Open Access Library Journal
2022, Volume 9, e8300
ISSN Online: 2333-9721
ISSN Print: 2333-9705

COVID-19: From Cough to Coffin

Patrick W. Chambers

Department of Pathology, Torrance Memorial Medical Center, Torrance, California, USA
Email: pwc@gte.net

How to cite this paper: Chambers, P.W. (2022) COVID-19: From Cough to Coffin. *Open Access Library Journal*, **9**: e8300.
https://doi.org/10.4236/oalib.1108300

Received: December 16, 2021
Accepted: January 24, 2022
Published: January 27, 2022

Abstract

The primary determinants of Covid severity are ACE genotype, the falciparum antigen (CD147), and vitamin D status. Specifically the I (insertion) and D (deletion) alleles, ACE polymorphisms determine the balance between the RAS (Renin Angiotensin System) and the KKS (Kallikrein Kinin System) in the response to SARS CoV2 (SARS2). CD147, the falciparum antigen, mediates the damage. Vitamin D modulates the immune response. The RAS and KKS connect Covid-19 to Kawasaki's Disease (KD) and Toxic Shock Syndrome (TSS). Covid-19 pathogenesis is embroiled in a nature versus nurture debate, as it seems to target people of color, unless you live in sub Saharan Africa. There are only three plausible explanations for the latter and they have all been selectively ignored/suppressed by mainstream medicine. This article speaks to the genotypic nature of Covid-19. Angiotensin II, bradykinin, ACE2, ACE and its two polymorphic alleles play vital roles. They predict disease severity. They portend the ARDS variants. They portend extra pulmonary disease or not. The heavily glycosylated CD147 epitope on the spike protein S is key. It has been dismissed as non-existent by flawed studies. Yet its interaction with CD147 receptors on erythrocytes and T lymphocytes cannot be denied and is at the heart of the myocarditis conundrum. Using this key, multiple dots are connected and a red alert issued, whether Covid-19 or vaccine related. These include thrombosis, immune deficit, cancer progression, autoimmune disease, and ADE (Antibody Dependent Enhancement) for those at risk. In susceptible vaccinees its deleterious effects are accelerated. Assessment of this and preventative approaches are explored.

Subject Areas

Pathology

Keywords

CD147, CD8, Lectin, Glycan, Epitope, Angioedema

1. Introduction

In early 2020 pulmonologists found that many of their patients did not fare well after initiating mechanical ventilation [1]. COVID-19 ARDS had a worse outcome than ARDS with mortality rates ranging from 65.7% to 94% in patients who required mechanical ventilation. When mechanically ventilated patients were anti-coagulated mortality dropped from 62.7% to 29.1% [2]. Then in April 2020 a research group in the Netherlands discovered the critical KKS contribution to Covid-19 pathogenesis [3]. This was quickly followed in July by a similar article from the Oak Ridge National Laboratory linking the RAS and KKS systems [4]. Recent 2021 articles have highlighted differences between Covid ARDS and typical ARDS [5] [6]. Once perspective is broadened from just the RAS to include the KKS clarity which begins to emerge. The impact of ACE polymorphisms is glimpsed. Correlating the physiology with the clinical findings becomes possible. There appears to be two types of Covid-19 ARDS that reflect the predominance of either the ACE I allele or the D allele. One tends toward angioedema (typical ARDS), the other toward microthrombosis (Covid ARDS). The dual angiotensin II/bradykinin nature to Covid-19 drives this. The evolutionary connection between these ACE polymorphisms and falciparum malaria is well known [7] (see **Figure 1**), as is the parasite's dependence on erythrocyte CD147 receptors for entry.

2. Discussion

The ACE DD genotype seems to have evolved in Africa over many millennia as protection against malaria. ACE is almost 70% higher in ACE DD v ACE II [9]

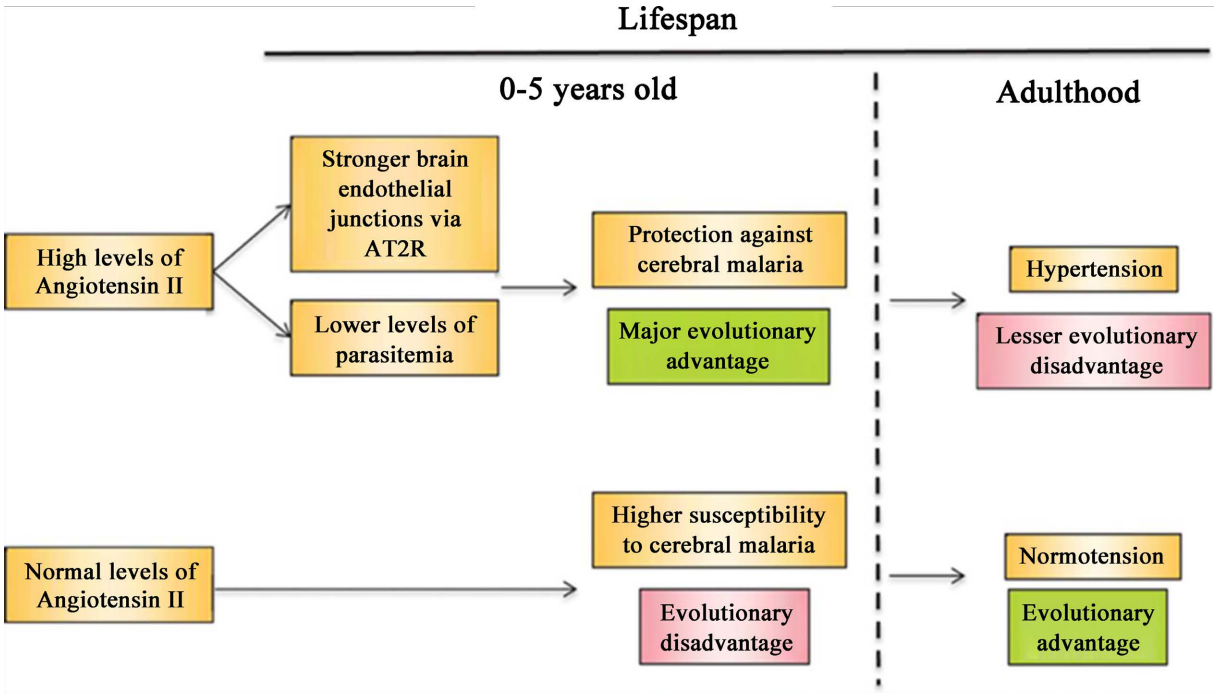

Figure 1. The evolutionary pressure of malaria [8].

[10]. This seems to work via angiotensin II and AT2Rs, enhancing endothelial tight junctions and preserving the blood brain barrier. Surviving cerebral malaria as a child was worth the risk of death due to hypertension as an adult. Given the overarching evolutionary pressure falciparum malaria has exerted on the ACE genotype and given the close clinical and lab parallels between malaria and Covid-19, more intense scrutiny of ARDS through the recently described KKS lens seems warranted.

2.1. ARDS

Covid-19 ARDS seems to swing between two forms: the traditional angioedema type as seen in SARS1/other viruses and something resembling a microthrombotic type of ARDS, kind of a "malarial pneumonia." The latter is driven by the RAS and angiotensin II (CD147, ACE D allele) and the former by the KKS and bradykinin (ACE2, ACE I allele). ACE2 receptors dominate via alveolar type 2 (AT2) cells before the blood-gas barrier, while CD147 receptors, up-regulated in the elderly, the obese, and the comorbid [11], are the primary determinants after the breach primarily via their receptors on lymphocytes, erythrocytes, platelets and endothelial cells. ACE2 receptors are not present on lymphocytes or erythrocytes and their presence on platelets [12] or endothelial cells [13] [14] is putative.

2.2. Covid Symptoms

Most exposed to Covid-19 have minimal symptoms (ACE I allele). Dry cough is one of its earliest signs and can indicate mild pulmonary edema [15]. In Covid-19 it is mediated by bradykinin [15] [16] [17] [18]. Anosmia, ageusia occur late and are good prognosticators [19] (KKS, ACE I allele). Dry cough and headache [19] are features of both early Covid (shorter clinical course) and long-haul Covid [20] (KKS, ACE I allele). It is another manifestation of bradykinin and the KKS. Estrogen down regulates ACE [21]. Brain fog and myalgias favors post Covid, non comorbid, non hospitalized Caucasian females [22] [23]. Indeed long-haul Covid may represent the new fibromyalgia/chronic fatigue syndrome [24]. Covid toes are also probably a skin manifestation of bradykinin. Bradykinin via B1R/B2R facilitates vascular permeability. ACE blocks BK access to B2Rs. Instead it is shunted to des-Arg9-bradykinin, which is metabolized by ACE2 (see **Figure 2**).

