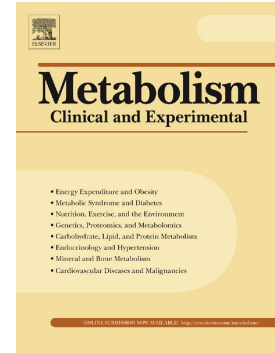# Journal Pre-proof

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COVID-19 and Diabetes Mellitus: What we know, how our patients should be treated now, and what should happen next

Angeliki M. Angelidi[a†], Matthew J. Belanger[b†], and Christos S. Mantzoros[a,c*]

[a]*Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA*

[b]*Department of Medicine Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA 02215, USA*

[c]*Section of Endocrinology, VA Boston Healthcare System, Harvard Medical School, Boston, MA 02115, USA*

[†] *These authors have contributed equally to this work as co-first authors and are listed here in alphabetical order.*

Keywords

COVID-19; Diabetes; Evidence-Based Practice; Renin-Angiotensin System; Risk; SARS-CoV-2; Therapy

Abbreviations

ACEI, ACE inhibitor; ACE2, angiotensin-converting enzyme 2; ARB, angiotensin II type-I receptor blocker; ARDS, acute respiratory distress syndrome; CDC, Center for Disease Control; ELISAs, enzyme-linked immunosorbent assays; FDA, Food and Drug Administration; MERS-CoV, Middle East respiratory syndrome coronavirus; RAAS, Renin–Angiotensin–Aldosterone System; RBD, receptor-binding domain; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

[*]Corresponding author at: Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215, United States of America.

E-mail address: cmantzor@bidmc.harvard.edu (C.S. Mantzoros)

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The novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into a worldwide crisis and was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. The rate of spread, range of clinical manifestations, morbidity, and mortality associated with COVID-19 has prompted special interest in understanding the factors that predispose individuals to infection and severe forms of the disease. Many of the early studies from China overlapped in finding that, in addition to older age, certain chronic medical conditions including hypertension, type 2 diabetes, and cardiovascular disease, are a risk factor for severe illness with COVID-19 [2-5]. Of note, according to a recent study, diverse haplotypes of SARS-CoV-2 were identified in distinct areas, probably due to different sources of exposure [6]. However, no evidence exists whether these haplotypes are responsible for differences in clinical manifestations of the disease.

The pandemic has spread worldwide, affecting more than 200 countries and territories. As of April 13, 2020, the number of global cases has surpassed 1.7 million, including over 110,000 deaths; the United States alone has reported over 500,000 cases and 20,444 deaths [7]. According to a recent study in Iceland, the percentage of people at high risk for infection (mainly patients with symptoms, those who had close contact with infected persons, and those who had recently traveled to areas where there is major community spread) who tested positive for SARS-CoV-2 infection was approximately 13%. In comparison, the percentage of infected individuals in the general population was 0.8%, which remained stable over the course of 20 days. It should be noted that children under ten years of age and females had a lower incidence of SARS-CoV-2 infection compared to adolescents or adults and males, respectively [6]. These initial data on incidence and prevalence are likely to change significantly over time with the progression of the pandemic and with the expected availability of better tests to confirm diagnosis as well as short and long-term immunity.

Emerging literature from Italy and the United States has also pointed to a higher burden of severe disease in individuals with chronic medical conditions. Preliminary data in the United

States identified diabetes as the most common risk factor for SARS-CoV-2 infection [8]. In this editorial, we review the clinical observations related to diabetes and COVID-19 in China, Italy, and the United States. We next review the pathogenesis of and immune response to SARS-CoV-2 infection. We then outline proposed mechanisms that may predispose individuals with diabetes both to infection and severe disease. Finally, we highlight areas that warrant further investigation and discuss management considerations for clinicians.

