Beyond just counting...Part 2 – the disease and the search for treatment

Why one should have sympathy with the decision-makers, in balancing the protection of the citizen and avoiding economic disaster, in view of the severity of the SARS-CoV-2 infection and the difficulty in finding a promising treatment.

Advertising the chance to gain three-digit millions in Bath, better in Dollar or Euro, at the next lottery draw, or to inform the public with five digits numbers of death, due to some infectious disease, is at least helpful for the governmental authorities but not necessarily helpful for an individual person. In the case of the lottery, millions, especially those at the lower end of the income scale, regularly buy lottery tickets in the hope to be lucky once in their lifetime. At the same time pay some sort of tax, which goes along with the price of the ticket, voluntarily to the government. In the case of the four-digit death numbers due to a pandemic of SARS-CoV-2, the danger of a sudden death leaps into the mind of those being informed in such a way. So, the readiness of the general public increases in following orders resulting in daily life restrictions, in view of the immediate danger. Who wants to dye unexpectantly? Yet, the chances to become super-rich or expecting to dye soon are not that easy to estimate, as one might think. To select 6 out of 49 numbers which will hit the jackpot is 1 to 13.983.816. The worlds total cases registered of COVID-19 on the 21st of March 2020 was 2.482.215 with a total death of 170.471. Expressed this as a rate per 1 Million population the number is high but less frightening with 318 individuals infected, and 21.9 death per 1 million people. All cases known so far for Thailand accounted for 40 and the death to 0.7 per 1 million population.

These provocative comparisons are made here to prepare for the expected heated debates when the economic fallout of the lockdown will become more and more painfully evident. One, however, should have some sympathy with those forced to make unpopular decisions, because whatever evolves they must take the blame. Admittingly, for those who are unlucky enough to fall seriously ill, they might face a very painful death. An Italian nurse is remembered in saying, that, while dying, you have the feeling of drowning being fully conscious.

<u>The disease</u>

Basic but also more detailed information about various aspects of the present pandemic is distributed through numerous media on a daily basis. This contribution aims to draw attention to some distinct features of the pathophysiology of the clinical cases, and the attack points, within the replication circle of the virus, chosen for treatment.

In *Science*, Wadman et al. recently published an overview with the expressive title '*How the coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes*'(1). Those unfortunate, approximately 5% of patients, falling critically ill might display clinical pictures in a combination 'no microbe humanity has ever seen'. Besides the lung, which is very much in focus, the heart, kidney, gut, and brain also might be involved in the infection. Important pathophysiological events such as the so-called 'cytokine storm', impeded oxygen uptake, blood clotting, alteration of hormones regulating blood pressure affect particular organs of the body. Experiences made during the SARS and MERS outbreak now helps to come up with assumptions about how the SARS-CoV-2 virus infection works (2). The way the virus attaches to the cell and reduplicates is briefly described in part1 of this contribution. There, the role of the angiotensin-converting enzyme 2 (ACE2) has been mentioned which is now known even to the general public.