2.3. MIS-C, MIS-A, KD, TSS

ACE/ACE2 increases with age, accelerated by comorbidities [25] [26]. Without a comorbidity pediatric ARDS is rare [27]. AT2Rs (facilitate tight endothelial junctions) and seemingly B2Rs (increase solute permeability) decrease with age [28] [29] and seem to cancel each other [30] Amongst 104 11 - 17 year olds bradykinin was negatively and des-Arg9-bradykinin positively correlated with body mass index (BMI) (increased ACE). Des-Arg9-BK was also positively correlated

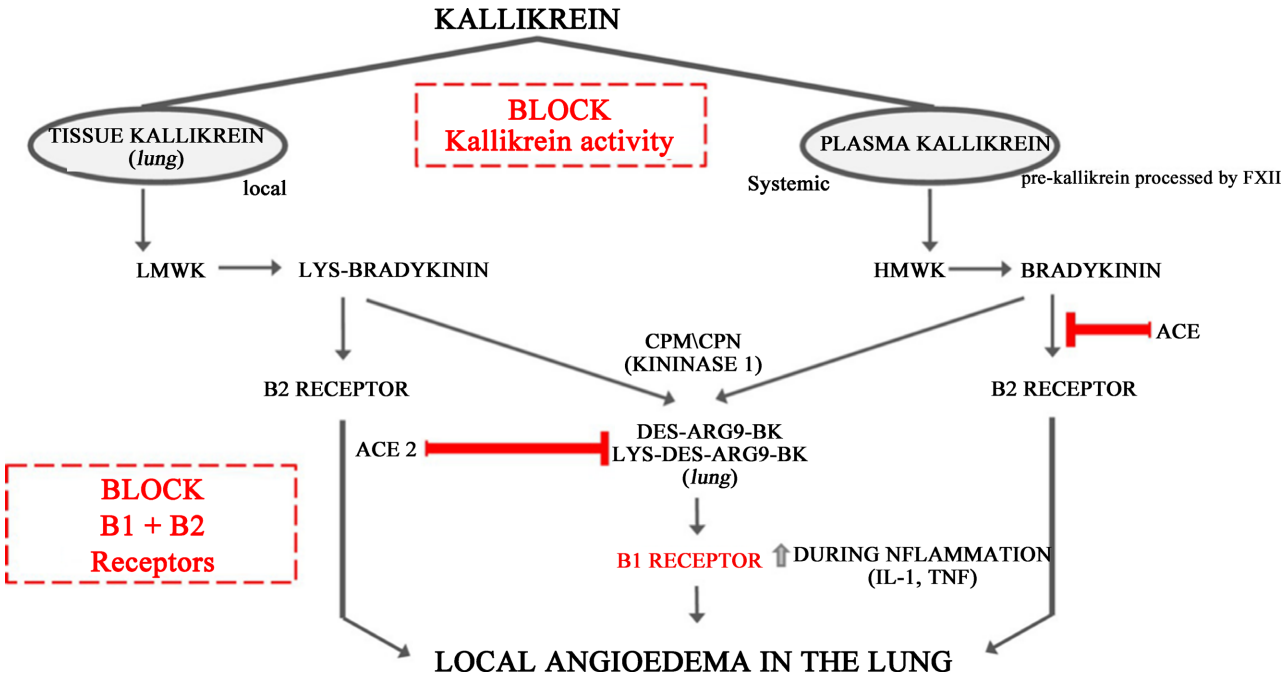

Figure 2. RAS and KKS are linked [3].

with systolic blood pressure (BP) [31]. Increasing pediatric BMI, diabetes, BP are burgeoning problems, especially amongst African Americans and Hispanics [32]. By correlating these age and gender related changes in children the KKS connection can be extrapolated to explain MIS-C [33] and MIS-A [34]. Children do not appear to express typical or Covid type ARDS, unless they have a comorbidity. But if their Th1/Th2 becomes imbalanced as seen in asthma/allergic atopy [35] or vitamin D deficiency [36], the balance can tip toward the KKS and higher risk [37]. The mucocutaneous erythema, edema, hypotension, and rash of MIS-C/MIS-A suggests the work of bradykinin and appealingly connects both KD and TSS [38] [39] to MIS-C. In MIS-A the slightly older (median age 21, predominantly male, noncomorbid, slightly overweight [40] status also seems symptomatically to represent a KKS response. CD147 and its glycan (sugar) shield interact with MBLs (Mannose Binding Lectins) and trigger the LCP (Lectin Complement Pathway) [41]. This ties the coronary arteritis and myocarditis of MIS-C/MIS-A to KD [42] [43] [44]. The staphylococcal and streptococcal toxins, although possessing no glycan shield, also invoke the LCP. Although myocarditis has been described in TSS, coronary arteritis has not. MIS-C/MIS-A, KD, and long haul Covid are probably best classified as post viral inflammatory/autoimmune states.

2.4. CD147

SARS2 in numbers removes ACE2 and increases ACE/ACE2 and Angiotensin II. Angiotensin II via AT1Rs activates TACE (Tumor necrosis factor Alpha Converting Enzyme) aka ADAM17 (A Disintegrin and Metalloproteinase 17) [45], which up-regulates TNF-α and IL6. TNF-α and IL-6 up-regulate CD 147 recep-

tors [46] [47]. TNF-α up-regulates high mannose glycans [48] due to TNF-α inhibition of mannosidase in the ER (endoplasmic reticulum) [48]. N-glycosylation in the ER of the heavily glycosylated spike S protein CD147 epitope (and the host CD147 receptors) then favors the high mannose N-glycan (sugar) for their glycan shield [49]. This then brings us to the CD147 epitope present on the SARS2 spike protein S [50]. Two recent widely referenced articles [51] [52] claimed not present, but have been discredited [53]. The CD147 epitope, whether on the emerging virus or on the manufactured spike protein S, is heavily N-glycosylated. MBLs are a prominent component of innate immunity especially in the young. They bind the high mannose glycans that are shielding the CD147 epitope, triggering complement and clotting cascades via the LCP. Fixed CD147 receptors are also involved in the pathogenesis of coronary artery disease [54].

2.5. ACE D ALLELE

ACE D allele is more frequently encountered in African-Americans and others, e.g., Italians, Iranians, differentially targeted by Covid-19 [55] [56]. The ACE D allele is more frequently encountered in elite athletes specializing in power sports [57]. The ACE I allele frequency correlates with stamina but only in male athletes [58]. CD147 receptors on erythrocytes are up regulated in quarter horses (power) versus Arabian horses (stamina) [59]. If quarter horses are likened to elite power athletes with the DD genotype, might this up-regulation also apply? The myocarditis appears to be mediated by CD147 receptors on cardiac pericytes [60] and CD147 epitopes on spike S. MBLs remove "immune complexes". After all CD147 is a member of the immunoglobulin super family. MASPs (MBL Associated Serine Proteases) increase endothelial inflammation, permeability and angioedema (up-regulate bradykinin) [61]. This would explain the myocarditis and pericardial effusion complication post vaccination in power athletes.

Age, gender, race, weight have significant impact on Covid phenotype. Furthermore other less easily quantified inputs, e.g., inoculum dose, vitamin D status, other polymorphisms, …, cannot be overlooked. The Covid-19 phenotype/ACE genotype linkage is strong but not absolute and not always direct. For example, elevated RDW (red cell distribution width) reflects spleen size and a poor prognosis. Perhaps pre-existing spleen size is also a negative determinant. The previous reference to increased CD147 receptors on erythrocytes in quarter horses indicated a close relationship between CD147 and MCT1 (monocarboxylate transporter). This relationship enables more efficient removal of lactic acid by erythrocytes. These erythrocytes can be stored in the spleen, as a reserve, when needed. Enlarged spleens due to chronic hypoxia are native to high altitude Sherpas and the free diving Bajau people (sea nomads) of Malaysia. ACE genotype does not dictate this, but the D allele does lead to higher ACE levels and more angiotensin II. This creates faster twitch, red fibers and gives its owner an advantage in power sports, which, if exploited with interval training, leads to more CD147-MCT1 receptors on erythrocytes stored in the spleen, as in quarter

horses. Since the Covid phenotype seems unduly harsh for the anaerobically trained athlete, perhaps the same is true for Sherpas and the Bajau. Covid 19 has devastated Nepal at the top of the world. The free diving Bajau peoples comprise barely 10% of the Malaysian population yet over 50% of the Covid deaths. This is even more striking, given their sea nomadic lifestyle and probably excellent vitamin D status in contrast to city dwelling Malaysians and the D allele is rare. Splenic release of these super sensitized CD147 laden erythrocytes could result in myocarditis if encountering increased CD147 antigens (epitopes) on the spike protein S (recent viral or vaccine exposure). In addition splenomegaly offers another connection to KD and coronary artery changes [62].

