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Hypoxia may be a determinative factor in COVID-19 progression

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ABSTRACT:

The disease which develops following SARS-CoV-2 virus infection, known as COVID-19, in most affected countries displays mortality from 1.5% to 9.8%. When leukocytosis due to granulocytosis, thrombocytopenia, and increased level of D-dimers are detected early during the disease course, they are accurate predictors of mortality. Based on the published observations that each of the aforementioned disturbances by itself may appear as a consequence of hypoxia, a hypothesis is presented that early hypoxia consequential to sleep apnea and/or blunted respiratory response to chemical stimuli is an early determinant of COVID-19 progression to the severe and critical stage. Further, it is noted that host-directed therapies which may counteract hypoxia and its early downstream effects are initiated only upon hospitalization of COVID-19 patients, which is too late to be fully effective. An example is anticoagulation treatment with low molecular weight heparin. Repurposing drugs which could counteract some early posthypoxic events, such as fluvoxamine, amantadine and N-acetylcysteine, for post-exposure prophylaxis of SARS-CoV-2 infection and early prehospital treatment of COVID-19, is indicated.

1. Introduction

In January 2020, a coronavirus of animal origin was identified as the causative agent of a new human contagious disease first detected in Wuhan, China (Yang X et al., 2020). On February 11 WHO announced "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" as the name of the new virus and "COVID-19" as the name of the disease which develops following this infection. Exactly one month later, on March 11 WHO declared COVID-19 as a pandemic. Since then, abundance of data have been published concerning various aspects of COVID-19 and the pathomechanisms involved. The disease is highly dangerous. According to Mortality Analyses - Johns Hopkins Coronavirus Resource Center (jhu.edu) case fatality ratios (CFR) in the most affected countries range from 1.5% to 9.8%.

An important aspect of research on COVID-19 is predicting disease severity and outcome. In a recent review (Tjendra Y. et al., 2020) predictive value of laboratory data such as blood counts, acute-phase reactants and other inflammatory markers, etc. is discussed. Although these blood-borne biomarkers are unspecific, they allow to prognosticate the outcome. However, they are not interpreted in terms of causation during early phase of the disease.

The aim of the present study is to analyze a chosen sets of published laboratory biomarker data gathered from patients suffering from COVID-19 during the early phase of the disease process and interpret them in terms of a hypothetical common causative factor driving the disease to its unfavorable outcome. We posit that such factor, present in a subset of patients already at the early phase of COVID-19, is hypoxic episodes caused by sleep apnea and/or blunted reactivity of the respiratory system to chemical stimuli.

2. Natural history of COVID-19 and predictors of mortality

The median incubation period, i.e. time from exposure to symptoms onset, is 4–5 days (only in 2.5% cases can be even longer than 11.5 days) (Lauer S. et al., 2020). Siddiqi and Mehra (Siddiqi HK et al., 2020) proposed to distinguish three consecutive stages in the COVID-19 (Fig. 1). The first, early infection, is characterized by mild to moderate influenza-like symptoms. In this stage, virus genes can usually be detected in nasopharyngeal swabs by RT-PCR. The majority of patients do not progress and encounter the virus clearance. In some, depending on factors not completely understood, the disease progresses to a second, pulmonary stage characterized by shortness of breath without or with overt signs of hypoxia. Characteristic pneumonia-like symptoms are radiologically detectable, described as lung opacities in chest radiography and glass opacities in CT. Patients in stage 2 can improve, but some progress to the third stage in which intubation and mechanical