Clinical Observations in China, Italy, and the United States

The first cluster of cases of pneumonia of unknown etiology appeared in Wuhan, China, in late December of 2019 [9]. Subsequent analysis identified the novel betacoronavirus, SARS-CoV-2, the seventh member of the coronavirus family that infects humans and includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), as the causative agent of COVID-19 [10]. An early single-center observational study in Wuhan of individuals with severe COVID-19 pneumonia described a high prevalence of chronic illness and a 22% prevalence of type 2 diabetes in individuals who did not survive the infection [2]. Another early large observational study identified type 2 diabetes as a common underlying condition in patients with severe illness (16.2%), second only to hypertension (23.7%) [3]. A meta-analysis that included these and other studies found that the incidence of diabetes was two-fold higher in those that developed severe disease compared with patients that experienced non-severe disease [5]. Subsequent studies have demonstrated an association between diabetes and poor prognosis and increased mortality. A recent retrospective cohort study of 174 patients admitted to Wuhan Union Hospital with COVID-19 found that 21.2% of patients had diabetes, and further identified diabetes as a risk factor for severe disease based on radiographic findings and biomarkers of inflammation and end-organ damage [11]. These findings are consistent with a summary report of over 72,000 cases across China from the Chinese Center for Disease Control (CDC) that showed an increased fatality rate of 7.3% in individuals with diabetes compared to an overall fatality rate of 2.3% [12]. Additionally, a recent multicenter retrospective cohort study of COVID-19 confirmed inpatients from Jinyintan Hospital and Wuhan Pulmonary Hospital found a statistically significant association between diabetes and increased mortality [13].

In Italy, the severity of disease and strain on the healthcare system related to COVID-19 has been noteworthy, with one recent estimated case fatality rate of 7.2% [14]. While factors unique to the Italian population may contribute to the higher case fatality rate, such as a relatively older population, emerging data has also highlighted the role that underlying chronic cardiometabolic disease has on the severity of illness. A retrospective case series of patients admitted to the intensive care unit (ICU) with COVID-19 in the Lombardy region found hypertension (49%), cardiovascular disease (21%), and diabetes (17%) to be common underlying medical conditions [15]. The Italian National Institute of Health reported the prevalence of diabetes in patients that died while infected with SARS-CoV-2 to be 35.5%, suggesting that diabetes may be a significant risk factor for mortality [16].

The first case of COVID-19 in the United States was confirmed on January 20, 2020, in Snohomish County, Washington [17]. Two early case series of critically ill patients admitted to ICUs in the Seattle-area found an incidence of diabetes of 58% and 33.3%, respectively [18, 19]. While more robust studies need to be completed, preliminary data from the United States CDC on March 28, 2020, estimated diabetes to be the most prevalent underlying health condition in individuals infected with SARS-CoV-2 at 10.9%, and further estimated that 32% of patients requiring ICU admission had diabetes [8]. What remains to be fully elucidated, given the nature and study designs of initial reports, is whether the reported associations are independent from potential confounding factors such as gender and age that are associated with both COVID-19 and diabetes. Additionally, the extent that admission to the hospital or ICU, or medications used in the ICU (such as steroids), may be contributing to the increased prevalence of diabetes and other metabolic syndrome-related comorbidities needs to be determined.

Pathogenesis and Immune Response to SARS-CoV-2 Infection

Coronaviruses are positive-sense, single-stranded RNA viruses, with a large 27 to 32 kilobase genome packaged inside a capsid formed by nucleocapsid protein (N). An envelope surrounds this helical structure and is associated with three structural proteins: membrane protein (M) and envelope protein (E), which are both involved in virion assembly, and spike protein (S), which mediates entry into host cells [20, 21]. The S protein is further characterized by a receptor-

binding domain (RBD) S1 subunit that facilitates binding to the host angiotensin-converting enzyme 2 (ACE2) receptor for both SARS-CoV and SARS-CoV-2, and an S2 subunit that is responsible for membrane fusion [22-24]. The RBD of MERS-CoV attaches to host cells via dipeptidyl peptidase 4 (DPP4) rather than ACE2 [25]. A recent study demonstrated that certain structural changes of the RBD unique to SARS-CoV-2 results in enhanced ACE2 receptor binding affinity in comparison to SARS-CoV [26]. Host cell factors further mediate viral entry through two serine proteases, TMPRSS2 and furin, which activate the S protein for membrane fusion through cleavage and assist in viral processing, respectively [21 22, 24].

