

SARS-CoV-2 infection: etiopathogenesis, clinical picture, current therapeutic options – the author’s observations

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Currently, the scenario of a self-contained disappearance of the epidemic (as it was in the case of SARS) is no longer taken into consideration, whilst the SARS-CoV-2 virus will stay with us forever, similarly to other coronaviruses or flu. It is quite likely that periodical exacerbations of the epidemics – their growth and decrease – depend on many factors, which comprise, among others, the approval of the restrictions by the society or the manner in the epidemiological supervision is carried out and whether it is consistent. We must be ready for about 18–24 months of a high activity of COVID-19 with periodic active hot spots in many world regions. This requires efficient health services and the access to efficacious medication. Without an effective prophylactic vaccine, it seems that we will not be able to prevent the spread of the pandemic

Key words: COVID-19, SARS-CoV-2, interstitial pneumonia

Introduction

The first, officially confirmed case of infection with the new beta-coronavirus SARS-CoV-2 was discovered on 1st December 2019 in China, in the city of Wuhan – a large industrial centre with a population of several million, which had numerous business connections practically with the entire world. Additionally, in the city, there is a renowned, highly-specialist scientific laboratory (BSL4), which also conducts research on coronaviruses. This laboratory was a French-Chinese joint venture, yet for some reasons, the French withdrew from the collaboration.

Probably the first cases of SARS-CoV-2 infections, undoubtedly of animal origin (bats), occurred slightly earlier than was officially reported (local authorities kept it secret). Unfortunately, it was not possible to contain the epidemic focus to the place of its origin and the virus disseminated quickly to other regions of the world. Even by 11th February the WHO had declared the virus a pandemic (mainly interstitial pneumonia leading in some patients to acute respiratory distress syndrome), naming it COVID-19.

SARS-CoV-2 is one of 7 known coronaviruses pathogenic for humans – the majority of which (about 20% cases) are responsible for a mild cold-like condition. Two other coronaviruses, with very strong genetic affinity to SARS-CoV-2, were or still are highly dangerous: virus connected with SARS (the epidemic in 2002–2003 with mortality at the level of 10%) and MERS (isolated cases from 2012 mainly on the Arabian Peninsula burdened with very high mortality – 30%). SARS-CoV-2 in comparison with these other two viruses is much more infectious, yet less virulent, with significantly lower mortality rates. Initially 5 genomes of the new virus have been isolated and described :

- betaCoV/Wuhan/IVDC-HB-01/2019;
- betaCoV/Wuhan/IVDC-HB-04/2020;
- betaCoV/Wuhan/IVDC-HB-05/2019;
- betaCoV/Wuhan/WIV04/2019;
- betaCoV/Wuhan/IPBCAMS-WH-01/2019.

However, the virus, when passing through consecutive human populations, gradually changes and the strains which

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are currently dominating are not the same as those which existed at the beginning of 2020. We see it clearly in our own clinical observations.

In spite of the large number of patients infected with SARS-CoV-2, which definitely exceeds hospitalisation and staff capacity of the health services, the rate of severe cases is lower than at the beginning of the epidemic, although definitely there are more cases in absolute numbers. Now, unfortunately, the self-contained disappearance of the epidemic (as it was in the case of SARS) is no longer taken into consideration, so the SARS-CoV-2 virus will stay with us forever, similarly to other coronaviruses or flu. It is quite likely that periodical exacerbations of epidemics – their growth and decrease – depend on many factors, which comprise, among others, the approval of the restrictions by the society or the manner in the epidemiological supervision is carried out and whether it is consistent. We must be ready for about 18–24 months of a high activity of COVID-19 with periodic active *hot spots* in many world regions [1, 2].

Etiopathogenesis

A dominating infection route is airborne and droplet transmission with conjunctival contamination being less frequent. Also alimentary transmission is possible by means of transmitting the virus particles from infected objects (e.g. from paper where the virus may survive for up to 40 hours) onto food or directly into the oral cavity. Although the presence of the virus was also detected in urine and faeces, the possibility of such a transmission, has not been confirmed.

A key role in the infection mechanism is played by the virus fusion protein (*S-spike*), which is present on its surface and manifests affinity with the ACE2 receptor protein (angiotensin-converting enzyme 2). The fusion of these two proteins allows the virus particles to penetrate into the cells of the host. ACE2 is a receptor existing on the mucosal membranes of the upper and lower respiratory tract, small intestine erythrocytes, in the kidneys, heart, testicles, cholangiocytes (but not hepatocytes) and – unfortunately – also in the vascular endothelium (that is why in severe cases it leads also to micro-thrombosis).

It was experimentally proven that other proteins: CD147, GRP78 and ADAM17, can also be receptors for SARS-CoV-2, whilst the very process of intracellular fusion requires the activation of glycoprotein S2 – via enzyme's cut with TMPRSS2, protein, cathepsin or furin. It was also proven that together with the ageing process and tobacco smoking, the ACE2 receptors count increases, which has a significant effect on the course of infection. These data form the foundation for the construction of various medications potentially helpful in the treatment of COVID-19 (numerous studies are in progress).

