Scientific Research Publishing

Advances in Infectious Diseases, 2022, 12, 568-631
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

COVID-19 Infection: The Virus and Its Origin, the Variants, the Immune Defense, the Multiorgan Autoimmune Reactions, and the Targeted Treatments

Vu Thuong Nguyen[1*], Lawrence S. Chan[2,3,4]

[1]Advanced Cosmeceuticals Enterprises, Inc., Sacramento, USA
[2]Department of Dermatology, University of Illinois, Chicago, USA
[3]Captain James Lovell Federal Health Care Center, North Chicago, USA
[4]Department of Dermatology, School of Medicine, University of California, Davis, USA
Email: *vu.dalat79@yahoo.com, *vutnguyen@lbcosmec.com

How to cite this paper: Nguyen, V.T. and Chan, L.S. (2022) COVID-19 Infection: The Virus and Its Origin, the Variants, the Immune Defense, the Multiorgan Autoimmune Reactions, and the Targeted Treatments. *Advances in Infectious Diseases*, **12**, 568-631.
https://doi.org/10.4236/aid.2022.123042

Received: July 5, 2022
Accepted: September 27, 2022
Published: September 30, 2022

Abstract

Background: SARS-CoV-2, the virus responsible for the current COVID-19 infection pandemic, has caused substantial damage and negative impacts in the world, including physical sickness, mental illness, death, society lock down, work interruption, and productivity reduction. From the onset in early 2020, the pandemic has not yet totally subsided as of July 2022. Although great efforts have been made to understand the nature of this pandemic by the medical and scientific communities, a comprehensive review of this pandemic has not been reported. **Purpose:** We aimed to perform a thorough review of the subject in order to come to a better understanding of the origin of the virus, its mutations and their corresponding health effects, its pathophysiology, and its responses to therapeutic intervention. A more comprehensive set of data on these subject matters, if available, would give healthcare providers a valuable tool in formulating the best methods to respond to the current disease and prevent the disease from spreading in the future. **Method:** An extensive literature search on the subjects of COVID-19 was conducted regarding the possible origin of the viral pathogen, its evolutionary changes and health impacts, the world's responses to COVID-19 and outcomes of their responses, and healthcare professional's actions to understand and manage the disease and the results of their actions. To gather these data, websites of PubMed and Google Scholar were utilized for the search with the following keywords: Pandemic, COVID-19, coronavirus, SARS, SARS-CoV, SARS-CoV-2, origin, pathogenesis, and treatment. **Results:** Our review revealed data that

points to an interesting autoimmune phenomenon where most seriously sick patients affected by COVID-19 were documented by an IgA-dominant immune response to the pathogen, along with a neutrophil-directed infiltration to the vital organ in the lung aveola, resulting in critical lung injury, leading to respiratory failure, multi-organ failure, and death. Surprisingly, this IgA-mediated and neutrophil-directed disease pattern is nearly identical to a group of IgA-mediated autoimmune skin diseases, such as dermatitis herpetiformis, IgA bullous dermatosis, and IgA pemphigus, which respond well to treatment by dapsone, a sulfone class of antibiotic/anti-inflammatory drug. Moreover, the usefulness of dapsone was supported by a small clinical study. In addition, systemic corticosteroid, a trusted anti-inflammatory medication, has been used in this pandemic with variable degrees of success. **Conclusion:** The data collected from our review of the subject, together with our prior search knowledge, compel us to conclude that the underlying pathophysiology that causes serious respiratory distress and multi-organ failure is most likely to be autoimmune in nature and that strategies to counter these multifacet autoimmune disorders would be the most valuable in life-saving. Specifically, we identified clinical and laboratory evidence pointing to IgA autoimmune reaction as a key factor that causes significant mortality in many patients. Accordingly, we proposed the utilization of a combination of dapsone, corticosteroid, and anti-thrombotic drugs in severely ill patients at the earliest point of the disease process. The autoimmune multi-organ syndrome may explain the pathogenesis of COVID-19 as well as Post-COVID conditions and may guide healthcare professionals in a better direction to manage the disease. The possible origin of the viral pathogen may shed light on a better understanding of the pathogenesis of the disease.

Keywords

COVID-19, Pathogenesis, Autoimmune, Mortality, ARDS, SARS-CoV-2, Origin, Delta Variant, Omicron Variant, Neutrophil, IgA, Neutrophil Adherence, Cytokine Storm, Dapsone, Methylprednisolone, Antithombotic, Treatment, Therapeutic Mechanism

1. The Origin of COVID-19 Virus

COVID-19 is caused by SARS-CoV-2 [1]. It erupted in Wuhan, China, in early November 2019 [2] and became epidermic in early December 2019, then pandemic in January 2020 [3]. The WHO declared the COVID-19 pandemic in March 2020.

Since 2002, SARS-CoV-2 has been the fourth coronavirus that is known to cause severe acute respiratory distress syndrome (SARS). Previous to the emergence of SARS-CoV in 2002, there were two prototype human coronaviruses, OC43 and 229E, etiologic agents of the common cold [4]. SARS-CoV was the first coronavirus that cause SARS in humans. In the SARS pandemic in 2003, the virus killed about 10% of about 8000 infected patients [5] [6]. The other two

SARS-causing coronaviruses are MERS-CoV, which first occurred in April 2012 that killed about 35% of about 3500 infected patients [7] [8] [9], and SARS-CoV-like virus that killed 3 of 6 mine workers in Mojang, Yunnan, China after they were infected in April 2012 at a bat-harboring mineshaft carrying SARS-CoV-like viruses and received treatments from 12 to 108 days from April to July 2012 at the First Affiliated Hospital of Kunming Medical University in Kunming, Yunnan, China [10]. Because the symptoms of these patients were similar to SARS, swab and serum samples of these patients were first sent to Chengdu Army Reserved Center for Disease Prevention and Control, Chengdu, China, to test for the presence of SARS-CoV and antibodies against the virus, and this institution reported a negative result. However, with the consultation of Dr. Zhong Nanshan, the leading SARS expert in China, patients' serum samples were sent to Wuhan Institute for Virology (WIV) in Wuhan, China, to test for IgM antibodies against SARS-CoV antigens using a very specific SARS-CoV ELISA developed by this institute, and the result was reported to be positive, which proved that these patients were actually acutely infected with a SARS-CoV-like virus [10] [11].

The Mojiang SARS-CoV-like virus may not be identical to SARS-CoV-2 because the old sera (2012) from these patients were stated to be tested again in 2020 and were claimed to be negative for a new SARS-CoV-2 specific ELISA, as shown in the addendum for the first publication for SARS-CoV-2, although there was no data shown in the addendum [12]. However, a thorough 60 pages of clinical and laboratory study presented in the master thesis of Dr. Li Xu, a physician in the team of doctors who directly took care of the six SARS patients from Mojiang mineshaft showed that these patients had very similar clinical presentation as patients with COVID-19 [10] [13] [14]. Still, the major difference is that SARS-CoV-2 only killed about 2% of infected patients in contrast to the Mojiang SARS-CoV-like virus that killed 3/6 infected patients, unless SARS-CoV-2 was the attenuated Mojiang SARS-CoV-like virus, that explains the negative test result reported in the addendum. Nevertheless, discoveries of SARS-CoV-like viruses in the same Mojiang mineshaft and the regions southern to Mojiang indicate that these coronaviruses and SARS-CoV-2 are closely related and may come from the same ancestors since their nucleic acid sequences share more than 95% identity [12] [15] [16] [17].

Similar to the first three SARS causing coronaviruses, SARS-CoV-2 is believed to originate from the tiny rufous horseshoe bat [1] [10] [18]. These viruses infect human cells via angiotensin-converting enzyme 2 (ACE-2), which is broadly expressed in vascular endothelium, respiratory epithelium, alveolar monocytes, and macrophages. Unlike SARS-CoV and MERS-CoV that the intermediate hosts were identified within a few months after the outbreak began [19] [20] [21]; there has been no identified intermediate host for COVID-19, despite an extensive testing effort of researchers in China with over 50,000 animal samples for more than two years from SARS-CoV-2 outbreak in Wuhan [2]. The failure to find any evidence of an intermediate host for SARS-CoV-2 has brought the attention of the scientific community back to the SARS-CoV-like virus men-

tioned in Dr. Li Xu's theses on the six patients with SARS from Mojiang mineshaft. Furthermore, after this incident in which the virus from bats infected directly to the mine workers, the research team led by Dr. Zhengli Shi at WIV found two more SARS-CoV-like viruses that could directly infect human cells via ACE-2 receptor [22] [23].

There is only one study that contradicts data from Dr. Li Xu's thesis on the 6 patients from the Mojiang mineshaft indicating the patients were infected with coronavirus similar to SARS-CoV. A publication by Wu *et al.* in 2014 reported that in June 2012, in the same mineshaft in Mojiang at the same time described in Dr. Xu's thesis, 3 persons got infected with the virus and all 3 patients died. Half a year later, they investigated the presence of novel zoonotic pathogens in natural hosts in this cave. For the investigation, they went to the same abandoned mineshaft and collected anal swab samples from 20 bats (Rhinolophus ferrumequinum), 9 rats (R. flavipectus), and 5 musk shrews (Crocidura dracula) from the mine for virome analysis. They found that 3 rats carried a novel henipa-like virus, MojV, belonging to the genus Henipavirus (family Paramyxoviridae) that have been associated with lethal neurologic and respiratory diseases in humans. They suggested that the viruses might infect more mammalian hosts [24]. The whole context of their report led readers to think that infection of MojV might be the cause of death of pneumonia patients from Mojiang.

The report by Wu *et al.* by itself contains a few fundamental loopholes. The authors claimed that they went to Mojiang mineshaft to obtain the samples in December 2012, which was the winter in Mojang Mountain and the freezing weather was not the time for a zoology field trip. They claimed that they collected anal swab samples from 20 bats belonging to the species *Rhinolophus ferrumequinum* in the mineshaft. Their claim contradicted data from a study by Ge *et al.* that the dominating bat species in the mineshaft they found during their visit in Fall 2012 were *Rhinolophus sinicus*, *Rhinolophus affinis*, *Hipposideros Pomona*, *Miniopterus schreibersii*, *Miniopterus fuliginosus*, and *Miniopterus fuscus* [15]. Thus, statistically it was unrealistic that Wu *et al.* could go to the same mineshaft and catch 20 bats belonging to only the species *Rhinolophus ferrumequinum*.

Wu *et al.* claimed that they caught 5 musk shrews belonging to the species *Crocidura dracula* from the mine on that winter field trip. According to a study by Chen *et al.*, *Crocidura Dracula* is the rarest and most speciose mammalian genus and in their 20 years of study, they could collect only 10 samples of this species and the nearest location of the sample to the Mojang mineshaft is more than 400 miles away [25]. Thus, it was extremely unlikely that Wu *et al.* could catch 5 *Crocidura Dracula* in their trip to the Mojiang mineshaft in winter 2012.

Wu *et al.* claimed that they caught 9 rats belonging to the species *R. flavipectus* in the same abandoned mineshaft in the Mojiang mountain area. A search by Google map shows that this abandoned mineshaft was far away from any civilian villages in Mojiang Autonomy of Yunnan. In a study by Yin *et al.* in Yunnan province, *R. flavipectus* is a house rat that normally lives in the village and depends on human food [26]. Thus, it was unusual that Wu *et al.* could catch *R. flavipectus* in

the abandoned mineshaft in the Mojiang mountain area that had no human food.

Since the publication by Wu *et al*. in 2014, a study by Rissanen *et al*. in 2016 using the nucleic sequence of MojV deposit on Genbank to reconstruct the MojV attachment glycoprotein (MojV-G) and confirm the inability of MojV-G to interact with known paramyxoviral receptors. MojV-G does not bind human CD150, the morbillivirus-specific cell surface receptor [27]. Thus, it was unclear if MojV could infect a human cell, what the entry receptor for MojV is, or even the true identity of the virus. Note that the Mojiang virus (MojV) is the first henipavirus identified in rodent and known only by sequence data. Another study by Cheliout *et al*. in 2021 utilized recombinant full-length and soluble forms of the MojV fusion (F) and attachment (G) glycoproteins in membrane fusion and receptor tropism studies. They found that MojV F and G were functionally competent and mediated cell-cell fusion in primate and rattine cells but only with low levels and slow fusion kinetics. Syncytia in cells co-expressing MojV F and G were much less extensive and were only observed 5 days post-transfection compared to control. Their exhaustive investigation of A- and B-class ephrin receptors indicated that none serve as a primary receptor for MojV [28]. Therefore, MojV cannot explain the rapid viral transmission among the 6 coworkers in the Mojiang mineshaft in 2012 that was described in Dr. Li Xu's thesis. While sera from the 6 Mojiang patients are available [12], until today, there is no evidence that sera from these patients contain antibodies to recombinant MojV proteins. In summary, MojV, if it truly exists, is very unlikely the pathogen causing death in 3 of 6 Mojiang patients.

Thus, the more critical question is how the virus is transmitted directly from a bat to a human causing severe pneumonia [10], leading to an outbreak and then a worldwide pandemic.

2. The Emergence of Delta Variant: An Evolutionally Unexpected Strain with Enhanced Virulence

When the COVID-19 pandemic began, scientists hoped and monitored with great interest that like other pandemics caused by a viral pathogen, SARS-CoV-2 would mutate and naturally attenuate over time [29]. Evolutionarily, while mutations in viruses occur randomly on errors, the selection of the surviving variants follows the rule of symbiosis, *i.e*., the virus would become less deadly to the host in order to survive in the host. This rule was, in fact, followed in the 1918 influenza pandemic that carried on for over 2 years from February 1918 to April 1920, in which most of the mortality occurred in the first year (February 1918-April 1919). The total world mortality was estimated at over 50 million (of a total population of about 1.8 billion); with which the highest mortality occurred in India with over 17 million deaths [30]. The 1918 influenza virus, studied by reconstruction of the virus in 2000, was very virulent. Mouse infected with the laboratory reconstructed 1918 influenza virus showed destruction of lung alveola with neutrophils infiltrated [31]. The neutrophil lung infiltrates in-

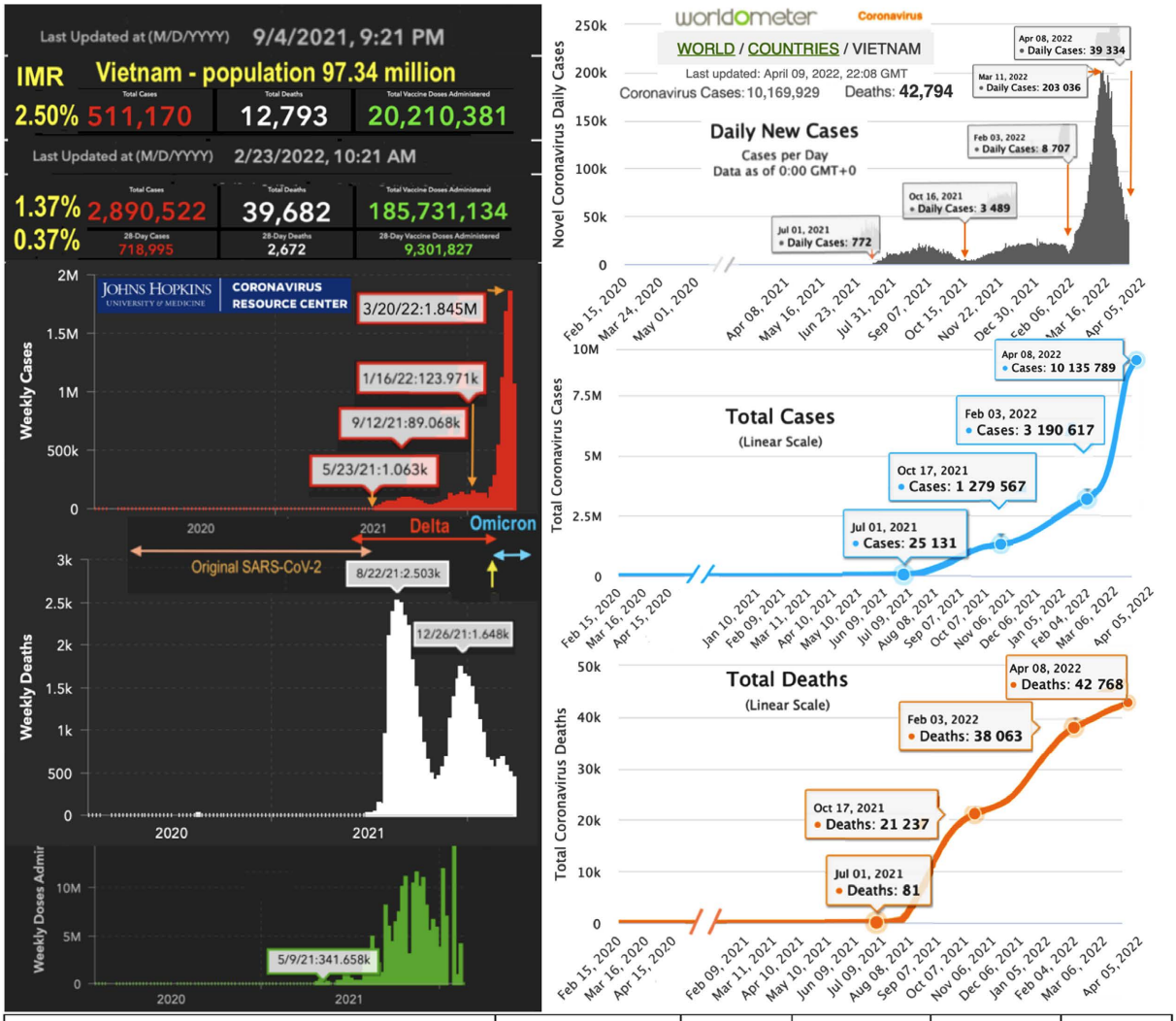
duced by laboratory reconstructed virus without bacteria or fungal superinfection is unique because it is only seen in severe COVID-19, but not in SARS-CoV infection cases [32], in influenza pneumonia or other viral pneumonia [33] [34], or in the early phase of SARS-CoV-2 infection [35] [36].

In the 1918 influenza pandemic the total mortality was highest in the second wave during winter 1918 due to the wide spread of the virus. The mortality decreased in the third wave in spring 1919 and became very small in the fourth wave in Spring 1920, probably due to the emergence of new and less virulent variants and the formation of herd immunity [30] [31] [32].

The experience of COVID-19 is similar, with a number of new variants emerging over time. One year from the beginning of the pandemic and after the second wave, it was thought that the pandemic had gone to its peak and the viral pathogen might begin its attenuated phase. Some countries like Vietnam and India thought that they had controlled the pandemic successfully [37] [38] [39] [40]. By July 1, 2021, there were only 18,830 confirmed COVID-19 cases in Vietnam. That data was likely far lower than the actual number of SARS-CoV-2 infected cases (due to untested asymptomatic and mild cases), producing the population infection rate (PIR) of less than 0.019%. There were only 81 COVID-19-related deaths recorded during that period of time, rounding up the infection mortality rate (IMR) of less than 0.43% (**Figure 1**) [41]. One additional significant factor that might help Vietnam achieve a very low COVID-19 PIR in its first three waves of the pandemic may be the routine yearly BCG vaccine that was believed to help the immune system be better trained against the original SARS-COV-2. Although BCG vaccine does not prevent SARS-CoV-2 infection per se [42], it may give some protection from severe COVID-19 infected with the original SARS-CoV-2 and reduce mortality [43] [44], thus may explain the extremely low PIR and IMR in Vietnam before 7/1/2021.

However, the rise of the unexpectedly more virulent Delta variant of SARS-CoV-2 has shocked the medical community (**Figure 1** and **Figure 2**). It was first recognized in India in December 2020 and this variant initiated the second wave of infection in India from March to August 2021 that killed many more victims [45] [46] [47] [48] (**Figure 2**). From May 2021 on, it became the world's dominant strain until it was replaced by the attenuated Omicron variant of the virus in early 2022. Delta variant of SARS-CoV-2 has been responsible for the world's second-year terror of COVID-19 (**Figure 3(a)**).

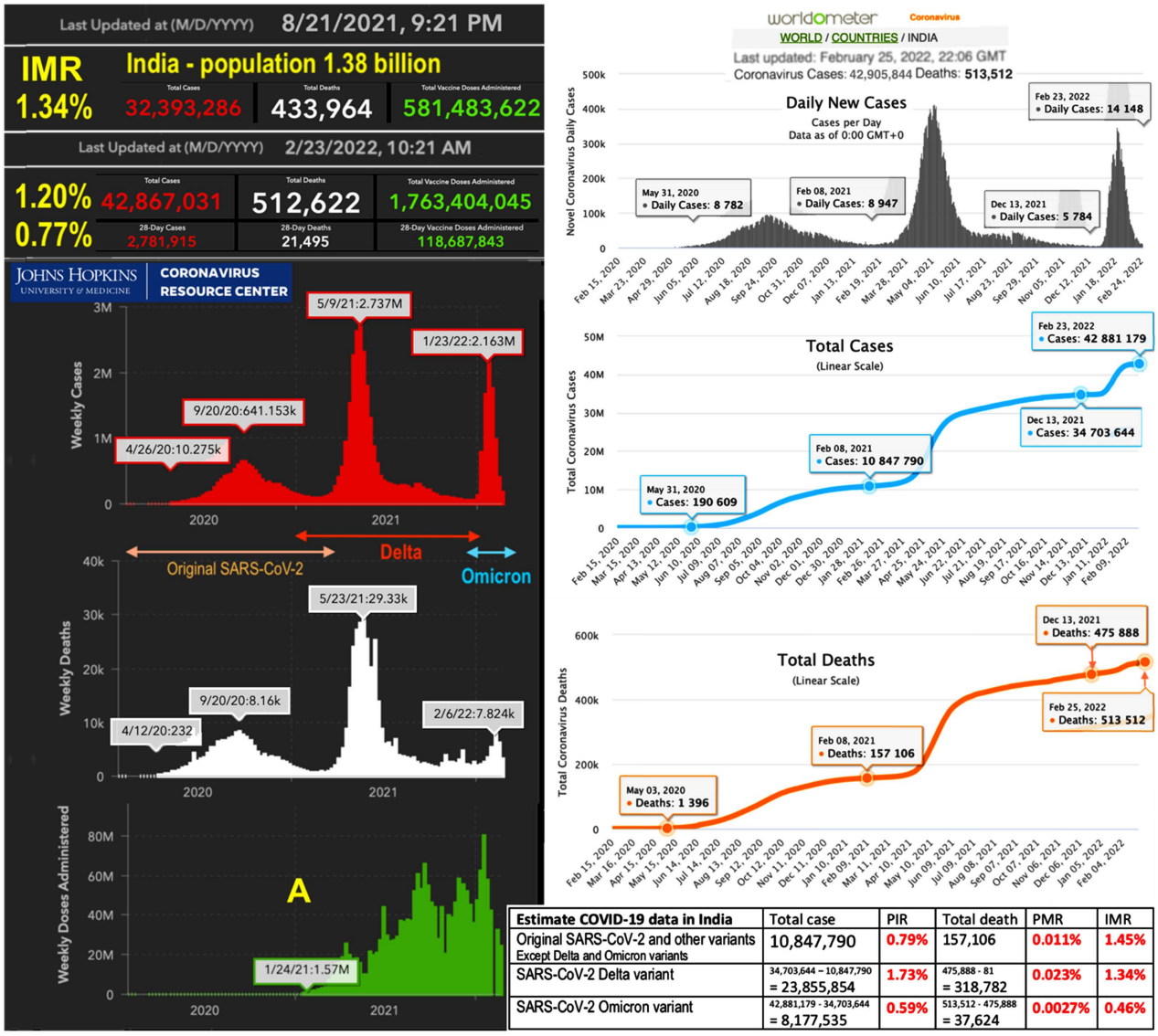
Vietnam is no exception. From July to October 16, 2021, despite the same anti-pandemic effort, the more virulent Delta SARS-CoV-2 took over 21,000 lives among 913,400 infected patients in the country's fourth wave of COVID-19 with an IMR of about 2.32%, compared to about and less than 0.43% in the first three waves [41] [49] [50] [51]. The fifth wave, still with Delta variant (second Delta variant infection wave), from October 2021 to the end of January 2022, when Vietnam reopened with the idea "to live with COVID", saw a larger amount of infection likely due to low number of vaccinations (**Figure 1**). The IMR, however,



Estimate COVID-19 data in Vietnam	Total case	PIR	Total death	PMR	IMR
Original SARS-CoV-2 and other variants Except Delta and Omicron variants	18,830	0.019%	81	0.00008 %	0.43%
First wave SARS-CoV-2 Delta variant	932,253 – 18,830 = 913,423	0.94%	21,237 - 81 = 21,156	0.023%	2.32%
Second wave SARS-CoV-2 Delta variant (Open-Live With COVID)	2,332,550 - 932,253 = 1,400,297	1.44%	38,063 - 21,237 = 16,826	0.0027%	1.20%
SARS-CoV-2 Omicron variant (to 4/08/2022)	10,135,789- 2,332,550 = 7,803,239	8.02%	42,768 - 38,063 = 4,705	0.0048%	0.060%

Figure 1. Overview of COVID-19 pandemic in Vietnam with three major variants of SARS-COV-2, 1) The SARS-COV-2 and variants other than Delta and Omicron, (Data before 7/1/2021), 2) Delta variant (first wave, 7/1-10/17/2021, second wave, 10/17/2-21-2/3/2022), and 3) Omicron variants of SARS-CoV-2 (2/3/2022-after). Left, data were downloaded from Johns Hopkins University, Coronavirus Resource Center. The graphs show weekly cases in thousands (Red), weekly deaths in thousands (White), and weekly vaccine doses administered in million (Green) [49]. Right, data downloaded from the Worldometer [82]. Data presented as total cases, population infection rate (PIR), population mortality rate (PMR), and infection mortality rate (IMR).

reduced from 2.48% to 1.2%, likely due to the available and flexible treatment modalities starting October 2021. There were only 16,826 actual deaths of over 1,400,000 infections instead of the expected 32,480 deaths (if IMR was 2.32% as seen in the first Delta wave) [52].



Estimate COVID-19 data in India	Total case	PIR	Total death	PMR	IMR
Original SARS-CoV-2 and other variants Except Delta and Omicron variants	10,847,790	0.79%	157,106	0.011%	1.45%
SARS-CoV-2 Delta variant	34,703,644 – 10,847,790 = 23,855,854	1.73%	475,888 - 81 = 318,782	0.023%	1.34%
SARS-CoV-2 Omicron variant	42,881,179 - 34,703,644 = 8,177,535	0.59%	513,512 - 475,888 = 37,624	0.0027%	0.46%

Figure 2. Overview of COVID-19 pandemic in India with three major variants of SARS-COV-2, 1) The SARS-COV-2 and variants other than Delta and Omicron (Data before 2/8/2021), 2) Delta variant (Data from 2/8/2021-12/13/2021), and 3) Omicron variants of SARS-CoV-2 (12/13/2021-2/23/2022). Left, data were downloaded from Johns Hopkins University, Coronavirus Resource Center. The graphs show weekly cases in million (Red), weekly deaths in thousands (White), and weekly vaccine doses administered in million (Green). Right, data downloaded from the Worldometer [82]. Data presented as total cases, population infection rate (PIR), population mortality rate (PMR), and infection mortality rate (IMR).

By the rule of symbiosis, the selection of the surviving variants favors the ones that could more easily infect the host cells and evade the host immune system but keeps the host surviving by mutating to be less virulent. The virus could become less virulent to the host by replicating more slowly, by increasing binding to less vital cell types, *i.e.*, epithelial cells of skin or oral mucosa or upper respiratory tracts, or by decreasing binding to more vital cell types such as lower respiratory tract epithelial cells.