Once infection with SARS-CoV-2 has occurred, a complex, orchestrated response of the innate and adaptive immune system ensues that correlates clinically to three proposed phases: a viremia phase, an acute phase, and a recovery phase [27]. The innate immune response involves the recognition of viral pathogen-associated molecular patterns by pattern recognition receptors (i.e., Toll-like receptors), resulting in the expression of type I interferons and inflammatory factors that potentiate macrophage and natural killer cell defense mechanisms [20]. Dendritic cells are tissue phagocytes that bridge the innate and adaptive immune response by activating T-lymphocytes and B-lymphocytes through antigen-presentation [20]. The adaptive immune system is essential for control of the persistent phase of infection and involves the production of neutralizing monoclonal antibodies to viral envelope glycoproteins by CD4+ T cells and the killing of viral-infected cells by cytotoxic CD8+ T cells [20]. In the acute phase of infection, SARS-CoV and SARS-CoV-2 invade CD4+ and CD8+ T-lymphocytes resulting in apoptosis and lymphocytopenia, a marker that is associated with severe outcomes [22, 27].

The specifics of the humoral response to SARS-CoV-2 infection is under investigation. A study of 173 hospitalized patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection showed a seroconversion rate for total antibody, IgM, and IgG of 93.1%, 82.7%, and 64.7%, respectively, and noted that the few patients with negative antibody findings did not have later stage blood samples available for analysis [28]. However, a subsequent study that analyzed the plasma of 175 patients who had recovered from mild COVID-19 illness showed that 30% of participants generated a very low level of neutralizing antibody and that elderly patients were more likely to generate a robust antibody response than

younger patients [29]. The implications of this regarding susceptibility to recurrent infection warrants further investigation, and ongoing studies are expected to shed more light on this topic.

Potential Mechanisms Underlying the Increased Risk of Severe COVID-19 in Diabetes

Individuals with diabetes are more susceptible to a broad range of infections [30]. In addition, several infections may result in less well-controlled diabetes. Numerous factors contribute to the immune dysfunction in individuals with diabetes, including hyperglycemia, inhibition of neutrophil chemotaxis, altered cytokine production, phagocytic cell dysfunction, impaired T-cell mediated immune responses, and ineffective microbial clearance [31-35].

The relationship between these known mechanisms of immune dysfunction in patients with diabetes and infection with SARS-CoV-2 will require further investigation. One recent study involving patients admitted for COVID-19 suggested that hypertension and diabetes resulted in delayed clearance of SARS-CoV-2 [36]. Investigations related to prior coronavirus outbreaks may also shed light on the pathophysiology of SARS-CoV-2 infection in patients with diabetes. For example, to understand the immune system response to MERS-CoV in individuals with diabetes, Kulcsar et al. created a transgenic mouse model that expressed human DPP4 (DPP4$^{H/M}$), the cellular binding site for MERS-CoV, and induced diabetes through a high-fat diet [37]. The diabetic DPP4$^{H/M}$ mice developed more severe disease and were found to have a dysregulated immune response after infection characterized by delayed and decreased recruitment of CD4+ T cells and inflammatory monocytes and macrophages in lung tissue. In addition to the decreased overall CD4+ T cell response, infected diabetic mice also displayed a more prominent Th17 response with increased levels of IL-17a, indicating that an alteration in cytokine profiles could be partly responsible for disease severity. This study is consistent with prior evidence that diabetes results in a shift toward Th17 responses and diminished regulatory T cells resulting in exaggerated inflammatory cascades [22, 34]. Notably, some patients infected with COVID-19 have developed a fatal hyperinflammatory syndrome resembling secondary hemophagocytic lymphohistiocytosis, thought to be mediated by pro-inflammatory cytokines such as IL-2, IL-6, IL-12, TNF-α, and IFN-γ [9, 38].