3. T Cells and Glycans

Covid-19 related lymphopenia is primarily of T cells, especially cytotoxic CD147+CD8+ T cells [63]. CD4/CD8 is increased in Covid-19 v AIDS, where it is decreased. This has important implications for complications, discussed below. Th17, a CD4+ T cell, is a marker for autoimmune disease (see **Figure 3**, **Figure 4**) and elevated Th17/Th1 is strongly associated with COVID mortality [37]. It is activated by IL-1,6,23 and produces IL-17. It is elevated in KD [64], Macrophage Activated Syndrome (MAS), and associated auto immune diseases, e.g., Stills Disease [65] and Juvenile Idiopathic Arthritis. Th17 in particular is associated with coronary ectasia [66], seen in almost all of these auto immune diseases. Coronary arteritis in MIS-C, MIS-A, KD involves CD147 receptor antibodies and appears to involve pericytes [60]. Although KD exhibits a Th17

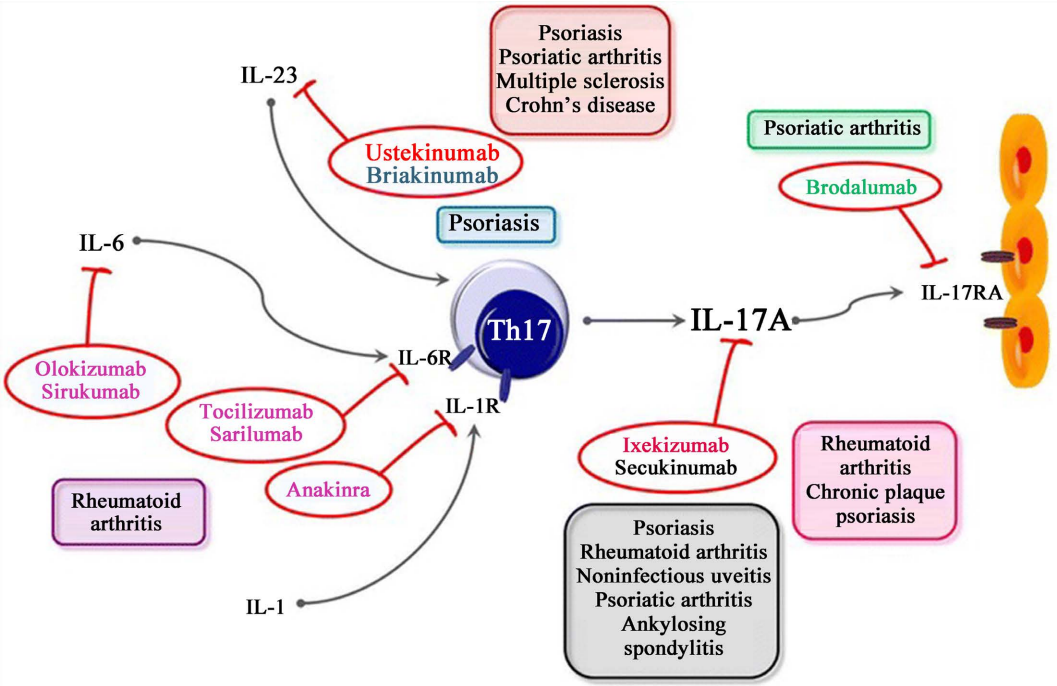

Figure 3. Many commercial monoclonal antibodies have been employed against Th17 and its autoimmune proclivities.

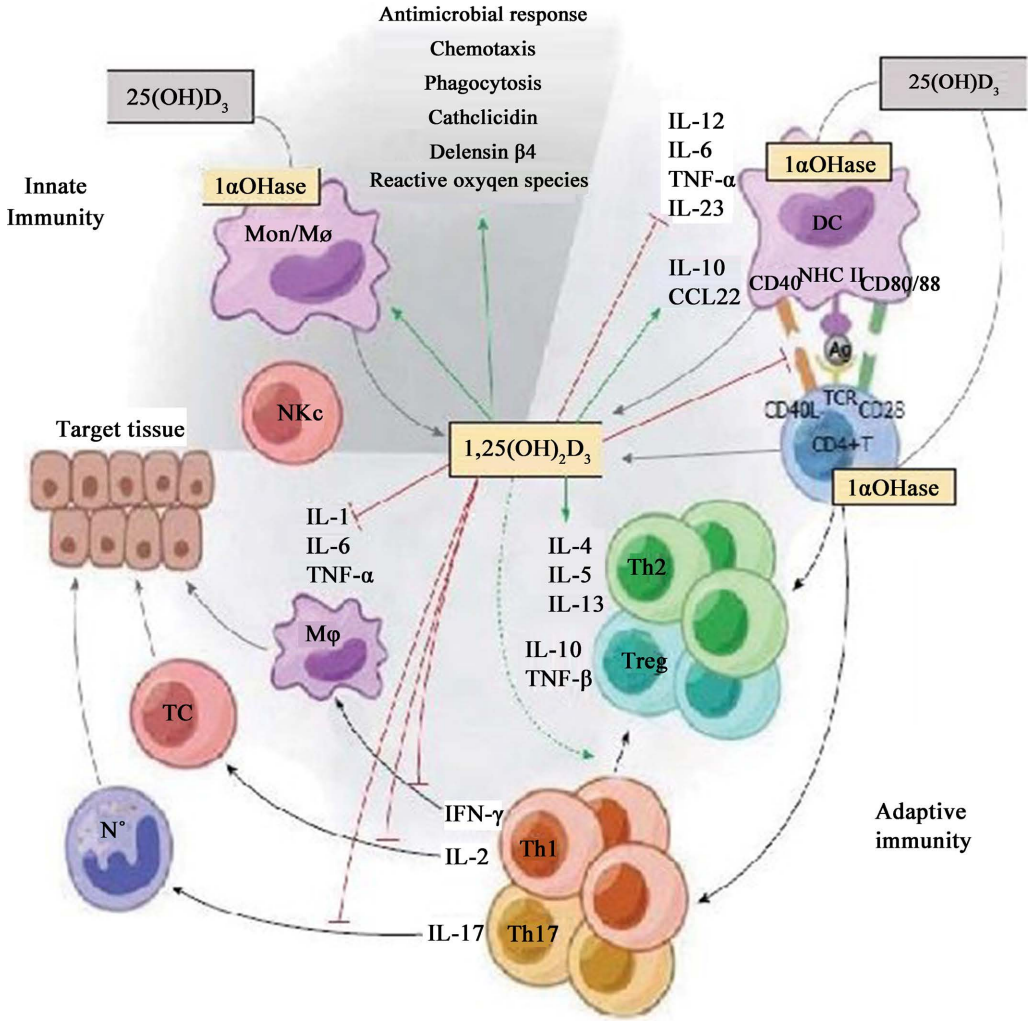

Figure 4. Vitamin D covers the action of all these Th17 related commercial monoclonal antibodies.

auto-immune type response, all KD patients with coronary aneurysms exhibited eosinophilia, a Th2 allergic type response [67]. So, TNF-alpha and IL-6, the two most critical cytokines to COVID-19 severity [68] [69], mediate both the MBL response and the Th-17 response. MASPs up-regulate bradykinin and cause cardiac angioedema [61]. This might explain the pericardial effusion that often accompanies the myocarditis in the young and otherwise healthy. These autoimmune and/or allergic effects are blocked by vitamin D (see **Figure 4**), which balances Th1/Th2 and suppresses Th17.