It is not surprising that the surviving Delta SARS-CoV-2 could become more infectious through mutations in the epitopes recognized by antibodies formed

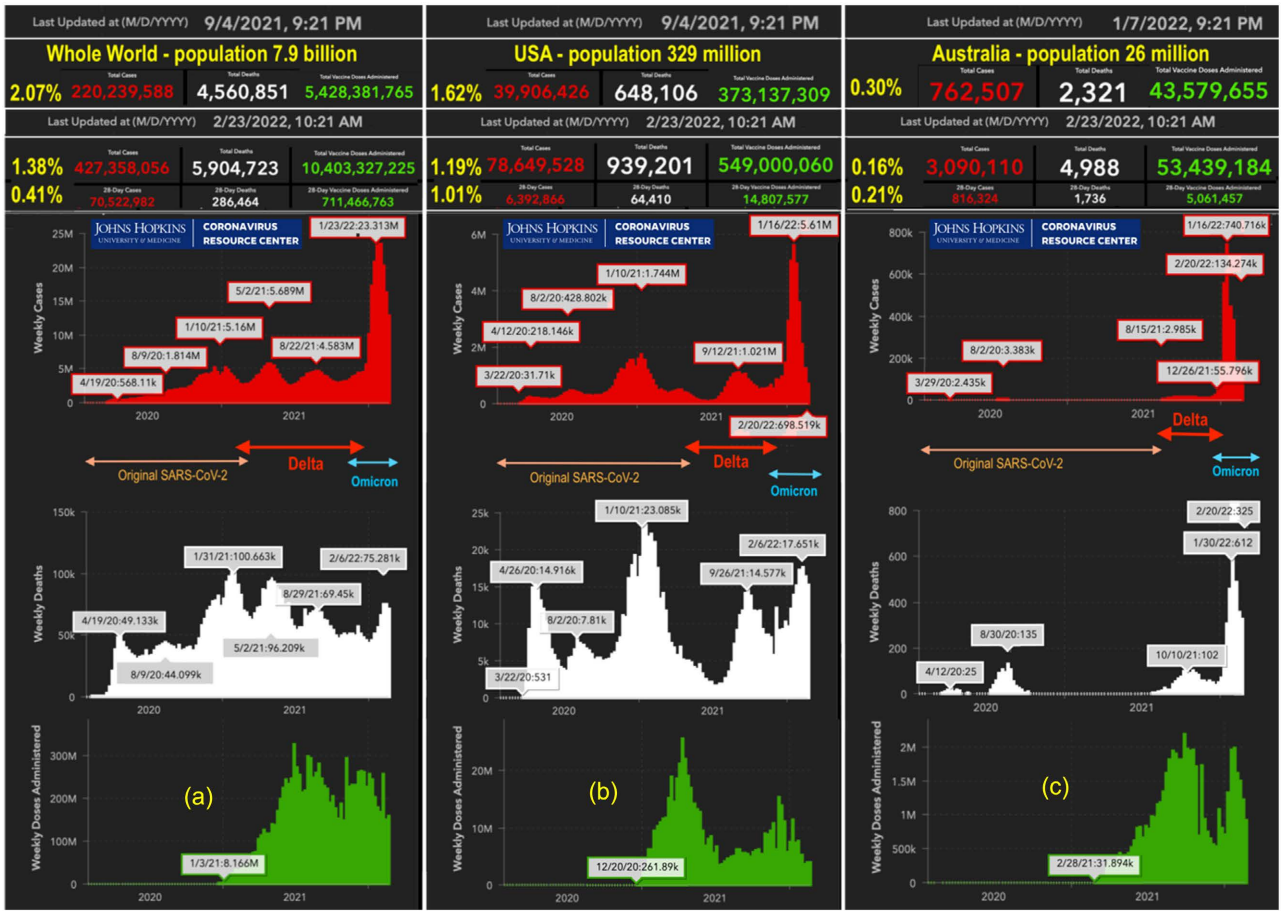


Figure 3. Overview of COVID-19 pandemic with original SARS-COV-2, Delta variant, and Omicron variant of SARS-CoV-2. The data were downloaded from Johns Hopkins University, Coronavirus Resource Center [49]. The infection mortality rate (IMR) of the whole world (a), USA (b), and Australia (c) before and after emergence of Omicron variant was compared.IMR of mixed variants including delta before 9/4/2021 was 2.07% (whole world), and 1.62% (USA) and 0.30% for Australia before 1/7/2022.IMR. IMR of mixed variants with Omicrondominant by 2/23/2022 was 1.38% (whole world),1.19% (USA), and 0.16% (Australia). IMR in the 28 days period before 2/23/2022 (mainly Omicron) was 0.41%(whole world),1.01% (USA), and 0.21% (Australia). The graphs of the whole world and the US show weekly cases in millions, weekly deaths in thousands, while that of Australia in scale of thousands and hundreds, respectively. Weekly vaccine doses administered was in millions.

from the previous infection or by vaccination, by obtaining higher avidity to ACE-2 receptor, by increasing the ability to fuse to host cell [53] [54] [55] [56], or by evading the host innate immune system [57]. These characteristics partly explain its heightened transmissibility. What is surprising, however, is the emergence of more virulent Delta SARS-CoV-2, which did not follow the rule of symbiosis and became more virulent. Overall, patients infected with Delta variant were younger, had lower rates of comorbidities, but with a higher risk for hospitalization, exhibited more severe symptoms, *i.e.*, needed more oxygen supplements and higher ICU admission, and suffered a higher mortality rate [58] [59] [60] [61] [62].

Unlike ordinary natural viral attenuation in the pandemic, Delta SARS-CoV-2 has increased virulence by increasing its replicability. Li *et al.* studied 167 delta SARS-CoV-2 infected patients in China. The average viral load in delta infection

is about 1000 times higher than the viral load in original SARS-CoV-2 infection in patients in China during the pandemic, pointing to faster viral replication [63]. A similar finding about the higher viral load in patients infected with Delta variant compared to other variants was documented by Teyssou *et al.* [64]. By *in vitro* experiments, Mlcochova *et al.* showed a higher replication rate of Delta variant in lung epithelial cells [65]. The very high viral load in delta SARS-CoV-2 infected patients is responsible for the rapid transmission of the variant in the community. The increased replicability while maintaining infectious preference for lung epithelial cells could be responsible for the increase of virulence of Delta SARS-CoV-2.

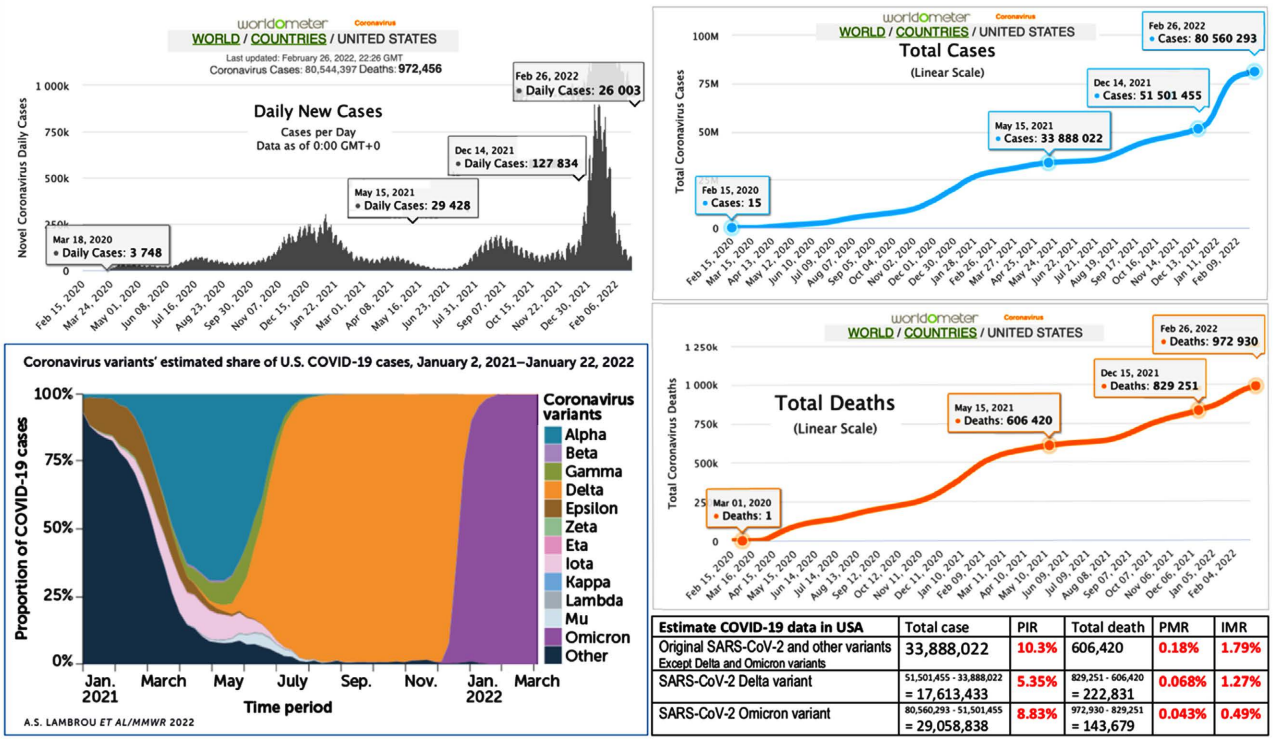
The paradoxical increase in virulence of Delta SARS-CoV-2 resembles an immune phenomenon termed "reversion to virulence". Many live-attenuated vaccines were created by passing the disease-causing virus through a series of cell cultures or animal embryos (typically chick embryos) in the laboratory without any genetic engineering manipulation. The virus would lose its pathogenicity by losing its ability to replicate in human cells [66]. Unfortunately, some live-attenuated vaccines exhibit reversion to virulence through back-mutation of attenuating mutations, compensatory mutations elsewhere in the genome, recombination or reassortment, or changes in quasi-species diversity [67]. For example, attenuated oral poliovirus vaccine (OPV) has been shown to replicate to high titers over long periods of time in some immunodeficient vaccinees, resulting in reversion to virulence. These immunodeficient vaccinated individuals also excrete polioviruses over long periods of time, increasing the likelihood of transmission to unvaccinated individuals in the community [68] [69].

3. The Emergence of Omicron Variant: An Evolutionarily Expected Strain with Attenuated Virulence

Since November 2021, Omicron SARS-Co-V2 has rapidly spread all over the world and has become the dominant strain. Omicron variant of SARS-CoV-2 was first recognized in South Africa and its neighbor India in mid-November 2021. The wave of Omicron infection in the US peaked in mid-December with about 145,500 new cases/week and gradually declined. The transmission rate of Omicron variant was about three times faster than Delta [70] [71], but there was a significant decrease in severity of COVID-19 disease in infected patients. The severe COVID-19 outcomes were reduced mostly due to protection conferred by prior infection and/or vaccination, but intrinsically reduced virulence in the virus may account for an approximately 25% reduced risk of severe hospitalization or death compared to Delta variant [72] [73] [74] [75]. In other countries during a period with both Delta and Omicron variants in circulation, SARS-CoV-2 infections with presumed Omicron variant being dominant were also associated with substantially reduced risk of severe clinical endpoints and shorter durations of hospital stay [76] [77].

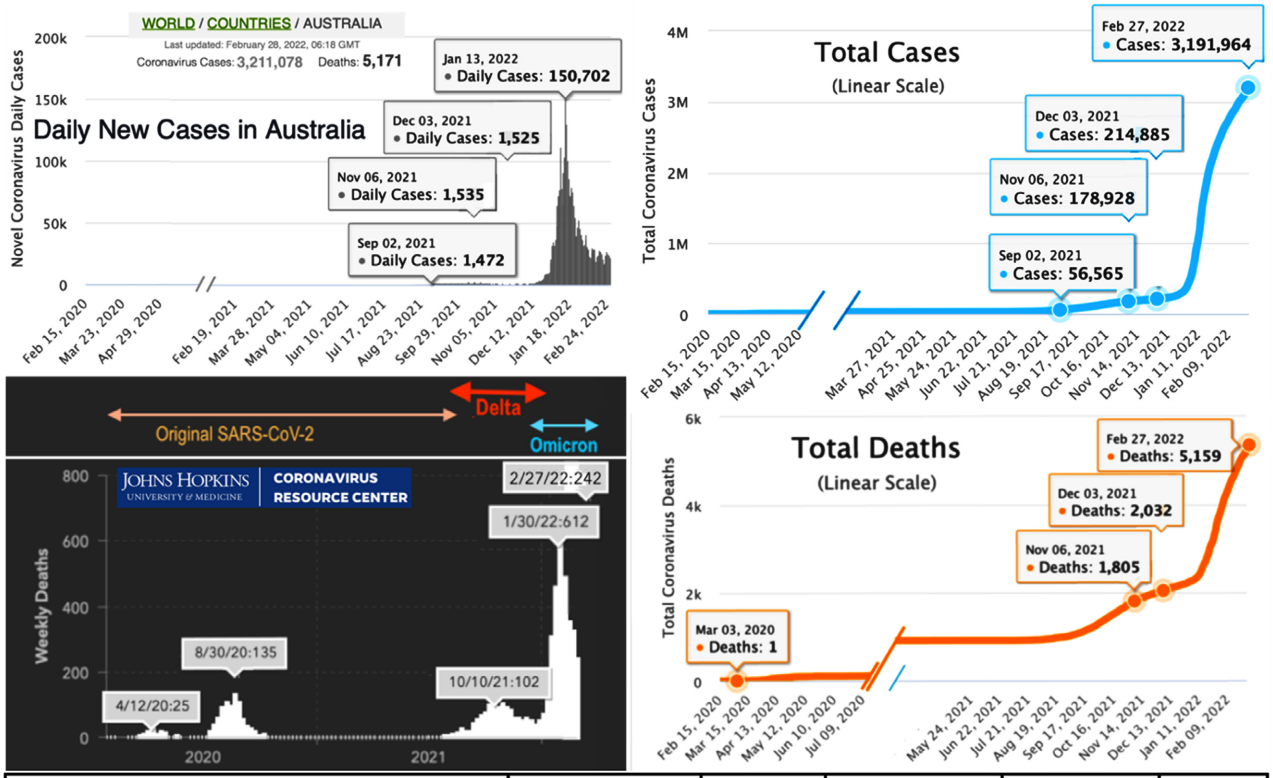
The IMR during the time period with mixed Delta and Omicron variants in

circulation therefore also significantly reduced, *i.e.*, 1/10 (or 10% of the rate during Delta wave) in South Africa [75] [76] [77]. With the emergence of omicron variant, the overall IMR of the whole world was reduced (**Figure 3**). In the US, the first Omicron infection was reported on December 1, 2021, and it spread quickly. Lambrou *et al.* graphed the SARS-CoV-2 variants' share of US COVID-19 cases between 2/2/2021-1/22/2022 and it showed Delta variant was the main infection between 5/15/2021-12/15/2021 and Omicron variant took over since mid-December 2021 [78]. Based on the data from the Worldometer updated on 2/26/2022, Delta variant infected about 17.6 million American (PIR~5.35%) with IMR of about 1.27% and Omicron variant infected about 290 million Americans (PIR~8.83%) with IMR dropped to about 0.49% [79] (**Figure 4**). From the beginning of the pandemic to 2/23/2022, the US had a total of about 973,000 deaths or population mortality rate (PMR) of 0.26%. Australia, on the other hand, with much more strict restrictions in traveling and handling COVID-19 and has no land border with other countries, has a very low total of about 4988 deaths or PMR of 0.019% from the beginning of the pandemic to 2/23/2022. The country kept its border tightly locked until the Omicron variant arrived. By 12/03/2021, there were only 2032 deaths (PMR~0.00063%) among 214,885 infections (PIR~1.73%), or IMR of 0.94%. Since then, the Omicron arrived and infected about 2,977,079 Australians (PIR~10.27%), with IMR dropping to 0.11% (**Figure 5**).



Estimate COVID-19 data in USA	Total case	PIR	Total death	PMR	IMR
Original SARS-CoV-2 and other variants Except Delta and Omicron variants	33,888,022	10.3%	606,420	0.18%	1.79%
SARS-CoV-2 Delta variant	51,501,455 - 33,888,022 = 17,613,433	5.35%	829,251 - 606,420 = 222,831	0.068%	1.27%
SARS-CoV-2 Omicron variant	80,560,293 - 51,501,455 = 29,058,838	8.83%	972,930 - 829,251 = 143,679	0.043%	0.49%

Figure 4. Overview of COVID-19 pandemic in the US with three major variants of SARS-COV-2, 1) The SARS-COV-2 and variants other than Delta and Omicron (Data before 5/15/2021), 2) Delta variant (Data from 5/15/2021- 12/15/2021), and 3) Omicron variants of SARS-CoV-2 (12/15/2021-after). Data were downloaded from the Worldometer [82]. Data presented as total cases, population infection rate (PIR), population mortality rate (PMR), and infection mortality rate (IMR). The graph for SARS-CoV-2 variants' estimated share of US COVID-19 cases is adopted from Lambrou *et al.*



Estimate COVID-19 data in Australia	Total case	PIR	Total death	PMR	IMR
Original SARS-CoV-2 and other variants Except Delta and Omicron variants	178,928	0.62%	1,850	0.0064%	1.03%
SARS-CoV-2 Delta variant	214,885 – 178,928 = 35,957	1.73%	2,032 – 1,850 = 182	0.00063%	0.51%
SARS-CoV-2 Omicron variant	3,191,964 – 214,885 = 2,977,079	10.27%	5,159 – 2,032 = 3,127	0.011%	0.11%

Figure 5. Overview of COVID-19 pandemic in Australia with three major variants of SARS-COV-2, 1) The SARS-COV-2 and variants other than Delta and Omicron (Data before 11/6/2021, first Delta case was reported on 10/29/2021), 2) Delta variant (Data from 11/6/2021-12/3/2021), and 3) Omicron variants of SARS-CoV-2 (12/3/2021-after, first Omicron case was reported on 11/27/2021). The graphs of weekly deaths in cases (White) were downloaded from Johns Hopkins University, Coronavirus Resource Center [49]. Other data were downloaded from the Worldometer [82]. Data presented as total cases, population infection rate (PIR), population mortality rate (PMR), and infection mortality rate (IMR).

India as a country has the hardest hit by Delta variant and has distinct periods of Delta and Omicron waves, as there was a gap between Delta wave bottom by early November 2021 and Omicron wave start by late December 2021. Delta variant infected about 23.8 million Indians (PIR~1.73%) with IMR of about 1.34% and Omicron variant infected about 8.18 million Indians (PIR~0.95%) with IMR dropped to about 0.46% (Figure 2). The Omicron arrived in Vietnam on 1/20/2022 when its second Delta wave dropped near the bottom. Omicron variant quickly spread and by 3/1/2022, it reached its peak at about 194,900 cases/day on 3/9/2022. So far by 4/8/2022, Omicron variant infected 7,803,239 Vietnamese with IMR dropped to 0.060% compared to 1.20% during its second Delta wave or 0.43% before Delta, clearly confirming attenuation of Omicron variants compared to the original SARS-CoV-2 (Figure 1). Note that the vaccination factor is

not in consideration for IMR because breakthrough infections only occurred in only less than 3% of vaccinated people [80] [81] [82].

Generally speaking, Omicron is the dominating SARS-CoV-2 strain causing infection in the world until July 2022. The data from Johns Hopkins University-COVID resource center, in the last 28 days of June 2022 there were over 17,000,000 COVID-19 infections with 40,700 deaths worldwide (IMR~ 0.24%). The IMR continue to drop from 0.27% in the last 28 days of January 2022, over 87,022,000 COVID-19 infections with 232,000 deaths worldwide, and a significant reduced number of infections pointing to the end of the pandemic.

Omicron itself has a total of 51 mutations across the entire genome including 37 mutations on its spike protein compared to the original SARS-CoV-2. Delta and Omicron variants have evolutionary diverged into distinct phylogroups and do not seem to share a common ancestry. Omicron shares common ancestry with variant of interest Lambda and its evolution is mainly derived from the non-synonymous mutations. Not evolving from Delta variant and with its sequence resembling that of SARS-CoV-2 during the early months of the pandemic, Omicron variant probably has been in circulation for some time. This supports a "long-term infection hypothesis" of Omicron SARS-CoV-2 origin. [83] [84].

The selective surviving Omicron variant of SARS-CoV-2 could evade the host immune system by having changes in the epitopes recognized by antibodies formed from the previous infection or by vaccination [85] [86] [87] [88] [89]. It was first thought that Omicron's ability to replicate faster; therefore increasing the viral loads as measured by PCR was responsible for the highly infectious and spreading ability. However, there was no significant difference in the infectious viral titer in Omicron compared to other variants, suggesting a different mechanism was involved [90]. The variant indeed has an increasing infectious ability and a lower ability to cause disease through its enhanced ability to interact with its S-protein to host ACE-2 receptor of host cells [91] [92], and the variant preferentially bond to epithelial cells of the upper respiratory tract instead of those alveola epithelial cells of the lower respiratory tract, and thereby resulting in decreased syncytia formation and less life-threatening. Omicron outcompeted Delta variant in nasal epithelial cells [93] [94] [95].

In harmony with evolutionary expectation, Omicron attenuated replication in alveola epithelial cells, in addition to attenuated pathogenicity. Shuai *et al.* showed that replication of the Omicron variant is dramatically attenuated in Calu3 lung cancer cells line, which are most closely related to alveola type II cells. They also showed that Omicron replication is markedly attenuated in both the upper and lower respiratory tract of infected K18-hACE2 transgenic mice expressing human ACE2 in comparison to that of the original SARS-CoV-2 and Delta variant, resulting in its dramatically ameliorated lung pathology that shown by histopathology of lung tissue. Omicron variant causes the least body weight loss and mortality rate when compared with original SARS-CoV-2 and other variants [96]. Similarly, independent studies by other investigators also

showed attenuated pathogenicity of Omicron variant using hamster animal model [97] [98] [99] [100]. Although Delta and the first Omicron variant have so far been identified as the major variants of COVID-19, other lesser virulent Omicron variants may surface in the future and become the dominant variant.

While less virulent, Omicron still cause many devastating symptoms to some patients. Some infected patients still end up in ICU, although mechanical ventilation is rarely needed [101]. The emergence of Omicron and its attenuated pathogenicity promotes a formation of herd immunity evidenced by the fact that Omicron infection enhances neutralizing immunity against the original SARS-CoV-2, Delta and other variants [102]. Together, the emergence of the less virulent and rapidly spreading Omicron variants, the availability of multiple vaccines, and the "to live with virus" policy enacted in many countries will hopefully establish herd immunity leading to an end of the pandemic.

4. The Immune Defense and the Multiorgan Autoimmune Reactions

When humans are infected with microorganisms, the human immune defense mechanism will initiate defense against the invading pathogens. Sometimes, these naturally defensive mechanisms will unfortunately result in autoimmune reactions against the infected hosts. Such is in the case of COVID-19 infection, which in some patients manifests with multiorgan autoimmune reactions. In the worst-case scenario, these severe autoimmune reactions against the human hosts, rather than the infection itself, became the leading cause of disease fatality.

4.1. Defining Autoimmune Reaction

The simplest definition of autoimmune disease is a dysfunctional immunological condition in which the patients' immune system mistakenly attacks their own bodies. Finding pathogenic autoantibodies to specific autoantigens is the hallmark of autoimmune diseases. Using *in vitro* assay such as cell culture and organ culture, or *in vivo* animal models to test the pathogenicity of autoantibodies provides more solid and functional evidence of autoimmune diseases [103]-[110]. In many life-threatening autoimmune diseases such as pemphigus vulgaris and paraneoplastic autoimmune multiorgan syndrome (PAMS) that we first described in 2001 [110], autoantibodies to many different antigens may act in constellation with or without the involvement of cell mediated immunity to cause these diseases, as we postulated in our "Multiple Hit theory" for the pathogenesis of pemphigus [106].

The presence of proven pathogenic autoantibodies to specific autoantigens, however, may not be found in some autoimmune diseases. For example, the specific autoantigens that form immune complexes as the granular deposition in dermal papillae in dermatitis herpetiformis (DH), a chronic, intensively itching and blistering skin disease related to gluten-sensitive enteropathy celiac disease, is not known [111] [112]. Similarly, membranous deposition of IgG immune

complex in the kidney glomerulus in systemic lupus erythematosus (SLE), observed by direct immunofluorescence of skin or kidney biopsy sections, is still unknown [113]. However, circulatory autoantibodies to many self-tissues and antigens are recognized by enzyme-linked immunosorbent assay (ELISA) or by indirect immunofluorescence [114] [115] [116]. Antinuclear, Anti-double stranded DNA, and anti-Smith (Sm) autoantibodies, etc., are commonly found in SLE with infiltration of monocytes. Anti-endomysium and anti-transglutaminase are commonly found with neutrophils infiltration in DH.

4.2. An Example of Factors That Can Trigger Autoimmune Diseases: Neoplasm

There are numbers of factors that can trigger autoimmune diseases. Neoplasm can trigger formation of autoantibodies to target many different autoantigens (self-antigens). For example, in PAMS, patients who have neoplasm-triggered autoimmunity develop autoantibodies to a whole host of keratinocyte proteins with different molecular weights, 250, 230, 210, 190, 170, 150, 130, 105, 95, 82, 75, 53, 47, 42 and 40 kDa. Some of these autoantigens are identified as envoplakin (210 kDa), periplakin (190 kDa), desmoplakin (250 kDa), Bullous Pemphigoid Antigen (dystonin, 230 kDa), desmoglein 4 (130 kDa), desmoglein 3 (130 kDa), and desmoglein 1 (150 kDa), and the 105 kDa tumor associate autoantigen. The identification of other smaller proteins targeted by PAMPS may be important signaling proteins that are yet to be determined [110]. Patients with small subsets of autoantibodies may cause a humoral effect with specific skin lesions, *i.e.*, pemphigus-like lesion in paraneoplastic pemphigus [117], pemphigoid-like lesion in paraneoplastic bullous pemphigoid [118], or overlapping subepidermal and intraepidermal vesicles in paraneoplastic lichen ruber pemphigoides [119], etc. Patients may also have full spectrum of autoantibodies that trigger both humoral and cellular responses. Autoantibodies can deposit in many organs such as skin and the epithelium lining of upper digestive and respiratory tract mucosae, kidney, urinary bladder, and smooth as well as striated muscle. In addition to autoantibodies, autoreactive cellular cytotoxicity mediated by skin and lung infiltration of CD8+ cytotoxic T lymphocytes, CD56+ natural killer cells, and CD68+ monocytes/macrophages are known in PAMS. Destructive cellular immune processes involve multiple organs, with the most devastating pulmonary involvement that leads to severe respiratory distress and death, occurring in nearly all patients with PAMS [110]. As we will discuss below, this autoantibody/inflammatory cell-mediated destructive pulmonary process documented in PAMS also occurred in severe COVID-19.

4.3. Infection as a Trigger for Autoimmune Reactions

Viral infections are another major factor that can trigger the development of autoimmune diseases. For example, Epstein-Barr virus (EBV), Cytomegalovirus, Rotavirus, Enterovirus, Coxsackievirus, and Parvovirus B19, etc., have been postulated to trigger autoimmunity in genetically predisposed individuals [120]. There

is an increased risk of celiac disease autoimmunity after a gastrointestinal Rotavirus infection in early life [121]. Under some circumstances, infections of Rotavirus, Cytomegalovirus, and Coxsackievirus can lead to autoimmune type 1 diabetes [122] [123] [124] [125]. EBV, also known as human herpesvirus 4 (HHV-4), a highly B cell-tropic virus and one of the most common DNA viruses found in humans, has been shown to associate with many autoimmune diseases including systemic lupus erythematosus (SLE), and autoimmune multiple sclerosis (MS) [126] [127] [128] [129]. MS is a chronic autoimmune-mediated disease with a complex etiology, involving a dysregulated immune system with intermittent peripheral inflammation as well as ongoing central nervous system compartmentalized inflammation, leading to loss of neural tissue and disability. SLE is a prototypic autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations. The primary pathological findings in patients with SLE are those of inflammation, vasculitis, vasculopathy, and immune complex deposition to many organs including skin and kidney. As we will discuss below, COVID-19 is similarly associated with vascular and kidney immune deposition and inflammation.