Another area of both scientific and clinical interest has centered on the relationship between ACE2 receptor expression and specific diseases such as diabetes. ACE2 is a transmembrane glycoprotein expressed on cells throughout the human body, including upper respiratory tract epithelium, type II alveolar pneumocytes, cardiac myocytes, and pancreatic islet cells. The renin-angiotensin-aldosterone (RAAS) signaling pathway comprises both angiotensin-converting enzyme (ACE), which metabolizes angiotensin I (Ang I) to angiotensin II (Ang II), and ACE2, which converts Ang II to angiotensin$_{(1-7)}$ (Ang 1-7) [39]. Ang II has both vasoconstrictive and inflammatory properties, which are counter-balanced by the vasodilatory and anti-inflammatory properties of Ang 1-7 [39, 40]. The ratio of the activity of ACE and ACE2, which are both highly expressed in the lung, has been shown to have implications on lung oxygenation and lung injury in acute respiratory distress syndrome (ARDS) [39, 41, 42]. Experimental models following the SARS-CoV epidemic showed that Spike protein binding results in decreased expression of ACE2 receptors in the lung, suggesting that lung injury may be mediated by a higher proportion of Ang II relative to Ang 1-7 [43]. Thus, the ACE2 receptor appears to have conflicting roles related to the pathophysiology of SARS-CoV-2 infection: one where ACE2 facilitates disease as the binding site for SARS-CoV-2, and another where reduced expression of ACE2 may contribute to severe lung injury after infection [40].

The effects that diabetes has on ACE2 expression in specific tissues need to be studied in more detail. Experimental models have primarily focused on ACE2 in the kidney of type 1 and type 2 diabetic mice and have shown increased ACE2 expression in early disease followed by decreased expression in later disease that coincides with the development of nephropathy [44-47]. Similarly, ACE2 has been shown to be decreased in the tubules of individuals with diabetic nephropathy [48]. An experimental model that investigated the effect of diabetes on the expression of ACE2 in tissues throughout the body found that the ratio of ACE2/ACE activity in the lung was decreased in late-stage diabetes [49]. Conversely, a recent phenome-wide Mendelian randomization study that investigated the association of disease states and ACE2 expression found that type 2 diabetes is causally associated with increased ACE2 expression in the lung [50]. Further investigation into the effects that both diabetes and SARS-CoV-2 infection have on ACE2 is warranted to guide therapeutic approaches.

Gaps in Our Knowledge Requiring Investigation

As discussed above, emerging information suggests that patients with diabetes are more susceptible to SARS-CoV-2 infection and are at risk of increased morbidity and mortality associated with COVID-19. However, it has been argued that the presence of diabetes may not predispose to an increased risk of SARS-CoV-2 infection, but rather a rapid progression and worse outcome of COVID-19 [16]. Thus, appropriately controlled large studies in both the inpatient and outpatient settings are needed to quantify the magnitude of these associations before and after therapy, and to assess whether such associations are causal or due to underlying confounding. For example, studies suggesting increased susceptibility to SARS-CoV-2 infection in individuals with diabetes could be confounded by a greater degree of testing in this population due to more frequent visits to the emergency department or hospitalizations for coexisting complications of diabetes such as other components of the metabolic syndrome and cardiovascular disease. Thus, it is necessary to clarify whether patients with diabetes are highly prone to SARS-CoV-2 infection or poor outcomes from COVID-19.