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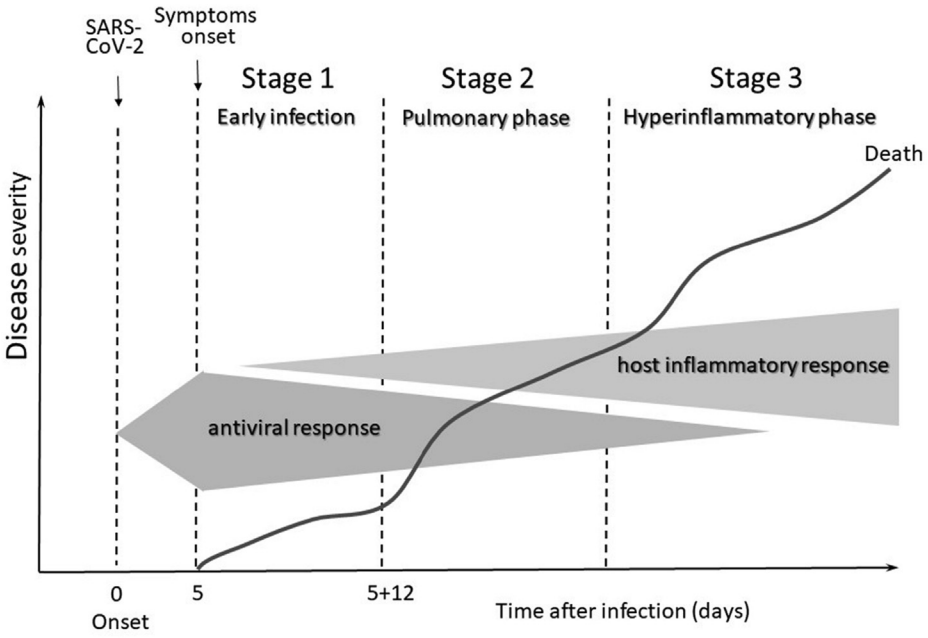

Fig. 1. Schematic representation of the natural history of COVID-19 (based on Fig. 1 in ref. (Siddiqi HK et al., 2020), modified). Three phases of the disease illustrate the worst-case scenario.

ventilation is necessary. This stage is characterized by hyper-inflammation, sepsis of lungs and multiorgan failure, resulting in a very high mortality. Along with the disease progression the relative importance of immediate responses to pathogenic virus decreases, whereas the relative importance of late inflammatory responses increases. In a small subgroup of patients the disease quickly progresses from stage 1–3, or even to death, because of the appearance of neurological symptoms, possibly caused by direct invasion of the virus to the brain, in particular to the brain stem respiratory centers (Li Y.C. et al., 2020).

An Italian study published in April (Ferrari D. et al., 2020). reported on the results of routine blood tests performed on patients with COVID-19-like symptoms (fever, cough and fatigue) who concomitantly were tested with RT-PCR for SARS-CoV-2 and found either positive (n = 105) or negative (n = 102). Table 1 shows excerpt of the data obtained in this study (for simplicity only mean values are shown). We may assume that RT-PCR-positive patients were at the early stage of COVID-19, whereas RT-PCR-negative patients were suffering from some other acute respiratory tract infection. Interestingly, RT-PCR-positive patients did not display increased leukocyte and neutrophil counts.

The fatal outcome of COVID-19 can be predicted early on the basis of some laboratory data. In the study published recently (Fu Y.-Q. et al., 2020) the entry records of 85 COVID-19 patients hospitalized in Wuhan in February 2020 were analyzed, and the data of 14 patients who deceased during hospital stay within the first week of hospitalization were compared with the data of 71 who survived and were discharged from the hospital before April 1st. The median time that elapsed between symptoms onset and hospitalization was similar for surviving and deceased patients, 12 and 11 days, respectively. Table 2 lists parameters

Table 1
Blood counts of patients positive and negative for SARS-CoV-2 RT-PCR test (RT-PCR(+) and RT-PCR(−), respectively). Excerpt of the data from Table 2 in ref. (Ferrari D. et al., 2020).

Parameter/group	RT-PCR(+)	RT-PCR(−)	P[a]
Leukocyte count [x109/L]	6.47	9.79	<0.001
Neutrophil count [x109/L]	4.76	7.18	0.001
Platelet count [x109/L]	208.1	232.8	n.s.

[a] statistical significance of the difference between the groups assessed with two-tailed, unequal variances *t*-test (Welch test).