Antibodies against EBV nuclear antigen-1 cross-react with the SLE associated antigens Sm, Ro, and EBV-EA/D antigens (molecular mimicry) [127] [128] [129]. Elevation of IgA autoantibody against Epstein-Barr virus early antigen diffuse (EBV-EA/D) was found in SLE patients [127]. Using protein microarray assays, several autoantibodies including those against nucleus (ANA), cytokine (ACA), chemokines, and growth factors, etc., have been described in SLE, pulmonary alveolar proteinosis, chronic mycobacterial infection, autoimmune polyendocrine syndrome type 1 (APS-1), and other immune disorders [130]. Viruses that trigger autoimmunity exhibit several characteristic features including a tendency to cause ubiquitous and/or persistent infection, as well as an ability to tip the host immune response toward loss of tolerance via production of autoreactive lymphocytes. Viruses may contribute to autoimmunity-prone immune responses in various ways. Examples include molecular and functional mimicry, superantigen activity, and stimulation of inflammatory signaling, including production of type I IFNs. Another example of molecular mimicry is myositis-specific autoantibodies in autoimmune inflammatory myopathies including dermatomyositis, polymyositis, and immune-mediated necrotizing myopathies, that manifest with muscle, skin or lung damage [131]. As we will discuss below, COVID-19 infection is similarly associated with autoantibodies to cytokines and other soluble proteins.

Similarly, bacterial and parasitic infections can trigger autoimmune diseases as seen in reactive arthritis (ReA), rheumatic fever (RF) and Lyme disease (LD) [132] [133] [134]. For example, there were cases of LD patients who developed SLE a couple of months after they were treated for the bacteria *Borrelia Burgdorferi* infection. These patients presented with episodes of fever, butterfly-like bilateral erythema on the cheek, diffuse alopecia, pain, and morning stiffness in

the metacarpophalangeal, interphalangeal and wrist joints, weight loss, pronounced chilliness of the fingers. Direct immunofluorescence shows deposition of a large globular immune complex along the basement membrane. Microscopic skin lesions were shown without pronounced lymphocytic infiltrates. Indirect immunoassays showed antinuclear antibodies (ANA), anti-nRNP, compliment C3 and C4, and lupus anticoagulant [134].

5. The Immune Defense and the Multiorgan Autoimmune Reactions in COVID-19

5.1. Patients with COVID-19 with History of Autoimmune Diseases Had More Severe COVID-19 with More Complications and Higher Mortality

Tan *et al.* conducted a multinational network cohort study by analyzing electronic health records data collected by Columbia University Irving Medical Center in the USA, Department of Veterans Affairs in the USA, and other international institutions on all patients with pre-existing autoimmune diseases, diagnosed and/or hospitalized for COVID-19 between January and June 2020, and compared with patients hospitalized with influenza in 2017-2018. The study outcomes were aimed at death and complications within 30 days of hospitalization. They found that patients with COVID-19 with a history of autoimmune diseases, different from flu patients with a history of autoimmune diseases, had more severe COVID-19, leading to more complications and higher mortality [135]. Similarly, in a community-based online survey collecting weekly data on 1518 COVID-19-positive participants, Dreyer *et al.* found that individuals with underlying autoimmune conditions appear to be particularly vulnerable to post-acute sequelae from COVID-19 [136]. Akiyama et al., in a systematic review and meta-analysis of 62 observational studies including a total of 319,025 patients with autoimmune diseases, found that the prevalence of COVID-19 was 0.011. The severity of COVID-19 in patients with existing autoimmune diseases was significantly higher than in control patients. In studies with 2766 patients with pre-existing autoimmune diseases infected with SARS-CoV-2. The rates of hospitalization and mortality were 0.35 and 0.066 respectively. In this group, previous use of glucocorticoids and combination (immunosuppressive) therapy is associated with higher COVID-19 adverse outcomes [137]. This observation does not contradict the fact that glucocorticoids such as methylprednisolone (MP) are the mainstay of treatment for COVID-19, as it will be discussed below. The use of glucocorticoids and a combination of drugs is common in severe autoimmune diseases. Thus, patients with more severe autoimmune diseases had a higher risk of COVID-19-related morbidity and mortality. Specifically, rather than exacerbating the existing autoimmune diseases, these COVID-19 patients developed a new kind of autoimmune disease that involved IgA and neutrophils typical of severe COVID-19. Consistent with this relationship, Chatterjee *et al.* found that demographically, countries with a higher incidence of autoimmune disorders correlated positively with COVID-19 mortality [138]. The prevalence

of autoimmune diseases is high in the US and northern European countries and the US had the highest prevalence of autoimmune diseases in 2019. This may partially explain the very high COVID-19 mortality rate in these countries.

5.2. SARS-CoV-2 Infection Caused New Onset Autoimmune Diseases

De novo autoimmune reactions in COVID-19 have been recognized since the early months of the pandemic. A search on PubMed on 2/8/2022 with two key words "COVID-19" and "autoimmune" provided 2430 publications within 2 years. The same search through Google Scholar resulted in a much larger number of publications. There were many cases of newly developed autoimmune diseases following SARS-CoV-2 infection such as antiphospholipid autoantibodies and thrombosis, Kawasaki-like disease, immune thrombocytopenic purpura, Guillian-Barrė syndrome, and Miller Fisher syndrome [139]. Guillain-Barré syndrome (GBS) is a group of autoimmune syndromes consisting of demyelinating and acute axonal degenerating forms of the disease. Patients exhibit progressive paralysis that reaches a plateau phase. In most patients, resolutions were complete or near complete when patients recovered from COVID-19 [139] [140]. The earliest cases were 5 patients of Guillain–Barr syndrome associated with SARS-CoV-2 infection, out of 1000 - 1200 COVID-19 patients admitted to three hospitals in northern Italy from February 28 through March 21, 2020, reported by Toscano *et al*. The new onset Guillain–Barr syndrome in these patients was abated with intravenous IgG immunoglobulin (IVIG) treatment [141].

Kawasaki disease (KD) is a very rare acute febrile childhood inflammatory disease, associated with coronary artery abnormalities. Recent studies on KD revealed endothelial damage and resultant thrombin generation, as well as B-cell activation during the acute phase. It affects medium-sized vessels and is characterized by hypercytokinemia. The disease is believed to result from an aberrant inflammatory response to an infectious trigger in genetically predisposed individuals. It was also thought that endothelial cell injury in KD was a consequence of T cell activation and cytotoxic effects of various proinflammatory cytokines. Several anti-endothelial cell autoantibodies have also been identified in KD patients that raised the concept of immunothrombosis as a potential pathogenic mechanism for KD. Intravenous immunoglobulin (IVIG) infusion and aspirin are the standard treatment of acute KD [142] [143] [144].

In Italy, between February 18, 2020, when the pandemic began to hit the country, through April 20, 2020, Verdoni *et al*. reported an outbreak of 10 patients with KD with SARS-CoV-2 infection. The incidence of the disease increased by 30-fold during that period of time, compared to pre-pandemic time with only 19 KD cases diagnosed between Jan 1, 2015, and Feb 17, 2020. Children diagnosed with KD after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of macrophage activation syndrome. All patients were administered IVIG at 2 g/kg. Patients were also treated with aspirin at 50 - 80

mg/kg per day for 5 days or aspirin at 30 mg/kg per day plus MP at 2 mg/kg per day for 5 days, followed by a tapering of MP over 2 weeks [145]. Outbreaks of Kawasaki disease were also reported in other countries. For example, Toubiana *et al.* reported 21 cases were admitted with features of Kawasaki disease over a 15 days period between April 27 to May 11, 2020 in general pediatric department of Necker Hospital for Sick Children in Paris. Of these 21 patients, 12 presented with Kawasaki disease shock syndrome and 16 had myocarditis, 17 required intensive care support, 19 had evidence of recent SARS-CoV-2 infection. All 21 patients received IVIG and 10 also received corticosteroids. The clinical outcome was favorable in all patients [146].

Because in many cases, the disease appears in a wider spectrum that involves inflammation of multiple organs besides the heart, the term Multisystem Inflammatory Syndrome in Children (MIS-C) has been described by many groups and standardized by the US Center of Disease Control (CDC) [147]. An International Survey was conducted by Bautista-Rodriguez *et al.* through retrospective data review of a case series of children who met the published definition for MIS-C and were discharged or died between March 1, 2020, and June 15, 2020. Through data collected from 33 participating European, Asian, and American hospitals that included 183 patients with MIS-C who had SARS-CoV-2 infection, they showed that these patients presented with fever, 117 patients (63.9%) had gastrointestinal symptoms, and 79 patients (43.2%) had shock, but only 27 patients (14.7%) fulfilled criteria for Kawasaki disease, suggesting the development of new onset of other new autoimmune reaction in most infected patients [148].

The development of new onset of autoimmune reaction increased several folds in the areas of active COVID-19 pandemic. Belhadjer and Bonnet described 35 children ages 2 - 16 years admitted to 12 hospitals for MIS-C with acute heart failure, located within the most active COVID-19 pandemic areas in France and 1 hospital in Switzerland from March 22, 2020 to April 30, 2020. The inclusion criteria were the presence of fever, cardiogenic shock, or acute left ventricular dysfunction with inflammatory state (C-reactive protein > 100 mg/mL). Gastrointestinal symptoms were prominent. Left ventricular ejection fraction was <30% in one-third of patients, and 80% of patients required inotropic support with 28% treated with extracorporeal membrane oxygenation. Inflammation markers were suggestive of cytokine storm. All patients received intravenous immunoglobulin, with adjunctive steroid therapy used in one-third. Left ventricular functions were restored in 25 of 35 of those discharged from the intensive care units with no mortality [149]. Similarly, Whittaker *et al.* described a case series of 58 children from 8 hospitals in England admitted between March 23 and May 16, 2020 [150]. Tolumay *et al.* reported 52 children with MIS-C admitted to the University of Health Sciences Adana City in Turkey from September 2020 to April 2021 [151]. Dufort *et al.* described 95 patients with confirmed and 4 with suspected MIS-C in New York up to May 10, 2020 [152]. Feldstein *et al.* reported case series of 186 patients with MIS-C in 26 states in the US between March 23 and May 16, 2020 [147].

COVID-19-associated MIS-C can be successfully treated in a similar way to the treatment of autoimmune diseases, *i.e.*, with glucocorticoids and/or IVIG. McArdle *et al.* performed an international observational cohort study of clinical and outcome data regarding suspected MIS-C that had been uploaded by physicians onto a Web-based database and found no difference in recovery in general from MIS-C after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone suggesting that glucocorticoids alone could be adequate for treatment of MIS-C [153]. Because IVIG is also a treatment of autoimmune disease in which passive transfer of IgG from healthy donors can suppress the production of autoantibodies in patients with severe autoimmune diseases of skin characterized with pathogenic IgG autoantibodies [154], successful treatment of COVID-19 associated MIS-C by IVIG supported a notion of autoimmune reaction in MIS-C. In concert, Consiglio *et al.* applied systems-level analyses of blood immune cells, cytokines, and autoantibodies in healthy children, children with Kawasaki disease enrolled prior to COVID-19, children infected with SARS-CoV-2, and children presenting with MIS-C and found that the inflammatory response in MIS-C shares several features with Kawasaki disease, but differs from the cytokine storm of severe acute COVID-19 with respect to T cell subsets, interleukin (IL)-17A, and biomarkers associated with arterial damage suggesting that autoimmune reaction in COVID-19 associated MIS-C is distinct from that of severe COVID-19. Autoantibody profiling suggests multiple autoantibodies that could be involved in the pathogenesis of MIS-C [155].

5.3. COVID-19-Mediated Autoimmune Reactions against Tissue Antigens

The earliest report of new onset autoantibodies detected in hospitalized COVID-19 patients by Zhou *et al.* in 4/2020 showed autoantibodies to 52 kDa SSA/Ro autoantigens, 60 kDa SSA/Ro autoantigens, and ANA in 20%, 25%, and 50% of hospitalized patients, respectively [156]. Another study by Gagiannis *et al.* posted on medRxiv in May 2020 showed common autoantibodies including ANA, anti-SS-B/La, anti-Scl-70, anti-CENP-B, anti-PM-Scl present in about 92% patients in ICU and about 36% of patients with milder clinical courses. These authors also showed that patients in ICU who had autoantibodies tend to have more severe diseases and the worst prognosis. In their settings, the mortality rate was about 18% of hospitalized patients [157]. In a different cohort however, Lerma *et al.* tested for the presence of autoantibodies against nuclear, vasculitis-associated, and phospholipid antigens and found the autoantibodies present in about 30% of the patients and ANA was only weakly reactive, the prevalence of antiphospholipid antibodies was low, and vasculitis-associated autoantibodies were not detected [158]. Although the autoantibodies against nucleus antigens tested in these studies were commonly found in patients with some autoimmune diseases and occasionally in healthy people, none of them has been proven to be pathogenic by passive transfer in animal models. Elevation of the level of these common autoimmune autoantibodies in patients, however, suggests certain on-

going dysfunctional immune activities.

5.4. COVID-19-Mediated Autoimmune Reactions against Functional Proteins of Immune System

To screen for autoantibodies against a wider spectrum of proteins, Wang *et al*. used rapid extracellular antigen profiling to screen a cohort of 194 individuals infected with SARS-CoV-2 for autoantibodies against 2770 extracellular and secreted proteins and found that patients with COVID-19 exhibit marked increases in autoantibody reactivities as compared to uninfected individuals and show a high prevalence of autoantibodies against immunomodulatory proteins including cytokines, chemokines, complement components and cell-surface proteins [159]. These authors also showed that these autoantibodies disturb immune function and impair virological control by inhibiting immunoreceptor signaling and by altering peripheral immune cell composition. They further used transgenic mice expressing human ACE2 to test for the effect of these autoantibodies. Mice pretreated with autoantibodies targeting type I IFNs presented in patients with severe COVID-19 were more susceptible to SARS-CoV-2 infection. These autoantibodies block of type I IFN signaling by impairing monocyte recruitment, maturation and proinflammatory macrophage differentiation in the lungs, and decreasing the relative frequency and an absolute number of activated (CD44+CD69+) natural killer cells and CD4+, CD8+ and $\gamma\delta$ T cells. Overall, these autoantibodies increased weight loss and reduced survival in mouse model infected with SARS-CoV-2. The finding by Wang *et al*. may explain the role of autoantibodies targeting IFNs, which were found in about 10% of patients with severe COVID-19 that was reported by others [160] [161] [162]. These authors also found that these experimental mice infected with SARS-CoV-2 immediately after passive transfer of anti-IL-18, anti-IL-1β, anti-IL-21R or anti-GM-CSF autoantibodies resulted in a significantly higher viral burden, a decreased frequency and number of effector natural killer cells with enhanced cytotoxic properties, more weight loss, and significantly decreased survival rate.

5.5. Documenting COVID-19 as a Trigger for Autoimmune Reactions in COVID-19 and Post-COVID Conditions

Patients with COVID-19 with no history of autoimmune diseases developed a new onset of autoantibodies, mostly of autoimmune rheumatologic autoimmune diseases that may be accountable for the rheumatologic symptoms during infection and common symptoms of "long haulers" or "long COVID-19" or "post-COVID-19 syndrome (PCS)" that persist for four weeks to six months, are present in about 10% people who have COVID-19 [163] [164] [165] [166]. Among many symptoms of multiorgan disorders, the most common lingering symptoms are fatigue, muscle pain, joint pain, and fever. These symptoms are usually self-resolved with supportive care. Acosta-Ampudia *et al*. have shown that the clinical manifestations of PCS are associated with the persistence of upregulated IFN-α, TNF-α, G-CSF, IL-17A, IL-6, IL-1β, and IL-13, whereas IP-10 was decreased. In

addition, PCS was characterized by increased levels of Th9, CD8+ effector T cells, naive B cells, and CD4+ effector memory T cells. Total levels of IgG S1-SARS-CoV-2 antibodies remained elevated over time. This long-term persistent immune activation may contribute to the development of the autoimmune PCS [167]. New onset autoimmunity in COVID-19 is not limited to common rheumatic diseases but also rare diseases such as new onset of anti-acetylcholine receptor and anti-MuSK in a few cases of myasthenia gravis after SARS-CoV-2 infection [168] [169]. We previously found that autoantibodies against a member of annexin family, annexin 31 or pemphaxin, a cholinergic receptor and alpha 9 acetylcholine receptor can be pathogenic in autoimmune skin disease [106] [107]. Here in COVID-19, Zuniga *et al*. found that anti-annexin A2 autoantibody in hospitalized COVID-19 patients and its level at admission strongly predicted mortality [170].

Chang *et al*. use bead-based antigen arrays with antigens selected based on literature searches that have implicated specific autoantigens in COVID-19 on serum from in serum from 147 hospitalized COVID-19 patients. They found that autoantibodies were identified in approximately 50% of patients compared to less than 15% of healthy controls. When present, autoantibodies largely target autoantigens associated with rare disorders such as myositis, systemic sclerosis and overlap syndromes. They detected the presence of autoantibodies at time day 0 and time day 7 and found a subset of autoantibodies targeting traditional autoantigens or cytokines developed *de novo* following SARS-CoV-2 infection suggesting that SARS-CoV-2 causes development of new-onset IgG autoantibodies that were positively correlated with immune responses to SARSCoV-2 proteins. RNA or DNA released from dying cells could also form immune complexes with viral or self-antigens that can promote autoantibody production [171]. A thorough review of new-onset rheumatic autoimmune diseases during or after SARS-CoV-2 infection is detailed elsewhere [139].

Autoantibodies may functionally inhibit or activate the functions of target antigens or simply form immune complexes, which could circulate and deposit to target organs to prime cellular immune response and take part in the pathogenesis of multiorgan syndrome in COVID-19. For example, most individuals with severe COVID-19 showed signs of myositis, and pathology study of muscle of COVID-19 autopsies show that about 17% of the cases showed a higher overall pathology score and higher inflammation score. Relevant expression of MHC class I antigens on the sarcolemma was present 55% of the cases and upregulation of MHC class II antigens in 17% of the case, compared to zero of the control samples. In some muscle specimens, SARS-CoV-2 RNA was detected by PCR, but no evidence for a direct viral infection of myofibers was found by immunohistochemistry and electron microscopy, suggesting that SARS-CoV-2-associated postinfectious, immune-mediated myopathy that maybe autoimmune in nature [172]. The presence of autoantibodies associated with the new onset of rheumatic autoimmune diseases such as myositis and systemic sclerosis may in part explain those long-term symptoms such as muscle weakness, muscle pain, joint

pains, etc. of COVID-19 patients persisting weeks to months after the initial onset of symptoms and extending beyond the original organ involvement, known as post-acute sequelae of COVID-19 (PASC) (long COVID). Autoimmunity induced by SARS-CoV-2 infection may indeed contribute to the multiorgan post-COVID-19 symptoms [173] [174] [175].

6. Severe COVID-19 Is IgA-Mediated and Neutrophil-Directed Disease

6.1. Severe COVID-19 Cases Are Characterized by Dysfunctional Immune Defense and Persisted Viral Load

Because over 80% of SARS-CoV-2 infected, people are either asymptomatic or only have mild symptoms since the outbreak in Wuhan; the virus spread quickly unnoticeable in this major crowded metropolitan city that has a population of more than 11 million people and connection to many major cities in the world, making it the second largest pandemic, one century from the flu pandemic between 1918-1920. The major virus spreaders are people aged from 20 - 45 [176] [177]. Unlike the first three SARS coronavirus that causes severe diseases in humans with very high IMR, SARS-COV-2 killed less than 2% of infected people. Only less than 20% of infected patients had severe symptoms, about 15% were hospitalized and about 5% ended up in intensive care units (ICU), in which about 30% died [49] [178] [179] [180] [181]. Nevertheless, COVID-19-related death is the leading cause of death in the United States in 2020 [182].

Unlike the 80% of infected people having no or mild symptoms that recovered, in whom the virus would be cleared by the immune system in about 10 days, in infected patients with the dysfunction immune response to the viruses, viruses in the respiratory tract continue to be viable and infectious up to 32 days. Folgueira *et al.* used cell culture experiments documenting viable SARS-CoV-2 in respiratory samples of severe COVID-19 patients [183].

In hospitalized patients, initial plasma SARS-CoV-2 RNA level is associated with increased disease severity and mortality [184] [185] [186]. Fajnzylber *et al.* measured the SARS-CoV-2 RNA level of samples from 88 hospitalized participants, 94 symptomatic individuals who were evaluated in a respiratory infection clinic, and 53 participants diagnosed with COVID-19 who had symptomatically recovered. They found that SARS-CoV-2 RNA level is associated with disease severity and laboratory abnormalities. The level of SARS-CoV-2 RNA detected in plasma, in general, is very small compared to those in respiratory tract, and generally associated with increased disease severity among hospitalized participants. Negative PCR testing for COVID-19 from upper respiratory samples was not uncommon in patients with severe COVID-19. Although their results also show a relatively high prevalence of plasma SARS-CoV-2 RNA in hospitalized individuals with severe disease, plasma SARS-CoV-2 RNA was also detected in symptomatic non-hospitalized participants. Higher levels of plasma SARS-CoV-2 RNA were also associated with markers of inflammation and disease severity,

including low lymphocyte counts, and elevated CRP and IL-6 levels [186]. The key to understand the relationship between plasma viremia and infection, however, lies in the infectious ability of these plasma viral RNAs as we will discuss below. This relationship, in turn, has major significance in our understanding of COVID-19-mediated autoimmunity.

6.2. SARS-CoV-2 RNAs in Patients' Plasma Represent Non-Viable and Non-Infectious Virus

Since severe pulmonary endotheliitis and multi-organ involvement correlated significantly with COVID-19-associated death [187] [188], one may speculate that the severity of the disease relates to the degree of plasma viremia from which the viruses may travel and infect other organs through circulation. Therefore, the critical question is whether inflammation of other organs is mediated by the circulating SARS-CoV-2 on the blood vessel with subsequent reach to these organs, since vascular endothelial cells also express ACE2 receptor. An alternative explanation is that multi-organ failure in severe COVID-19 resembles autoimmune disease such as PAMS. In this case, the organ-deposited antibody-antigen immune complexes were formed by COVID-induced autoantibodies and destructed lung tissue antigens and subsequently traveled via the circulation and deposited in other organs [110].

It is important to note, that the so called "plasma viremia" is measured by PCR for the level of SARS-CoV-2 RNA and not the actual virion or viable virion, and that the plasma viral RNA load in these patients is very small compared to the viral RNA load in their respiratory tract samples. SARS-CoV RNA has also been reported previously in SARS pandemic in 2003 and MERS pandemic in 2012. However there has not been any evidence that the virus RNAs detected in patients' plasma is infectious or disease-transmissible [189]. Study by Andersson *et al*. demonstrated that SARS-CoV-2 RNA detected in blood products from patients with COVID-19 is in fact non-infectious. These authors inoculated into cell culture the viral RNAs isolation from a subset of RNA-positive COVID-19 patient's sera samples. PCR-positive sera did not produce any cytopathic effect or yield an increase in detectable SARS-CoV-2 RNA [190].

Studies by many groups show no evidence that endothelial cells or muscle cells of organs infected with SARS-CoV-2 despite these cells express ACE-2. Study on postmortem biopsies of the COVID-19 autopsies by Diao *et al*. showed that SARS-CoV-2 infected kidney ACE2+ kidney tubules epithelium, but not glomerulus endothelium, suggesting SARS-CoV-2 RNA in plasma only represent viral RNA fragment, not viable virus that could have infected endothelial cells, while renal epithelial cell infection is most likely through urethral tract [191]. Thus, plasma SARS-CoV-2 RNA load ("viremia") does not represent viable virus or infectious capability. More likely, the plasma SARS-CoV-2 RNA represents the released product of protease-induced damage by over-reacting neutrophils that destroy infected lung epithelial cells and epithelial-endothelial barrier of the lower respiratory tract caused, as we will discuss below. Multi-organ involve-

ment that causes death in COVID-19 is, therefore, most likely caused by inflammation of multiple organs induced by the inflammatory products originating from the lung where dysfunctional reaction of cell-mediated immune system against SARS-CoV-2 invasion occurred. The multi-organ involvement that causes death in Covid-19 patients thus resembles the multi-organ involvement that causes death in autoimmune PAMS. This delineation would help medical community in formulating targeted treatments as we will discuss in the sessions below.

6.3. Paradoxical Lower Respiratory-Tract Viral Load in Severe COVID-19 Patients than in Mild COVID-19 Patients

The speed of viral replication in the respiratory tract epithelial cells determines the viral load. If the destruction of respiratory epithelial cell is directly caused by SARS-CoV-2 infection and replication in the cells, the respiratory tract viral load should be the indicator of severity leading to death of the disease. If this was the case, treatment by antiviral drugs that inhibit viral replication should be able to abate mortality. Paradoxically it is not the case of severe SARS-CoV-2 infection. In a study on the respiratory tract samples of 205 COVID-19 patients in New York, Argyropoulos *et al.* found that respiratory tract viral load was significantly lower in hospitalized patients than in patients not hospitalized [192]. Their results suggest that the mechanism for the destruction of respiratory epithelial cells in severe COVID-19 may relate to an abnormal immune response rather than the direct destruction caused by infected viruses. The unique potential lethal abnormal immune response occurs in severe cases that make up only a small portion of total people infected with SARS-CoV-2 [193]. This observation explains the limited efficacy of antiviral drugs in the effort to stop COVID-19 mortality in ICU.

6.4. The Pulmonary Pathophysiology in Severe COVID-19 Represents Neutrophil-Directed Destruction of Alveolar Tissue without Bacterial Infection

Acute respiratory distress syndrome (ARDS) is the most common cause of death in COVID-19 patients, but coagulation induced by excessive inflammation, thrombosis, and disseminated intravascular coagulation (DIC) also induces death by multiple-organ dysfunction syndrome. Postmortem autopsy pathology study by Elezkurtaj *et al.* on 26 SARS-CoV-2-associated deaths in early pandemic, between March and June 2020 showed septic shock (16/26) and multi-organ failure (4/26) were the most common immediate cause of death. However, their data showed none was described as fungal superinfection and only two cases (2/26) were specifically defined as bacterial super infection, which may actually be secondary infection. Respiratory failure due to diffuse alveolar damage presented as immediate cause of death in fewer cases. Several comorbidities, such as hypertension, ischemic heart disease, and obesity were present in vast majority of patients who died [194].

Witchmann *et al*. found deep venous thrombosis in 7 of 12 autopsies (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients [195]. Findings by Witchmann *et al*. raised a question of thromboembolism events in fact following the destruction of endothelial-epithelial barrier at the alveola. In another study on 6 SARS-CoV-2-associated deaths, Fox *et al*. found the presence of thrombosis and microangiopathy in the small vessels and capillaries of the lungs, with associated hemorrhage, significantly contributed to death. Features of diffuse alveolar damage, including hyaline membranes, were present, even in patients who had not been ventilated. Cardiac findings included individual cell necrosis without lymphocytic myocarditis. Also, there was no evidence of secondary pulmonary infection by microorganisms [196]. The findings by Fox *et al*. suggest that pulmonary superinfection is not the initial reason for neutrophils infiltration in alveola that is found by others. Haberecker *et al*. studied 15 SARS-CoV-2 positive autopsies with focus on vascular, thromboembolic, and ischemic changes in pulmonary and in extrapulmonary sites. They found that extensive pulmonary endotheliitis and multi-organ involvement are characteristic autopsy features in fatal COVID-19-associated deaths [197]. In a larger study on 735 SARS-CoV-2-associated deaths in Germany, Fitzek *et al*. found the majority died of pneumonia and/or diffuse alveolar damage (73.6%). Thromboses in lower extremities and pulmonary embolism were found in 39.2% and 22.1% patients, respectively in one study [198].

In a more detailed study, Borczuk *et al*. systematically evaluated lungs of 68 autopsies from 2 institutions in USA and 1 institution in Italy in March and April 2020, when the two countries were heavily hit by the pandemic. The most common symptoms at onset were shortness of breath (80%), fever (65%), and cough (47%). Premortem laboratory results showed elevated levels of D-dimer in 92% of patients with testing, mild thrombocytopenia in 31%, and lymphopenia in 79%. IL-6 level was increased 94%, and C-Reactive Protein was elevated in 98% of patients. The authors used pathology sections stained for light microscopy and prepared for electron microscopy. Immunohistochemistry was carried out to detect the platelet component of microthrombi and SARS-CoV-2. SARS-CoV-2 RNA was detected in trachea and lung by RNAscope technology. Virus was seen in airway epithelium and type 2 pneumocytes in alveola. Microscopic evaluation of different anatomic lung areas (airways, alveoli, and vascular bed) for patterns of injury showing frequent presence of airways inflammation and alveolar zones with hyaline membranes and type 2 pneumocyte (AT2 cell) hyperplasia. Pneumocytes frequently appeared atypical, enlarged, and sometimes multinucleated with syncytial features [199].