It should be noted that challenges have been encountered with the quality and availability of PCR-based diagnostic tests that are currently used to make the diagnosis. Furthermore, the first antibody-based tests for diagnosing recent infection (IgM) or more remote infection (IgG), and possibly immunity, are only now emerging. Initial antibody-based tests, mainly enzyme-linked immunosorbent assays (ELISAs), were characterized by a lack of specificity due to cross-reactivity with other coronaviruses. These deficiencies need to be corrected for the tests to be clinically useful, and their availability needs to significantly increase since they are not currently available for screening the asymptomatic population.

The deployment of large-scale antibody testing is imperative not only to understand the frequency of infection in specific subpopulations (such as individuals with diabetes) but also to obtain an accurate assessment of the case fatality rate of COVID-19. Serological testing could provide necessary read-outs regarding the efficacy of vaccines or other medications currently in clinical trials. It will also be an essential part of assessing who among the general population could be allowed to return to work safely and thus will inform public policy decisions regarding easing restrictions and re-opening the workforce [51]. Taking all the above into account, more accurate and widely available diagnostic tools are needed to expand the study sample and

identify the percentage of undiagnosed individuals, including those who are asymptomatic and sub-symptomatic. Notably, the Food & Drug Administration (FDA) recently granted emergency authorization for the first rapid antibody test released to authorized laboratories. Genetic epidemiology studies that fully map the haplotypes/clades of the virus will assist in case finding and case tracing and may not only enhance public health efforts to contain the spread of the virus but also may help prevent any future recurrences. Careful association studies of viral haplotypes in relation to clinical manifestations may also provide information regarding the possibility of mutations occurring over time and the potential clinical implications thereof.

Due to the fact that ACE2 is the cellular receptor of SARS-CoV-2, many investigators have expressed concern whether patients treated with ACE inhibitors (ACEIs), angiotensin II type-I receptor blockers (ARBs), or other drugs that increase ACE2 expression may exhibit a worse prognosis and have questioned whether physicians should discontinue these drugs in patients that take them for hypertension or complications of diabetes [52, 53]. On the other hand, some evidence emphasizes the protective effects of ACE2 on the cardiovascular system and in ARDS [39, 42]. SARS-CoV-2-induced impaired ACE2 activity may hypothetically attenuate the cardioprotective role of ACE2, exaggerate inflammation, and contribute to severe lung injury in COVID-19. As discussed above, ACE2 in humans is not well understood, but evidence suggesting that ACE2 expression may be reduced in the elderly, or individuals with hypertension or diabetes, provides an argument for the continuation of ACEIs/ARBs and for clinical trials investigating the therapeutic effects of initiating these medications in severe cases of COVID-19 [40]. Furthermore, different RAAS inhibitors may demonstrate different effects on ACE2 levels and COVID-19 outcomes, and the discontinuation of ACEIs and ARBs may result in adverse health outcomes related to poor control of chronic conditions [54-57]. This is an area of active investigation from both an epidemiological risk factor perspective as well as from a novel drug development point of view.

Moreover, multicenter observational studies should be conducted to estimate the prevalence and the case fatality ratio of the disease, which appears to be different among different populations. Potential explanations for the observed differences include measurement errors (since the denominator of the ratio is affected by the quality and number of measurements in each case), genetic susceptibility of the populations of interest, and differential virulence of the

known haplotypes/variants of the virus. In addition, more experimental and rigorous clinical trials are of vital importance to clarify and further explore the findings of the observational studies. Furthermore, trials using multi-omics approaches and big data analytics are urgently needed to examine the characteristics of these subpopulations and to identify potential risk factors, i.e., sex, race, ethnicity, presence of preexisting disorders, or comorbidities. Interventional trials should also focus on the efficacy and safety of the different types of RAAS inhibitors and elucidate their role and mechanism of action in the disease milieu. Whether different classes of antidiabetic drugs that may affect the levels of ACE2 (such as DPP4 inhibitors) can reduce the risk of infection or modify disease progression should be investigated [52, 58]. A more in-depth understanding of the disease is crucial for the development of effective vaccines and therapeutic strategies against SARS-CoV-2.