Table 2
Hospital entry data of SARS-CoV-2 positive patients who survived or deceased. Excerpt of the data from Table 1 in ref. (Fu Y.-Q. et al., 2020).

Parameter/group	Survival group	Death group	P[a]
PaO2/FiO2	219	128	<0.001
Leukocyte count [x109/L]	5.71	11.2	<0.001
Neutrophil count [x109/L]	3.96	10.10	<0.001
Platelet count [x109/L]	224	161	0.004
CRP > 60 mg/L [%]	29.6	78.6	0.001

[a] statistical significance of the difference between the groups assessed with Mann-Whitney *U* test.

for which differences between survivors and deceased were highly statistically significant, despite the modest group sizes (here the median values are shown). This tally tells us that, independent on the primary causes of the differences between surviving and deceased, patients' fate had been decided within 12 days after onset of symptoms.

In the other study performed in UK (Goodall J.W. et al., 2020) association between results of clinical assessment and laboratory tests performed on admission and in-hospital death over subsequent 4 weeks was explored in a cohort of almost thousand COVID-19 patients hospitalized between March 12th and April 15th, using Cox proportional hazards modelling. In multivariable analysis decreased platelet counts, increased serum C-reactive protein (CRP), alkaline phosphatase and lactate, as well as increased respiratory rate, presence of hypoxia and low Glasgow Coma Scale score (<15) were highly statistically significantly associated with an increased risk of death.

3. Major determinants of mortality in SARS-Cov-2 are related to early hypoxia

In a recent Perspective paper on metabolic aspects of COVID-19 Ayres (Ayres J.S., 2020a) presented an important opinion on the pathophysiology of COVID-19. One of her first remarks is that the virulence of SARS-CoV-2 is a continuum: most individuals who acquire the infection experience mild disease, whereas a subset of individuals progress to severe, or even to critical disease, driven by the host response to the infection. Later she points at the metabolism as a critical regulator of

susceptibility to, and recovery from and survival after COVID-19, and presents a model of the disease stages. The model is not linear but rather "multi-storey", the three stages of sickness do not follow each other but are shown as trajectories which are common at the beginning, but quickly branch and follow independent paths. The explanation why patients with comorbidities such as metabolic syndrome and diabetes are more prone to severe and critical phases of COVID-19 may lie in the heightened baseline inflammatory state in patients with preexisting compromised metabolic health.

Oxygen delivery to tissues must be kept in balance with tissue demand for oxygen uptake. Imbalance between O2 delivery and uptake because of inadequate oxygen availability is called "hypoxia". In appreciation of a key importance of oxygen uptake for the body metabolism we propose to substitute the term "health" in the Ayres's model with the "degree of hypoxia" (Fig. 2).

Now let's look again at the parameters in Table 2, values of which (as discussed previously) decide on patients survival or death already at day 12 after symptoms onset. Increased leukocyte count in deceased patients is caused by increased neutrophil count; exposure to hypoxia has been shown (in healthy people) to quickly induce granulocytosis (Hitomi Y et al., 2003). It is also well known that hypoxia induces inflammation and both these phenomena are intertwined at the molecular, cellular, and clinical levels (Eltzschig H.K et al., 2011), these associations provide a direct link between hypoxia and high CRP. Hypoxia-induced thrombocytopenia had been described many years ago in mice (Birks J.W. et al., 1975), and a similar phenomenon has been found in the human neonatal respiratory distress syndrome (Kohelet D. et al., 1990).