4. Lectins

Unfortunately this spike S/CD147 (BSG) interaction has dire consequences for those with comorbidities. Destruction of ACE2 receptor bearing cells by SARS2 increases ACE/ACE2. Although SARS2 may also enter cells after attaching to CD147 receptors [50], their high mannose glycan shield may be more problematic [49]. The RBD (Receptor Binding Domain) is extensively shielded from antibody recognition by its glycan cover, with the notable exception of the ACE2

receptor binding domain [70] [71]. This translates to plenty of ACE2 antibodies, but few CD147 antibodies. The poorly shielded ACE2 epitope provides easy access for antibody production. CD147 antibodies but not mRNA induced antibodies are protective against all the variants [72]. Vaccines trigger antibodies to the predominant strains, clearing the field and encouraging the rise of variants simple Darwinian survival of the most resistant, not unlike disruption of the normal balance of gut flora by antibiotics, thereby providing a gap for pathogenic microorganisms. Natural immunity is non-discriminating and attacks all strains old and new as they appear. Mutations are not granted special status and usually get diluted. Many recent studies have reported overwhelming superiority of natural immunity over vaccine immunity (Johns Hopkins and Israeli reports). This spike protein S, whether viral or vaccine related, presents plenty of high mannose glycans for the MBLs [73]. The efficacy of meplazumab (antibody against CD147) [74] and an LCP inhibitor [75] [76] lends additional mechanistic support. The glycan shield on the RBD of SARS2 triggers the LCP via circulating MBLs [77] [78]. Complement triggered by CD147 is also a prominent player in malaria [79]. Complement fixing MBLs are strongly correlated to plasma D-dimer levels, a marker of COVID19 coagulopathy [80] [81] [82]. IVM and other lectins (red algae [83]) bind and saturate not only these high mannose glycan shields but also the high mannose glycans on CD147 receptors on erythrocytes, platelets, lymphocytes, and endothelial cells, intermediating the complement and clotting cascades (microthrombotic and cardiovascular pathology). Lending credence to this hypothesis is an ongoing clinical trial involving Rhodophyta, a red algae. Rhodophyta (Gigartina) contain mannose specific lectins that bind spike glycoprotein specific to SARS-CoV2 to inhibit viral entry. This leaves MBLs inactivated and dormant. This would seem protective whether facing Covid-19 or its vaccines [84].

5. Vaccines (Pfizer and Moderna)

The blood-gas barrier seems to separate typical ARDS from microthrombotic type. Once the blood gas barrier is bypassed by the vaccine, the introduction of large numbers of CD147 bearing S spike-proteins accelerates the process in the susceptible. Vaccines bypass this barrier in a manner analogous to the bite of an Anopheles mosquito injecting P falciparum. Both the protozoan and the S protein attach to the CD147 receptors on erythrocytes, platelets, and endothelial cells, causing thrombosis and vasculitis. No replication required. Knowing Avogadro's number, the 30 microgram Pfizer/100 microgram Moderna load of mRNA with 150 kD molecular weight, one can calculate the number S units produced (12 trillion for Pfizer and 40 trillion for Moderna). S antigen was detected as early as day 1 post-vaccination, and peak levels were detected on average 5 days after the first injection. S in all participants declined and became undetectable by day 14 [85]. According to analysis of a Japanese biodistribution study of the Pfizer mRNA vaccine, the S1 subunit can be found in spleen, bone

marrow, the liver, adrenal glands, ovaries, heart and brain [86]. Each new administration represents a CD147/MBL booster and is the reason D-dimers are acutely slightly elevated post vaccination. Richard Hoffe, MD reported July 2021 mildly elevated D-dimers in 62% after 4-7 days in the 900 tested [87]. Vaccines create a mismatch between circulating spike protein S with their high mannose glycan shielded CD147 epitopes and host CD147 receptors on T cells, erythrocytes, and endothelial cells. Many otherwise healthy with enlarged spleens, e.g., athletes, Sherpas, Bajau people, may face dire consequences upon release of these CD147 receptor upregulated erythrocytes that are sequestered in the spleen. Vitamin D deficiency would compound this.

6. Covid-19 and Vaccine Complications

We know the short term risks of Covid-19, but those of its vaccines are less clear. What might be the intermediate and long term consequences?

6.1. Thrombosis

Clearly Covid-19 causes TMA (Thrombotic Microangiopathy) in those susceptible, *i.e.*, the elderly, the obese, and the comorbid (RAS dominant). However, outside this group those with the ACE DD genotype and those with anaerobically induced splenomegaly are also at risk. The large number of vaccinees has highlighted the problem of thrombosis amongst the otherwise healthy. The AZ and JJ [88] vaccine adverse reactions appear to be more platelet activating and thrombotic and less cytotoxic, whereas the mRNA vaccine adverse reactions seem to favor the MBL pathway. The thrombotic reactions can be either HIT [89] or VITT. Heparin antibodies are present in about 5.4% of the population [90]. Thrombosis could also be triggered without heparin. After the first AZ/JJ dose CD147 epitopes on the inactivated virus could activate platelets. These activated platelets then release platelet factor 4. PF4 combines with endothelial heparan sulfate (a heparin analogue) to form complexes [91] on the endothelial cells (no exogenous heparin needed). These immunogenic complexes have a clearance time of about 50 days [89]. They could trigger thrombosis if Covid-19 exposure was recent or this could theoretically follow the second dose, depending on the timing. Instead of HIT, it's called vaccine-induced immune thrombotic thrombocytopenia (VITT) and involves primarily 20 to 50 year old Caucasian females [88]. This may be unrelated to the RAS/KKS balance. However, one can speculate about the role of birth control pills in this thrombotic process. The increase in PF4 seems to be mediated by the S spike protein [88] [90]. VITT post AZ/JJ vaccines is probably due to an antibody to the immunogenic PF4/heparan complex (not just PF4 [92] [93]). See **Figure 5**.

6.2. Immune Compromise

CD8+ T cells are selectively but not solely reduced by SARS CoV2, increasing CD4+/CD8+ [63]. In one study of 88 children with chicken pox (varicella) and

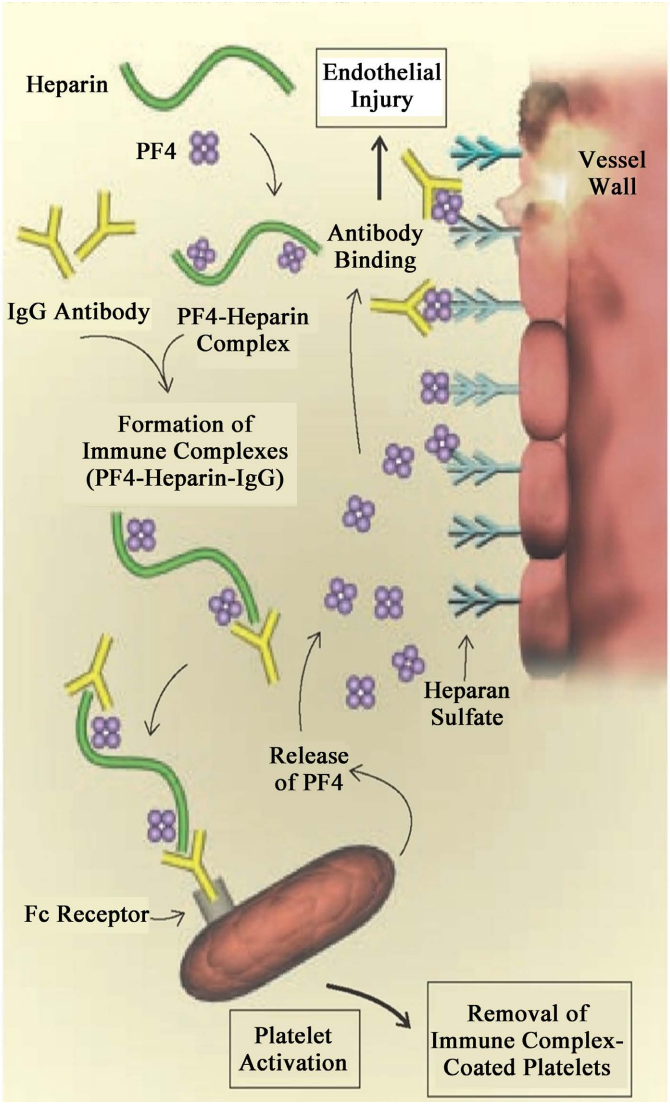

Figure 5. Endothelial heparan sulfate, like heparin, is an anticoagulant, but under certain circumstances it can become a pro-coagulant.

60 without, a significant decrease in the level of CD8 positive cells was found in those with viral DNA. CD4 differed insignificantly [94]. Reactivation of herpes zoster is often seen in the immunocompromised, e.g., those undergoing chemotherapy, the elderly, the stressed, … Reactivation of herpes zoster (HZ) post Covid-19 has been described [95]. European EudraVigilance database reported 4103 cases of HZ after receiving the Pfizer vaccine [96]. This has also been seen after both the Moderna and inactivated viral vaccines as well [97]. CD4+ and cytolytic CD8+ T cell responses play an important role in controlling HZ replication [98] [99].