Histologically showed mucosal ulceration with mixed inflammatory cell infiltration including neutrophils and fibrin. Large airway inflammation was seen in 92% of patients who were never intubated, including acute inflammation in 45% and chronic inflammation in 47% of patients. The presence of an associated or superimposed bacterial or fungal pneumonia by antemortem or postmortem

culture with consistent histological examination, or by special stains for microorganisms was seen in only 26.5% of patients. While neutrophils may reflect superinfection and ventilator associated pneumonia, a subset of cases had rapid progression to severe respiratory failure without evidence of superinfection and without mechanical ventilation. In these cases, neutrophils were seen in association with capillary proliferation with alveolar wall injury, necrosis, and microthrombi, suggesting an endotheliitis was not directly mediated by infection per se [199]. The aseptic neutrophil infiltration and activation causing destruction of epithelia-endothelial barrier may represent a common early stage of alveolitis and endotheliitis in all cases, eventually obscured by diffuse acute lung injury. If this neutrophil-mediated endotheliitis is not directly driven by infection, we then need to provide a more valid explanation as we will discuss below.

6.5. Severe COVID-19 Is Mediated by Dysfunctional and Dysregulated Neutrophils

In a normal immune response to virus infection of the lung, the first line of defense system (innate immunity, cell mediated) attacks the viruses, *i.e.*, neutrophils destroy the virus intracellularly within phagolysosomes to digest phagocytized microorganisms, *i.e.*, complex of neutralized viruses by IgM, in combination with microbicidal peptides and the membrane-associated NADPH oxidase system, which produces reactive oxygen metabolites. Viruses that escape the first line of defense could infect the epithelial cells and replicate. Replication of virus in epithelial cell induces the cells to release cytokines and chemotaxis factor to recruit additional neutrophils from circulation. The increase of neutrophils normally parallels the increase of regulatory lymphocytes; therefore, the ratio is unchanged.

During this initial period, the adaptive immune system exposes to the pathogen and begins to learn the virus so that it quickly forms the low avidity anti SARS-CoV-2 IgM; then in about a week, patients begin to produce IgA, then IgG. The later response to the rapidly replicating virus could be mediated by neutrophils, which adhere to IgAs that bind to the virus expressed on the infected epithelial cell membrane. The neutrophils are recruited to the site of action by chemotactic factors, cytokines, released from epithelial cells or by other immune cells such as T helper cells, other mononucleated cells, and/or macrophages, etc. While other cytokines recruit neutrophils to the site of action, GCSF and GMCSF stimulate neutrophils to adhere to antibody that already bind to the viral antigen expressed on the surface of infected epithelial cells. Activated neutrophils then secrete proteases to destroy the infected cells containing newly replicated viruses, the reservoir of viral pathogen that otherwise could further infect other lung cells, by neutrophil extracellular traps (NET) mechanism. NET is made of a web-like structure of DNA meshwork of chromatin fibers decorated with granule-derived antimicrobial peptides and enzymes such as neutrophil elastase and neutrophil serine proteases secreted by activated neutrophils. The chromatin fibers bound to positively charged molecules, such as histones and

NSPs, and serve as physical barriers that trap and kill extracellular pathogens, thus preventing further spreading [200].

Also present in a normal response process, serine proteases neutrophil elastase, proteinase 3, and cathepsin G, three major components of neutrophil azurophilic granules participate in the nonoxidative pathway of intracellular and extracellular pathogen destruction. The key modulator of the acute phase immune response in humans to control the extracellular action of neutrophil is protein $\alpha - 1$ antitrypsin (AAT), a 52 kD glycoprotein that is synthesized primarily in the liver, would act as a serine protease inhibitor and a potent anti-inflammatory [200] [201] [202] [203] [204]. AAT also regulates neutrophil degranulation and autoimmunity [205] [206]. Thus, under the normal condition that happens to more than 80% of infected people, their immune response to SARS-CoV-2 can clear the viruses in about 10 days. Infected people are usually asymptomatic or only have mild symptoms.

In contrast, in severe COVID-19 cases, the neutrophils response to SARS-CoV-2 bizarrely abnormal. The finding of neutrophils infiltration and alveolar wall damage in COVID-19 autopsy pathology is parallel with the finding of dysfunctional and dysregulated neutrophils activity. Dysfunctional and dysregulated neutrophils in the pathophysiology of inflammation are well documented including the followings: coagulopathy, organ damage, and immunothrombosis that characterize severe cases of COVID-19 are marked by the high blood level of neutrophils/lymphocyte ratio and more prominent in ICU patients, high mortality [207] [208] [209] [210] [211], neutrophil over-activation, arginine depletion, tryptophan metabolites accumulation correlated with T cell dysfunction in critical patients [212], and imbalance between NET formation/ degradation marked by elevation of plasma free DNA level [213] [214]. In addition, McElvaney *et al.* measured the level of serum immunometabolic markers of neutrophils, PKM2, phosphorylated PKM2, and HIF-1a, and showed that neutrophils undergo metabolic reprogramming in severe COVID-19 patients and that the AAT level in severe COVID-19 patients remained unchanged despite the highly elevated level of cytokine IL-6 [215]. Thus, the overreacted neutrophils allow their overdriven NET mechanism unchecked, leading to massive destruction of infected epithelial cells as well as the epithelial-endothelial barrier. The result is the leaking of cell-free DNA into the circulation, which explains finding by Hammad *et al.* documenting circulating cell-free DNA associated with severity of COVID-19 [214].

While T lymphocytes and NK cells are the key cells causing epithelial damage in PAMS, neutrophils play the key role in causing damage to alveola in severe COVID-19. Chen et al., by measuring the level of inflammatory cells infiltrate in bronchoalveolar lavage fluid of hospitalized COVID-19 patients, found that significantly higher neutrophil, but lower macrophage in lung was observed along with markedly increased cytokines expression in severe COVID-19 patients, compared with healthy controls and patients with mild COVID-19. By contrast, neutrophil and macrophage returned to normal level whilst more T and NK cells

accumulation were observed in patients with mild COVID-19 [216]. The data from the study by Chen *et al.* also suggest that in COVID-19, the release of cytokines from epithelial cells rather than macrophages could be the key mechanism for the cytokine storm (down regulation of macrophages due to too high level of cytokines in severe cases, return to normal level in mild cases) and that neutrophils rather than T cells or NK cells play a critical role in causing alveolar epithelial cell and tissue damage.

6.6. Severe COVID-19 Associates with Dysfunctional and Dysregulated NET

Since the beginning of the pandemic, dysregulation of neutrophil and NET formation has been recognized as the key factor that causes the damage of alveola epithelial-endothelial barriers and disseminate thrombosis [217]-[222]. Elevated levels of serum NETs in many hospitalized patients with COVID-19 were assessed for cell-free DNA, myeloperoxidase-DNA (MPO-DNA) complexes, or citrullinated histone H3 (Cit-H3) [218] [223] [224]. Since the occurrence of ST-elevated myocardial infarction (STEMI) is a serious cardiac manifestation of COVID-19, Blasco *et al.* studied the coronary thrombus samples that were aspirated during the primary coronary intervention of 5 patients with STEMI and COVID-19 and found that NET was detected in the thrombi of all 5 patients. NET was found in thrombi of about 68% of STEMI in the pre-COVID-19 era, *i.e.*, in 2015 [224]. SARS-CoV-2 infection, as well as down regulation of ACE2 upon the cell entry of SARS-CoV-2 triggers neutrophil infiltration in the lungs. Veras *et al.* have further shown by *in vitro* experiments, that SARS-CoV-2 can directly infect and induce neutrophils to form NET and that neutrophils isolated from COVID-19 patients produced more NET than those isolated from healthy individuals [225].

Because NET dysregulation has been shown to associate with many diseases especially acute respiratory distress syndrome, NET has been proposed to be the primary driving force of COVID-19 and targeting NETs directly and/or indirectly with existing drugs may reduce the clinical severity of COVID-19 [226]. Before COVID-19, some NET inhibitors such as Sivelestat were approved to treat ARDS in Japan and South Korea, but they did not increase survival when used for ARDS [227]. Since April 2020, publication by Barnes *et al.* has proposed numbers of modalities for NET therapeutic for COVID-19 such as inhibitors of NETs synthesis or promoters of NETs fragmentation, targeting key enzymes in the formation of NETs such as neutrophil elastase (NE) (which degrades intracellular proteins and triggers nuclear disintegration), and peptidyl arginine deiminase type 4 (PAD4) (which citrullinates histones to facilitate the decondensation and release of the chromosomal DNA) [228]. A review of potential NET-targeted therapy can be found in Al-Kuraishy *et al.* [229]. Some NET inhibitors such as R406, a potent SYK inhibitor and the metabolically active component of fostamatinib, a drug for adults with immune thrombocytopenia, can inhibit NET formation *in vitro* by neutrophils isolated from healthy people in-

duced by plasma from COVID-19 patients [230]. However, until today there is no report of NET therapy that shows reduced COVID-19 mortality. Thus, there is still another key factor besides NET that is critical in causing death in the disease.

6.7. Severe COVID-19 Associates with Cytokine Storm

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if unchecked or inadequately treated. In cytokine storm, immune response to the injuries induced by pathogen, but not the pathogen itself, can contribute to multiorgan dysfunction [231]. Similar to SARS and MERS, and probably the 1918-1919 influenza pandemic, an exaggerated immune response cytokine storm was suspected of contributing to the lethality of COVID-19. The reason why only a small portion of SARS-CoV-2 infections developed Cytokine storm is still needs to be elucidated. But very likely cytokine storm links to the viscous cycle of SARS-CoV-2/Epithelial cells/IgA/Neutrophil epithelial-endothelial barrier destruction.

The earliest publication in January 2020 by Huang *et al.* reported the typical development of severe symptoms of COVID-19 patients in hospital in Wuhan. The most common symptoms at the onset of illness were fever, cough, and myalgia or fatigue. More than half of patients developed dyspnea. The median time from onset of symptoms to first hospital admission was 7 days, to shortness of breath was 8 days, to acute respiratory distress syndrome (ARDS) was 9 days, to mechanical ventilation was 10 days, and to ICU admission was 10.5 days. At the time of hospital admission, plasma IL1-β, IL1RA, IL6, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, TNFα, PDGF, TNFα, IL2, IFNγ and VEGF levels were higher in both ICU and non-ICU patients than in healthy adults. Moreover, plasma IL2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were higher in ICU patients than non-ICU patients [232]. Subsequently, the similar findings of cytokine storm with more cytokines in severe COVID-19 patients were reported by several other groups in other countries such as one by Notz *et al.* in Germany [233]. Analysis of cytokine storm in COVID-19 compared to SARS and MERS shows that immunological and pathologic features of COVID-19 have something in common with SARS and MERS. For example, all of these viruses can cause lymphopenia and influenza-like symptoms in the early stage. SARS and COVID-19 do not lead to the upregulation of TNF-a, but the increase of IL-6 and IL-10 is more prevalent in COVID-19. Thus, IL-6 may play a crucial role in the pathologic of COVID-19, including the chemotaxis of neutrophils and lymphocyte necrosis.

Due to the recognized important role of cytokine storm in the pathophysiology of the disease, number of treatment strategies have been brought out targeting its key mechanism [234] [235]. Similar to other coronavirus infections, SARS [236], MERS [237], and Mojiang SARS-CoV-like coronavirus [10], glucocorti-

coid therapy such as MP is used widely among critically ill patients infected with SARS-CoV-2. Besides immunosuppression effect, glucocorticoids strongly diminish the production of the "initial phase" cytokines IL-1 beta and TNF-alpha and the "immunomodulatory" cytokines IL-2, IL-3, IL-4, IL-5, IL-10, IL-12 and IFN-gamma, as well as of IL-6, IL-8 and the growth factor GM-CSF [238]. Glucocorticoids can act directly on the cell to change its gene expression, thus preventing unwanted effects [239].

There is the number of anti-cytokine drugs have been considered. The most effective anti-cytokine drugs used in COVID-19 is IL-6 antagonists such as tocilizumab and sarilumab that could lower 28-day all-cause mortality, as shown in the study by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group on 10,930 patients in 27 clinical trials [240]. However, with all available drugs that showed benefits for hospitalized COVID-19 patients, even used in combination, the overall mortality of severe COVID-19 patients is still very high. For example, the daily new SARS-CoV-2 infected cases in the US as of October 1, 2021, is 121,049 with 1821 deaths or about 1.5%, about the same compared to those of 2020 [49]. The unchanged mortality per infections ratio in the US may simply be due to the same treatments that have been used since the beginning of the pandemic. In 28 days prior to February 23, 2022, there were 286,464 COVID-19 deaths in the world, which included 67,410 in the US [49]. A surprise statistic was IMR of the whole world in this period was 0.41% but that of the US, which having the best medical care in the world, was 1.01% (**Figure 3**). Thus, there is still another key factor beside NET and cytokine storm that is critical in causing death in the disease.

6.8. Severe COVID-19 Is an IgA-Mediated Immune Reaction

Unlike SARS-CoV, MERS-CoV, influenza virus infection or in asymptomatic SARS-CoV-2 infection, in which IgA class antibodies do not appear significantly earlier or in higher quantity than IgG [241] [242] [243] [244], in symptomatic SARS-CoV-2 infection, the first seroconversion of IgA against the virus occurred in 1-2 days after onset of the initial symptoms (fever), much earlier than seroconversion of IgM and IgG that occurred in 5 days after onset. The relative levels of IgA and IgG were markedly higher in severe patients compared with non-severe patients [245] [246] [247] [248] [249].

Since the beginning of the pandemic, Padoan *et al.* in Italy studied the kinetics of IgA and IgM of 19 hospitalized patients monitored from the onset of symptoms (fever). The serum sample was taken every 2 days in 42 days. They found that the average levels of IgM and IgA antibodies increased since 6 - 8 days from the onset of COVID-19. Compared to IgM, IgA showed persistently higher levels for the whole observation period, with a peak level at 20 - 22 days. IgM levels peaked at 10 - 12 days and significantly declined after 18 days [245]. This IgA kinetic is unique to COVID-19 compared to that in SARS study by Woo *et al.* [241] and Hsueh *et al.* [242] in China in 2004.

In another study, Yu *et al.* in China compared the kinetics of IgA, IgM and

IgG between severe and non-severe COVID-19 patients and found that the first seroconversion day of IgA was 2 days after the onset of the initial symptoms, and the first seroconversion day of IgM and IgG was 5 days after onset. The positive rate of antibodies in the 183 samples was 98.9%, 93.4% and 95.1%, for IgA, IgM and IgG classes, respectively. The levels of both Ag-specific IgA and IgG markedly increased about 2 weeks after symptom onset and remained continuously elevated for the following 2 weeks. In contrast, the levels and time-dependent changes of IgM were minimal. The relative levels of IgA and IgG were markedly higher in severe patients compared with non-severe patients. There were also significant differences in the relative levels of IgA and IgG between the severe and non-severe patient groups. Moreover, there is a significantly positive association between the level of SARS-CoV-2-specific IgA and the Acute Physiology and Chronic Health Evaluation (APACHE)-II score in critically ill patients with COVID-19, while the level of SARS-CoV-2-specific IgG and IgM did not show correlations with disease severity [246]. In a study on 87 COVID-19 patients in China, Ma *et al.* also found that IgA levels in severe cases were significantly higher than those in mild or moderate cases [247]. Similar result was obtained by Barzegar Amini *et al.* in Iran [248], and Zervou *et al.* in New York [249].

The deposition of IgA immune complexes in many organs causing multiorgan syndrome in COVID-19 has been described. There have been several reports of newly onset autoimmune IgA vasculitis and nephritis cases in COVID-19 patients. In these cases, the nephritis or vasculitis can occur during or post SARS-CoV-2 infection [250]-[260]. Despite endothelial cells have been known to express ACE-2 [261], vasculitis and nephritis, particularly glomerulitis in COVID-19 are not caused by direct infection of SARS-CoV-2 because SARS-CoV-2 RNA found in COVID-19 "viremia" does not represent viable and infectious virus as mentioned previously, and there has been no report that shows SARS-CoV-2 infected vascular endothelial cells. Instead, the deposition of IgA immune complexes or a part of thrombosis is more likely the cause, in which it resembles IgA-mediated autoimmunity in which the patients also develop some common IgA autoantibodies such as anti-phospholipid. Zuo *et al.* reported that up to 52% of hospitalized COVID-19 patients have anti-phospholipid antibodies. They further showed that these autoantibodies have the capacity to cause clots in mouse models [262]. Hasan Ali reported that severe COVID-19 is associated with elevated serum IgA and IgA class anti-phospholipid antibodies [263]. Thus, it is possible that the IgA immune complex formed by SARS-CoV-2 proteins or DNA, bound by IgA autoantibodies including to those against component of NET fragments, play a major role in the pathophysiology of vasculitis and multiorgan inflammation. The pathogenesis of IgA vasculitis may involve generating IgA immunocomplexes and deposition on small vessels, followed by IgA-directed activation of mannan-binding lectin and alternative complement pathways. More details of the mechanisms for autoimmune IgA mediated vasculitis and potential treatment can be found elsewhere [250].

6.9. The DH-Like IgA-Directed Neutrophil-Mediated Autoimmune Reaction in Severe COVID-19

The mechanism of lung injury in severe COVID-19 by SARS-CoV-2 infection is far more severe than that observed in vasculitis and it involves destruction of the alveola tissue and even the epithelial-endothelial barrier by IgA-mediated neutrophil-directed mechanism. Using immunostaining of biopsies from lung of COVID-19 autopsies, Hou YJ *et al.* found SARS-CoV-2 infected both alveolar cells type 2 (AT2) and alveolar cells type 1 (AT2) and there is hyperplasia of AT2 [264]. Correspondingly, high levels of IgG and both dimeric and monomeric IgA against SARS-CoV-2 have been found in alveola in samples of bronchoalveolar lavage fluid from COVID-19 patients by Sterlin *et al.* [265]. Histopathology sections of lung tissue from autopsies of COVID-19 show alveolar tissue destruction with neutrophil infiltrate [194]-[199]. Evidence of Polymorphonuclear neutrophils adhered to syncytial alveola cells can be seen in the photo of histopathology section by Borczuk *et al.* [199].

The mechanism of lung injury in severe COVID-19 by SARS-CoV-2 infection, however, is quite similar to that of skin disease DH and IgA bullous dermatoses where IgA deposits in skin function as ligands to mediate adherence of activated neutrophils and trigger neutrophil to release proteases that destroy the tissue [111] [112] [266] [267] [268] [269]. Specifically, severe COVID-19 is significantly similar to DH in that both diseases are characterized by critically increased levels of autoantibodies against tissue transglutaminase (tTG), an endomysial autoantigen and a specific predictor for celiac disease and DH [270] [271]. Lingel *et al.* conducted a prospective study of 80 acute and former SARS-CoV-2 infected individuals and 39 unexposed donors to evaluate autoantibody responses and immune composition. They found that autoantibody levels against cyclic citrullinated peptide (CCP), a specific predictor for rheumatoid arthritis (RA), were significantly elevated in convalescents only. However, both acute COVID-19 patients and long-term convalescents showed critically increased levels of anti-tissue transglutaminase (tTG). Both anti-CCP and anti-tTG antibody levels were still detectable after 4 - 8 months post-infection. Anti-tTG antibodies occurred predominantly in aged patients in a context of a post-SARS-CoV-2-specific immune composition. They also showed that increased anti-CCP and anti-tTG autoantibody levels could remain long-term after recovering even from mildly experienced COVID-19. Thus, they suggest that the inter-relationship between the lung (portal of viral entry) and autoimmunity indicates that a SARS-CoV-2-infection could be a relevant environmental factor in autoimmune disease pathogenesis [271].

Autoantibodies to endomysium may indirectly involve in the pathogenesis of DH. However, the existence of IgA anti-tTG antibodies in DH does not necessarily mean that the granular IgA deposits in skin, which represent immune complexes, are due to excess antibodies reacting with tTG or tTG-containing complexes. tTG has been shown to be involved in the intermolecular cross-linking

activities, for example, epidermal transglutaminase. tTG also expresses in another organ such as lung and heart [272]. In COVID-19, cross linking activities of lung epithelial cell transglutaminase may involve in the generation of IgA anti-SARS-CoV-2 complexes. In DH, the complex of IgA and unknown antigen deposit to the dermal papillae, may activate complement system, that in turn attracts neutrophils to the site of action. Neutrophils are stimulated by cytokines such as GMSF or GMCSF to adhere to the Fc portion of fixed IgA, which activates neutrophils to release protease to destroy the tissue and cause skin blisters [269]. Treated with dapsone, the DH lesions resolve and patients have clear skin. Since the similar IgA-mediated neutrophil-directed mechanism occurs in the COVID-19-affected lung alveola and destroy this vital organ for oxygenation and cause fatality, same medication, like dapsone, may help to reverse that.

In COVID-19, hyperplasia of AT2 cells increases the number of SARS-CoV-2 highly infectable cells in alveola therefore increasing targets for neutrophils adhere to SARS-CoV-2 antibody that binds to the virus expressed on alveolar cells. The replication of the virus induces epithelial cells to release cytokines and chemotactic factors, further attracting neutrophils to the site of action to destroy infected cells (and cause lung tissue damage). In severe COVID-19, necrotic cell death of lower respiratory tract epithelial cells, as well as NET formation, further releases damage-associated molecular patterns and alarmins in the surrounding extracellular space then into the circulation due to destruction of epithelial-endothelial barrier. Together, these immune events induce a cascade of production of a pro-inflammatory cytokines-driven vicious cycle, setting up a loop of necroinflammation that is responsible for a larger cytokine storm that cause further endothelial injury and necroinflammation via complement activation, recruiting platelet deposition at the damaged vasculature as well as promote the venous thrombus formation. As such, many medical literatures reported that COVID-19-infected patients developed multiorgan failure [197] [273].

Thus, in severe COVID-19, the initial event leading to tissue destruction in alveola is the adherence of neutrophil to Fc portion of the immunoglobulin in IgA complexes that activate neutrophil destructive activity in alveola. A dysfunctional over-reaction of neutrophils can severely damage the epithelial liner in the lung and consequently impair the ability to exchange O_2/CO_2 of the lung epithelium, while release the immune complex (IgA-SARS-CoV-2 proteins and IgG-SARS-CoV-2 proteins), viral proteins and RNA, and NET materials to the circulation through the damaged epithelial-endothelial barrier, triggers further microthrombi formation, together with neutrophil/IgA and neutrophil/IgG vasculitis and vasculitis by other inflammatory mechanisms lead to multiorgan syndrome in COVID-19, and ultimately death.

Therefore, the most specific therapy to save lives in severe Covid-19 cases should be stopping the initial event causing damage to the respiratory tract epithelial cells and epithelial-endothelial barrier, which is the adherence of neutrophil to IgA or IgG at the site of action (bronchioles and alveoli). This adhesion

will follow by activation that initiates the destruction of tissue by neutrophils (Figure 2). Thus, timely treatment is critical.

7. Treatment Strategies for Severe COVID-19

7.1. Glucocorticoids as a Mainstay Therapy for Autoimmune Diseases and Autoimmune Reactions in COVID-19

Glucocorticoids such as methylprednisolone (MP) are the mainstay of treatment for several autoimmune diseases [274] [275]. In addition to immunosuppression, we have previously showed that MP exhibits its direct effects on target organ such as the epidermis in pemphigus vulgaris by altering expression of several genes in keratinocytes targeted by pathogenic autoantibodies [239]. MP can induce reciprocal effects on the targeted cells against the effect of pathogenic autoantibody. For example, in pemphigus vulgaris (PV), a potential lethal autoimmune disease in which patients develop autoantibodies against the membrane proteins of their keratinocytes that make these cells detach from one another (acantholysis), inflammation and skin blisters. In this disease autoantibodies alone on keratinocytes could induce acantholysis (break down of cell-cell adhesion) [105] [106] [107] [108] [109]. High dose systemic corticosteroids, such as MP, are life-saving for these patients, before the availability of other immunosuppressive medications. MP reverses acantholysis while both antibodies and inflammatory cells still exist at the site of action suggesting that MP could assert its anti-acantholytic effect directly on epithelial cells. In 2002 we used DNA array assay with a set gene chips of 15,000 genes to test the effect of MP on the cells in the presence or absence of pathogenic antibodies, we concluded that the drug asserts its therapeutic effect directly on epithelial cells (keratinocytes in our study) by altering the cell expression of several genes including cell adhesion, signaling, cytokines and pro-inflammatory factors. Its effects are directly countering to those actions caused by pathogenic autoantibody on the cells [239].

Unlike the experience with SARS and MERS [236] [237] and meta-analyses from influenza pneumonia studies [276] [277] that discourage their widespread empirical use, glucocorticoids have been commonly used as treatment in COVID-19. In COVID-19 pneumonia, low-dose dexamethasone reduced mortality among ventilated patients [278] [279]. Wang *et al.* studied 46 severe patients with COVID-19 pneumonia at the isolation ward of Union Hospital in Wuhan, China, from January 20 to February 25, 2020. Three patients died during the hospitalization, and the other 43 patients were successfully discharged. Oxygen therapy, antiviral therapy, immunoenhancement therapy, prevention of bacterial infection, relieving cough eliminating phlegm (respiratory mucus during disease and inflammation), and nutritional support were commonly used for all 46 patients. While 26 of them received extra low-dose MP treatment with the dosage of 1 - 2 mg/kg/day for 5 - 7 days via intravenous corticosteroid administration. The authors showed that early, low-dose and short-term application of

MP was associated with better clinical outcomes in severe patients with COVID-19 pneumonia, and they suggest that corticosteroid should be considered before the onset of ARDS [280].

From a retrospective cohort study on 447 severe COVID-19 patients from the record of 1019 COVID-19 patients who were admitted to Stony Brook University Hospital (Stony Brook, NY, USA) from March 1st to April 15th 2020, Papamanoli *et al.* showed that MP does not reduced mortality, but it significantly reduced needs for mechanical ventilation and intensive care in patients with severe COVID-19 pneumonia [281]. Edalatifard *et al.* conducted a single-blind, randomized controlled clinical trial involving 68 severe hospitalized patients in Iran with confirmed COVID-19 at the early pulmonary phase of the illness, on the other hand, it showed that intravenous administration, 250 mg MP a day for 3 days significantly lower the mortality [282]. In another study, Salton *et al.* conducted a multicenter observational study to explore the association between exposure to prolonged, low-dose MP treatment and need for ICU referral, intubation, or death within 28 days (composite primary end point) in patients with severe COVID-19 pneumonia admitted to Italian respiratory high-dependency units between February 27 and April 24, 2020. Their study's secondary outcomes were invasive mechanical ventilation-free days and changes in C-reactive protein levels. The authors used a loading dose of 80 mg intravenously at study entry, followed by an infusion of 80 mg/d in 240 mL of normal saline at 10 mL/h for at least 8 days, until achieving either a PaO_2:FiO_2 > 350 mmHg or a CRP < 20 mg/L. Following that, oral administration at 16 mg or 20 mg twice daily until CRP reached < 20% of the normal range or a PaO_2:FiO_2 > 400 (alternative $SatHbO_2 \geq 95\%$ on room air). The data from 80 patients with MP and 90 patients without MP show that early administration of prolonged MP treatment was associated with a significantly lower hazard of death and decreased ventilator dependence [283].