The other well described predictor of severity and mortality in COVID-19 patients is blood level of D-dimers. The D-dimer is a unique marker of fibrin degradation (Adam S.S. et al., 2009), and it is well established that in advanced COVID-19, following the activation of coagulation pathways, blood levels of D-dimers are increased (Teuwen L.A. et al., 2020). Associations between endothelial dysfunction, hypoxia, and thrombus formation are well established in the septic microvasculature, and hypoxia may be both a consequence and cause of microthrombosis because of a positive feedback loop between thrombus formation and inflammation (Gupta N. et al., 2019). When admission data of 5279 COVID-19 patients in New York were correlated with the outcome over the next 50 days, D-dimer plasma level of more than 1 mg/mL predicted death or hospice care in almost 50% of cases (Petrilli C.M. et al., 2020). This data imply that D-dimer increase is yet another parameter which early increase in COVID-19 heralds serious consequences, and which is also hypoxia-dependent.

Most patients infected with SARS-CoV-2 encounter asymptomatic or mild course, and those who deteriorate, usually do so at around day eight after symptoms onset. Hypoxia is recognized as an important clinical parameter which shall be identified early in order to initiate higher-level care (Greenhalgh T. et al., 2020). A characteristic feature of many patients suffering from COVID-19, in particular those of older age, is the so-called "happy hypoxemia", i.e. hypoxia and hypocapnia without signs of respiratory distress (Brouqui P. et al., 2020). The cause of this phenomenon is not clear, but it has been proposed that its presence is unveiled when a COVID-19 patient encounters a ≥3%–5% drop in SpO2 after approximately 60 s of mild activity/ambulation (Galwankar S.C. et al., 2020). One possible explanation of such "happy hypoxemia" may be preexisting, infection-independent blunted reactivity of the respiratory system to chemical stimuli (hypoxia, hypercapnia), or a kind of habituation to recurrent episodes of apnea.

SARS-CoV-2 is similar to SARS-CoV and MERS-CoV, the other human respiratory coronaviruses characterized by high fatality rates. All 3 enter a human organism with respiratory droplets and target cells using viral spike protein S which bind to receptor proteins at the cell surface. MERS-CoV virus binds to dipeptidyl peptidase 4 (DPP4), whereas both SARS-CoV and SARS-CoV-2 bind to angiotensin-1 converting enzyme 2 (ACE2) located in apical cellular membranes of epithelial cells located along the upper and lower parts of respiratory tract (Kronenberg R.S. et al., 1973). An important issue concerning the pathomechanism of COVID-19 encompasses two types of events that may initiate hypoxia early in the corurse of infection.

The first is SARS-CoV-2 entry to both type 1 and type 2 pneumocytes in lung alveoli. A characteristic feature of severe cases COVID-19 in the advanced stage is lung involvement, visible radiologically as ground-glass opacites (Noman A. et al., 2021) and in autopsy material as diffuse alveolar damage and intravascular thrombosis (Landete P. et al., 2020). There is paucity of human data on the picture of lung involvement in the early stage of COVID-19, but when cynomolgus macaques were inoculated with SARS-CoV-2, four days after inoculation and in the absence of overt clinical signs of infection the virus was detected in type I and II pneumocytes in the foci of diffuse alveolar damage affecting up to 10% of lung volume (Bösmüller H. et al., 2020). Thus, it may be expected that damage of pneumocytes in human patients is an early event, and it is tempting to assume that it will to some extent compromise alveolar gas exchange.