Cytokine storm

Virus laden droplets, inhaled through nose and throat, meet cells rich of the cell-surface receptor ACE2 enabling the virus to start to duplicate. For some time, the virus might delay the response of the immune system to the infection. This would explain the long incubation period lasting up to 14 days. Initiating macrophages, neutrophils and dendritic cells are the non-specific response of the immune system. One of the first in place is interferon proteins regulating the system. It was found, that the response of one type of the interferon system, called I IFN, is delayed or suppressed during the initial infection (2). Unfortunately, as observed often, is the dangerous 'overreaction' of the system, by releasing proinflammatory cytokines. Cytokines, as such, regulate the immune response and help in reducing inflammation and healing (3). Proinflammatory cytokines, however, are harmful to the host, especially in severe infections, and has been singled out as one of the indications of a severe COVID-19 infection with a bad prognosis. Through the 'cytokine storm' also named 'cytokine release syndrome' (CRS), the lung is seriously damaged, resulting in acute respiratory distress syndrome (ARDS) (4). The pathways to the CRS are complex and one of the elevated proinflammatory cytokine is the interleukine-6 (IL-6), which is a target for the treatment of the CRS. The medicine, siltuximab, is an anti-IL-6 chimeric (derived from human and mouse) monoclonal antibody and has already been used for patients suffering from SARS-CoV and MERS-CoV, as well as for other diseases, i.e. leukemia patients treated with 'engineered T cell' therapy. (As a side effect of the cancer therapy a CRS was observed.) The therapy is thought to reduce the 'out of proportion inflammatory response of the virus' resulting in the ARDS. The damage is done to the alveoli, filling them with fluids and dead cells, resulting in the interruption of the exchange of oxygen to the capillaries. Some experts are suspicious as far as the benefit of the treatment with the drug is concerned. The drug aims at a part of the immune system and to diminish the cytokine response might 'backfire'. However, controlling the

CRS is important, since it not only attacks healthy tissue but makes blood vessels leak and form blood clots. Blood clots might cause heart attacks and pulmonary embolism, and stroke.

The brain and nervous system

The 'sympathic storm' is another 'storm' threatening the COVID-19 patients. The term was formerly used by nurses caring for patients with acute multiple trauma. The mental signs are caused by hypothalamic stimulation of the sympathic nervous system and adrenal glands in increasing corticoids and catecholamines. Symptoms are agitation, posturing, extreme sweating, tachycardia, and hypertension. Not only the brain but also the nervous system can be involved. Seizures might be due to encephalitis and a sign of the involvement of the nervous system is losing the sense of smell and the phenomenon that patients with a very low oxygen saturation of the blood don't gasp for breath.

Comorbidities

The danger of patients with comorbidities dying from the infection could be explained by the effect the virus has on the balance of hormones regulating blood pressure and constricts blood vessels. (Low blood oxygen saturation is not only due to the impairment of the function of the lung but might also due to constricted blood vessels.) Patients with obesity tend to suffer from the 'metabolic syndrome' with hypertension and diabetes mellitus. One of the diseases in the course of diabetes involves the kidney. Acute kidney injury (AKI), going along the COVID-19 infection is very common. The virus might attack the organ directly and by this might aggravate an already existing disease. The patient will finally dye of renal failure.

Also affected could be the liver and the intestine. The liver might be damaged either by the 'cytokine storm' or because of the side effects of treatment attempts. The lower gastrointestinal tract is rich in ACE2 receptors and diarrhea in infected patients are common. By no means, the clinical features of the disease are fully understood and seem to comprise the entire system of our organism.

Prospective treatment methods

Up to now, the desperate search for a promising treatment for severely ill patients was not very successful. In the second half of March, the World Health Organization (WHO) started an initiative to collect reliable information about treatment efforts around the world, a project which is called SOLIDARITY (5). In a number of countries too many patients severely ill did end up in intensive care units (ICU). This especially happened at the high peak of the pandemic. Different treatments were applied all over the world. Because of the sudden increase of the need for ICU beds appropriate care of patients broke down in several countries. Often patients with ARDS under sedation should have been treated with ventilators, which were not available in required numbers. On the other hand, it was claimed, that mechanical ventilation might be harmful

because of the lungs of COVID-19 patients are easily damaged. Providing oxygen by ‘less-invasive respiratory supports, like breathing masks and nasal tubes’ might be safer.