6.3. Cancer Acceleration

In addition to erythrocytes and platelets SARS2 and its vaccines impact T lymphocytes. T cell lymphopenia is well described in malaria and a poor prognosti-

cator. CD147 receptors are expressed on CD4+ (T helper) and CD8+ (T cytotoxic) cells. CD8+ T cells are selectively but not solely reduced by SARS CoV2, increasing CD4+/CD8+ [63]. This is the inverse of HIV where the ratio decreases [100]. Both viruses utilize highly glycosylated CD147. Loss of CD8+ T cells translates to loss of control over progression of CA (growth, metastasis,…) [101] [102] [103] and CD147 is specifically involved. This is because CD4+ T cells monitor premalignant cells, *i.e.*, dysplasia and carcinoma in situ. CD8+ T cells suppress those that actually invade (loss of p53 function) [101]. In short loss of CD4+ T cells renders an individual susceptible to opportunistic infections. Loss of CD8+ T cells renders an individual susceptible to cancer recurrence. Presence of cytotoxic CD8+ expressing CD147 receptors limits cancers expressing CD147 antigens [102] [103] [104] [105]. This is why cancer is spiking post Covid 19 vaccine [106].

6.4. Autoimmune Disease and Antibody Dependent Enhancement (ADE)

The cause of autoimmune disease is multifactorial but appears to involve Th17 [107]. Vitamin D deficiency is clearly contributory [45]. Some consider autoimmune disease to be the longterm sequelae of a viral infection. Others have shown a distinct link with CD8+ T cell deficiency. So the low CD8+ T cell count (CD4/CD8 is increased) in SARS2 [108] is worrisome.

ADE was first seen with the Dengue virus about 40 years ago. It has also been described with Yellow fever, Zika, West-Nile fever, respiratory syncytial virus, influenza, measles, HIV, SARS, and MERS [109] [110]. CD8+ T cells can block Dengue [111] and Zika virus ADE [109]. The ADE potential for SARS2 has already been documented in the lab, using the Wuhan strain and the delta strain [112]. IVM [113] [114] [115], and Vitamin D [4] have much to offer.

7. Early Diagnosis

D-dimers, RDW, platelet, lymphocyte and eosinophil counts are good proxies for early diagnosis of the more lethal microthrombotic ARDS (angiotensin II dominant) or extra-pulmonary TMA. The CD147 epitope on the spike protein S interacts with CD147 receptor bearing erythrocytes. These erythrocytes, which now lack available CD147 receptors, are entrapped in the spleen [116], which itself enlarges. RDW parallels splenic size [117] [118] [119]. This same interaction between CD147 receptors on platelets (releasing PF4) and endothelial cells triggers the LCP with angioedema and thrombosis, producing the D-dimers and thrombocytopenia. The same process drives cerebral malaria [120]. ACE2 receptors are probably not involved. But the answer is probably moot [121]. All four cell types, erythrocytes, platelets, lymphocytes, and endothelial cells, conspire for a poor prognosis [119] [122] [123] [124] [125] [126]. All four are rich in CD147 with poor/no ACE2 receptor component. Covid-19 has had little impact in sub-Saharan Africa. There are only three plausible explanations for this

and all three have been denigrated to some extent by mainstream medicine. 1) falciparum antibodies [127] [128]; 2) IVM cross coverage for malaria/river blindness [129]; 3) adequate vitamin D.

IVM is a horse dewormer! Many parasitic helminths, e.g., Onchocerca volvulus (cause of a filariasis known as river blindness), horse worms like Ascaris, … employ glycan shields against bacteria as their larval or filarial forms migrate through the bloodstream. Ascaris employs an N-glycan shield [130]. P. falciparum's RH5 epitope is also heavily glycosylated. Given its efficacy for river blindness (Nobel Prize) and as a horse dewormer (not to mention anti-malarial), IVM may also bind these glycans, pre-empting MBLs without the inflammation and thrombosis.

Vitamin D levels were lower in north and south Africa compared with sub-Saharan Africa, in urban areas compared with rural areas, in women compared with men, and in newborn babies compared with their mothers [131]. Amongst Brazilians over 50 years 25% were vitamin D deficient and 62% were vitamin D insufficient [132]. In one unpublished study 88% of Filipinos were vitamin D deficient (<20 ng/ml) or insufficient (<30 ng/ml). In India 80% - 90% were deficient [133]. Adequate vitamin D counters the development of either phenotype [4]. IL6 and severity/mortality are inversely and independently related to Vitamin D levels. Adequate vitamin D counters MIS-C and MIS-A. IL-6 and TNF-α are the prime cytokines of COVID-19. TNF-α inhibits mannosidase, increasing high mannose glycans on the RBD of the spike protein S [48] and IL-6 up-regulates CD147 [47]. These oligomeric glycans involve not only the RBD on circulating S protein of viral or vaccine origin but also the native CD147 receptors. They are upregulated by cytokines, especially IL-6, interact with MBLs, which initiate the LCP and thrombosis, and accelerate atherosclerosis [134] [135].

8. Therapy

There have been many studies evaluating the efficacy of vitamin D for prevention and therapy of COVID19. The vast majority have been positive [136] [137] [138] [139]. Those that have been less favorable, when reviewed, have obvious errors in structure, e.g., low levels accepted as sufficient, insufficient time for adequate levels to develop, … Vitamin D is helpful in the vaccinated and the unvaccinated. Vitamin D also addresses the influenza risk. Using 2017-18 data from the CDC website [140] one can calculate the NNT for the flu shot to be about 40. The NNT for vitamin D during the winter (less than 25 nmol/L or 10 ng/ml) is just above 4 [141] (see **Figure 6**). NNT is the number needed to treat to eliminate one case of the flu. This translates to a vitamin D flu efficacy nearly an order of magnitude greater than that of the flu shot.

Vitamin D deficiency rickets was first described in the 1920s. Vitamin D resistant magnesium deficient rickets wasn't described until 50 years later in the 1970s (see **Figure 7**). Vitamin D deficiency can also impact allergy and autoimmune

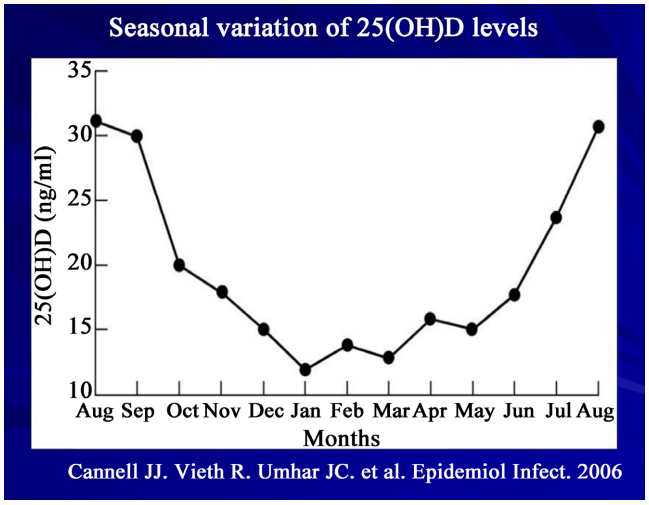

Figure 6. During the flu season in the northern tier of the US vitamin D levels are less than 15 ng/ml.

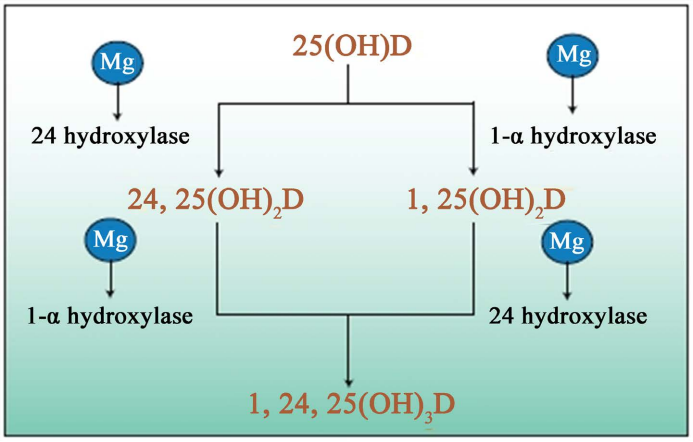

Figure 7. Magnesium is critical in producing the active form of vitamin D [142].

risks [143] [144] [145].

9. Conclusion

The ACE I/D polymorphisms seem to predict which Covid-19 ARDS variant will manifest in the few that do develop ARDS. A preliminary CD4/CD8 might provide some insight into susceptibility. Those without comorbidities that are KKS inclined generally escape severe ARDS, while those with comorbidities that are RAS mediated upregulate TNF-α and IL6. CD147 then takes center stage. D-dimers, RDW, lymphocyte, platelet and eosinophil counts should help in early diagnosis. There are numerous considerations, e.g., vitamin D status, polymorphisms, age, gender, inoculum dose, …, that impact the clinical course. Vitamin D, IVM, red algae might assist in prevention and treatment of symptoms, whether vaccinated or not. In summary circulating MBLs attack the glycan shield on the CD147 epitope. This supercharges CD147 induced damage and triggers microthrombosis. In the susceptible consequences can be devastating.