The second type of events that may initiate and/or aggravate hypoxia

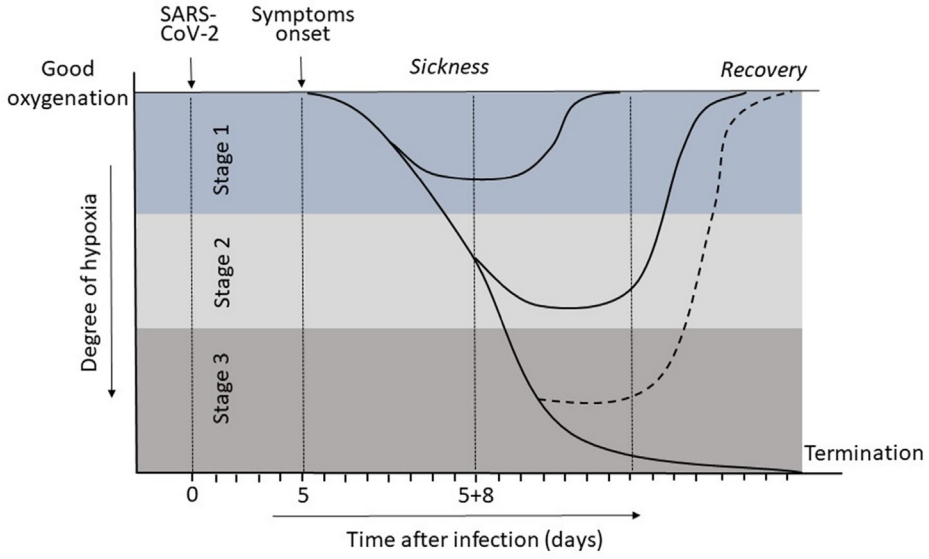

Fig. 2. Three stages of COVID-19 presented as different disease trajectories (based on fig.1 in Ayres J.S., 2020a, modified).

in COVID-19 relates to neuroinvasive potential of the virus. Several animal and human coronaviruses, including SARS-CoV and MERS-CoV, were shown to be able to invade central nervous system. Whereas hematogenous route seemed improbable, the evidence was mounting that these coronaviruses may enter brain using transsynaptic route, reaching medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways (Rockx B. et al., 2020). Anosmia and aegusia, which according to some authors are the most common early symptoms of COVID-19 (Li Y.C. et al., 2020; Freni F. et al., 2020), are related to the previously found presence of ACE2 receptors in cells of nasal and tongue epithelia (Vaira L.A. et al., 2020). Although direct entry of SARS-CoV-2 to brain stem respiratory centers remains controversial, a possible virus-related depression of the respiratory generator during the early course of COVID-19 cannot be excluded.

If hypoxia initiates progression to severe and critical stages of COVID-19, one would expect that patients with blunted reactivity of respiratory system to hypoxia or suffering from recurrent hypoxia episodes prior to SARS-CoV-2 infection will be more likely to progress to severe and critical stages of COVID-19. Such associations, indeed, exist. Old age is a strong risk factor of death in COVID-19 patients. Respiratory responses to hypoxemia and hypercapnia are significantly diminished in older adults (Hamming I. et al., 2004), and reduced cerebrovascular and ventilatory reactivity to hypoxia in older adults has been described (Hartmann S.E. et al., 2015). Sleep apnea is prevalent in subjects after age 60 (Launois S.H. et al., 2007), but its most common form, obstructive sleep apnea (OSA), is frequent in younger patients, too. OSA of various intensity is present in approximately 25% of the US adult general population (Gottlieb D.J. et al., 2020), and most cases remain undiagnosed. Recent data from the U.S. healthcare system identified diagnosed sleep apnea as a risk factor for COVID-19 mortality (Cade B.E. et al., 2020). Obesity, a risk factor for disease severity in COVID-19, has an adverse effect on respiratory physiology is frequently associated with sleep apnea (Kimura T. et al., 2020). Also, a significant fraction of obese patients suffer from obesity hypoventilation syndrome (Randerath W.J. et al., 2020). Last but not least, diabetes is a strong risk factor of death in the course of COVID-19 (Azar W.S. et al., 2020). In adults with diabetes type 2 ventilatory responses to isocapnic hypoxia are blunted, although the ventilatory response to hypercapnia is well preserved. Moreover, diabetes affects breathing during sleep and is an independent risk factor for sleep apnea (Lecube A. et al., 2017).

It is usually assumed that hypoxia in COVID-19 results from lung inflammation. However, as discussed above, hypoxia may as well be the initiating factor of granulocytosis, decrease in platelet counts, activation of coagulation pathways and lung endothelial dysfunction (Fig. 3). These factors, interconnected with a network of positive feedback loops, may run out of control, but they also could be amenable to pharmacological control.