Fernández-Cruz *et al.* performed a single-center retrospective cohort study in a university hospital in Madrid, Spain, during March of 2020. The authors reported their study on 463 hospitalized patients, of whom 396 and 67 patients were treated and untreated with steroids respectively and showed that in-hospital mortality was lower in patients treated with steroids than in controls [284]. In a multi-center study by Chaudhuri *et al.* including 2826 patients from 19 clinical trials in Canada, USA, Denmark, China, France, the authors showed that corticosteroids reduce mortality in ARDS patients. This effect was consistent between patients with COVID-19 and non-COVID-19 ARDS, corticosteroid types, and dosages [285]. In a prospective triple-blinded randomized controlled trial, Ranjbar K *et al.* enrolled 86 hospitalized COVID-19 patients from August to November 2020, in Shiraz, Iran to compare the effectiveness of MP and dexamethasone and found that in hospitalized hypoxic COVID-19 patients, MP demonstrated better results compared to dexamethasone [286]. In Vietnam, during the first Delta wave, inexpensive MP/Aspirin combination was widely used by local doctors for SARS-CoV-2 infection in out-patient settings and

seemed to help reduce hospitalization.

In summary, treatment with corticosteroids such as MP for hospitalized COVID-19 patients is favorable. However, the overall mortality of severe COVID-19 patients is still very high in hospitalized patients even in case corticosteroid used in combination with medicine such as IL-6 antagonists. Carbonell *et al.* studied the mortality comparison between the first and second/third waves among 3795 critical COVID-19 patients with pneumonia admitted to the ICU in a multi-center retrospective cohort study. The authors found that despite substantial changes in supportive care and management, overall ICU mortality was about 31%, without significant differences between the first wave (31.7%), second and third waves (28.8%) [287].

A good solution to end this pandemic is to have herd immunity against the virus. Since February 2022, living with virus policy with the rapid spread of the less lethal Omicron may be a way to achieve herd immunity. Vaccine is one of the ways to obtain herd immunity without sacrificing many more lives. But we still face the challenge that unvaccinated people may get infected and may end up in ICU. Moreover, vaccine availability is also an issue in some countries. In addition, currently available vaccines do not provide perfect protection. We need a specific treatment to stop mortality.

7.2. Dapsone, the Specific Treatment for Autoimmune DH Could Be Life-Saving for Severe COVID-19

Because the pathomechanism of tissue destruction of alveola in COVID-19 is significantly similar to that of tissue destruction of skin in DH, dapsone, the specific drug excellent for treating autoimmune DH that can stop tissue destruction in skin, can also be used for treating severe COVID-19 to stop tissue destruction in alveola, thus saving lives.

Dapsone (diaminodiphenyl sulfone, DDS), an FDA-approved medication for DH and leprosy and a sulfone class of medication developed in 1908, has been extensively and confidently utilized by dermatology physicians over a century. It is on the World Health Organization's list of essential medicine as the safest and most effective medicines needed in a health system. The oral formulation of dapsone is available as a generic drug and inexpensive [288] [289]. Initially dapsone was used as an antibiotic in 1937 to treat gonococcal and streptococcal infection. Then in 1945, it began to be used for leprosy. In 1950 the drug was first used to treat DH, then it was subsequently adapted to treat several skin diseases that are pathologically characterized by tissue deposition of IgA and infiltration of neutrophils. For DH, dapsone is considered the first-line medication because it is uniquely effective in treatment of the disease. Dapsone therapy produces relief of pruritus and clearing of skin lesions within 24 to 48 hours. Symptoms recur with equal rapidity when treatment is discontinued [266]. Because the characteristic of dapsone treatment in DH is the drug reverses the skin blisters while the IgA complex still present at the site of action.

To specifically delineated the mechanism, we utilized a modified neutrophil adherence assay in open chambers which contained an IgA complex model with IgA binding to skin basement membrane zone (BMZ) antigen, allowing addition of activators at various times. This IgA complex model system enabled us to examine the effects of neutrophil chemokine GM-CSF and dapsone on the binding of neutrophils to the IgA complex. Incubating IgA-BMZ antigen complexes with dapsone prior to exposing them to neutrophils revealed that dapsone inhibited neutrophil adherence by direct impact on IgA rather than cytotoxic effect on neutrophils [112]. On the molecular level, dapsone, with its unique chemical structure diaminodiphenyl sulfone, could bind to the IgA protein and interfere the IgA's Fc portion, the binding site for neutrophils, so that IgA could no longer interact with the Fc receptor (Fc*α*RI) of neutrophils. This could explain the rapid effect of dapsone in the treatment of IgA-mediated neutrophil-directed skin diseases. The molecular mechanism regarding IgA and its interaction with Fc*α*RI on inflammatory cells in diseases has been delineated extensively [290]. The understanding of interference of dapsone on neutrophil adherence to IgA immune complex, either by inducing some conformational changes or by steric hindrance on the Fc of IgA, would add a new therapeutic opportunity for other pathological conditions where IgA immune complex also plays a critical role.

In severe COVID-19, even being treated with the combination of glucocorticoids and anti-cytokine drugs, the IgA complex with SARS-CoV-2 loaded in alveola and neutrophils infiltrate remained intact as observed in autopsy tissue of the lung. Thus, these drugs cannot stop activation of neutrophils that subsequently destroy alveola tissue. Therefore, it becomes clear that dapsone could be the best and target-specific candidate drug to stop destruction of this vital organ. Consider the similarity in pathological mechanism between DH and ARDS of COVID-19 infection with the presence of all critical players, neutrophils, IgA-antigen complex, and GCSF/GMCSF, dapsone should be tried for severe COVID-19 patients as a target-specific modality to stop the damage initiated by neutrophils/IgA action. We previously proposed that since dapsone could inhibit IgA-mediated neutrophil-directed skin injury, it should be tried on severe COVID-19 patients to block lung injury (**Figure 6**). Dapsone therapy should be used for hospitalized COVID-19 patients who have elevated serum anti-SARS-CoV-2 IgA and should be initiated in a timely fashion before lung injury occurs [291]. Additional therapeutic benefits for dapsone therapy have been reviewed by Wozel and Blasum [288].

In fact, our proposal is supported by the results of a small study. A recent clinical trial of 44 COVID-19 patients in ICU with similar clinical condition documented that in the group of dapsone-treated patients, all 22 patients survived, whereas in the group of who patients did not receive dapsone, 8 of 22 patients did not survive [292]. The news of successful short course trial in the US has been followed by two large clinical trials of dapsone for COVID-19 that are currently undergoing at the Hunt Regional Medical Center in Texas, USA and the McGill

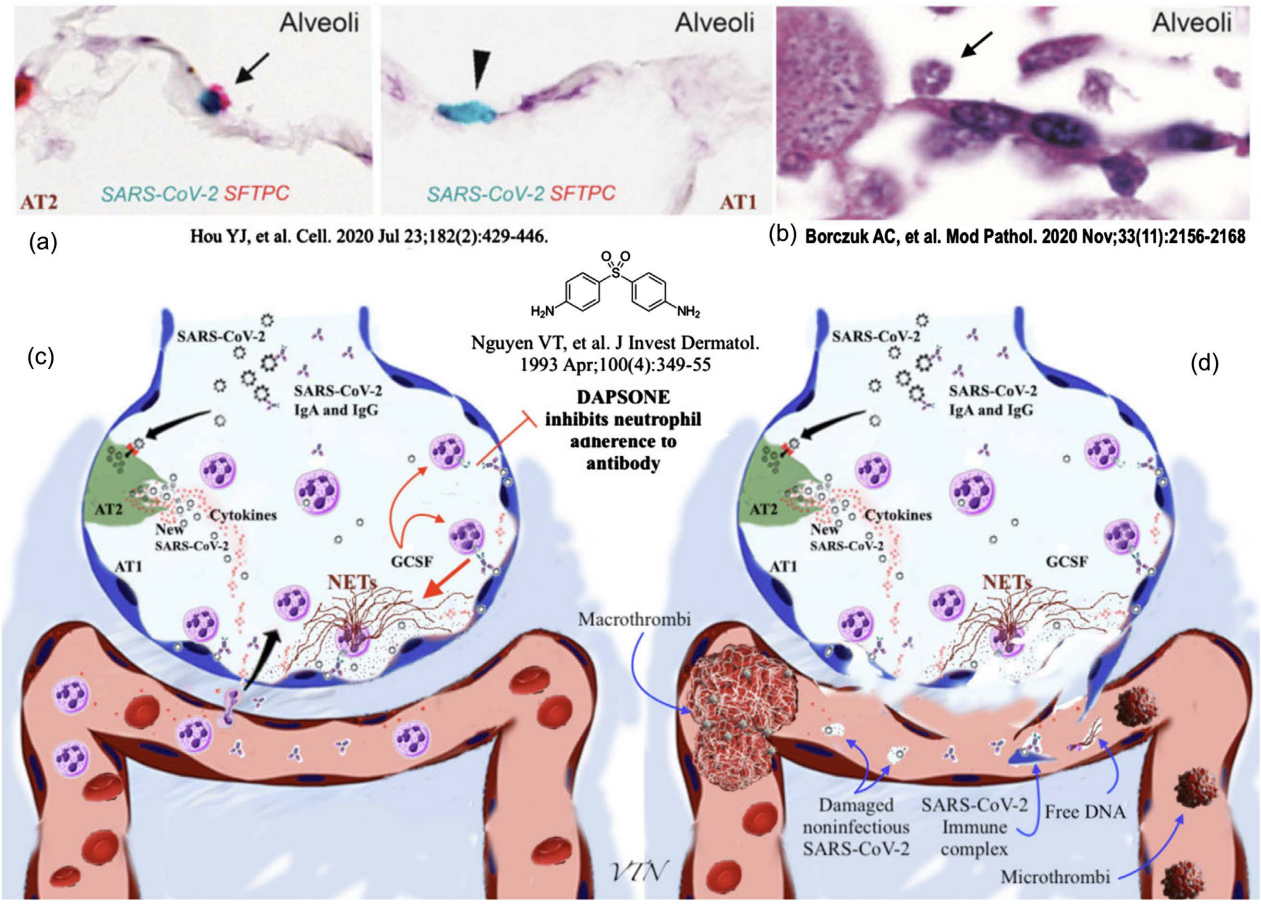


Figure 6. Illustration of the mechanism of IgA/Neutrophil destruction of pulmonary alveola and vasculature in severe COVID-19. (a) and (b): evidence form autopsy of COVID-19 victims. In (a), Hou YJ, *et al.* show SARS-CoV-2 infected alveolar cells type 2 (AT2, labeled with SFTPC) and alveolar cells type 1 (AT1). High level of dimeric and monomeric IgA and IgG against SARS-CoV-2 in has been found in respiratory mucosa alveola by sampling bronchoalveolar lavage fluid of COVID-19 patients by Sterlin D *et al.* (b) shows a polymorphonuclear neutrophil adhere to a syncytial alveola cell in a microscopic histopathology photograph by Borczuk AC, *et al.* (c) shows a known mechanism how neutrophils adhere to fixed antibodies and get activated to destroy pathogens. (d) show dysfunctional overactive neutrophils that activated by adherence to fixed antibodies, especially IgA can destroy alveola as well as lung epithelial-endothelial barrier leading to leaking of damaged noninfectious SARS-CoV-2, SARS-CoV-2 immune complex, free DNA, and other debris to the circulation. Damaged endothelial cell initials formation of macro and microthrombi that further migrate to other organs leading to multiorgan syndrome in severe COVID-19 (Adopted with correction from Nguyen VT and Chan LS, *Advances in Infectious Diseases*, *Vol.12 No.1*, *2022*).

University Health Centre in Quebec, Canada, with estimated primary completion dates of December 31, 2021 and March 31, 2022, respectively. The results of these trials are not yet available as of February 20, 2022 [293] [294]. Interestingly, the observation of COVID-19 in leprosy community also supports the possible use of dapsone in COVID-19. Cerqueira *et al.* performed a prospective real-world cohort study of the influence of leprosy-related clinical and epidemiological variables in the occurrence and severity of COVID-19. Among the 406 included patients on dapsone treatment, 69 were infected with SARS-CoV-2 during the course of study, 7 were admitted to ICU, none needed mechanical ventilation, and no death [295]. Also in this study, these authors noted that dapsone did not prevent SARS-CoV-2 infection, and this finding is consistent

with the possible therapeutic effect of dapsone in COVID-19 on inhibition of neutrophil adherence to IgA, rather than blocking the virus binding to the lung. Therefore, the essential key is to start the dapsone treatment early enough to block the neutrophil binding to IgA. Once neutrophils bind to IgA and initiate the destructive process, dapsone's effects will be substantially diminished.

7.3. Treatment Proposal for Severe COVID-19

In the last 28 days ending on March 27, 2022 there were over 184,700 people in the world who died related to COVID-19, significantly reduced from 291,000 COVID-19 deaths in 28 days proceeding February 24, 2022 [1]. While waiting for the results from the large clinical trial that may give the medical community more evidence in support for dapsone therapy in the COVID-19 setting, select use of this medication, guided by clinical condition and IgA data, at this time may be called for in cases of impending respiratory compromise on an emergency basis. Saving life for patients with severe COVID-19 infection requires our urgent actions. As we have identified the critical autoimmune features of severe COVID-19 (**Figure 6**) and the suitable general and specific drugs that are used to treat autoimmunity, we propose a combination of dapsone and MP with antithrombotic drugs for treatment of severe COVID-19.

Specifically, we recommend that COVID-19 patients, who have severe disease and are admitted to the hospital, should be checked for their serum IgA levels. If their IgA levels are elevated, dapsone at the dose of 200 mg per day should be administered during the acute disease phase. After the acute phase, a lower dose of dapsone (50 - 100 mg per day) for two more weeks should be utilized to prevent relapse [291]. This regiment should be used together with the concurrent uses of glucocorticoids such as MP (1 - 2 mg/kg/day for 5 - 7 days via intravenous injection) [278]-[286], and antithrombotic drugs such as aspirin for out patients and heparin for hospitalized COVID-19 patients as guided by the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health [296].

After a century of usage, dapsone is generally recognized as a safe medication. Other than the infrequent occurrence of the following side effects (usually after a long-term usage), blood oxygen level reduction, white blood cells decrease, hypersensitivity, psychosis, and neuropathy, dapsone has a very good safety profile and is readily available and inexpensive [288] [289]. Careful monitoring these side effects, especially for usage in a short-term basis, should be sufficient to ensure no major problem would occur in the patients receiving dapsone.

The treatment regiments of dapsone in combination with MP and antithrombotic drugs for severe COVID-19 played a significant role in reducing the IMR in the second Delta wave in Vietnam, as mentioned, from 2.4% of the first Delta wave to 1.2% of the second Delta wave. There was no other explanation for this significant drop of IMR. In this pandemic emergency situation, Dr. Nguyen began to share his idea of using Dapsone regiment to treat severe COVID-19 with many physicians and hospitals in Vietnam after the first delta variant wave

hit the country so hard with too many deaths. Since October 2021 he has been repeatedly sharing his thought on using dapsone in combination with MP and antithrombotic drugs to physicians and hospitals in Vietnam and over 2000 physicians and scientists around the world who have published their studies on COVID-19 though email communication. Since these drugs are very inexpensive and available everywhere, doctors in third-world countries may have tried them when they encountered dying severe COVID-19 patients [52].

8. Theories for the Pathogenesis of Multi-Organ Autoimmunity of COVID-19

Similar to other infection induce autoimmune diseases, both molecular mimicry and bystander activation have been proposed to be occurring in COVID-19-triggered autoimmune reactions. Manifestation of T cell bystander activation has been identified in COVID-19 patients [297] [298], but it is still unknown if these activations could lead to autoimmunity in COVID-19. By bioinformatic approach, there are many studies assessing the sequence similarity between peptide sequence stretching about 5 - 9 amino acids in SARS-CoV-2 and the human proteome that identified many sequence similarities [299]-[304]. Another approach is using anti-SARS-CoV-2 monoclonal antibodies to assess their cross activity with human proteins. Potential molecular mimicry suggested by these approaches may partially explain the existence of some autoantibodies in COVID-19 but may not be able to explain the broad spectrum of autoantibodies that have been identified in COVID-19 [305] [306] [307] [308] [309].

The characteristic delay in the onset of respiratory distress caused by SARS-COV-2, approximately 6 to 12 days after the start of early symptoms, which is somewhat atypical for other severe viral respiratory infections, and the occurrence of the enhanced virulent delta variant in COVID-19 may suggest similarity to reversion to virulence through back-mutation of attenuating mutations of a virus. We postulate additional theories of "attenuated viral pathogen" and "anti-evolution". Mojiang SARS-CoV like virus that killed 3 of 6 infected patients in 2012 has viral relatives with nucleic acid sequences that share more than 96% identity with that of SARS-CoV-2, the similarity of the clinical presentation, and the history of the research on the virus, suggests that the origin of SARS-CoV-2 could be the attenuated form of Mojiang SARS-CoV like virus. The existence of multiple autoantibodies in COVID-19 reminds us of PAMS. Autoimmunity may be a natural mechanism for the body that aims to eliminate dysregulated tissue growth like neoplasm. Autoimmunity could normally function at a minuscule level but when it is activated to an excessive level, it induces tissue damage and causes disease. This mechanism must be tightly regulated and perfectly maintained through evolution. The immune system has evolved through billion years to deal with natural micro-organisms which also have evolved through over a billion years. Thus, when it encounters micro-organisms that act against evolution such as a live-attenuated virus exhibiting reversion to virulence through back-mutation of attenuating mutations, the immune system may be confused

and act wildly, leading to a multi-facet autoimmune disease occurs. Vaccination could be critical to help the immune system to prevent surprises and confusion when an encounter the COVID-19 pathogen in the pandemic.

9. Summary

The COVID-19 pandemic has brought us many surprises. It now becomes clear that autoimmunity plays a central role in the pathogenesis of the disease and its sequelae. The published data that significantly support the role of autoimmune responses in the pathophysiology of COVID-19 are far more than what we could cite in this paper. While the central role of neutrophils and IgA is critical in the pathogenesis of severe COVID-19 that leads to high mortality, dapsone is the most effective drug that specifically blocks the interaction of neutrophil to IgA that initiate the process of neutrophil-directed damage to the alveola tissue and could be a life-saving drug. Other autoimmune facets of COVID-19 may be accountable for many symptoms during and after SARS-CoV-2 infection and post-COVID-19 conditions; thus, clinicians should consider autoimmune reactions in their treatment strategies.

Contributions

1) Vu Thuong Nguyen: Idea conception, literature review, composed the first draft, reviewed, revised and finalized the manuscript, 2) Lawrence S. Chan: Review and revision of the manuscript.

Conflicts of Interest

Dr. Nguyen is the founder of Advanced Cosmeceuticals Enterprises, Inc. (Dr. Vu Cosmeceuticals) and La Belle Cosmeceuticals, Inc., a California USA cosmeceutical company. He has no conflict of interest to declare. Dr. Chan is the Dr. Orville J. Stone Professor of Dermatology, former Head of the Department of Dermatology, College of Medicine, University of Illinois at Chicago, USA, and Professor of Dermatology of the Department of Dermatology, School of Medicine, University of California at Davis, USA. He also has no conflict of interest to declare. This work is dedicated to millions of patients victimized by the SARS-CoV-2 pathogen.

References

[1] Zhou, P., Yang, X.L., Wang, X.G., Hu, B., *et al.* (2020) A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature*, **579**, 270-273. https://doi.org/10.1038/s41586-020-2012-7

[2] Bloom, J.D. (2021) Recovery of Deleted Deep Sequencing Data Sheds More Light on the Early Wuhan SARS-CoV-2 Epidemic. *Molecular Biology and Evolution*, **38**, 5211-5224. https://doi.org/10.1093/molbev/msab246

[3] Allam, Z. (2020) The First 50 Days of COVID-19: A Detailed Chronological Timeline and Extensive Review of Literature Documenting the Pandemic. In: Allam, Z., *Surveying the COVID-19 Pandemic and its Implications*, Elsevier, Amsterdam, 1-7. https://doi.org/10.1016/B978-0-12-824313-8.00001-2

[4] Weiss, S.R. and Navas-Martin, S. (2005) Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. *Microbiology and Molecular Biology Reviews*: *MMBR*, **69**, 635-664. https://doi.org/10.1128/MMBR.69.4.635-664.2005

[5] Peiris, J.S., Yuen, K.Y., Osterhaus, A.D. and Stöhr, K. (2003) The Severe Acute Respiratory Syndrome. *The New England Journal of Medicine*, **349**, 2431-2441. https://doi.org/10.1056/NEJMra032498

[6] Sampathkumar, P., Temesgen, Z., Smith, T.F. and Thompson, R.L. (2003) SARS: Epidemiology, Clinical Presentation, Management, and Infection Control Measures. *Mayo Clinic Proceedings*, **78**, 882-890. https://doi.org/10.4065/78.7.882

[7] Centers for Disease Control and Prevention. Middle East Respiratory Syndrome (MERS). https://www.cdc.gov/coronavirus/mers/about/index.html

[8] Azhar, E.I., Hui, D., Memish, Z.A., Drosten, C. and Zumla, A. (2019) The Middle East Respiratory Syndrome (MERS). *Infectious Disease Clinics of North America*, **33**, 891-905. https://doi.org/10.1016/j.idc.2019.08.001

[9] Ramadan, N. and Shaib, H. (2019) Middle East Respiratory Syndrome Coronavirus (MERS-CoV): A Review. *Germs*, **9**, 35-42. https://doi.org/10.18683/germs.2019.1155

[10] Li, X. (2013) Analysis of Six Patients with Unknown Viruses. Master Thesis, Kunming Medical University, Kunming. https://www.documentcloud.org/documents/6981198-Analysis-of-Six-Patients-With-Unknown-Viruses.html

[11] Yuan, J.-F., Li, Y., Zhang, H.-J., Zhou, P., Ke, Z.-H., Zhang, Y.-Z. and Shi, Z.-L. (2009) Indirect Enzyme-Linked Immunosorbent Assay Based on the Nucleocapsid Protein of SARS-Like Coronaviruses. *Virologica Sinica*, **24**, 146-151. https://doi.org/10.1007/s12250-009-3037-0

[12] Zhou, P., Yang, X. L., Wang, X. G., Hu, B., *et al.* (2020) Addendum: A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature*, **588**, E6. https://doi.org/10.1038/s41586-020-2951-z

[13] Rahalkar, M.C. and Bahulikar, R.A. (2020) Lethal Pneumonia Cases in Mojiang Miners (2012) and the Mineshaft Could Provide Important Clues to the Origin of SARS-CoV-2. *Frontiers in Public Health*, **8**, Article ID: 581569. https://doi.org/10.3389/fpubh.2020.581569

[14] Speciale, A.C. (2021) Commentary: Lethal Pneumonia Cases in Mojiang Miners (2012) and the Mineshaft Could Provide Important Clues to the Origin of SARS-CoV-2. *Frontiers in Public Health*, **9**, Article ID: 702199. https://doi.org/10.3389/fpubh.2021.702199

[15] Ge, X.Y., Wang, N., Zhang, W., Hu, B., *et al.* (2016) Coexistence of Multiple Coronaviruses in Several Bat Colonies in an Abandoned Mineshaft. *Virologica Sinica*, **31**, 31-40. https://doi.org/10.1007/s12250-016-3713-9

[16] Mallapaty S. (2021) Closest Known Relatives of Virus behind COVID-19 Found in Laos. *Nature*, **597**, 603. https://doi.org/10.1038/d41586-021-02596-2

[17] Zhou, H., Ji, J., Chen, X., Bi, Y., *et al.* (2021) Identification of Novel Bat Coronaviruses Sheds Light on the Evolutionary Origins of SARS-CoV-2 and Related Viruses. *Cell*, **184**, 4380-4391.E14. https://doi.org/10.1016/j.cell.2021.06.008

[18] Hu, B., Ge, X., Wang, L.F. and Shi, Z. (2015) Bat Origin of Human Coronaviruses. *Virology Journal*, **12**, Article No. 221. https://doi.org/10.1186/s12985-015-0422-1

[19] Guan, Y., Zheng, B.J., He, Y.Q., Liu, X.L., *et al.* (2003) Isolation and Characterization of Viruses Related to the SARS Coronavirus from Animals in Southern China.

Science (New York, N.Y.), **302**, 276-278. https://doi.org/10.1126/science.1087139

[20] Lau, S.K., Woo, P.C., Li, K.S., Huang, Y., *et al.* (2005) Severe Acute Respiratory Syndrome Coronavirus-Like Virus in Chinese Horseshoe Bats. *Proceedings of the National Academy of Sciences of the United States of America*, **102**, 14040-14045. https://doi.org/10.1073/pnas.0506735102

[21] Al Mutair, A. and Ambani, Z. (2020) Narrative Review of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection: Updates and Implications for Practice. *The Journal of International Medical Research*, **48**. https://doi.org/10.1177/0300060519858030

[22] Ge, X.Y., Li, J.L., Yang, X.L., Chmura, A.A., *et al.* (2013) Isolation and Characterization of a Bat SARS-Like Coronavirus That Uses the ACE2 Receptor. *Nature*, **503**, 535-538. https://doi.org/10.1038/nature12711

[23] Yang, X.L., Hu, B., Wang, B., Wang, M.N., *et al.* (2015) Isolation and Characterization of a Novel Bat Coronavirus Closely Related to the Direct Progenitor of Severe Acute Respiratory Syndrome Coronavirus. *Journal of Virology*, **90**, 3253-3256. https://doi.org/10.1128/JVI.02582-15

[24] Wu, Z., Yang, L., Yang, F., Ren, X., *et al.* (2014) Novel Henipa-Like Virus, Mojiang Paramyxovirus, in Rats, China, 2012. *Emerging Infectious Diseases*, **20**, 1064-1066. https://doi.org/10.3201/eid2006.131022

[25] Chen, S., Qing, J., Liu, Z., Liu, Y., *et al.* (2020) Multilocus Phylogeny and Cryptic Diversity of White-Toothed Shrews (Mammalia, Eulipotyphla, Crocidura) in China. *BMC Evolutionary Biology*, **20**, Article No. 29. https://doi.org/10.1186/s12862-020-1588-8

[26] Yin, J.X., Geater, A., Chongsuvivatwong, V, *et al.* (2008) Predictors for Presence and Abundance of Small Mammals in Households of Villages Endemic for Commensal Rodent Plague in Yunnan Province, China. *BMC Ecology*, **8**, Article No. 18. https://doi.org/10.1186/1472-6785-8-18

[27] Rissanen, I., Ahmed, A.A., Azarm, K., *et al.* (2017) Idiosyncratic Mòjiāng Virus Attachment Glycoprotein Directs A Host-Cell Entry Pathway Distinct from Genetically Related Henipaviruses. *Nature Communications*, **8**, Article No. 16060. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5510225/pdf/ncomms16060.pdf https://doi.org/10.1038/ncomms16060

[28] Da Silva, S.C., Yan, L., Dang, H.V., Xu, K., *et al.* (2021) Functional Analysis of the Fusion and Attachment Glycoproteins of Mojiang Henipavirus. *Viruses*, **13**, Article 517. https://www.mdpi.com/1999-4915/13/3/517/htm https://doi.org/10.3390/v13030517

[29] Armengaud, J., Delaunay-Moisan, A., Thuret, J.Y., van Anken, E., *et al.* (2020) The Importance of Naturally Attenuated SARS-CoV-2 in the Fight against COVID-19. *Environmental Microbiology*, **22**, 1997-2000. https://doi.org/10.1111/1462-2920.15039

[30] Taubenberger, J.K. and Morens, D.M. (2006) 1918 Influenza: The Mother of All Pandemics. *Emerging Infectious Diseases*, **12**, 15-22. https://doi.org/10.3201/eid1209.05-0979

[31] Tumpey, T.M., Basler, C.F., Aguilar, P.V., Zeng, H., *et al.* (2005) Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. *Science* (New York, N.Y.), **310**, 77-80. https://doi.org/10.1126/science.1119392

[32] Yang, W., Petkova, E. and Shaman, J. (2014) The 1918 Influenza Pandemic in New York City: Age-Specific Timing, Mortality, and Transmission Dynamics. *Influenza and Other Respiratory Viruses*, **8**, 177-188. https://doi.org/10.1111/irv.12217

[33] Hsueh, P.R., Huang, L.M., Chen, P.J., Kao, C.L. and Yang, P.C. (2004) Chronological Evolution of IgM, IgA, IgG and Neutralisation Antibodies after Infection with SARS-Associated Coronavirus. *Clinical Microbiology and Infection*, **10**, 1062-1066. https://doi.org/10.1111/j.1469-0691.2004.01009.x