Long-term impact of Covid-19 is unknown. But the commonality of CD147 between the virus and the vaccine raises some disturbing possibilities, including compromised immune function, autoimmune disease, accelerated progression of cancer, and ADE. There are many trillions of spike protein S units created by each mRNA dose/booster. CD147 epitopes are on each S unit, despite flawed articles claiming otherwise. This article constitutes a red alert on the lurking dangers that are becoming more apparent. Warning: Cough not required!

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Gosangi, B., Rubinowitz, A.N., Irugu, D., Gange, C., Bader, A. and Cortopassi, I. (2021) COVID-19 ARDS: A Review of Imaging Features and Overview of Mechanical Ventilation and Its Complications. *Emergency Radiology*. https://doi.org/10.1007/s10140-021-01976-5

[2] Welker, C., Huang, J., Gil, I.N. and Ramakrishna, H. (2021) Acute Respiratory Distress Syndrome Update, with Coronavirus Disease 2019 Focus. *Journal of Cardiothoracic and Vascular Anesthesia*, 1-8. (In Press) https://doi.org/10.1053/j.jvca.2021.02.053

[3] van De Veerdonk, F.L., Netea, M.G., van Deuren, M., van der Meer, J.W.M., De Mast, Q., *et al.* (2020) KKS Blockade in Patients with COVID-19 to Prevent Acute Respiratory Distress Syndrome (Apr 2020). *ELife*, **9**, Article ID: E57555. https://doi.org/10.7554/eLife.57555

[4] Garvin, M.R., Alvarez, C., Miller, J.I., Prates, E.T. and Walker, A.M. (2020) A Mechanistic Model and Therapeutic Interventions for COVID-19 Involving a RAS Mediated Bradykinin Storm. *ELife*, **9**, Article ID: E59177. https://doi.org/10.7554/eLife.59177

[5] Middleton, E.A. and Zimmerman, G.A. (2021) COVID-19-Associated Acute Respiratory Distress Syndrome: Lessons from Tissues and Cells. *Critical Care Clinics*, **37**, 777-793. https://doi.org/10.1016/j.ccc.2021.05.004

[6] Science Daily (2021, April 15) Two Distinct Types of COVID-19-Associated Acute Respiratory Distress Syndrome Identified. https://www.sciencedaily.com/releases/2021/04/210415090727.htm

[7] Volpe, M., Battistoni, A. and Mancia, G. (2016) Angiotensin II-Linked Hypothesis to Understand the Advantage of the Coevolution of Hypertension and Malaria. *Circulation Research*, **119**, 1046-1048. https://doi.org/10.1161/CIRCRESAHA.116.309855

[8] Gallego-Delgado, J., Walther, T. and Rodriguez, A. (2016) The High Blood Pressure-Malaria Protection Hypothesis. *Circulation Research*, **119**, 1071-1075. https://doi.org/10.1161/CIRCRESAHA.116.309602

[9] Biller, H., Zissel, G., Ruprecht, B., Nauck, M., Busse Grawitz, A. and Müller-Quernheim, J. (2006) Genotype-Corrected Reference Values for Serum Angiotensin-Converting Enzyme. *European Respiratory Journal*, **28**, 1085-1091. https://doi.org/10.1183/09031936.00050106

[10] Rigat, B., Corvol, P. and Soubrier, F. (1990) An Insertion/deletion Polymorphism in the Angiotensin I-Converting Enzyme Gene Accounting for Half the Variance of

Serum Enzyme Levels. *Journal of Clinical Investigation*, **86**, 343-1346. https://doi.org/10.1172/JCI114844

[11] Radzikowska, U., Ding, M., Tan, G., Zhakparov, D., Peng, Y., Wawrzyniak, P., *et al.* (2020) Distribution of ACE2, CD147, CD26, and Other SARS-CoV-2 Associated Molecules in Tissues and Immune Cells in Health and in Asthma, COPD, Obesity, Hypertension, and COVID-19 Risk Factors. *Allergy*, **75**, 2828-2845. https://doi.org/10.1111/all.14429

[12] Manne, B.K., Denorme, F., Middleton, E.A., Portier, I., Rowley, J.K., *et al.* (2020) Platelet Gene Expression and Function in Patients with COVID-19. *Blood*, **136**, 1317-1329. https://doi.org/10.1182/blood.2020007214

[13] McCracken, I.R., Saginc, G., He, L., Huseynov, A., Daniels, A., *et al.* (2021) Lack of Evidence of Angiotensin-Converting Enzyme 2 Expression and Replicative Infection by SARS-CoV-2 in Human Endothelial Cells. *Circulation*, **143**, 865-868. https://doi.org/10.1161/CIRCULATIONAHA.120.052824

[14] Ganier, C., Du-Harpur, X., Harun, N., Wan, B., Arthurs, C., *et al.* (2020) CD147 (BSG) But Not ACE2 Expression Is Detectable in Vascular Endothelial Cells Within Single Cell RNA Sequencing Datasets Derived from Multiple Tissues in Healthy Individuals (bioRxiv Preprint). https://doi.org/10.1101/2020.05.29.123513

[15] Zwaveling, S., van Wijk, R.G. and Karim, F. (2020) Pulmonary Edema in COVID-19: Explained by Bradykinin? *Journal of Allergy and Clinical Immunology*, **146**, 1454-1455. https://doi.org/10.1016/j.jaci.2020.08.038

[16] Takahashi, T., Yamaguchi, E., Furuya, K. and Kawakami, Y. (2001) The ACE Gene Polymorphism and Cough Threshold for Capsaicin after Cilazapril Usage. *Respiratory Medicine*, **95**, 130-135. https://doi.org/10.1053/rmed.2000.1005

[17] Bas, M., Hoffmann, T.K., Tiemann, B., Thao-Vi Dao, V., Bantis, C., *et al.* (2010) Potential Genetic Risk Factors in Angiotensin-Converting Enzymeinhibitor-Induced Angio-Edema. *British Journal of Clinical Pharmacology*, **69**, 179-186. https://doi.org/10.1111/j.1365-2125.2009.03567.x

[18] Mukae, S., Itoh, S., Aoki, S., Iwata, T., Nishio, K., Sato, R., *et al.* (2002) Association of Polymorphisms of the Renin-Angiotensin System and Bradykinin B2 Receptor with ACE-Inhibitor-Related Cough. *Journal of Human Hypertension*, **16**, 857-863. https://doi.org/10.1038/sj.jhh.1001486

[19] Vahey, G.M., Marshall, K.E., McDonald, E., Martin, S.W., Tate, J.E., *et al.* (2021). Symptom Profiles and Progression in Hospitalized and Nonhospitalized Patients with Coronavirus Disease, Colorado, USA, 2020. *Emerging Infectious Diseases*, **27**, 385-395. https://doi.org/10.3201/eid2702.203729

[20] Raveendran, A.V., Jayadevan, R. and Sashidharan, S. (2021) Long COVID: An Overview. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, **15**, 869-875. https://doi.org/10.1016/j.dsx.2021.04.007

[21] Gallagher, P.E., Li, P., Lenhart, J.R., Chappell, M.C., Bridget, K., *et al.* (1999) Estrogen Regulation of Angiotensin-Converting Enzyme MRNA. *Hypertension*, **33**, 323-328. https://doi.org/10.1161/01.HYP.33.1.323

[22] Graham, E.L., Clark, J.R., Orban, Z.S., Lim, P.H., Szymanski, A.L., *et al.* (2021) Persistent Neurologic Symptoms and Cognitive Dysfunction in Nonhospitalized Covid19 "long Haulers". *Annals of Clinical and Translational Neurology*, **8**, 1073-1085. https://doi.org/10.1002/acn3.51350

[23] Becker, J.H., Lin, J.J., Doernberg, M., Stone, K., Navis, A., Festa, J.R., *et al.* (2021) Assessment of Cognitive Function in Patients after COVID-19 Infection. *JAMA Network Open*, **4**, Article ID: E2130645.

https://doi.org/10.1001/jamanetworkopen.2021.30645

[24] Brusco, I., Justino, A.B., Silva, C.S., Fischer, S., Cunha, T.M, *et al.* (2019) Kinins and Their B1 and B2 Receptors Are Involved in Fibromyalgia-Like Pain Symptoms in Mice. *Biochemical Pharmacology*, **168**, 119-132. https://doi.org/10.1016/j.bcp.2019.06.023