4. Host-directed therapies to counteract hypoxia and its downstream effects in COVID-19

Currently, no specific therapy is recommended for the persons infected with SARS-CoV-2 who develop symptoms but do not require hospitalization. Elderly patients and those with prevailing chronic medical conditions such as lung disease, heart failure, cancer, renal disease, diabetes, etc. are considered in risk for developing severe illness (Almaghaslah D. et al., 2020) and require close monitoring in order to start active treatment when the disease progresses. However, as argued previously, a good or even the best opportunity to change the trajectory of COVID-19 and avoid a fatal outcome is at the very beginning of the disease process. Such early intervention could be aimed directly at the proliferating virus, but the use of remdesivir, the only antiviral drug accepted currently for the treatment of SARS-CoV-2 infection, is (paradoxically) saved for advanced cases, at which stage the major driver of the disease is the host response.

A viable alternative may be host-directed therapies (HDT), strategies of targeting host factors rather than attacking a pathogen directly (Zumla A. et al., 2016; Kaufmann S.H.E. et al., 2018). HDT may employ various commonly used drugs with good safety profiles, repurposed to the new indication. There are many ways through which HDT can reduce morbidity and mortality in infectious diseases. One possible mechanism is targeting pathogen-perturbed pathways leading to hyper-inflammation. Examples of HDT applications and related benefits for patients mostly concern chronic infectious diseases such as tuberculosis or AIDS, but such strategy can also be used for treatment of acute

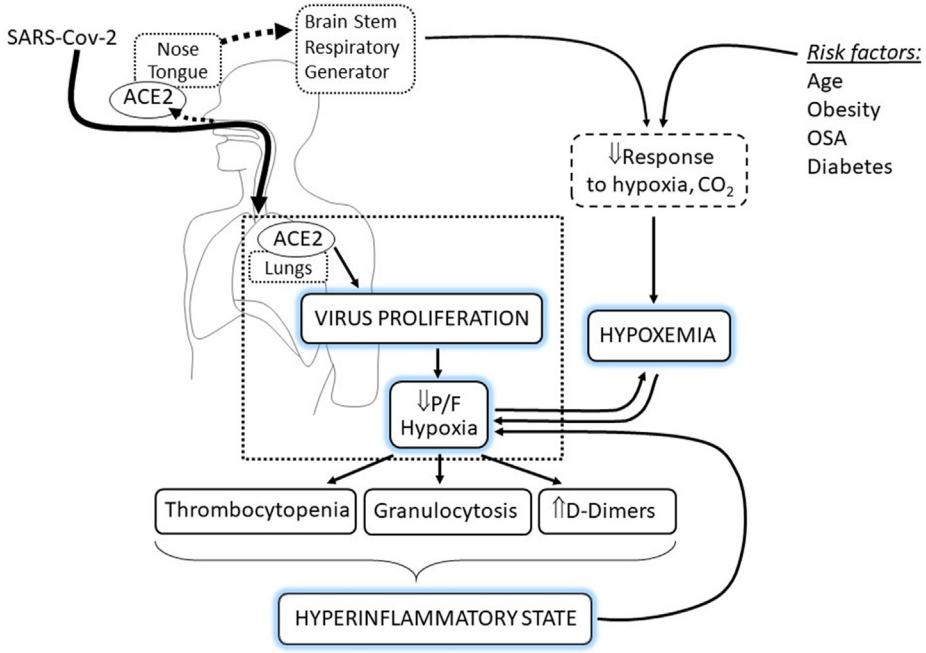

Fig. 3. Scheme indicating the central role of hypoxia in the development of severe/critical stage (phase) of COVID-19. P/F, the ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2), is the main determinant of hypoxemia and lung tissues hypoxia.

diseases, e.g. sepsis.