[34] Ko, J.H., Müller, M.A., Seok, H., Park, G.E., *et al.* (2017) Suggested New Breakpoints of Anti-MERS-CoV Antibody ELISA Titers: Performance Analysis of Serologic Tests. *European Journal of Clinical Microbiology & Infectious Diseases*, **36**, 2179-2186. https://doi.org/10.1007/s10096-017-3043-3

[35] Padoan, A., Sciacovelli, L., Basso, D., Negrini, D., *et al.* (2020) IgA-Ab Response to Spike Glycoprotein of SARS-CoV-2 in Patients with COVID-19: A Longitudinal Study. *Clinica Chimica Acta*, **507**, 164-166. https://doi.org/10.1016/j.cca.2020.04.026

[36] Yu, H.Q., Sun, B.Q., Fang, Z.F., Zhao, J.C., *et al.* (2020) Distinct Features of SARS-CoV-2-Specific IgA Response in COVID-19 Patients. *The European Respiratory Journal*, **56**, Article ID: 2001526. https://doi.org/10.1183/13993003.01526-2020

[37] Tran, T., Le, T.H., Nguyen, T. and Hoang, V.M. (2020) Rapid Response to the COVID-19 Pandemic: Vietnam Government's Experience and Preliminary Success. *Journal of Global Health*, **10**, Article ID: 020502. https://doi.org/10.7189/jogh.10.020502

[38] Ha, B., Ngoc Quang, L., Mirzoev, T., Tai, N.T., Thai, P.Q. and Dinh, P.C. (2020) Combating the COVID-19 Epidemic: Experiences from Vietnam. *International Journal of Environmental Research and Public Health*, **17**, Article 3125. https://doi.org/10.3390/ijerph17093125

[39] Mallapaty, S. (2021) Has COVID Peaked? Maybe, but It's Too Soon to Be Sure. *Nature*, **591**, 512-513. https://doi.org/10.1038/d41586-021-00705-9

[40] Bhattacharjee, A., Kumar, M. and Patel, K.K. (2021) When COVID-19 Will Decline in India? Prediction by Combination of Recovery and Case Load Rate. *Clinical Epidemiology and Global Health*, **9**, 17-20. https://doi.org/10.1016/j.cegh.2020.06.004

[41] Vu, D., Nguyen, T. and Hoang, A. (2021) Spatial Clustering Analysis of the COVID-19 Pandemic: A Case Study of the Fourth Wave in Vietnam. *Geography, Environment, Sustainability*, **14**, 140-147. https://doi.org/10.24057/2071-9388-2021-086

[42] Fukui, M., Kawaguchi, K. and Matsuura, H. (2020) Does TB Vaccination Reduce COVID-19 Infection? No Evidence from a Regression Discontinuity Analysis. *medRxiv* 2020.04.13.20064287. https://doi.org/10.1101/2020.04.13.20064287

[43] Escobar, L.E., Molina-Cruz, A. and Barillas-Mury, C. (2020) BCG Vaccine Protection from Severe Coronavirus Disease 2019 (COVID-19). *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 17720-17726. (Erratum in: *Proceedings of the National Academy of Sciences of the United States of America*, 2020, **117**, 27741-27742). https://doi.org/10.1073/pnas.2008410117

[44] Urashima, M., Otani, K., Hasegawa, Y. and Akutsu, T. (2020) BCG Vaccination and Mortality of COVID-19 across 173 Countries: An Ecological Study. *International Journal of Environmental Research and Public Health*, **17**, Article 5589. https://doi.org/10.3390/ijerph17155589

[45] Thangaraj, J., Yadav, P., Kumar, C. G., Shete, A., *et al.* (2022) Predominance of Delta Variant among the COVID-19 Vaccinated and Unvaccinated Individuals, India, May 2021. *The Journal of Infection*, **84**, 94-118. https://doi.org/10.1016/j.jinf.2021.08.006

[46] Yang, W. and Shaman, J. (2022) COVID-19 Pandemic Dynamics in India, the SARS-CoV-2 Delta Variant and Implications for Vaccination. *Journal of the Royal*

Society Interface, **19**, Article ID: 20210900. https://doi.org/10.1098/rsif.2021.0900

[47] Del Rio, C., Malani, P.N. and Omer, S.B. (2021) Confronting the Delta Variant of SARS-CoV-2, Summer 2021. *JAMA*, **326**, 1001-1002. https://doi.org/10.1001/jama.2021.14811

[48] Novelli, G., Colona, V.L. and Pandolfi, P.P. (2021) A Focus on the Spread of the Delta Variant of SARS-CoV-2 in India. *The Indian Journal of Medical Research*, **153**, 537-541. https://doi.org/10.4103/ijmr.ijmr_1353_21

[49] Johns Hopkins University, Coronavirus Resource Center. https://coronavirus.jhu.edu/map.html

[50] Le, H.T. (August 11, 2021) Delta Variant Outbreak Challenges Vietnam's COVID-19 Response Strategy. Brookings Institution. https://www.brookings.edu/blog/order-from-chaos/2021/08/11/delta-variant-outbreak-challenges-vietnams-covid-19-response-strategy/

[51] Nguyen, T.P., Wong, Z.S., Wang, L., Thanh, T.T., Van Nguyen, H. and Gilmour, S. (2021) Rapid Impact Assessments of COVID-19 Control Measures against the Delta Variant and Short-Term Projections of New Confirmed Cases in Vietnam. *Journal of Global Health*, **11**, Article ID: 03118. https://doi.org/10.7189/jogh.11.03118

[52] Nguyen, V.T. (2022) "ĐẠI DỊCH COVID-19: Nguồn gốc Vi rút Gây Bệnh, Vi rút Gây Bệnh và Các Biến Thể, Cơ Chế Gây Bệnh, Hệ Thống Phòng Thủ Miễn Dịch, Các Phản Ứng Tự Khảng Đa Cơ Quan Và Các Phương Pháp Điều Trị" (COVID-19 Pandemic: Origin of the Viral Pathogen, Pathogenesis, Treatments…). *The Vietnamese Journal of Medicine*. (Presented at the Symposium For COVID-19 and Post-COVID Management, Hanoi, Vietnam April 22, 2022) (In Vietnamese)

[53] Augusto, G., Mohsen, M.O., Zinkhan, S., Liu, X., Vogel, M. and Bachmann, M.F. (2022) *In Vitro* Data Suggest That Indian Delta Variant B.1.617 of SARS-CoV-2 Escapes Neutralization by Both Receptor Affinity and Immune Evasion. *Allergy*, **77**, 111-117. https://doi.org/10.1111/all.15065

[54] McCallum, M., Walls, A.C., Sprouse, K.R., Bowen, J.E., *et al.* (2021) Molecular Basis of Immune Evasion by the Delta and Kappa SARS-CoV-2 Variants. *Science*, **374**, 1621-1626. https://doi.org/10.1126/science.abl8506

[55] Zhang, J., Xiao, T., Cai, Y., Lavine, C.L., *et al.* (2021) Membrane Fusion and Immune Evasion by the Spike Protein of SARS-CoV-2 Delta Variant. *Science* (New York, N.Y.), **374**, 1353-1360. https://doi.org/10.1126/science.abl9463

[56] Mlcochova, P., Kemp, S.A., Dhar, M.S., Papa, G., *et al.* (2021) SARS-CoV-2 B.1.617.2 Delta Variant Replication and Immune Evasion. *Nature*, **599**, 114-119. https://doi.org/10.1038/s41586-021-03944-y

[57] Thorne, L.G., Bouhaddou, M., Reuschl, A.K., Zuliani-Alvarez, L., *et al.* (2022) Evolution of Enhanced Innate Immune Evasion by SARS-CoV-2. *Nature*, **602**, 487-495. https://doi.org/10.1038/s41586-021-04352-y

[58] Bast, E., Tang, F., Dahn, J. and Palacio, A. (2021) Increased Risk of Hospitalisation and Death with the Delta Variant in the USA. *The Lancet: Infectious Diseases*, **21**, 1629-1630. https://doi.org/10.1016/S1473-3099(21)00685-X

[59] Butt, A.A., Dargham, S.R., Chemaitelly, H., Al Khal, A., *et al.* (2022) Severity of Illness in Persons Infected with the SARS-CoV-2 Delta Variant vs Beta Variant in Qatar. *JAMA Internal Medicine*, **182**, 197-205. https://doi.org/10.1001/jamainternmed.2021.7949

[60] Ong, S., Chiew, C.J., Ang, L.W., Mak, T.M., *et al.* (2021) Clinical and Virological Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants of Concern: A Retrospective Cohort Study Comparing B.1.1.7 (Alpha),

B.1.351 (Beta), and B.1.617.2 (Delta). *Clinical Infectious Diseases*, **75**, e1128-e1136. https://doi.org/10.1093/cid/ciab721

[61] Twohig, K.A., Nyberg, T., Zaidi, A., Thelwall, S., *et al.* and COVID-19 Genomics UK (COG-UK) Consortium (2022) Hospital Admission and Emergency Care Attendance Risk for SARS-CoV-2 Delta (B.1.617.2) Compared with Alpha (B.1.1.7) Variants of Concern: A Cohort Study. *The Lancet. Infectious Diseases*, **22**, 35-42.

[62] Ryu, B.H., Hong, S.I., Lim, S.J., Cho, Y., *et al.* (2021) Clinical Features of Adult COVID-19 Patients without Risk Factors before and after the Nationwide SARS-CoV-2 B.1.617.2 (Delta)-Variant Outbreak in Korea: Experience from Gyeongsangnam-Do. *Journal of Korean Medical Science*, **36**, e341. https://doi.org/10.3346/jkms.2021.36.e341

[63] Li, B., *et al.* (2022) Viral Infection and Transmission in a Large, Well-Traced Outbreak Caused by the SARS-CoV-2 Delta Variant. *Nature Communications*, **13**, Article No. 460. https://doi.org/10.1038/s41467-022-28089-y

[64] Teyssou, E., Delagrèverie, H., Visseaux, B., Lambert-Niclot, S., *et al.* (2021) The Delta SARS-CoV-2 Variant Has a Higher Viral Load than the Beta and the Historical Variants in Nasopharyngeal Samples from Newly Diagnosed COVID-19 Patients. *The Journal of Infection*, **83**, e1-e3. https://doi.org/10.1016/j.jinf.2021.08.027

[65] Mlcochova, P., Kemp, S.A., Dhar, M.S., Papa, G., *et al.* (2021) SARS-CoV-2 B.1.617.2 Delta Variant Replication and Immune Evasion. *Nature*, **599**, 114-119. https://doi.org/10.1038/s41586-021-03944-y

[66] Rodrigues, A.F., Soares, H.R., Guerreiro, M.R., Alves, P.M. and Coroadinha, A.S. (2015) Viral Vaccines and Their Manufacturing Cell Substrates: New Trends and Designs in Modern Vaccinology. *Biotechnology Journal*, **10**, 1329-1344. https://doi.org/10.1002/biot.201400387

[67] Hanley, K.A. (2011) The Double-Edged Sword: How Evolution Can Make or Break a Live-Attenuated Virus Vaccine. *Evolution*, **4**, 635-643. https://doi.org/10.1007/s12052-011-0365-y

[68] Kew, O.M., Sutter, R.W., de Gourville, E.M., Dowdle, W.R. and Pallansch, M.A. (2005) Vaccine-Derived Polioviruses and the Endgame Strategy for Global Polio Eradication. *Annual Review of Microbiology*, **59**, 587-635. https://doi.org/10.1146/annurev.micro.58.030603.123625

[69] Odoom, J.K., Yunus, Z., Dunn, G., Minor, P.D. and Martín, J. (2008) Changes in Population Dynamics during Long-Term Evolution of Sabin Type 1 Poliovirus in an Immunodeficient Patient. *Journal of Virology*, **82**, 9179-9190. https://doi.org/10.1128/JVI.00468-08

[70] Liu, Y., Yu, Y., Zhao, Y. and He, D. (January 16, 2022) Reduction in the Infection Fatality Rate of Omicron (B.1.1.529) Variant Compared to Previous Variants in South Africa. https://ssrn.com/abstract=4010080 https://doi.org/10.2139/ssrn.4010080

[71] Viana, R., Moyo, S., Amoako, D.G., Tegally, H., *et al.* (2022) Rapid Epidemic Expansion of the SARS-CoV-2 Omicron Variant in Southern Africa. *Nature*, **603**, 679-686.

[72] Wolter, N., Jassat, W., Walaza, S., Welch, R., *et al.* (2022) Early Assessment of the Clinical Severity of the SARS-CoV-2 Omicron Variant in South Africa: A Data Linkage Study. *The Lancet*, **399**, 437-446. https://doi.org/10.1016/S0140-6736(22)00017-4

[73] Abdullah, F., Myers, J., Basu, D., Tintinger, G., *et al.* (2022) Decreased Severity of Disease during the First Global Omicron Variant COVID-19 Outbreak in a Large

Hospital in Tshwane, South Africa. *International Journal of Infectious Diseases*, **116**, 38-42. https://doi.org/10.1016/j.ijid.2021.12.357

[74] Jassat, W., Karim, S.A., Mudara, C., Welch, R., *et al.* (2021) Clinical Severity of COVID-19 Patients Admitted to Hospitals in Gauteng, South Africa during the Omicron-Dominant Fourth Wave. DATCOV Author and Blumberg, Lucille and Cohen, Cheryl, Clinical Severity of COVID-19 Patients Admitted to Hospitals in Gauteng, South Africa During the Omicron-Dominant Fourth Wave (December 29, 2021). https://doi.org/10.2139/ssrn.3996320

[75] Davies, M.-A., Kassanjee, R., Rosseau, P., Morden, E., *et al.* (2022) Outcomes of Laboratory-Confirmed SARS-CoV-2 Infection in the Omicron-Driven Fourth Wave Compared with Previous Waves in the Western Cape Province, South Africa. *Tropical Medicine & International Health*, **27**, 564-573. https://doi.org/10.1111/tmi.13752

[76] Lewnard, J.A., Hong, V.X., *et al.* (2022) Clinical Outcomes among Patients Infected with Omicron (B.1.1.529) SARS-CoV-2 Variant in Southern California. *medRxiv* 2022.01.11.22269045.

[77] Kim, M.K., Lee, B., Choi, Y.Y., Um, J., Lee, K.-S., *et al.* (2022) Clinical Characteristics of 40 Patients Infected with the SARS-CoV-2 Omicron Variant in Korea. *Journal of Korean Medical Science*, **37**, e31. https://doi.org/10.3346/jkms.2022.37.e31

[78] Lambrou, A.S., *et al.* (2022) Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants—United States, June 2021-January 2022. *Morbidity and Mortality Weekly Report*, **71**, 206-211. https://doi.org/10.15585/mmwr.mm7106a4

[79] The World Ometer. https://www.worldometers.info/coronavirus/

[80] Bergwerk, M., Gonen, T., Lustig, Y., Amit, S., *et al.* (2021) Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *The New England Journal of Medicine*, **385**, 1474-1484. https://doi.org/10.1056/NEJMoa2109072

[81] Jung, J., Sung, H. and Kim, S.H. (2021) Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *The New England Journal of Medicine*, **385**, 1629-1630. https://doi.org/10.1056/NEJMc2113497

[82] Amit, S., Gonen, T. and Regev-Yochay, G. (2021) Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. Reply. *The New England Journal of Medicine*, **385**, 1630-1631. https://doi.org/10.1056/NEJMc2113497

[83] Hahn, G., Lee, S., Prokopenko, D., *et al.* (2021) Unsupervised Genome-Wide Cluster Analysis: Nucleotide Sequences of the Omicron Variant of SARS-CoV-2 Are Similar to Sequences from Early 2020. *bioRxiv* 2021.12.29.474469. https://doi.org/10.1101/2021.12.29.474469

[84] Bansal, K. and Kumar, S. (2022) Mutational Cascade of SARS-CoV-2 Leading to Evolution and Emergence of Omicron Variant. *Virus Research*, **315**, Article ID: 198765. https://doi.org/10.1016/j.virusres.2022.198765

[85] Planas, D., Saunders, N., Maes, P., Guivel-Benhassine, F., *et al.* (2022) Considerable Escape of SARS-CoV-2 Omicron to Antibody Neutralization. *Nature*, **602**, 671-675 https://doi.org/10.1038/d41586-021-03827-2

[86] Dejnirattisai, W., Huo, J., Zhou, D., Zahradník, J., *et al.* (2021) Omicron-B.1.1.529 Leads to Widespread Escape from Neutralizing Antibody Responses. *bioRxiv*: The Preprint Server for Biology, 2021.12.03.471045.

[87] Ikemura, N., Hoshino, A., Higuchi, Y., Taminishi, S., Inaba, T. and Matoba, S. (2021) SARS-CoV-2 Omicron Variant Escapes Neutralization by Vaccinated and Convalescent Sera and Therapeutic Monoclonal Antibodies. *medRxiv* 2021.12.13.21267761.

https://doi.org/10.1101/2021.12.13.21267761

[88] Rössler, A., Riepler, L., Bante, D., von Laer, D. and Kimpel, J. (2022) SARS-CoV-2 Omicron Variant Neutralization in Serum from Vaccinated and Convalescent Persons. *The New England Journal of Medicine*, **386**, 698-700. https://doi.org/10.1056/NEJMc2119236

[89] Hoffmann, M., Krüger, N., Schulz, S., Cossmann, A., *et al.* (2021) The Omicron Variant Is Highly Resistant against Antibody-Mediated Neutralization: Implications for Control of the COVID-19 Pandemic. *Cell*, **185**, 447-456.E11. https://doi.org/10.1101/2021.12.12.472286

[90] Puhach, O., Adea, K., Hulo, N., Sattonnet, P., *et al.* (2022) Infectious Viral Load in Unvaccinated and Vaccinated Patients Infected with SARS-CoV-2 WT, Delta and Omicron. *medRxiv* 2022.01.10.22269010. https://doi.org/10.1101/2022.01.10.22269010

[91] Golcuk, M., Yildiz, A. and Gur, M. (2022) Omicron BA.1 and BA.2 Variants Increase the Interactions of SARS-CoV-2 Spike Glycoprotein with ACE2. *Journal of Molecular Graphics and Modelling*, **117**, Article ID: 108286. https://doi.org/10.1016/j.jmgm.2022.108286

[92] Mannar, D., Saville, J.W., Zhu, X., Srivastava, S.S., *et al.* (2022) SARS-CoV-2 Omicron Variant: Antibody Evasion and Cryo-EM Structure of Spike Protein-ACE2 Complex. *Science* (New York, N.Y.), **375**, 760-764. https://doi.org/10.1126/science.abn7760

[93] Lamers, M.M., Mykytyn, A.Z., Breugem, T.I., Groen, N., *et al.* (2022) SARS-CoV-2 Omicron Efficiently Infects Human Airway, but Not Alveolar Epithelium. *bioRxiv* 2022.01.19.476898. https://doi.org/10.1101/2022.01.19.476898

[94] Peacock, T.P., Brown, J.C., Zhou, J., Thakur, N., *et al.* (2021) The SARS-CoV-2 Variant, Omicron, Shows Rapid Replication in Human Primary Nasal Epithelial Cultures and Efficiently Uses the Endosomal Route of Entry. *bioRxiv* 2021.12.31.474653.

[95] Nie, C., Sahoo, A.K., Herrmann, A., Ballauff, M., Netz, R.R. and Haag, R. (2022) Charge Matters: Mutations in Omicron Variant Favor Binding to Cells. *ChemBioChem*, **23**, e202100681. https://doi.org/10.1002/cbic.202100681

[96] Shuai, H., Chan, J.FW., Hu, B., *et al.* (2022) Attenuated Replication and Pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. *Nature*, **603**, 693-699. https://doi.org/10.1038/s41586-022-04442-5

[97] McMahan, K., Giffin, V., Tostanoski, L.H., Chung, B., *et al.* (2022) Reduced Pathogenicity of the SARS-CoV-2 Omicron Variant in Hamsters. *Clinical and Translational Report*, **3**, 262-268.E4. https://doi.org/10.1016/j.medj.2022.03.004

[98] Abdelnabi, R., Foo, C.S., Zhang, X., Lemmens, V., *et al.* (2022) The Omicron (B.1.1.529) SARS-CoV-2 Variant of Concern Does Not Readily Infect Syrian Hamsters. *Antiviral Research*, **198**, Article ID: 105253. https://doi.org/10.1016/j.antiviral.2022.105253

[99] Halfmann, P.J., Iida, S., Iwatsuki-Horimoto, K., *et al.* (2022) SARS-CoV-2 Omicron Virus Causes Attenuated Disease in Mice and Hamsters. *Nature*, **603**, 687-692. https://doi.org/10.1038/s41586-022-04441-6

[100] Sato, K., Suzuki, R., Yamasoba, D., Kimura, I., Wang, L., Kishimoto, M., *et al.* (2022) Attenuated Fusogenicity and Pathogenicity of SARS-CoV-2 Omicron Variant. https://doi.org/10.21203/rs.3.rs-1207670/v1

[101] Lewnard, J.A., Hong, V.X., Patel, M.M., Kahn, R., Lipsitch, M. and Tartof, S.Y. (2022) Clinical Outcomes among Patients Infected with Omicron (B.1.1.529) SARS-CoV-2 Variant in Southern California. *medRxiv*.

[102] Khan, K., Karim, F., Cele, S., San, J.E., *et al.* (2022) Omicron Infection Enhances Delta Antibody Immunity in Vaccinated Persons. *Nature*, **607**, 356-359. https://doi.org/10.1038/s41586-022-04830-x

[103] Chan, L.S., Hammerberg, C. and Cooper, K.D. (1990) Cicatricial Pemphigoid. Identification of Two Distinct Sets of Epidermal Antigens by IgA and IgG Class Circulating Autoantibodies. *Archives of Dermatology*, **126**, 1466-1468. https://doi.org/10.1001/archderm.1990.01670350080013

[104] Chan, L.S., Fine, J.D., Briggaman, R.A., Woodley, D.T., Hammerberg, C., Drugge, R.J. and Cooper, K.D. (1993) Identification and Partial Characterization of a Novel 105-kDalton Lower Lamina Lucida Autoantigen Associated with a Novel Immune-Mediated Subepidermal Blistering Disease. *The Journal of Investigative Dermatology*, **101**, 262-267.

[105] Nguyen, V.T., Ndoye, A., Shultz, L.D., Pittelkow, M.R. and Grando, S.A. (2000) Antibodies against Keratinocyte Antigens Other than Desmogleins 1 and 3 Can Induce Pemphigus Vulgaris-Like Lesions. *Journal of Clinical Investigation*, **106**, 1467-1479. https://doi.org/10.1172/JCI10305

[106] Nguyen, V.T., Ndoye, A. and Grando, S.A. (2000) Pemphigus Vulgaris Antibody Identifies Pemphaxin. A Novel Keratinocyte Annexin-Like Molecule Binding Acetylcholine. *Journal of Biological Chemistry*, **275**, 29466-29476. https://doi.org/10.1074/jbc.M003174200

[107] Nguyen, V.T., Ndoye, A. and Grando, S.A. (2000) Novel Human Alpha9 Acetylcholine Receptor Regulating Keratinocyte Adhesion Is Targeted by Pemphigus Vulgaris Autoimmunity. *The American Journal of Pathology*, **157**, 1377-1391. https://doi.org/10.1016/S0002-9440(10)64651-2

[108] Kljuic, A., Bazzi, H., Sundberg, J.P., Panteleyev, A.A., Nguyen, V.T. and Christiano, A.M. (2003) Desmoglein 4 in Hair Follicle Differentiation and Epidermal Adhesion: Evidence from Inherited Hypotrichosis and Acquired Pemphigus Vulgaris. *Cell*, **113**, 249-260. https://doi.org/10.1016/S0092-8674(03)00273-3

[109] Nguyen, V.T. (2003) Chapter 19: Experimental Mouse Model of Pemphigus Vulgaris: Passive Transfer of Nondesmoglein 1 and 3 Antibodies. In: Chan, L.S., Ed., *Animal Models of Human Inflammatory Skin Diseases*, CRC Press LLC, Boca Raton, FL.

[110] Nguyen, V.T., *et al.* (2001) Classification, Clinical Manifestations, and Immunopathological Mechanisms of the Epithelial Variant of Paraneoplastic Autoimmune Multiorgan Syndrome: A Reappraisal of Paraneoplastic Pemphigus. *Archives of Dermatology*, **137**, 193-206.

[111] Mendes, F.B., Hissa-Elian, A., Abreu, M.A. and Gonçalves, V.S. (2013) Review: Dermatitis Herpetiformis. *Anais Brasileiros de Dermatologia*, **88**, 594-599. https://doi.org/10.1590/abd1806-4841.20131775

[112] Nguyen, V.T., Kadunce, D.P., Hendrix, J.D., Gammon, W.R. and Zone, J.J. (1993) Inhibition of Neutrophil Adherence to Antibody by Dapsone: A Possible Therapeutic Mechanism of Dapsone in the Treatment of IgA Dermatoses. *Journal of Investigative Dermatology*, **100**, 349-355. https://drive.google.com/file/d/1QqBjj9lVYVplqdEXjTrFYGrGyG25rqmp/view?usp=sharing https://doi.org/10.1111/1523-1747.ep12471811

[113] Tsokos G.C. (2011) Systemic Lupus Erythematosus. *The New England Journal of Medicine*, **365**, 2110-2121. https://doi.org/10.1056/NEJMra1100359

[114] Clarindo, M.V., Possebon, A.T., Soligo, E.M., Uyeda, H., *et al.* (2014) Dermatitis Herpetiformis: Pathophysiology, Clinical Presentation, Diagnosis and Treatment.

Anais Brasileiros de Dermatologia, **89**, 865-877. https://doi.org/10.1590/abd1806-4841.20142966

[115] Chorzelski, T.P., Beutner, E.H., Sulej, J., Tchorzewska, H., Jablonska, S., Kumar, V. and Kapuscinska, A. (1984) IgA Anti-Endomysium Antibody. A New Immunological Marker of Dermatitis Herpetiformis and Coeliac Disease. *The British Journal of Dermatology*, **111**, 395-402. https://doi.org/10.1111/j.1365-2133.1984.tb06601.x

[116] Mok, C.C. and Lau, C.S. (2003) Pathogenesis of Systemic Lupus Erythematosus. *Journal of Clinical Pathology*, **56**, 481-490. https://doi.org/10.1136/jcp.56.7.481

[117] Anhalt, G.J., Kim, S.C., Stanley, J.R., Korman, N.J., *et al.* (1990) Paraneoplastic Pemphigus. An Autoimmune Mucocutaneous Disease Associated with Neoplasia. *The New England Journal of Medicine*, **323**, 1729-1735. https://doi.org/10.1056/NEJM199012203232503

[118] Jackson, S.R., Koestenbauer, J., Carroll, A.P., Oo, T.H., Chou, S. and Indrajit, B. (2020) Paraneoplastic Bullous Pemphigoid—A Sign of Clear Cell Renal Carcinoma. *Urology Case Reports*, **30**, Article ID: 101119. https://doi.org/10.1016/j.eucr.2020.101119

[119] Pachinger, W. (1983) Zum paraneoplastischen Lichen ruber pemphigoides [Paraneoplastic Lichen Ruber Pemphigoides]. *Zeitschrift fur Hautkrankheiten*, **58**, 1024-1037.