[25] Joshi, S., Gomez, S., Duran-Mendez, M., Quiroz-Olvera, J., Garcia, C., *et al.* (2019) Aging Healthy, Or with Diabetes, Is Associated with ACE2/ACE Imbalance in the Hematopoietic Stem Progenitor Cells. *The FASEB Journal*, **33**, 514.7-514.7. https://doi.org/10.1096/fasebj.2019.33.1_supplement.514.7

[26] Bank, S., Kumar De, S., Bankura, B., Maiti, S., Das, M., *et al.* (2021) ACE/ACE2 Balance Might Be Instrumental to Explain the Certain Comorbidities Leading to Severe COVID-19 Cases. *Bioscience Reports*, **41**, Article ID: BSR20202014. https://doi.org/10.1042/BSR20202014

[27] Diorio, C., Henrickson, S.E., Vella, L.A., McNerney, K.O., Chase, J., *et al.* (2020) Multisystem Inflammatory Syndrome in Children and COVID-19 Are Distinct Presentations of SARS–CoV-2. *Journal of Clinical Investigation*, **130**, 5967-5975. https://doi.org/10.1172/JCI140970

[28] Mirabito, K.M., Hilliard, L.M., Kett, M.M., Brown, R.D., Booth, S.C., *et al.* (2014) Sex- and Age-Related Differences in the Chronic Pressure Natriuresis Relationship: Role of the Angiotensin Type 2 Receptor. *American Journal of Physiology—Renal Physiology*, **307**, F901-F907. https://doi.org/10.1152/ajprenal.00288.2014

[29] Feng, W., Xu, X., Zhao, G., Zhao, J. and Dong, R. (2016) Increased Age-Related Cardiac Dysfunction in Bradykinin B2 Receptor Deficient Mice. *The Journals of Gerontology*: *Series A*, **71**, 178-187. https://doi.org/10.1093/gerona/glu210

[30] Abadir, P.M., Periasamy, A., Carey, R.M. and Siragy, H.M. (2006) Angiotensin II Type 2 Receptor-Bradykinin B2 Receptor Functional Heterodimerization. *Hypertension*, **48**, 316-322. https://doi.org/10.1161/01.HYP.0000228997.88162.a8

[31] Fernandes, F.B., Fernandes, A.B., Febba, A.C.S., Leite, A.P.O., Leite, C.A., Vitalle, M.S.S., *et al.* (2021) Association of Ang-(1-7) and Des-Arg^{9}BK as New Biomarkers of Obesity and Cardiometabolic Risk Factors in Adolescents. *Hypertension Research*, **44**, 969-977. https://doi.org/10.1038/s41440-021-00618-0

[32] Yanes Cardozo, L.L. and Romero, D.G. (2021) Novel Biomarkers of Childhood and Adolescent Obesity. *Hypertension Research*, **44**, 1030-1033. https://doi.org/10.1038/s41440-021-00651-z

[33] Rafferty, M.S., Burrows, H., Joseph, J.P., Leveille, J., Nihtianova, S. and Amirian, S. (2021) Multisystem Inflammatory Syndrome in Children (MIS-C) and the Coronavirus Pandemic: Current Knowledge and Implications for Public Health. *Journal of Infection and Public Health*, **14**, 484-494. https://doi.org/10.1016/j.jiph.2021.01.008

[34] Most, Z.M., Hendren, N., Drazner, M.H. and Perl, T.M. (2021) Striking Similarities of Multisystem Inflammatory Syndrome in Children and a Myocarditis-Like Syndrome in Adults. *Circulation*, **143**, 4-6. https://doi.org/10.1161/CIRCULATIONAHA.120.050166

[35] Berger, A. (2000) T Lymphocytes Are a Major Source of Cytokines. *BMJ*, **321**, 424. https://doi.org/10.1136/bmj.321.7258.424

[36] Maalmi, H., Berraïes, A., Tanguouru, E., Ammar, J., Abid, H., *et al.* (2012) The Impact of Vitamin D Deficiency on Immune T Cells in Asthmatic Children: A Case-Control Study. *Journal of Asthma and Allergy*, **5**, 11-19. https://doi.org/10.2147/JAA.S29566

[37] Pavel, A., Glickman, J.W., Michels, J.R., Kim-Schultze, S., Miller, R.L., *et al.* (2021) Th2/Th1 Cytokine Imbalance Is Associated with Higher COVID-19 Risk Mortality. *Frontiers in Genetics*, **12**, Article ID: 706902. https://doi.org/10.3389/fgene.2021.706902

[38] Sriskandan, S. and Cohen, J. (2000) Kallikrein-Kinin System Activation in Streptococcal Toxic Shock Syndrome. *Clinical Infectious Diseases*, **30**, 961-962. https://doi.org/10.1086/313827

[39] Bengtson, S.H., Phagoo, S.B., Norrby-Teglund, A., Pa̋hlman, L., Mőrgelin, M., *et al.* (2006) Kinin Receptor Expression during *Staphylococcus aureus* Infection. *Blood*, **108**, 2055-2063. https://doi.org/10.1182/blood-2006-04-016444

[40] Patel, P., DeCuir, J., Abrams, J., Campbell, A.P., Godfred-Cato, S. and Belay, E.D. (2021) Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults a Systematic Review. *JAMA Network Open*, **4**, Article ID: E2126456. https://doi.org/10.1001/jamanetworkopen.2021.26456

[41] Fodil, S. and Annane, D. (2021) Complement Inhibition and COVID-19: the Story So Far. *ImmunoTargets and Therapy*, **10**, 273-284. https://doi.org/10.2147/ITT.S284830

[42] Biezeveld, M.H., Kuipers, I.M., Geissler, J., Lam, J., Ottenkamp, J.J., *et al.* (2003) Association of Mannose-Binding Lectin Genotype with Cardiovascular Abnormalities in Kawasaki Disease. *The Lancet*, **361**, 1268-1270. https://doi.org/10.1016/S0140-6736(03)12985-6

[43] Polycarpou, A., Grigoriadou, S., Klavinskis, L. and Sacks, S. (2021) Does the Lectin Complement Pathway Link Kawasaki Disease and SARSCoV-2? *Frontiers in Immunology*, **11**, Article ID: 604512. https://doi.org/10.3389/fimmu.2020.604512

[44] Qi, Y., Xu, J., Lin, Z., Tao, Y., Zheng, F., *et al.* (2021) The Network of Pro-Inflammatory Factors CD147, DcR3, and IL33 in the Development of Kawasaki Disease. *Journal of Inflammation Research*, **14**, 6043-6053. https://doi.org/10.2147/JIR.S338763

[45] Chambers, P.W. (2020) COVID-19, ARDS, ACOVCS, MIS-C, KD, PMIS, TSS, MIS-A: Connecting the Alphabet? (See Figures 4,5). *Clinical in Medicine*, **2**, Article No. 1027. http://doi.org/10.33597/2688-6731-V2-id1027

[46] Kollias, G. and Sfikakis, P.P. (2010) TNF Pathophysiology. Molecular and Cellular Mechanisms. Current Directions in Autoimmunity, Vol. 11, Karger, Basel, 145-156. https://doi.org/10.1159/isbn.978-3-8055-9384-7

[47] Hu, J., Lei, L., Wang, Y., Wang, K., Hu, X., *et al.* (2016) Interleukin-6 Drives Multiple Myeloma Progression by Up-Regulating of CD147/Emmprin Expression. *Blood*, **128**, 5632. https://doi.org/10.1182/blood.V128.22.5632.5632

[48] Regal-McDonald, K. and Patel, R.P. (2020) Selective Recruitment of Monocyte Sub-Sets by Endothelial Nglycans. *The American Journal of Pathology*, **190**, 947-957. https://doi.org/10.1016/j.ajpath.2020.01.006

[49] Heller, M., von der Ohe, M., Kleene, R., Mohajer, H. and Schachner, M. (2003) The Immunoglobulin-Superfamily Molecule Basigin Is a Binding Protein for Oligomannosidic Carbohydrates: An Anti-Idiotypic Approach. *Journal of Neurochemistry*, **84**, 557-565. https://doi.org/10.1046/j.1471-4159.2003.01537.x

[50] Wang, K., Chen, W., Zhang, Z., Deng, Y., Lian, J.Q., Du, P., *et al.* (2020) CD147-Spike Protein Is a Novel Route for SARS-CoV-2 Infection to Host Cells. *Signal Transduction and Targeted Therapy*, **5**, Article No. 283. https://doi.org/10.1038/s41392-020-00426-x