Finally the clinical picture and patient history influence the character and type of immunological response to the infection – which depends on many factors, including:

- individual genetic predisposition of each patient;

- specific immunological response to infections;
- viral load which the infected person received from another infected person (it has been proven that the use of personal protection measures reduces the number of severe cases of COVID-19 by 60%).

In about 5% of infections, a cytokine storm takes place. This is a general systemic response of a relatively healthy immune system which leads to a quick release of more than 150 known mediators of inflammatory reaction: among others, proinflammatory cytokines (e.g. tumour necrosis factor alpha, interleukin-1 and interleukin-6) and anti-inflammatory cytokines (e.g. interleukin-10 and interleukin-1 receptor blockers), numerous oxygen free radicals and coagulation factors. Cytokines signal and activate the cells of the immune system, including macrophages and T-cells to migrate in the direction of the locus of infection. The cytokines, which are located in the locus of infection, in turn, activate a mechanism within the cells which encourages them to produce even more cytokines. A correctly functioning immune system keeps this feedback loop within reasonable limits. Unfortunately, in some patients with COVID-19, especially in those with multimorbidity, the immunological response is uncontrolled – by means of activating other cells of the immune system in one location. The exact cause of the situation has not been completely clarified, yet it is definitely connected with a large number of virus particles. It may also be caused by the excessive reaction of the immune system, when it encounters a new, more aggressive pathogen and also by individual genetic predispositions of an infected person. In some way, it is imitated by the hemophagocytic syndrome.

Finally, the patient's fate is determined by the following factors:

- the stage of the pulmonary lesions, and also the lesions in other organs (heart and kidneys in particular),
- interstitial involvement,
- slowing down the blood flow within the patient's organism
- coagulopathy with the formation of micro- and macro-thrombosis [1, 3–5].

A clinical picture of the disease

According to world data, in 80% of infected persons there are no clinical symptoms or the clinical symptoms are mild. In other patients, i.e. about 20% of infected persons, the symptoms of severe interstitial pneumonia with various intensity are dominating, with the critical course concerning about 5% of this population (cytokine storm). Yet, mortality does not exceed 2–4% of all cases of infection. These statistical data are reflected in our own observations – among people who must be hospitalised.

Groups of increased risk of infection and also of a more severe course of the disease comprise the following:

- **Patients staying in nursing homes and extended care facilities.** Also other patients, in all age groups, hospitali-

sed for many reasons (nevertheless, in clinical practice this group comprises most frequently old-age persons with multi-morbidity, including advanced stages of oncological disease). Mortality for COVID-19 in the patient group >80 reaches 14–20% of all cases; yet in the cases of people very advanced in age (>95 years) the infection, for unknown reasons has a subclinical course.

- **With decreased immunity:** cancer patients (in particular with onco-haematologic conditions, patients in immuno-, chemo- or radiotherapy and 5 years after the completion of oncological treatment), HIV patients (in our practice – only untreated or with a low D4 cell count), patients with chronic unspecific colitis (e.g. Crohn's disease or ulcerative colitis), patients with some types of arthritis, systemic connective tissue diseases or dermatologic diseases, persons after cell or solid organ transplants and also persons chronically treated with glucocorticosteroids or other immunosuppressive medication.
- **Patients with cardiovascular conditions,** in particular with coronary disease and arterial hypertension.
- **Patients with respiratory diseases** – such as chronic obstructive pulmonary disease, asthma (moderate to severe form).
- **Obese persons** (with a BMI \geq 40 or higher), also diabetics, patients with chronic renal disease (during dialysis therapy) or those suffering from chronic liver diseases.

The group at increased risk of infection and its severe course comprises also Afro-Americans and Latinos – yet in practice this does not concern Poland [4, 5].

General and local problems in the care of patients with COVID-19

The most important areas which must be stressed in this context:

1. The general failure in preparing many health systems to deal with the enormous scale of the epidemic (with regards to organisation, equipment and staff). The epidemic of SARS-CoV-2 exposed in many countries those areas which had been underinvested and with shortages of staff, especially with regard to infectious disease care.
2. The negative attitude of some (fortunately small) part of the medical staff (quitting the job, prolonged medical leave, reluctance of primary care doctors to offer individual consultations for patients with a suspicion of COVID-19). The effect of these superficial telephone consultations was the influx of patients to the ER departments in the hospitals for infectious diseases which had a negative influence on their efficiency.
3. Significant problems with medical transport.
4. Lack of consequence in capitalising on the effects on the lockdown in spring. Premature easing of the restrictions and the failure to observe those existing already (and to impose them again), as well as a reluctance to withdraw

from loosening the restrictions, high risk of infections (weddings, open restaurants and clubs, church services, funerals). In spite of the almost 4-month holiday period and the number of infections being curbed, the country was not prepared for the expected typical exacerbation of the epidemic in the autumn and winter period.

5. The lack of a credible system to inform society about the causes and purposes of upholding the restrictions.
6. The lack of a definite reaction to the scandalous – in social and medical terms – activity of the “anti-COVID” movements, which deny the existence of the epidemic.