[120] Smatti, M.K., Cyprian, F.S., Nasrallah, G.K., Al Thani, A.A., Almishal, R.O. and Yassine, H.M. (2019) Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses*, **11**, Article 762. https://doi.org/10.3390/v11080762

[121] Kemppainen, K.M., Lynch, K.F., Liu, E., Lönnrot, M., *et al.* and TEDDY Study Group (2017) Factors That Increase Risk of Celiac Disease Autoimmunity after a Gastrointestinal Infection in Early Life. *Clinical Gastroenterology and Hepatology*, **15**, 694-702.e5. https://doi.org/10.1016/j.cgh.2016.10.033

[122] Blomqvist, M., Juhela, S., Erkkila, S., Korhonen, S., *et al.* (2002) Rotavirus Infections and Development of Diabetes-Associated Autoantibodies during the First 2 Years of life. *Clinical and Experimental Immunology*, **128**, 511-515. https://doi.org/10.1046/j.1365-2249.2002.01842.x

[123] Pane, J.A., Webster, N.L., Graham, K.L., Holloway, G., Zufferey, C. and Coulson, B.S. (2013) Rotavirus Acceleration of Murine Type 1 Diabetes Is Associated with a T Helper 1-Dependent Specific Serum Antibody Response and Virus Effects in Regional Lymph Nodes. *Diabetologia*, **56**, 573-582. https://doi.org/10.1007/s00125-012-2798-4

[124] Pak, C.Y., Eun, H.M., McArthur, R.G. and Yoon, J.W. (1988) Association of Cytomegalovirus Infection with Autoimmune Type 1 Diabetes. *The Lancet* (London, England), **332**, 1-4. https://doi.org/10.1016/S0140-6736(88)92941-8

[125] Laitinen, O.H., Honkanen, H., Pakkanen, O., Oikarinen, S., *et al.* (2014) Coxsackievirus B1 Is Associated with Induction of β-Cell Autoimmunity That Portends Type 1 Diabetes. *Diabetes*, **63**, 446-455. https://doi.org/10.2337/db13-0619

[126] Moon, U.Y., Park, S.J., Oh, S.T., Kim, W.U., *et al.* (2004) Patients with Systemic Lupus Erythematosus Have Abnormally Elevated Epstein-Barr Virus Load in Blood. *Arthritis Research & Therapy*, **6**, R295-R302.

[127] Draborg, A.H., Jørgensen, J.M., Müller, H., Nielsen, C.T., *et al.* (2012) Epstein-Barr Virus Early Antigen Diffuse (EBV-EA/D)-Directed Immunoglobulin A Antibodies in Systemic Lupus Erythematosus Patients. *Scandinavian Journal of Rheumatology*, **41**, 280-289. https://doi.org/10.3109/03009742.2012.665944

[128] Gross, A.J., Hochberg, D., Rand, W.M. and Thorley-Lawson, D.A. (2005) EBV and Systemic Lupus Erythematosus: A New Perspective. *Journal of Immunology* (Baltimore, MD.: 1950), **174**, 6599-6607. https://doi.org/10.4049/jimmunol.174.11.6599

[129] Bar-Or, A., Pender, M.P., Khanna, R., Steinman, L., *et al.* (2021) Epstein-Barr Virus in Multiple Sclerosis: Theory and Emerging Immunotherapies: (Trends in Molecular Medicine, 26:3 p:296-310, 2020). *Trends in Molecular Medicine*, **27**, 410-411. https://doi.org/10.1016/j.molmed.2021.01.004

[130] Price, J.V., *et al.* (2013) Protein Microarray Analysis Reveals BAFF-Binding Autoantibodies in Systemic Lupus Erythematosus. *Journal of Clinical Investigation*, **123**, 5135-5145. https://doi.org/10.1172/JCI70231

[131] Adler, B.L. and Christopher-Stine, L. (2018) Triggers of Inflammatory Myopathy: Insights into Pathogenesis. *Discovery Medicine*, **25**, 75-83.

[132] Girschick, H.J., Guilherme, L., Inman, R.D., Latsch, K., *et al.* (2008) Bacterial Triggers and Autoimmune Rheumatic Diseases. *Clinical and Experimental Rheumatology*, **26**, S12-S17.

[133] Seidel, M.F., Domene, A.B. and Vetter, H. (2007) Differential Diagnoses of Suspected Lyme Borreliosis or Post-Lyme-Disease Syndrome. *European Journal of Clinical Microbiology & Infectious Diseases*, **26**, 611-617. https://doi.org/10.1007/s10096-007-0342-0

[134] Yehudina, Y. and Trypilka, S. (2021) Lyme Borreliosis as a Trigger for Autoimmune Disease. *Cureus*, **13**, e18648. https://doi.org/10.7759/cureus.18648

[135] Tan, E.H., Sena, A.G., Prats-Uribe, A., You, S.C., *et al.* (2021) COVID-19 in Patients with Autoimmune Diseases: Characteristics and Outcomes in a Multinational Network of Cohorts across Three Countries. *Rheumatology* (Oxford), **60**, SI37-SI50. https://doi.org/10.1093/rheumatology/keab250

[136] Dreyer, N., Petruski-Ivleva, N., Albert, L., Mohamed, D., Brinkley, E., Reynolds, M. and Toovey, S. (2021) Identification of a Vulnerable Group for Post-Acute Sequelae of SARS-CoV-2 (PASC): People with Autoimmune Diseases Recover More Slowly from COVID-19. *International Journal of General Medicine*, **14**, 3941-3949. https://doi.org/10.2147/IJGM.S313486

[137] Akiyama, S., Hamdeh, S., Micic, D. and Sakuraba, A. (2021) Prevalence and Clinical Outcomes of COVID-19 in Patients with Autoimmune Diseases: A Systematic Review and Meta-Analysis. *Annals of the Rheumatic Diseases*, **80**, 384-391. https://doi.org/10.1136/annrheumdis-2020-218946

[138] Chatterjee, B., Karandikar, R.L. and Mande, S.C. (2021) Mortality Due to COVID-19 in Different Countries Is Associated with Their Demographic Character and Prevalence of Autoimmunity. *Current Science*, **120**, 501-508. https://doi.org/10.18520/cs/v120/i3/501-508

[139] Gracia-Ramos, A.E., Martin-Nares, E., Hernández-Molina, G., *et al.* (2021) New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. *Cells*, **10**, Article 3592. https://doi.org/10.3390/cells10123592

[140] Israeli, E., Agmon-Levin, N., Blank, M., Chapman, J. and Shoenfeld, Y. (2012) Guillain-Barré Syndrome—A Classical Autoimmune Disease Triggered by Infection or Vaccination. *Clinical Reviews in Allergy & Immunology*, **42**, 121-130. https://doi.org/10.1007/s12016-010-8213-3

[141] Toscano, G., *et al.* (2020) Guillain-Barré Syndrome Associated with SARS-CoV-2. *The New England Journal of Medicine*, **382**, 2574-2576. https://doi.org/10.1056/NEJMc2009191

[142] Newburger, J.W., Takahashi, M. and Burns, J.C. (2016) Kawasaki Disease. *Journal of the American College of Cardiology*, **67**, 1738-1749. https://doi.org/10.1016/j.jacc.2015.12.073

[143] Galeotti, C., Kaveri, S.V., Cimaz, R., Kon-Paut, I. and Bayry, J. (2016) Predisposing Factors, Pathogenesis, and Therapeutic Intervention of Kawasaki Disease. *Drug Discovery Today*, **21**, 1850-1857. https://doi.org/10.1016/j.drudis.2016.08.004

[144] Sakurai, Y. (2019) Autoimmune Aspects of Kawasaki Disease. *Journal of Investigational Allergology & Clinical Immunology*, **29**, 251-261. https://doi.org/10.18176/jiaci.0300

[145] Verdoni, L., Mazza, A., Gervasoni, A., Martelli, L., Ruggeri, M., Ciuffreda, M., Bonanomi, E. and D'Antiga, L. (2020) An Outbreak of Severe Kawasaki-Like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic: An Observational Cohort Study. *The Lancet* (London, England), **395**, 1771-1778. https://doi.org/10.1016/S0140-6736(20)31103-X

[146] Toubiana, J., Poirault, C., Corsia, A., Bajolle, F., *et al.* (2020) Kawasaki-Like multisystem Inflammatory Syndrome in Children during the Covid-19 Pandemic in Paris, France: Prospective Observational Study. *BMJ*, **369**, m2094. https://doi.org/10.1136/bmj.m2094

[147] Feldstein, L.R., Rose, E.B., Horwitz, S.M., Collins, J.P., *et al.* and CDC COVID-19 Response Team (2020) Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *The New England Journal of Medicine*, **383**, 334-346. https://doi.org/10.1056/NEJMoa2021680

[148] Bautista-Rodriguez, C., Sanchez-de-Toledo, J., Clark, B.C., Herberg, J., *et al.* (2021) Multisystem Inflammatory Syndrome in Children: An International Survey. *Pediatrics*, **147**, e2020024554. https://doi.org/10.1542/peds.2020-024554

[149] Belhadjer, Z., Méot, M., Bajolle, F., Khraiche, D., *et al.* (2020) Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation*, **142**, 429-436. https://doi.org/10.1161/CIRCULATIONAHA.120.048360

[150] Whittaker, E., Bamford, A., Kenny, J., Kaforou, *et al.* and PIMS-TS Study Group and EUCLIDS and PERFORM Consortia (2020) Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. *JAMA*, **324**, 259-269. https://doi.org/10.1001/jama.2020.10369

[151] Tolunay, O., Çelik, Ü., Arslan, İ., Orgun, A., Demir, H., Demir, O. and Dağdelen, E.Ç. (2021) Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: A Case Series Experience in a Tertiary Care Hospital of Southern Turkey. *Journal of Tropical Pediatrics*, **67**, fmab050. https://doi.org/10.1093/tropej/fmab050

[152] Dufort, E.M., Koumans, E.H., Chow, E.J., Rosenthal, *et al.* and New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team (2020) Multisystem Inflammatory Syndrome in Children in New York State. *The New England Journal of Medicine*, **383**, 347-358. https://doi.org/10.1056/NEJMoa2021756

[153] McArdle, A.J., Vito, O., Patel, H., Seaby, E.G., *et al.* and BATS Consortium (2021) Treatment of Multisystem Inflammatory Syndrome in Children. *The New England Journal of Medicine*, **385**, 11-22. https://doi.org/10.1056/NEJMoa2102968

[154] Hoffmann, J. and Enk, A.H. (2019) High-Dose Intravenous Immunoglobulin in Skin Autoimmune Disease. *Frontiers in Immunology*, **10**, Article 1090.

https://doi.org/10.3389/fimmu.2019.01090

[155] Consiglio, C.R., Cotugno, N., Sardh, F., Pou, C., *et al.* (2020) The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell*, **183**, 968-981.e7. https://doi.org/10.1016/j.cell.2020.09.016

[156] Zhou, Y., Han, T., Chen, J., Hou, C., Jia, E., *et al.* (2020) Clinical and Autoimmune Characteristics of Severe and Critical Cases of COVID-19. *Clinical and Translational Science*, **13**, 1077-1086. https://doi.org/10.1111/cts.12805

[157] Gagiannis, D., Steinestel, J., Hackenbroch, C., *et al.* (2020) COVID-19-Induced Acute Respiratory Failure—An Exacerbation of Organ-Specific Autoimmunity? *medRxiv* 2020.04.27.20077180. https://doi.org/10.1101/2020.04.27.20077180

[158] Lerma, L.A., Chaudhary, A., Bryan, A., Morishima, C., Wener, M.H. and Fink, S.L. (2020) Prevalence of Autoantibody Responses in Acute Coronavirus Disease 2019 (COVID-19). *Journal of Translational Autoimmunity*, **3**, Article ID: 100073. https://doi.org/10.1016/j.jtauto.2020.100073

[159] Wang, E.Y., Mao, T., Klein, J., *et al.* (2021) Diverse Functional Autoantibodies in Patients with COVID-19. *Nature*, **595**, 283-288. https://doi.org/10.1038/s41586-021-03631-y

[160] Bastard, P., Rosen, L.B., Zhang, Q., *et al.* (2020) Autoantibodies against Type I IFNs in Patients with Life-Threatening COVID-19. *Science*, **370**, eabd4585. https://doi.org/10.1126/science.abd4585

[161] Solanich, X., Rigo-Bonnin, R., Gumucio, V.D., *et al.* (2021) Pre-Existing Autoantibodies Neutralizing High Concentrations of Type I Interferons in Almost 10% of COVID-19 Patients Admitted to Intensive Care in Barcelona. *Journal of Clinical Immunology*, **41**, 1733-1744. https://doi.org/10.1007/s10875-021-01136-x

[162] Troya, J., Bastard, P., Planas-Serra, L. *et al.* (2021) Neutralizing Autoantibodies to Type I IFNs in >10% of Patients with Severe COVID-19 Pneumonia Hospitalized in Madrid, Spain. *Journal of Clinical Immunology*, **41**, 914-922. https://doi.org/10.1007/s10875-021-01036-0

[163] Tang, K.T., Hsu, B.C. and Chen, D.Y. (2021) Autoimmune and Rheumatic Manifestations Associated with COVID-19 in Adults: An Updated Systematic Review. *Frontiers in Immunology*, **12**, Article ID: 645013. https://doi.org/10.3389/fimmu.2021.645013

[164] Garg, M., Maralakunte, M., Garg, S., Dhooria, S., Sehgal, I., *et al.* (2021) The Conundrum of 'Long-COVID-19': A Narrative Review. *International Journal of General Medicine*, **14**, 2491-2506. https://doi.org/10.2147/IJGM.S316708

[165] Ramani, S.L., Samet, J., Franz, C.K., Hsieh, C., Nguyen, C.V., Horbinski, C. and Deshmukh, S. (2021) Musculoskeletal Involvement of COVID-19: Review of Imaging. *Skeletal Radiology*, **50**, 1763-1773. https://doi.org/10.1007/s00256-021-03734-7

[166] Ahmed, S., Zimba, O. and Gasparyan, A.Y. (2021) COVID-19 and the Clinical Course of Rheumatic Manifestations. *Clinical Rheumatology*, **40**, 2611-2619. https://doi.org/10.1007/s10067-021-05691-x

[167] Acosta-Ampudia, Y., Monsalve, D.M., Rojas, M., Rodríguez, Y., Zapata, E., Ramírez-Santana, C. and Anaya, J.M. (2022) Persistent Autoimmune Activation and Proinflammatory State in Post-COVID Syndrome. *The Journal of Infectious Diseases*, **225**, 2155-2162. https://doi.org/10.1093/infdis/jiac017

[168] Restivo, D.A., Centonze, D., Alesina, A. and Marchese-Ragona, R. (2020) Myasthenia Gravis Associated with SARS-CoV-2 Infection. *Annals of Internal Medicine*, **173**, 1027-1028. https://doi.org/10.7326/L20-0845

[169] Assini, A., Gandoglia, I., Damato, V., Rikani, K., Evoli, A. and Del Sette, M. (2021)

Myasthenia Gravis Associated with Anti-MuSK Antibodies Developed after SARS-CoV-2 Infection. *European Journal of Neurology*, **28**, 3537-3539. https://doi.org/10.1111/ene.14721

[170] Zuniga, M., Gomes, C., Carsons, S.E., Bender, M.T., Cotzia, P., Miao, Q.R., Lee, D.C. and Rodriguez, A. (2021) Autoimmunity to Annexin A2 Predicts Mortality among Hospitalised COVID-19 Patients. *The European Respiratory Journal*, **58**, Article ID: 2100918. https://doi.org/10.1183/13993003.00918-2021

[171] Chang, S.E., Feng, A., Meng, W., Apostolidis, S.A., *et al.* (2021) New-Onset IgG Autoantibodies in Hospitalized Patients with COVID-19. *Nature Communications*, **12**, Article No. 5417. https://doi.org/10.1038/s41467-021-25509-3

[172] Aschman, T., Schneider, J., Greuel, S., Meinhardt, J., *et al.* (2021) Association between SARS-CoV-2 Infection and Immune-Mediated Myopathy in Patients Who Have Died. *JAMA Neurology*, **78**, 948-960. https://doi.org/10.1001/jamaneurol.2021.2004

[173] Proal, A.D. and VanElzakker, M.B. (2021) Long COVID or Post-Acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Frontiers in Microbiology*, **12**, Article ID: 698169. https://doi.org/10.3389/fmicb.2021.698169

[174] Huang, Y., Pinto, M.D., Borelli, J.L., Mehrabadi, M.A., *et al.* (2021) COVID Symptoms, Symptom Clusters, and Predictors for Becoming a Long-Hauler: Looking for Clarity in the Haze of the Pandemic. *medRxiv*: The Preprint Server for Health Sciences, 2021.03.03.21252086. https://doi.org/10.1101/2021.03.03.21252086

[175] Nalbandian, A., Sehgal, K., Gupta, A., *et al.* (2021) Post-Acute COVID-19 Syndrome. *Nature Medicine*, **27**, 601-615. https://doi.org/10.1038/s41591-021-01283-z

[176] Oran, D.P. and Topol, E.J. (2020) Prevalence of Asymptomatic SARS-CoV-2 Infection. *Annals of Internal Medicine*, **173**, 362-367. https://doi.org/10.7326/M20-3012

[177] Davies, N.G., Klepac, P., Liu, Y., *et al.* (2020) Age-Dependent Effects in the Transmission and Control of COVID-19 Epidemics. *Nature Medicine*, **26**, 1205-1211. https://doi.org/10.1038/s41591-020-0962-9

[178] Guan, W.J., Ni, Z.Y., Hu, Y., Zhong, N.S., *et al.* (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England Journal of Medicine*, **382**, 1708-1720. https://doi.org/10.1056/NEJMoa2002032

[179] Jiang, F., Deng, L., Zhang, L., Cai, Y., *et al.* (2020) Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). *Journal of General Internal Medicine*, **35**, 1545-1549. https://doi.org/10.1007/s11606-020-05762-w

[180] de Roquetaillade, C., Bredin, S., Lascarrou, J.B., Soumagne, T., *et al.* (2021) Timing and Causes of Death in Severe COVID-19 Patients. *Critical Care* (London, England), **25**, Article No. 224. https://doi.org/10.1186/s13054-021-03639-w

[181] Verity, R., Okell, L.C., Dorigatti, I., Winskill, P., *et al.* (2020) Estimates of the Severity of Coronavirus Disease 2019: A Model-Based Analysis. *The Lancet*: *Infectious Diseases*, **20**, 669-677. https://doi.org/10.1016/S1473-3099(20)30243-7

[182] Woolf, S.H., Chapman, D.A. and Lee, J.H. (2021) COVID-19 as the Leading Cause of Death in the United States. *JAMA*, **325**, 123-124. https://doi.org/10.1001/jama.2020.24865

[183] Folgueira, M.D., *et al.* (2021) Prolonged SARS-CoV-2 Cell Culture Replication in Respiratory Samples from Patients with Severe COVID-19. *Clinical Microbiology and Infection*, **27**, 886-891. https://doi.org/10.1016/j.cmi.2021.02.014

[184] Prebensen, C., *et al.* (2021) Severe Acute Respiratory Syndrome Coronavirus 2 RNA

in Plasma Is Associated with Intensive Care Unit Admission and Mortality in Patients Hospitalized with Coronavirus Disease 2019. *Clinical Infectious Diseases*, **73**, e799-e802. https://doi.org/10.1093/cid/ciaa1338

[185] Li, Y., Schneider, A.M., Mehta, A., *et al.* (2021) SARS-CoV-2 Viremia Is Associated with Distinct Proteomic Pathways and Predicts COVID-19 Outcomes. *Journal of Clinical Investigation*, **131**, e148635. https://doi.org/10.1172/JCI148635

[186] Fajnzylber, J., *et al.* (2020) Massachusetts Consortium for Pathogen Readiness. SARS-CoV-2 Viral Load Is Associated with Increased Disease Severity and Mortality. *Nature Communications*, **11**, Article No. 5493. https://doi.org/10.1038/s41467-020-19057-5

[187] Matsuishi, Y., Mathis, B.J., Shimojo, N., Subrina, J., Okubo, N. and Inoue, Y. (2021) Severe COVID-19 Infection Associated with Endothelial Dysfunction Induces Multiple Organ Dysfunction: A Review of Therapeutic Interventions. *Biomedicines*, **9**, Article 279. https://doi.org/10.3390/biomedicines9030279

[188] Chen, T., Wu, D., Chen, H., Yan, W., *et al.* (2020) Clinical Characteristics of 113 Deceased Patients with Coronavirus Disease 2019: Retrospective Study. *BMJ*, **368**, m1091. https://doi.org/10.1136/bmj.m1091

[189] Katz, L.M. (2020) Is SARS-CoV-2 Transfusion Transmitted? *Transfusion*, **60**, 1111-1114. https://doi.org/10.1111/trf.15831

[190] Andersson, M.I., *et al.* (2020) SARS-CoV-2 RNA Detected in Blood Products from Patients with COVID-19 Is Not Associated with Infectious Virus. *Wellcome Open Research*, **5**, 181. https://doi.org/10.12688/wellcomeopenres.16002.2

[191] Diao, B., Wang, C., Wang, R., Feng, Z., *et al.* (2021) Human Kidney Is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Nature Communications*, **12**, Article No. 2506. https://doi.org/10.1038/s41467-021-22781-1

[192] Argyropoulos, K.V., Serrano, A., Hu, J., Black, M., *et al.* (2020) Association of Initial Viral Load in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Patients with Outcome and Symptoms. *The American Journal of Pathology*, **190**, 1881-1887. https://doi.org/10.1016/j.ajpath.2020.07.001

[193] Verity, R., Okell, L C., Dorigatti, I., Winskill, P., *et al.* (2020) Estimates of the Severity of Coronavirus Disease 2019: A Model-Based Analysis. *The Lancet*: *Infectious Diseases*, **20**, 669-677. https://doi.org/10.1016/S1473-3099(20)30243-7

[194] Elezkurtaj, S., Greuel, S., Ihlow, J., Michaelis, E.G., *et al.* (2021) Causes of Death and Comorbidities in Hospitalized Patients with COVID-19. *Scientific Reports*, **11**, Article No. 4263. https://doi.org/10.1038/s41598-021-82862-5

[195] Wichmann, D., Sperhake, J.P., Lütgehetmann, M., Steurer, S., *et al.* (2020) Autopsy Findings and Venous Thromboembolism in Patients with COVID-19: A Prospective Cohort Study. *Annals of Internal Medicine,* **173**, 268-277. https://doi.org/10.7326/M20-2003

[196] Fox, S.E., Akmatbekov, A., Harbert, J.L., Li, G., Quincy Brown, J. and Vander Heide, R.S. (2020) Pulmonary and Cardiac Pathology in African American Patients with COVID-19: An Autopsy Series from New Orleans. *The Lancet*: *Respiratory Medicine*, **8**, 681-686. https://doi.org/10.1016/S2213-2600(20)30243-5

[197] Haberecker, M., Schwarz, E.I., Steiger, P., Frontzek, K., *et al.* (2022) Autopsy-Based Pulmonary and Vascular Pathology: Pulmonary Endotheliitis and Multi-Organ Involvement in COVID-19 Associated Deaths. *Respiration*, **101**, 155-165. https://doi.org/10.1159/000518914

[198] Fitzek, A., Schädler, J., Dietz, E., Ron, A., *et al.* (2021) Prospective Postmortem Evaluation of 735 Consecutive SARS-CoV-2-Associated Death Cases. *Scientific Re-*

ports, **11**, Article No. 19342. https://doi.org/10.1038/s41598-021-98499-3

[199] Borczuk, A.C., Salvatore, S.P., Seshan, S.V., Patel, S.S., *et al.* (2020) COVID-19 Pulmonary Pathology: A Multi-Institutional Autopsy Cohort from Italy and New York City. *Modern Pathology*, **33**, 2156-2168. https://doi.org/10.1038/s41379-020-00661-1

[200] Mayadas, T.N., Cullere, X. and Lowell, C.A. (2014) The Multifaceted Functions of Neutrophils. *Annual Review of Pathology*, **9**, 181-218. https://doi.org/10.1146/annurev-pathol-020712-164023

[201] Korkmaz, B., Horwitz, M.S., Jenne, D.E. and Gauthier, F. (2010) Neutrophil Elastase, Proteinase 3, and Cathepsin G as Therapeutic Targets in Human Diseases. *Pharmacological Reviews*, **62**, 726-759. https://doi.org/10.1124/pr.110.002733

[202] Cicco, S., Cicco, G., Racanelli, V. and Vacca, A. (2020) Neutrophil Extracellular Traps (NETs) and Damage-Associated Molecular Patterns (DAMPs): Two Potential Targets for COVID-19 Treatment. *Mediators of Inflammation*, **2020**, Article ID: 7527953. https://doi.org/10.1155/2020/7527953

[203] Bucurenci, N., Blake, D.R., Chidwick, K. and Winyard, P.G. (1992) Inhibition of Neutrophil Superoxide Production by Human Plasma Alpha 1-Antitrypsin. *FEBS Letters*, **300**, 21-24. https://doi.org/10.1016/0014-5793(92)80156-B

[204] Hurley, K., Lacey, N., O'Dwyer, C.A., Bergin, D.A., *et al.* (2014) Alpha-1 Antitrypsin Augmentation Therapy Corrects Accelerated Neutrophil Apoptosis in Deficient Individuals. *The Journal of Immunology*, **193**, 3978-3991. https://doi.org/10.4049/jimmunol.1400132

[205] Bergin, D.A., *et al.* (2010) α-1 Antitrypsin Regulates Human Neutrophil Chemotaxis Induced by Soluble Immune Complexes and IL-8. *Journal of Clinical Investigation*, **120**, 4236-4250. https://doi.org/10.1172/JCI41196

[206] Bergin, D.A., *et al.* (2014) The Circulating Proteinase Inhibitor α-1 Antitrypsin Regulates Neutrophil Degranulation and Autoimmunity. *Science Translational Medicine*, **6**, 217ra1. https://doi.org/10.1126/scitranslmed.3007116

[207] Sun, S., *et al.* (2020) Abnormalities of Peripheral Blood System in Patients with COVID-19 in Wenzhou, China. *Clinica Chimica Acta*, **507**, 174-180. https://doi.org/10.1016/j.cca.2020.04.024

[208] Liu, J., *et al.* (2020) Longitudinal Characteristics of Lymphocyte Responses and Cytokine Profiles in the Peripheral Blood of SARS-CoV-2 Infected Patients. *eBioMedicine*, **55**, Article ID: 102763. https://doi.org/10.1016/j.ebiom.2020.102763

[209] Kong, M., Zhang, H., Cao, X., Mao, X. and Lu, Z. (2020) Higher Level of Neutrophil-to-Lymphocyte Is Associated with Severe COVID-19. *Epidemiology & Infection*, **148**, e139. https://doi.org/10.1017/S0950268820001557

[210] Pakos, I.S., *et al.* (2020) Characteristics of Peripheral Blood Differential Counts in Hospitalized Patients with COVID-19. *European Journal of Haematology*, **105**, 773-778. https://doi.org/10.1111/ejh.13509

[211] Vafadar Moradi, E., Teimouri, A., Rezaee, R., Morovatdar, N., *et al.* (2020) Increased Age, Neutrophil-to-Lymphocyte Ratio (NLR) and White Blood Cells Count Are Associated with Higher COVID-19 Mortality. *The American Journal of Emergency Medicine*, **40**, 11-14. https://doi.org/10.1016/j.ajem.2020.12.003

[212] Wu, P., *et al.* (2021) The Trans-Omics Landscape of COVID-19. *Nature Communications*, **12**, Article No. 4543. https://doi.org/10.1038/s41467-021-24482-1

[213] Ackermann, M., Anders, H.J., Bilyy, R., Bowlin, G.L., *et al.* (2021) Patients with COVID-19: In the Dark-NETs of Neutrophils. *Cell Death and Differentiation*, **28**, 3125-3139. https://doi.org/10.1038/s41418-021-00805-z

[214] Hammad, R., *et al.* (2021) Circulating Cell-Free DNA, Peripheral Lymphocyte Subsets Alterations and Neutrophil Lymphocyte Ratio in Assessment of COVID-19 Severity. *Innate Immunity*, **27**, 240-250. https://doi.org/10.1177/1753425921995577

[215] McElvaney, O.J., *et al.* (2020) Characterization of the Inflammatory Response to Severe COVID-19 Illness. *American Journal of Respiratory and Critical Care Medicine*, **202**, 812-821. https://doi.org/10.1164/rccm.202005-1583OC

[216] Chen, H., Liu, W., Wang, Y., Liu, D., Zhao, L. and Yu, J. (2021) SARS-CoV-2 Activates Lung Epithelial Cell Proinflammatory Signaling and Leads to Immune Dysregulation in COVID-19 Patients. *eBioMedicine*, **70**, Article ID: 103500. https://doi.org/10.1016/j.ebiom.2021.103500