In case of COVID-19 certain HDTs may be efficacious at early stages of the disease process, when hypoxia and its downstream effects determine disease progression. An example of therapy currently recommended only for hospitalized patients which could prove useful also in the early phase of COVID-19 is heparin use. Already in March 2020 International Society of Thrombosis and Haemostasis (ISTH) issued interim guidance providing an algorithm for the management of coagulopathy in COVID-19 based on simple laboratory markers (Thachil J. et al., 2020). According to this algorithm COVID-19 patients with normal prothrombin time and platelet count without markedly raised D-dimer but hospitalized for other clinical reasons (unspecified) should be started with low molecular weight heparin (LMWH) in prophylactic dose similarly to those who are admitted to hospital because of coagulopathy symptoms. Considering that hypoxia, which in COVID-19 patients frequently occurs prior to hospitalization, is a likely contributor to the thrombotic complications, safety and efficacy of prophylaxis with LMWH in mild to moderate COVID-19 cases prior to hospitalization shall deserve prospective evaluation.

A unique example of potentially successful HDT for COVID-19 operating downstream from the putative hypoxic trigger of the serious disease is fluvoxamine, a popular and relatively well tolerated antidepressant. Fluvoxamine acts as a selective serotonin reuptake inhibitor in brain neurons, and also as agonist for sigma-1 receptor (S1R) with low-nanomolar affinity to these receptors (Hindmarch I. et al., 2010). S1R is a chaperone protein at the endoplasmic reticulum acting as an inter-organelle signaling modulator acting on mitochondria and nucleus (Su T.P et al., 2010; Chu U.B. et al., 2016). Fluvoxamine protected mice from lethal septic shock and dampened inflammatory response in human blood leukocytes (Rosen D.A. et al., 2020). In a randomized placebo-controlled study on 152 adult outpatients with symptomatic COVID-19 fluvoxamine intake nullified the likelihood of clinical deterioration over 15 days with very few side effects (Lenze E.J. et al., 2020). Recently similar results were reported in the prospective "real world" trial where the drug was offered to asymptomatic or symptomatic patients infected with SARS-CoV-2 virus in an occupational setting with congregate living. At 14 days none of 65 patients treated was hospitalized and all were symptom-free, whereas of 48 patients not taking the drug 6 were hospitalized and 29 exhibited residual symptoms (Seftel D. and Boulware D.R., 2021).

Another example is amantadine, a HDT which may attenuate the development of COVID-19 while acting also the SARS-CoV-2 virus life cycle. Originally amantadine had been developed and widely used for prophylaxis and treatment of influenza A, but these viruses become resistant. Later it has been found that the drug displays a multi-faceted pharmacological activity (Danysz W. et al., 2021). It may still be active against some RNA viruses, such as Chikungunya (Dey D. et al., 2019) and hepatitis C (HCV). An in-silico molecular docking predictions suggested possible interaction of amantadine with the amino acids of the receptor binding domain of SARS-CoV-2 spike protein (Baig A.M. et al., 2010), and in the other study it was discovered that the drug may reduce this virus entry to cells through lysosomal effects (Smieszek S. et al., 2020). In few small studies amantadine drug has been tested on patients with chronic hepatitis C, evoking significant decreases in serum alanine transaminase levels probably related to its antiinflammatory activity (Carreño V., 2014). Several preclinical studies evidenced its antiinflammatory effects in neuroinflammation induced by sepsis and by lipopolysaccharides, experimental models of multiple sclerosis, spinal cord injury, and respiratory diseases (Jiménez-Jiménez F.J. et al., 2020). Amantadine has been successfully repurposed to become a useful drug in neurology, indicated for Parkinson's disease and disorders of consciousness, also prescribed off-label to multiple sclerosis patients suffering from fatigue (Ma H.M. et al., 2020). Neurological effects of amantadine are related to its ability to cross the blood-brain barrier and antagonize NMDA receptors at the central level, but similar mechanism may also be effective at the periphery and prevent acute lung injury and respiratory distress developing early in the course of COVID-19 (Butterworth R.F., 2020). Last but not least, amantadine is similar to fluvoxamine in that it is also a potent agonist of the sigma-1 receptors (Peeters M. et al., 2004). In a questionnaire-based study multiple sclerosis and Parkinsons disease patients taking amantadine were found infected with SARS-CoV-2 but none of them developed clinical manifestations of COVID-19 (Rejdak K. and Grieb P., 2020). Besides putative antiviral and effects, anti-fatigue and arousal-enhancing effects of the drug may counteract respiratory depression and development of hypoxia in COVID-19 (Grieb P. et al., 2020).