The potential benefits of several other agents against SARS-CoV-2 are currently being investigated (i.e., hydroxychloroquine, chloroquine, azithromycin, corticosteroids, anti-inflammatory agents, antiviral drugs, convalescent plasma transfusion) and numerous compounds are in development. Randomized clinical trials should be designed to examine the safety and efficacy of these drugs on chemoprophylaxis and treatment, including patients with diabetes, and the possibility of a quick interim analysis from these studies should be considered [59-61]. With global attention focused on the COVID-19 pandemic and urgent requests for emergency access to potential therapies, there is an understandable temptation to use drugs without fully proven safety and efficacy against the disease. As a result, a greater emphasis on the drug-evaluation process and evidence-based decision making is needed to protect patients not only from possibly ineffective drugs but also potentially unsafe treatments, which may induce complications and have side effects [62].Trials with long-term follow up are essential to evaluate the effects of different therapeutic strategies on patient-centered outcomes such as intermediate-term and long-term mortality. Studies should also be designed to examine the long-term cardiometabolic sequelae of SARS-CoV-2 infection among individuals that have recovered from COVID-19. Of note, one small study evaluated 25 individuals 12 years after recovery from SARS-CoV infection and found a higher amount of altered glucose and lipid metabolism and significant differences in serum metabolomes compared to age-matched healthy controls [63].

Metabolism has issued a call for papers and letters to the editor to enhance the scientific dialogue and facilitate dissemination of critically needed useful information in this area. At the same time, it should be acknowledged that the urgent need for information about this global public health crisis has led to an increased number of published papers and data with several limitations (including sampling issues, methodological constraints, limited peer-review process, and potential publication and researcher bias) that may affect the validity of the findings and their interpretation [64]. It is essential for future studies to have predefined and standardized criteria regarding study hypothesis, sample population, clinical syndromes, disease severity, and patient-centered outcomes both for observational and interventional studies. Thus, in order to elucidate the impact of diabetes mellitus as a risk factor for COVID-19 as well as to explore the best prophylactic and therapeutic strategies for this high-risk population, it is critical to design and conduct high-quality, robust observational studies and clinical trials.

Implications for Clinicians

Given the current situation, the paucity of robust scientific evidence, and the lack of specific treatments, COVID-19 has become a crucial worldwide health problem. At present, quarantine, isolation, social distancing, and stringent restrictions on domestic and international travel are the most effective preventive strategies, along with practicing good hygiene. However, due to a potential lack of access to medications and supplies, individuals with diabetes may experience difficulties in acquiring essential medical supplies as well as consumable medical devices such as insulin, alcohol wipes, glucose test strips, etc. As a result, metabolic dysregulation and inadequate control of coexisting cardiometabolic conditions, such as hypertension and dyslipidemia, may occur in patients with diabetes [65].

Notably, ACE2 is also expressed in pancreatic and liver tissues, both of which may be potential targets for SARS-CoV-2, leading to further worsening of hyperglycemia during the COVID-19 infection. According to this hypothesis, both COVID-19 as an acute illness and SARS-CoV-2 per se may worsen glycemic control [22, 66]. Given that individuals with diabetes, especially those with comorbidities and complications, are considered high-risk patients, it is evident that risk factors such as hyperglycemia and hypertension should be optimized.

Clinicians should be proactive in addressing the needs of patients using telemedicine technologies, including phone calls and video visits if available. The United States government has notably decreased regulatory thresholds to make video health visits easier to provide during this pandemic. We anticipate that establishing care through these technologically advanced means may have a lasting impact on how we treat and follow up with patients with diabetes in the long-term. Both patients and physicians will be adopting and benefiting from novel technological advancements [67-69].