[217] Tomar, B., Anders, H.J., Desai, J. and Mulay, S.R. (2020) Neutrophils and Neutrophil Extracellular Traps Drive Necroinflammation in COVID-19. *Cells*, **9**, Article 1383. https://doi.org/10.3390/cells9061383

[218] Zuo, Y., Yalavarthi, S., Navaz, S.A., Hoy, C.K., *et al.* (2021) Autoantibodies Stabilize Neutrophil Extracellular Traps in COVID-19. *JCI Insight*, **6**, e150111. https://doi.org/10.1172/jci.insight.150111

[219] Wang, J., Li, Q., Yin, Y., Zhang, Y., *et al.* (2020) Excessive Neutrophils and Neutrophil Extracellular Traps in COVID-19. *Frontiers in Immunology*, **11**, Article 2063. https://doi.org/10.3389/fimmu.2020.02063

[220] Yang, J., Wu, Z., Long, Q., Huang, J., Hong, T., Liu, W. and Lin, J. (2020) Insights into Immunothrombosis: The Interplay Among Neutrophil Extracellular Trap, von Willebrand Factor, and ADAMTS13. *Frontiers in Immunology*, **11**, Article 610696. https://doi.org/10.3389/fimmu.2020.610696

[221] Reusch, N., De Domenico, E., Bonaguro, L., Schulte-Schrepping, J., Baßler, K., Schultze, J.L. and Aschenbrenner, A.C. (2021) Neutrophils in COVID-19. *Frontiers in Immunology*, **12**, Article ID: 652470. https://doi.org/10.3389/fimmu.2021.652470

[222] Rothan, H.A. and Byrareddy, S.N. (2020) The Epidemiology and Pathogenesis of Coronavirus Disease (COVID-19) Outbreak. *Journal of Autoimmunity*, **109**, Article ID: 102433. https://doi.org/10.1016/j.jaut.2020.102433

[223] Middleton, E.A., He, X.Y., Denorme, F., *et al.* (2020) Neutrophil Extracellular Traps Contribute to Immunothrombosis in COVID-19 Acute Respiratory Distress Syndrome. *Blood*, **136**, 1169-1179. https://doi.org/10.1182/blood.2020007008

[224] Blasco, A., Coronado, M.J., Hernández-Terciado, F., Martín, P., *et al.* (2021) Assessment of Neutrophil Extracellular Traps in Coronary Thrombus of a Case Series of Patients with COVID-19 and Myocardial Infarction. *JAMA Cardiology*, **6**, 469-474. https://doi.org/10.1001/jamacardio.2020.7308

[225] Veras, F.P., Pontelli, M.C., Silva, C.M., *et al.* (2020) SARS-CoV-2-Triggered Neutrophil Extracellular Traps Mediate COVID-19 Pathology. *The Journal of Experimental Medicine*, **217**, e20201129. https://doi.org/10.1084/jem.20201129

[226] Janiuk, K., Jabłońska, E. and Garley, M. (2021) Significance of NETs Formation in COVID-19. *Cells*, **10**, Article 151. https://doi.org/10.3390/cells10010151

[227] Tagami, T., Tosa, R., Omura, M., Fukushima, H., *et al.* (2014) Effect of a Selective Neutrophil Elastase Inhibitor on Mortality and Ventilator-Free Days in Patients with Increased Extravascular Lung Water: A Post Hoc Analysis of the PiCCO Pulmonary Edema Study. *Journal of Intensive Care*, **2**, Article No. 67. https://doi.org/10.1186/s40560-014-0067-y

[228] Barnes, B.J., Adrover, J.M., Baxter-Stoltzfus, A., *et al.* (2020) Targeting Potential Drivers of COVID-19: Neutrophil Extracellular Traps. *The Journal of Experimental Medicine*, **217**, e20200652. https://doi.org/10.1084/jem.20200652

[229] Al-Kuraishy, H.M., Al-Gareeb, A.I., Al-Hussaniy, H.A., Al-Harcan, N.A.H., Alexiou, A. and Batiha, G.E. (2022) Neutrophil Extracellular Traps (NETs) and Covid-19: A New Frontiers for Therapeutic Modality. *International Immunopharmacology*, **104**, Article ID: 108516. https://doi.org/10.1016/j.intimp.2021.108516

[230] Strich, J.R., Ramos-Benitez, M.J., Randazzo, D., Stein, S.R., *et al.* (2021) Fostamatinib Inhibits Neutrophils Extracellular Traps Induced by COVID-19 Patient Plasma: A Potential Therapeutic. *The Journal of Infectious Diseases*, **223**, 981-984. https://doi.org/10.1093/infdis/jiaa789

[231] Fajgenbaum, D.C. and June, C.H. (2020) Cytokine Storm. *The New England Journal of Medicine*, **383**, 2255-2273. https://doi.org/10.1056/NEJMra2026131

[232] Huang, C., Wang, Y., *et al.* (2020) Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *The Lancet*, **395**, 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[233] Notz, Q., Schmalzing, M., Wedekink, F., Schlesinger, T., *et al.* (2020) Pro- and Anti-Inflammatory Responses in Severe COVID-19-Induced Acute Respiratory Distress Syndrome—An Observational Pilot Study. *Frontiers in Immunology*, **11**, Article ID: 581338. https://doi.org/10.3389/fimmu.2020.581338

[234] Tang, Y., Liu, J., Zhang, D., Xu, Z., Ji, J. and Wen, C. (2020) Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Frontiers in Immunology*, **11**, Article 1708. https://doi.org/10.3389/fimmu.2020.01708

[235] Yang, L., Xie, X., Tu, Z., *et al.* (2021) The Signal Pathways and Treatment of Cytokine Storm in COVID-19. *Signal Transduction and Targeted Therapy*, **6**, Article No. 255. https://doi.org/10.1038/s41392-021-00679-0

[236] Stockman, L.J., Bellamy, R. and Garner, P. (2006) SARS: Systematic Review of Treatment Effects. *PLOS Medicine*, **3**, e343. https://doi.org/10.1371/journal.pmed.0030343

[237] Arabi, Y.M., Mandourah, Y., Al-Hameed, F., *et al.* (2018) Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *American Journal of Respiratory and Critical Care Medicine*, **197**, 757-767. https://doi.org/10.1164/rccm.201706-1172OC

[238] Brattsand, R. and Linden, M. (1996) Cytokine Modulation by Glucocorticoids: Mechanisms and Actions in Cellular Studies. *Alimentary Pharmacology & Therapeutics*, **10**, 81-92. https://doi.org/10.1046/j.1365-2036.1996.22164025.x

[239] Nguyen, V.T., Arredondo, J., Chernyavsky, A.I., Kitajima, Y., Pittelkow, M. and Grando, S.A. (2004) Pemphigus Vulgaris IgG and Methylprednisolone Exhibit Reciprocal Effects on Keratinocytes. *Journal of Biological Chemistry*, **279**, 2135-2146. https://doi.org/10.1074/jbc.M309000200

[240] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, *et al.* (2021) Association between Administration of IL-6 Antagonists and Mortality among Patients Hospitalized for COVID-19: A Meta-Analysis. *JAMA*, **326**, 499-518.

[241] Woo, P.C., Lau, S.K., Wong, B.H., Chan, K.H., *et al.* (2004) Longitudinal Profile of Immunoglobulin G (IgG), IgM, and IgA Antibodies against the Severe Acute Respiratory Syndrome (SARS) Coronavirus Nucleocapsid Protein in Patients with Pneumonia Due to the SARS Coronavirus. *Clinical and Diagnostic Laboratory Immunology*, **11**, 665-668. https://doi.org/10.1128/CDLI.11.4.665-668.2004

[242] Hsueh, P.R., Huang, L.M., Chen, P.J., Kao, C.L. and Yang, P.C. (2004) Chronological Evolution of IgM, IgA, IgG and Neutralisation Antibodies after Infection with SARS-Associated Coronavirus. *Clinical Microbiology and Infection*, **10**, 1062-1066.

https://doi.org/10.1111/j.1469-0691.2004.01009.x

[243] van de Sandt, C.E., Kreijtz, J.H. and Rimmelzwaan, G.F. (2012) Evasion of Influenza A Viruses from Innate and Adaptive Immune Responses. *Viruses*, **4**, 1438-1476. https://doi.org/10.3390/v4091438

[244] Ko, J.H., Müller, M.A., Seok, H., Park, G.E., *et al.* (2017) Suggested New Breakpoints of Anti-MERS-CoV Antibody ELISA Titers: Performance Analysis of Serologic Tests. *European Journal of Clinical Microbiology & Infectious Diseases*, **36**, 2179-2186. https://doi.org/10.1007/s10096-017-3043-3

[245] Padoan, A., Sciacovelli, L., Basso, D., Negrini, D., *et al.* (2020) IgA-Ab Response to Spike Glycoprotein of SARS-CoV-2 in Patients with COVID-19: A Longitudinal Study. *Clinica Chimica Acta*, **507**, 164-166. https://doi.org/10.1016/j.cca.2020.04.026

[246] Yu, H.Q., Sun, B.Q., Fang, Z.F., Zhao, J.C., *et al.* (2020) Distinct Features of SARS-CoV-2-Specific IgA Response in COVID-19 Patients. *European Respiratory Journal*, **56**, Article ID: 2001526. https://doi.org/10.1183/13993003.01526-2020

[247] Ma, H., Zeng, W., He, H., Zhao, D., *et al.* (2020) Serum IgA, IgM, and IgG Responses in COVID-19. *Cellular & Molecular Immunology*, **17**, 773-775. https://doi.org/10.1038/s41423-020-0474-z

[248] Barzegar-Amini, M., Mahmoudi, M., Dadgarmoghaddam, M., Farzad, F., Najafabadi, A.Q. and Jabbari-Azad, F. (2022) Comparison of Serum Total IgA Levels in Severe and Mild COVID-19 Patients and Control Group. *Journal of Clinical Immunology*, **42**, 10-18. https://doi.org/10.1007/s10875-021-01149-6

[249] Zervou, F.N., Louie, P., Stachel, A., Zacharioudakis, I.M., Ortiz-Mendez, Y., Thomas, K. and Aguero-Rosenfeld, M.E. (2021) SARS-CoV-2 Antibodies: IgA Correlates with Severity of Disease in Early COVID-19 Infection. *Journal of Medical Virology*, **93**, 5409-5415. https://doi.org/10.1002/jmv.27058

[250] Sugino, H., Sawada, Y. and Nakamura, M. (2021) IgA Vasculitis: Etiology, Treatment, Biomarkers and Epigenetic Changes. *International Journal of Molecular Sciences*, **22**, Article 7538. https://doi.org/10.3390/ijms22147538

[251] Suso, A.S., Mon, C., Oñate Alonso, I., Galindo Romo, K., *et al.* (2020) IgA Vasculitis with Nephritis (Henoch-Schönlein Purpura) in a COVID-19 Patient. *Kidney International Reports*, **5**, 2074-2078. https://doi.org/10.1016/j.ekir.2020.08.016

[252] AlGhoozi, D.A. and AlKhayyat, H.M. (2021) A Child with Henoch-Schonlein Purpura Secondary to a COVID-19 Infection. *BMJ Case Reports*, **14**, e239910. https://doi.org/10.1136/bcr-2020-239910

[253] Hoskins, B., Keeven, N., Dang, M., Keller, E. and Nagpal, R. (2021) A Child with COVID-19 and Immunoglobulin A Vasculitis. *Pediatric Annals*, **50**, e44-e48. https://doi.org/10.3928/19382359-20201211-01

[254] Allez, M., Denis, B., Bouaziz, J.D., Battistella, M., *et al.* (2020) COVID-19-Related IgA Vasculitis. *Arthritis & Rheumatology* (Hoboken, N.J.), **72**, 1952-1953. https://doi.org/10.1002/art.41428

[255] Jacobi, M., Lancrei, H.M., Brosh-Nissimov, T. and Yeshayahu, Y. (2021) Purpurona: A Novel Report of COVID-19-Related Henoch-Schonlein Purpura in a Child. *The Pediatric Infectious Disease Journal*, **40**, e93-e94. https://doi.org/10.1097/INF.0000000000003001

[256] Sandhu, S., Chand, S., Bhatnagar, A., Dabas, R., Bhat, S., Kumar, H. and Dixit, P.K. (2021) Possible Association between IgA Vasculitis and COVID-19. *Dermatologic Therapy*, **34**, e14551. https://doi.org/10.1111/dth.14551

[257] Li, N.L., Papini, A.B., Shao, T. and Girard, L. (2021) Immunoglobulin-A Vasculitis with Renal Involvement in a Patient with COVID-19: A Case Report and Review of

Acute Kidney Injury Related to SARS-CoV-2. *Canadian Journal of Kidney Health and Disease*, **8**. https://doi.org/10.1177/2054358121991684

[258] Zhang, Z., Zhang, G., Guo, M., Tao, W., Liu, X., Wei, H., Jin, T., Zhang, Y. and Zhu, S. (2021) The Potential Role of an Aberrant Mucosal Immune Response to SARS-CoV-2 in the Pathogenesis of IgA Nephropathy. *Pathogens*, **10**, Article 881. https://doi.org/10.3390/pathogens10070881

[259] Barbetta, L., Filocamo, G., Passoni, E., Boggio, F., Folli, C. and Monzani, V. (2021) Henoch-Schönlein Purpura with Renal and Gastrointestinal Involvement in Course of COVID-19: A Case Report. *Clinical and Experimental Rheumatology*, **39**, 191-192. https://doi.org/10.55563/clinexprheumatol/5epvob

[260] Jedlowski, P.M. and Jedlowski, M.F. (2022) Coronavirus Disease 2019-Associated Immunoglobulin A Vasculitis/Henoch-Schönlein Purpura: A Case Report and Review. *The Journal of Dermatology*, **49**, 190-196. https://doi.org/10.1111/1346-8138.16211

[261] Guney, C. and Akar, F. (2021) Epithelial and Endothelial Expressions of ACE2: SARS-CoV-2 Entry Routes. *Journal of Pharmacy & Pharmaceutical Sciences*, **24**, 84-93. https://doi.org/10.18433/jpps31455

[262] Zuo, Y., Estes, S.K., Ali, R.A., Gandhi, A.A., *et al.* (2020) Prothrombotic Autoantibodies in Serum from Patients Hospitalized with COVID-19. *Science Translational Medicine*, **12**, eabd3876. https://doi.org/10.1126/scitranslmed.abd3876

[263] Hasan Ali, O., Bomze, D., Risch, L., Brugger, S.D., *et al.* (2021) Severe Coronavirus Disease 2019 (COVID-19) Is Associated with Elevated Serum Immunoglobulin (Ig) A and Antiphospholipid IgA Antibodies. *Clinical Infectious Diseases*, **73**, e2869-e2874. https://doi.org/10.1093/cid/ciaa1496

[264] Hou, Y.J., Okuda, K., Edwards, C.E., Martinez, D.R., *et al.* (2020) SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. *Cell*, **182**, 429-446.E14. https://doi.org/10.1016/j.cell.2020.05.042

[265] Sterlin, D., Mathian, A., Miyara, M., Mohr, A., *et al.* (2021) IgA Dominates the Early Neutralizing Antibody Response to SARS-CoV-2. *Science Translational Medicine*, **13**, eabd2223. https://doi.org/10.1126/scitranslmed.abd2223

[266] Zone, J.J. (1991) Dermatitis Herpetiformis. *Current Problems in Dermatology*, **3**, 6-41. https://doi.org/10.1016/1040-0486(91)90003-M

[267] Diaz, M.S., Morita, L., Ferrari, B., Sartori, S., Greco, M.F., Sobrevias Bonells, L., *et al.* (2019) Linear IgA Bullous Dermatosis: A Series of 17 Cases. *Actas Dermo- Sifiliográficas*, **110**, 673-680. https://doi.org/10.1016/j.ad.2018.06.017

[268] Wang, J., Kwon, J., Ding, X., Fairley, J.A., Woodley, D.T. and Chan, L.S. (1997) Nonsecretory IgA1 Autoantibodies Targeting Desmosomal Component Desmoglein 3 in Intraepidermal Neutrophilic IgA Dermatosis. *The American Journal of Pathology*, **150**, 1901-1907.

[269] Hendrix, J.D., Mangum, K.L., Zone, J.J. and Gammon, W.R. (1990) Cutaneous IgA Deposits in Bullous Diseases Function as Ligands to Mediate Adherence of Activated Neutrophils. *Journal of Investigative Dermatology*, **94**, 667-672. https://doi.org/10.1111/1523-1747.ep12876246

[270] Dieterich, W., Laag, E., Bruckner-Tuderman, L., Reunala, T., Schuppan, D., *et al.* (1999) Antibodies to Tissue Transglutaminase as Serologic Markers in Patients with Dermatitis Herpetiformis. *The Journal of Investigative Dermatology*, **113**, 133-136. https://doi.org/10.1046/j.1523-1747.1999.00627.x

[271] Lingel, H., Meltendorf, S., Billing, U., Thurm, C., *et al.* (2021) Unique Autoantibody Prevalence in Long-Term Recovered SARS-CoV-2-Infected Individuals. *Journal of*

Autoimmunity, **122**, Article ID: 102682. https://doi.org/10.1016/j.jaut.2021.102682

[272] Penumatsa, K.C., Toksoz, D., Warburton, R.R., Kharnaf, M., *et al.* (2017) Transglutaminase 2 in Pulmonary and Cardiac Tissue Remodeling in Experimental Pulmonary Hypertension. *American Journal of Physiology*: *Lung Cellular and Molecular Physiology*, **313**, L752-L762. https://doi.org/10.1152/ajplung.00170.2017

[273] Mokhtari, T., Hassani, F., Ghaffari, N., Ebrahimi, B., Yarahmadi, A. and Hassanzadeh, G. (2020) COVID-19 and Multiorgan Failure: A Narrative Review on Potential Mechanisms. *Journal of Molecular Histology*, **51**, 613-628. https://doi.org/10.1007/s10735-020-09915-3

[274] Ronchetti, S., Ayroldi, E., Ricci, E., Gentili, M., Migliorati, G. and Riccardi, C. (2021) A Glance at the Use of Glucocorticoids in Rare Inflammatory and Autoimmune Diseases: Still an Indispensable Pharmacological Tool? *Frontiers in Immunology*, **11**, Article ID: 613435. https://doi.org/10.3389/fimmu.2020.613435

[275] Flammer, J.R. and Rogatsky, I. (2011) Minireview: Glucocorticoids in Autoimmunity: Unexpected Targets and Mechanisms. *Molecular Endocrinology* (Baltimore, MD), **25**, 1075-1086. https://doi.org/10.1210/me.2011-0068

[276] Ni, Y.-N., Chen, G., Sun, J., Liang, B.-M. and Liang, Z.-A. (2019) The Effect of Corticosteroids on Mortality of Patients with Influenza Pneumonia: A Systematic Review and Meta-Analysis. *Critical Care*, **23**, Article No. 99. https://doi.org/10.1186/s13054-019-2395-8

[277] Zhou, Y., Fu, X., Liu, X., *et al.* (2020) Use of Corticosteroids in Influenza-Associated Acute Respiratory Distress Syndrome and Severe Pneumonia: A Systemic Review and Meta-Analysis. *Scientific Reports*, **10**, Article No. 3044. https://doi.org/10.1038/s41598-020-59732-7

[278] RECOVERY Collaborative Group, Horby, P., Lim, W.S., Emberson, J.R., *et al.* (2021) Dexamethasone in Hospitalized Patients with Covid-19. *The New England Journal of Medicine*, **384**, 693-704. https://doi.org/10.1056/NEJMoa2021436

[279] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, *et al.* (2020) Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-Analysis. *JAMA*, **324**, 1330-1341. https://doi.org/10.1001/jama.2020.17023

[280] Wang, Y., Jiang, W., He, Q., Wang, C., *et al.* (2020) A Retrospective Cohort Study of Methylprednisolone Therapy in Severe Patients with COVID-19 Pneumonia. *Signal Transduction and Targeted Therapy*, **5**, Article No. 57. https://doi.org/10.1038/s41392-020-0158-2

[281] Papamanoli, A., Yoo, J., Grewal, P., Predun, W., Hotelling, J., *et al.* (2021) High-Dose Methylprednisolone in Nonintubated Patients with Severe COVID-19 Pneumonia. *European Journal of Clinical Investigation*, **51**, e13458. https://doi.org/10.1111/eci.13458

[282] Edalatifard, M., *et al.* (2020) Intravenous Methylprednisolone Pulse as a Treatment for Hospitalised Severe COVID-19 Patients: Results from a Randomised Controlled Clinical Trial. *European Respiratory Journal*, **56**, Article ID: 2002808. https://doi.org/10.1183/13993003.02808-2020

[283] Salton, F., *et al.* (2020) Prolonged Low-Dose Methylprednisolone in Patients with Severe COVID-19 Pneumonia. *Open Forum Infectious Diseases*, **7**, ofaa421. https://doi.org/10.1093/ofid/ofaa421

[284] Fernández-Cruz, A., Ruiz-Antorán, B., Muñoz-Gómez, A., Sancho-López, A., *et al.* (2020) Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality. *Antimicrobial Agents and Chemo-*

therapy, **64**, e01168-20. https://doi.org/10.1128/AAC.01168-20

[285] Chaudhuri, D., Sasaki, K., Karkar, A., Sharif, S., *et al.* (2021) Corticosteroids in COVID-19 and Non-COVID-19 ARDS: A Systematic Review and Meta-Analysis. *Intensive Care Medicine*, **47**, 521-537. https://doi.org/10.1007/s00134-021-06394-2

[286] Ranjbar, K., Moghadami, M., Mirahmadizadeh, A., Fallahi, M.J., *et al.* (2021) Methylprednisolone or Dexamethasone, Which One Is Superior Corticosteroid in the Treatment of Hospitalized COVID-19 Patients: A Triple-Blinded Randomized Controlled Trial. *BMC Infectious Diseases*, **21**, Article No. 337. https://doi.org/10.1186/s12879-021-06045-3

[287] Carbonell, R., Urgelés, S., Rodríguez, A., Bodí, M. and COVID-19 SEMICYUC Working Group (2021) Mortality Comparison between the First and Second/Third Waves among 3,795 Critical COVID-19 Patients with Pneumonia Admitted to the ICU: A Multicentre Retrospective Cohort Study. *The Lancet Regional Health—Europe*, **11**, Article ID: 100243. https://doi.org/10.1016/j.lanepe.2021.100243

[288] Wozel, G. and Blasum, C. (2014) Dapsone in Dermatology and Beyond. *Archives of Dermatological Research*, **306**, 103-124. https://doi.org/10.1007/s00403-013-1409-7

[289] World Health Organization (2022) World Health Organization Model List of Essential Medicines: 21st List 2019. World Health Organization, Geneva. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

[290] Breedveld, A. and van Egmond, M. (2019) IgA and Fc*α*RI: Pathological Roles and Therapeutic Opportunities. *Frontiers in Immunology*, **22**, Article 553. https://doi.org/10.3389/fimmu.2019.00553

[291] Nguyen, V.T. and Chan, L.S. (2022) Dapsone: A Century-Old Medicine and a New Hope for Severe COVID-19. *Advances in Infectious Diseases*, **12**, 50-56. https://doi.org/10.4236/aid.2022.121004

[292] Kanwar, B., Lee, C.J. and Lee, J.H. (2021) Specific Treatment Exists for SARS-CoV-2 ARDS. *Vaccines* (Basel), **9**, Article 635. https://doi.org/10.3390/vaccines9060635

[293] Critical Care Results of SARS-CoV-2 ARDS by Dapsone and Standard COVID-19 Treatment. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04918914?term=Dapsone&cond=COVID-19&draw=2&rank=2

[294] Dapsone Coronavirus SARS-CoV-2 Trial (DAP-CORONA) COVID-19 (DAP-CORONA). Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04935476?term=Dapsone&cond=COVID-19&draw=2&rank=1

[295] Cerqueira, S.R.P.S., Deps, P.D., Cunha, D.V., Bezerra, N.V.F., *et al.* (2021) The Influence of Leprosy-Related Clinical and Epidemiological Variables in the Occurrence and Severity of COVID-19: A Prospective Real-World Cohort Study. *PLOS Neglected Tropical Diseases*, **15**, e0009635. https://doi.org/10.1371/journal.pntd.0009635

[296] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/

[297] Bergamaschi, L., Mescia, F., Turner, L., Hanson, A.L., *et al.* (2021) Longitudinal analysis Reveals That Delayed Bystander CD8+ T Cell Activation and Early Immune Pathology Distinguish Severe COVID-19 from Mild Disease. *Immunity*, **54**, 1257-1275.e8. https://doi.org/10.1016/j.immuni.2021.05.010

[298] Gregorova, M., Morse, D., Brignoli, T., Steventon, J., *et al.* (2020) Post-Acute COVID-19 Associated with Evidence of Bystander T-Cell Activation and a Recurring Antibiotic-Resistant Bacterial Pneumonia. *eLife*, **9**, e63430. https://doi.org/10.7554/eLife.63430.sa2

[299] Kanduc, D. (2020) From Anti-SARS-CoV-2 Immune Responses to COVID-19 via Molecular Mimicry. *Antibodies* (Basel), **9**, Article 33. https://doi.org/10.3390/antib9030033

[300] Angileri, F., Légaré, S., Marino Gammazza, A., Conway de Macario, E., Macario, A. and Cappello, F. (2020) Is Molecular Mimicry the Culprit in the Autoimmune Haemolytic Anaemia Affecting Patients with COVID-19? *British Journal of Haematology*, **190**, e92-e93. https://doi.org/10.1111/bjh.16883

[301] Marino Gammazza, A., Légaré, S., Lo Bosco, G., Fucarino, A., *et al.* (2020) Human Molecular Chaperones Share with SARS-CoV-2 Antigenic Epitopes Potentially Capable of Eliciting Autoimmunity against Endothelial Cells: Possible Role of Molecular Mimicry in COVID-19. *Cell Stress & Chaperones*, **25**, 737-741. https://doi.org/10.1007/s12192-020-01148-3

[302] Lucchese, G. and Flöel, A. (2020) Molecular Mimicry between SARS-CoV-2 and Respiratory Pacemaker Neurons. *Autoimmunity Reviews*, **19**, Article ID: 102556. https://doi.org/10.1016/j.autrev.2020.102556

[303] Adiguzel, Y. (2021) Molecular Mimicry between SARS-CoV-2 and Human Proteins. *Autoimmunity Reviews*, **20**, Article ID: 102791. https://doi.org/10.1016/j.autrev.2021.102791

[304] Vojdani, A. and Kharrazian, D. (2020) Potential Antigenic Cross-Reactivity between SARS-CoV-2 and Human Tissue with a Possible Link to an Increase in Autoimmune Diseases. *Clinical Immunology* (Orlando, FL), **217**, Article ID: 108480. https://doi.org/10.1016/j.clim.2020.108480

[305] Vojdani, A., Vojdani, E. and Kharrazian, D. (2021) Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins with Tissue Antigens: Implications for Autoimmune Diseases. *Frontiers in Immunology*, **11**, Article ID: 617089. https://doi.org/10.3389/fimmu.2020.617089

[306] Lyons-Weiler, J. (2020) Pathogenic Priming Likely Contributes to Serious and Critical Illness and Mortality in COVID-19 via Autoimmunity. *Journal of Translational Autoimmunity*, **3**, Article ID: 100051. https://doi.org/10.1016/j.jtauto.2020.100051

[307] Ehrenfeld, M., Tincani, A., Andreoli, L., Cattalini, M., Shoenfeld, Y., *et al.* (2020) Covid-19 and Autoimmunity. *Autoimmunity Reviews*, **19**, Article ID: 102597. https://doi.org/10.1016/j.autrev.2020.102597

[308] Moody, R., Wilson, K., Flanagan, K.L., Jaworowski, A. and Plebanski, M. (2021) Adaptive Immunity and the Risk of Autoreactivity in COVID-19. *International Journal of Molecular Sciences*, **22**, Article 8965. https://doi.org/10.3390/ijms22168965

[309] Galeotti, C. and Bayry, J. (2020) Autoimmune and Inflammatory Diseases Following COVID-19. *Nature Reviews Rheumatology*, **16**, 413-414. https://doi.org/10.1038/s41584-020-0448-7.