The other popular drug which may prove particularly useful as HDT for post-prophylaxis and early treatment of COVID-19 is N-acetylcysteine (NAC). This acetylated variant of the amino acid L-cysteine is a cell membrane-permeable donor of L-cysteine required for glutathione (GSH) synthesis. NAC is used in medicine for more than 5 decades, first of all as a mucolytic and a remedy for acetaminophen poisoning, but many other indications have been proposed (Kelly G.S., 1998). Besides antioxodant and antiinflammatory effects NAC displays beneficial vasodilatory effects on the microcirculation and could potentially benefit some patients with sepsis and septic shock (Chertoff, 2017). As in other respiratory viral infections, virus-induced ROS production and disturbed cellular redox balance are important triggers of inflammation in COVID-19 (Wu J., 2020). Therapeutic potential of NAC in COVID-19 has been the subject of few recent reviews (De Flora S. et al., 2020; Shi Z. and Puyo C.A., 2020; Luo P. et al., 2021). It has been suggested that older individuals and patients with comorbidities are more prone to serious manifestations of COVID-19 because of glutathione deficiency (Polonikov A., 2020). According to the ClinicalTrals.gov database few studies assessing NAC as a post-prophylaxis or early treatment of COVID-19 are currently ongoing.

In the context of COVID-19 it is also worth to mention pharmacologically active methylxanthines. Two recent papers (Monji F. et al., 2020; Liu L. et al., 2020) suggested that pentoxyfilline, and first of all caffeine, widely available traditional drugs displaying pleiotropic effects (respiratory stimulating, anti-inflammatory, antioxidant, immunomodulatory and even antiviral) could also be used as potentially beneficial adjuvant treatments of COVID-19 patients. The aforementioned examples of HDTs suitable for early intervention in SARS-CoV-2 certainly do not encompass all possibilities.

5. Concluding remarks

In an editorial which appeared one month prior to the aforementioned Perspective paper Ayres (Ayres J.S., 2020b) remarked that scientists are wrongly focused on developing antivirals instead on drugs that promote physiological function during the infection. Antivirals will likely be effective only in patients that develop "mild" cases of COVID-19, and for the patients who require hospitalization and develop severe and critical stages of the disease only supportive care is offered. These remarks are, indeed, true.

Two central questions concerning COVID-19 are: (i) why some individuals become mortally sick and others not, and (ii) what can be done to prevent or at least reduce mortality of this disease. The data cited and discussed above seem to indicate that although the root cause of symptomatic COVID-19 is infection with SARS-CoV-2 virus, the most likely trigger of disease worsening is an inadequate respiratory response to hypoxia, and mortality seems less dependent on the virus itself, but more so on host factors. These factors in most cases are related to the preexisting risks (e.g. diabetes, sleep apnea, glutathione deficiency, etc.) and become dominant at the advanced stage of the disease. However, hypoxemia appearing at the early phase of the disease may be a decisive factor for the development of uncontrolled host-dependent sequelae such as thrombocytopenia, coagulopathy, granulocytosis, etc., leading to a highly mortal hyperinflammatory state. Post-exposure prophylaxis and early (prehospital) treatment of COVID-19 by host-directed therapies aimed at hypoxia-derived pathomechanisms could be the most effective measure to decrease mortality related to this disease. Such treatments

should be urgently tested in controlled clinical trials.

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CRediT authorship contribution statement

Pawel Grieb: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Maciej Swiatkiewicz:** Writing – original draft, Writing – review & editing, Visualization. **Katarzyna Prus:** Writing – original draft, Writing – review & editing. **Konrad Rejdak:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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