Therapy for those with only mild symptoms of an ordinary cold, the usual ‘self-help’ with cough syrup, nasal spray and paracetamol, or the old fashion aspirin seemed to be working. Ibuprofen is often in use as well, but its side effects, especially to the kidney, should be a concern. For the severe sick patient drugs attacking the virus directly are in need. Early at the beginning of the epidemic, a small study with chloroquine made the headline in various media. That study was heavily criticized because the standard methods to test the therapy was not observed. Chloroquine and hydrochloroquine, formerly used to treat malaria, have side effects harming the heart, but still is in use now for treating COVID-19 patients. The drug attacks the virus in endocytosis. Another therapeutic suggestion is to use monoclonal antibodies derived from the plasma of individuals, who already got the disease and recovered. The idea is to booster immunity so that the attachment of the virus at the ACE2 receptor might be prevented. To inhibit the attachment of the virus to another cell surface receptor (TMPRSS2), a proteinase inhibitor (camostat mesylate), is tested. There are several drugs used for HIV treatment and tested during the SAARS and MERS epidemic. One of the drugs (lopinavir-ritonavir) ‘cleaves the protein chain during the assembly of the new virus’ and another one (remdesivir) is effective against the RNA dependent RNA polymerase. Also, a drug used for the treatment of the flu (favipiravir) is being included in the SOLIDARITY project of the WHO (5).

A major problem in testing the different regimes for COVID-19 is that very often the patients are already critically ill before treatment starts. It would be better to start the therapy at the early stage of the disease for patients, supposed to get worse. The difficulty is how to define this point.

Health problems after recovery

Yet, even the elderly, critically ill patients are surviving. Those who survive might suffer from the aftereffects of the ordeal when released from the hospital (6). As mentioned above, COVID-19 might not only harm the lung but also many other organs as well, such as the kidney, brain, heart, and blood vessel. ARDS patients may suffer from breathing problems for a long time and could be stricken by stroke, heart attack, and chronic kidney disease. Cognitive and mental diseases due to treatment with sedatives for ‘suppressing violent cough’ or being on a ventilator for days and longer than that. To be exposed to medical personal ‘all gowned up’ and without family members visiting could be frightening. Among mental health problems are memory deficits and the risk to fall into delirium. Those in need of ventilation ‘are prone to muscle atrophy and weaknesses. Physical therapists to treat these patients during their stay in the hospital need to protect themselves from virus infection. In those countries with an overburden of hospital patients the necessary equipment was only available for medical doctors and nurses attending the patients in the ICU wards, but not for the therapists.

Conclusion

In order to reduce the transmission of the virus, the authorities in charge use more or less drastic measures not being tolerated before the crisis. Looking at the numbers of more and more people are infected and dyeing the general population is willing to obey to follow ‘orders’, as in Thailand even to refrain from their daily glass of beer. Of course, the authorities in power are aware, that the ‘lockdown’ of a country will have serious aftereffects, not only on the economy but on society as a whole. Just on the 26th of April, it was published that the president of the The German parliament, a Mr. Schäuble (one of the most senior politicians of the country) remarked, that the state can not solve all problems of the corona crisis and ‘one cannot do the outermost to protect human life (literally translated he was saying: ‘one cannot subordinate everything to protect human life’). Actually, he was directing the view towards what in public health already the undergrad student will learn, namely to judge about the seriousness of a situation, such as a health problem, how many people are involved measured against a given total. Actually, one should look at ‘rates’ as well, and not only just count. A rate consists of a nominator and a denominator. As mentioned above all over the world up to now 318 Persons per 1 Million population has been infected and 21.9 Persons per 1 Million population dyed. There are countries, of course, exceeding these numbers but others, including Thailand, are much better off, in that presently 40 individuals per 1 million got the infection and less than 1 person (0.7) per million dyed. At the moment nobody can foresee what will happen in the following weeks and months. As it is outlined here, the disease caused by the virus can be deadly, but is it worthwhile to take the chance to ruin the country economic wise. It is not an easy decision for the ‘decision-makers’! In one of the numerous publications spread all over the media day by day, it was assumed that ‘ SARS-CoV-2 is probably here to stay, and the high transmission rate will continue to force a choice between widespread infection and social disruption, at least until a vaccine is available (7). The prospects whether we even will have a vaccine once will be discussed in the following contribution to this Journal Club.

Literature

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