Positive attitudes:

1. The great commitment of the majority of medical staff on many levels as well as local administration in the region of Lower Silesia (also high-level one) in their battle with the epidemic (not only in a clinical sense).
2. The development of social solidarity in fighting epidemics and the organisation of support for healthcare staff.

Therapeutic procedure options

The therapeutic procedures depend on the stage of COVID-19 and the presence of comorbidities. The ordinal scale for SARS-CoV-2/COVID in its version announced by the WHO in 2020 may be useful here: this scale divides the patients infected with coronavirus into 8 functional groups:

1. Patients without hospitalisation and without any restriction of their activity;
2. Patients without hospitalisation, yet requiring restriction of their activity;
3. Patients who require hospitalisation but without oxygen therapy;
4. Patients who require unconditional hospitalisation and a low flow of oxygen through a face mask or nasal cannulas;
5. Patients who require unconditional hospitalisation and a high flow of oxygen (\geq 15 l/min), CPAP2, BIPAP3, non-invasive ventilation;
6. Patients who require unconditional hospitalisation and intubation and mechanical ventilation (without additional organ support);
7. Patients who require unconditional hospitalisation at the Intensive Care Unit and mechanical ventilation with additional organ support (e.g. vasopressors, RRT4, ECMO5);
8. Patients who die of SARS-CoV-2.

In clinical practice, a 4-stage scale is used whilst therapeutic procedures were defined by some scientific associations. The most complete and regularly updated recommendations in Poland seem to be the recommendations of PTEILCH (the Polish Association of Epidemiologists and Doctors of Infectious Diseases) and those which are close to them – although expanded with experimental therapies (clinical trials) – the recommendations of local therapeutic committees. In our case, the treatment of COVID-19 in the region of Lower Silesia

is coordinated by J. Gromkowski Regional Specialist Hospital in Wrocław [6].

Stage I of COVID-19 disease – an asymptomatic patient or with a subclinical infection (applies to 80% of all infected persons) does not require hospitalisation, and therapeutic procedures are limited to the recommendations concerning isolation, rest, appropriate hydration, the use of anti-fever medication and saturation control – with respect to the possibility of a sudden progression of the disease. The use of glucocorticoids at this stage may increase viral replication and is clinically unadvisable.

Stage II with full symptoms – the patient requires hospitalisation (usually they already have interstitial pneumonia at a various stage of intensification) with regards to the necessity to apply oxygen therapy (various techniques), the prophylaxis of thromboembolic complications (low molecular weight heparin) and anti-viral treatment. At this point the recommendations from the first stage of the disease are still valid.

Currently the only known medication with a proven anti-viral action which is used in our centre (apart from the medical in therapeutic clinical trials), are remdesivir and the convalescent plasma – agents with a limited efficacy and not always available [7–10]. A significant completion of the therapy consists in adding antibiotic therapy (cephalosporins) and the administration of glucocorticosteroids – dexamethasone at the daily dose of 6–8 mg/day, started within the period between the second and the fifth day of the first administration of remdesivir or plasma.

The use of dexamethasone reduces the risk of death (evaluation within 28 days of randomisation) in patients with mechanical ventilation and in oxygen therapy – by 35% and 20% respectively. The use of remdesivir in patients who do not require oxygen therapy and more than a week after the appearance of symptoms does not make any sense and does not bring any clinical effects. So far the effectiveness of other drugs with potential anti-viral activity has not been proven – these drugs comprise lopinavir/ritonavir (used for HIV infections), baloxavir, marboxil, favipiravir (used in the treatment of flu), umifenovir (used in the treatment of flu), camostat mesylate (serine protease inhibitors), interferon, ribavirin, losartan (hydroxy) chloroquine, darunavir, nitazoxanide (antiparasitic drug), oseltamivir (used in the treatment of flu), azithromycin, sofosbuvir, daclatasvir, verdinexor and selinexor (its analogue). A number of other preparations are currently undergoing clinical trials.

Stage III – a patient with respiratory distress (the onset of a cytokine storm). The procedures are like in stage II plus additional high-flow oxygen therapy and anti-cytokine medication. In practice, the only approved preparations comprise tocilizumab (in patients with an increased concentration of IL-6) and sarilumab. There are also many other anti-cytokine medications undergoing clinical trials: IL-1 inhibitor (anakinra), human monoclonal antibody IgG1k: against IL-6 (sirukumab), against IL12/23 (ustekinumab), human monoclonal antibody

p/GM-CSF (otilimab), immunoglobulins *i.v.*, inhibitors (baricitinib, ruxolitinib).

It appears that the use of remdesivir and convalescent plasma at this stage of disease is not justified with regards to aetiopathogenesis.

Stage IV – this is acute respiratory distress syndrome (ARDS) which requires mechanical ventilation and, possibly, extracorporeal membrane oxygenation (ECMO). The patient must be treated at the intensive care unit. At this stage of disease, remdesivir and convalescent plasma are not justified with regards to aetiopathogenesis (the lack of active viral replication) [6–11].

Conflict of interest: none declared

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