Innovative public health interventions are also being explored, such as a mobile phone contact tracing App that could be used as a strategy to mitigate pre-symptomatic transmission, also considering the limitations of this theoretical model (minimum number of registers, potential privacy compliance issues, ethical requirements) [70]. Health care providers, in general, should use telemedicine and telehealth services to minimize physical contact and simultaneously provide individualized care, support, and feedback. Moreover, they should also ensure close monitoring, maintenance of healthy lifestyle practices, treatment adherence, and aim to remotely address rising health issues in an efficient and timely manner. Due to this uncertain situation and the extremely challenging circumstances, individuals may not only undergo physical health deterioration, but also may experience various anxieties, psychological pressure, distress, and vulnerability. A multidisciplinary group of experienced professionals both from health and social services should assist patients with diabetes as well as their families and caregivers, taking advantage of the new communication-based social networking platforms.

The immediate management considerations surrounding medications such as ACEIs and ARBs continues to be debated and investigated. Due to lack of strong evidence and given the beneficial organ-protective effects of ACEIs and ARBs, as well as the potential adverse outcomes of SARS-CoV-2 on the cardiovascular system [5, 56, 71], the Heart Failure Society of America, the American College of Cardiology, and the American Heart Association, as well as the European Society of Cardiology recommend against the discontinuation of RAAS inhibitors [72, 73]. It should be noted that several clinical trials are underway to examine the safety and efficacy of RAAS inhibitors in COVID-19.

There have been a number of reports regarding the role of corticosteroids during severe acute illness due to SARS-CoV-2 [2, 13, 74, 75]. Corticosteroids may attenuate pulmonary

inflammation and subsequent acute lung injury by reducing the inflammatory response and modulating the activity of the immune system [76]. However, concerns exist whether corticosteroid use is associated with viral rebound, prolonged replication, and increased rates of mechanical ventilation and mortality [77-79]. Therefore, according to the WHO, corticosteroid treatment is not routinely recommended as a therapeutic option for COVID-19 pneumonia outside of clinical trials [80].

At this point, we would also like to note that based on the currently proposed mechanisms of SARS-CoV-2 pathogenesis, APN01, a recombinant soluble human ACE2 (rhACE2), recently received regulatory approvals to be studied in the context of a Phase II clinical trial to treat patients with severe COVID-19. APN01 alleviates the detrimental effects of acute inflammation in the lungs and may exhibit a protective role against acute lung injury and ARDS induced by SARS-CoV-2. Due to the similarity of APN01 with human ACE2, the virus binds to the soluble APN01 and inhibits entry into human cells by serving as a decoy receptor [81]. In our opinion, and based on mechanisms of action, we believe that this is the most promising compound among all medications currently in development. In this context, it should also be noted that the activity of TMPRSS2, a molecule downstream of ACE2, is essential for viral entry into primary target cells in addition to viral spread and pathogenesis in the infected host. According to recent data, camostat mesylate, a transmembrane serine protease serine 2 inhibitor developed for the treatment of acute pancreatitis, is active against TMPRSS2 and prevents cellular entry of the virus [24]. Data regarding additional drugs of this class, such as nafamostat, are also expected in the near future from planned trials [82]. The above drugs are promising therapeutic agents, and further data are urgently needed as no specific treatment for COVID-19 is currently approved.

The ongoing COVID-19 pandemic is rapidly evolving. Fast, efficient, but also unbiased, reliable, and valid studies are of paramount importance to provide evidence-based information and guidance to these unanswered questions. At the same time, close monitoring of the data is crucial to identify the best strategies in terms of prevention, early diagnosis, and treatment of this globally challenging health problem. Given that several viruses of increasing infectivity, virulence, and lethality have emerged over the past three decades from hot spots around the world, coordinated public health efforts centered on preventing the transmission of zoonotic diseases to humans as well as early detection of potential threats are needed to avoid similar

future outbreaks. Ultimately, nations and international organizations, including the WHO, will need to come together as a community to prioritize these global preparedness initiatives to ensure that an event like this does not occur again. It is never too early to start building the foundations to more effectively prevent and address future threats as we are fighting this evolving and dangerous pandemic.

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