac surgery **[31-33]**.

No drug or vaccine has yet been approved for treatment of COVID 19. Despite ongoing search. Current regimen includes anti-bacterial drug (Azithromycin), inflammation control with Dexamethasone & restorative compounds or oligonucleotide based therapies **[24]**.

The global innovative pharmaceutical industry has accelerated its efforts to search for application of known medicinalproducts with a known antiviral effect and to develop new antiviral drugs. About 30 antiviral drugs at various stages of development or use are currently being studied by innovative pharmaceutical companies to determine their effectivity against COVID 19. The effects are related for acceleration of the development of therapeutic tools to deal with current and future coronavirus outbreaks. Clinical trials

for investigation of the effectiveness of HIV/AIDS drugs and of antiviral combinations: Daclatasvir/Sofosbuvir, Lopinavir/Ritonavir, nucleoside analogues (Favipiravir, Galidesivir, Remdesivir, Ribavirin) have been launched. Oseltamivir, Stopcivir and Umifenovir are under clinical investigations too **[34]**. Ribavirin, Remdesivir, Galidesivir, Sofosbuvir and Tenofovir show promising results for application against COVID 19 **[15]**.

In depth immunological studies are needed to understand the pathogenesis, improve the treatment of the disease and improve the prognosis. More and more attention is being paid to the role of immunomodulatory drugs: monoclonal antibodies, vaccines, convalescent plasma, Apilimod against autoimmune diseases, herbal immunomodulators, recombinant Bacillus Calmette–Guérin (BCG) vaccine VPM1002 **[35]**.

Already in the first months of the coronavirus pandemic in the United States there was a serious decline in the number of patients seeking medical care in the Emergency Department (49.3%) compared to 2019. A disproportionate decline is observed in pediatric patients, elderly patients and women. Conditions such as syncope, cerebrovascular accidents, renal colic, abdominal pain and back pain are increasingly rare reasons for examinations at the Emergency Centers. The symptoms of shortness of breath, chest pain, as well as associated with upper respiratory tract infections predominate in the complaints of patients seeking emergency medical care. This is an interesting phenomenon indirectly related to the COVID 19 pandemic. The situation thus the attention of specialists on coronavirus infection life-threatening conditions and the severe consequences of delayed or untimely adequate care for these conditions within the scope of emergency medicine **[15, 23]**.

This tendency to reduce the number of patient visits is also observed in the Multi profile emergency department of "N.I.Pirogov" UMBALSM. Compared to 2018 and 2019, after March 2020, there has been a significant decrease in emergency examinations. This decline coincides with the declaration of a state of emergency in the Republic of Bulgaria. The main reason for seeking medical help are complaints from the respiratory system. RT PCR tests should be carefully interpreted. Negative results from Oro-nasopharyngeal PCR tests, combined with clinical laboratory and radiology changes indicating possible SARR CoV2 infection, the diagnosis of COVID 19 cannot be overruled. The attention and efforts of the good clinician should be directed towards the treatment of the disease rather than the positive PCR test. The following laboratory parameters can be indicated as predictors of disease severity: elevated transaminases, D-dimers and fibrinogen, high CRP, lymphocytopenia, elevated LDH and ferritin. The fight against COVID 19 requires complete dedication and significant efforts from the treating physician especially in the conditions of lack of etiological treatment and constantly changing guidance and recommendations for treatment. The basic clinical postulates remain on the forefront despite the newness of COVID forthe mankind.

At the moment, the epidemic situation worldwide is still extremely dynamic. Both

densely populated areas and areas with low population density are affected. We should not underestimate the fact that even in the reality of modern civilization, there are parts of the world where epidemiological studies are unthinkable to be done, let alone take specific medical measures. It is difficult to predict the epidemic behavior of this new disease for the human population. Many consistent and in-depth studies are needed on both the spread of the disease and the complications associated with it. It is necessary to trace the nature of these complications, the periods in which they occur and the severity with which they involve the target organs and systems of man. Long term algorithms need to be developed to prevent and reduce disabling effects. It is necessary to monitor and analyze the possible mortality in the convalescent Post Covid period which may be directly related to the experienced coronavirus infection.

Our experience showed that timely diagnosis and decision for hospitalization as well as implementation of proper therapeutic strategies leads to a reduction of both hospital stay and convalescent (Post COVID) period. New studies are needed to develop effective strategies to adequately monitor patients especially in the first six months after suffering from a complicated coronavirus infection. Long term and in-depth studies are also needed. Complications of a psychopathological and psychiatric nature are also "tera incognita" to this day. After conducting in depth and long-term studies of patients with mild, moderate and severe forms of the disease, including asymptomatic cases. It is possible to put on the agenda the question of possible prooncogenic activity of the human coronavirus. Questions may arise whether such effects may not be related to some of the diagnostic and therapeutic procedures used and to the frequency and duration of their use in treatment of COVID infection.

CONCLUSION

We can safely conclusion that extension of the monitoring period to 12 months (and maybe more) after illness is absolutely justified from both a scientific and a purely practical point of view.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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