[51] Ragotte, R.J., Pulidoa, D., Donnellana, F.R., Hill, M.L., Gorini, G., Davies, H., *et al.*

(2021) Human Basigin (CD147) Does Not Directly Interact with SARS-CoV-2 Spike Glycoprotein. *MSphere*, **6**, Article ID: E00647-21. https://doi.org/10.1128/mSphere.00647-21

[52] Shilts, J., Crozier, T.W.M., Greenwood, E.J.D., Lehner, P.J. and Wright, G.J. (2021) No Evidence for Basigin/CD147 as a Direct SARS-CoV-2 Spike Binding Receptor. *Scientific Reports*, **11**, Article No. 413. https://doi.org/10.1038/s41598-020-80464-1

[53] Chambers, P.W. (2021) Basigin Binds Spike S on SARS2. *Open Access Library Journal*, **8**, Article No. E8064. https://doi.org/10.4236/oalib.1108064

[54] Ahmetaj-Shala, B., Vaja, R., Atanur, S.S., George, P.M., Kirkby, N.S., *et al.* (2020) Cardiorenal Tissues Express SARS-CoV-2 Entry Genes and Basigin (BSG/CD147) Increases with Age in Endothelial Cells. *JACC*: *Basic to Translational Science*, **5**, 1111-1123. https://doi.org/10.1016/j.jacbts.2020.09.010

[55] Sarangarajan, R., Winn, R., Kiebish, M.A., Bountra, C., Granger, E. and Narain, N.R. (2021) Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers. *Journal of Racial and Ethnic Health Disparities*, **8**, 973-980. https://doi.org/10.1007/s40615-020-00853-0

[56] Al-Hinai, A.T., Hassan, M.O., Simsek, M., Al-Barwani, H. and Bayoumi, R. (2002) Genotypes and Allele Frequencies of Angiotensin Converting Enzyme (ACE) Insertion/deletion Polymorphism among Omanis, Table 2. *SQU Journal for Scientific Research*: *Medical Sciences*, **4**, 25-27. https://applications.emro.who.int/imemrf/SQUMJ_2002_4_1_2_25.pdf

[57] Kranes, S., Gove, T., Dodson, K., Jacobson, A., Latourelle, S. and Elwess, N. (2021) The Polymorphic ACE Gene and Resulting Genotypes and Allele Frequencies Within Specific Groups. *SUNY Plattsburgh's Scientia Discipulorum Journal of Undergraduate Research*, **8**, 1-7. http://hdl.handle.net/20.500.12648/1281

[58] Min, S.K.K., Takahashi, K., Ishigami, H., Hiranuma, K., Mizuno, M., Ishii, T., *et al.* (2009) Is There a Gender Difference between ACE Gene and Race Distance? *Applied Physiology*, *Nutrition*, *and Metabolism*, **34**, 926-932. https://doi.org/10.1139/H09-097

[59] Regatieria, I.C., Almeida, M.L.M., Neto, A.R.T., Curi, R.A., Ferraz, G.C. and Queiroz-Neto, A. (2016) Quantification of MCT1 and CD147 in Red Blood Cells of Arabian and Quarter Horses. *Journal of Equine Veterinary Science*, **43**, 66-71. https://doi.org/10.1016/j.jevs.2016.05.004

[60] Avolio, E., Carrabba, M., Milligan, R., Williamson, M.K. and Beltrami, A.P. (2021) The SARS-CoV-2 Spike Protein Disrupts Human Cardiac Pericytes Function Through CD147-Receptor-Mediated Signaling: A Potential Noninfective Mechanism of COVID-19 Microvascular Disease. *Clinical Science*, **135**, 2667-2689. https://doi.org/10.1042/CS20210735

[61] Debreczeni, M.L., Németh, Z., Kajdácsi, E., Schwaner, E., Makó, V., *et al.* (2019) MASP-1 Increases Endothelial Permeability. *Frontiers in Immunology*, **10**, Article No. 991. https://doi.org/10.3389/fimmu.2019.00991

[62] Kang, D. and Kim, S. (2019) Clinical Aspects of Splenomegaly as a Possible Predictive Factor of Coronary Artery Changes in Kawasaki Disease. *Cardiology in the Young*, **29**, 297-302. https://doi.org/10.1017/S1047951118002238

[63] Urra, J.M., Cabrera, C.M., Porras, L. and Rodenas, I. (2020) Selective CD8 Cell Reduction by SARS-CoV-2 Is Associated with a Worse Prognosis and Systemic Inflammation in COVID-19 Patients. *Clinical Immunology*, **217**, Article ID: 08486. https://doi.org/10.1016/j.clim.2020.108486

[64] Zhang, K., Li, Z., Li, M., Zhang, Y., Wu, S. and Chen, C. (2017) Increase in T Helper Type 17 Cells in Children with Kawasaki Disease Is NR4A2 Dependent. *European Journal of Inflammation*, **16**, 1-8. https://doi.org/10.1177/2058739218760945

[65] Mavragani, C.P., Spyridakis, E.G. and Koutsilieris, M. (2012) Adult-Onset Still's Disease: from Pathophysiology to Targeted Therapies. *International Journal of Inflammation*, **2012**, Article ID: 879020, 10 p. https://doi.org/10.1155/2012/879020

[66] Uyguna, T., Demir, B., Tosuna, V., Ungan, I., Kural, A., *et al.* (2019) Relationship between Interleukin-17A and Isolated Coronary Ectasia. *Cytokine*, **115**, 84-88. https://doi.org/10.1016/j.cyto.2018.11.015

[67] Cogan, E., Foulon, P, Cappeliez, O., Dolle, N., Vanfraechem, G. and De Backer, D. (2020) Multisystem Inflammatory Syndrome with Complete Kawasaki Disease Features Associated with SARS-CoV-2 Infection in a Young Adult. A Case Report. *Frontiers in Medicine*, **7**, Article No. 428. https://doi.org/10.3389/fmed.2020.00428

[68] Axis, M., Fatima, R. and Assaly, R. (2020) An Inflammatory Cytokine Signature Predicts COVID-19 Severity and Survival. *Journal of Medical Virology*, **92**, 2283-2285. https://doi.org/10.1002/jmv.25948

[69] Aliza, M. (2020) Elevated Interleukin-6 and Severe COVID-19: A Meta-Analysis. *Journal of Medical Virology*, **92**, 2283-2285. https://doi.org/10.1002/jmv.25948

[70] Grant, O.C., Montgomery, D., Ito, K. and Woods, R.J. (2020) Analysis of the SARS-CoV-2 Spike Protein Glycan Shield Reveals Implications for Immune Recognition. *Scientific Reports*, **10**, Article No. 14991. https://doi.org/10.1038/s41598-020-71748-7

[71] Bullen, G., Galson, J.D., Hall, G., Villar, P. and Moreels, L. (2021) Cross-Reactive SARS-CoV-2 Neutralizing Antibodies from Deep Mining of Early Patient Responses. *Frontiers in Immunology*, **15**, Article No. 678570. https://doi.org/10.3389/fimmu.2021.678570

[72] Geng, J., Chen, L., Yuan, Y., Wang, K., Wang, Y., Qin, C., *et al.* (2021) CD147 Antibody Specifically and Effectively Inhibits Infection and Cytokine Storm of SARS-CoV-2 and Its Variants Delta, Alpha, Beta, and Gamma. *Signal Transduction and Targeted Therapy*, **6**, Article No. 347. https://doi.org/10.1038/s41392-021-00760-8

[73] Federica Defendi, F., Leroy, C., Epaulard, O., Clavarino, G., Vilotitch, A., *et al.* (2021) Complement Alternative and Mannose-Binding Lectin Pathway Activation Is Associated with COVID-19 Mortality. *Frontiers in Immunology*, **10**, Article No. 742446. https://doi.org/10.3389/fimmu.2021.742446

[74] Bian, H., Zheng, Z.H., Wei, D., Wen, A., Zhang, Z., Lian, J.Q., *et al.* (2021) Safety and Efficacy of Meplazumab in Healthy Volunteers and COVID-19 Patients: A Randomized Phase 1 and an Exploratory Phase 2 Trial. *Signal Transduction and Targeted Therapy*, **6**, Article No. 194. https://doi.org/10.1038/s41392-021-00603-6

[75] Rambaldi, A., Gritti, G., Micò, M.C., Frigeni, M., Borleri, G., *et al.* (2020) Endothelial Injury and Thrombotic Microangiopathy in COVID-19: Treatment with the Lectin-Pathway Inhibitor Narsoplimab. *Immunobiology*, **225**, Article ID: 152001. https://doi.org/10.1016/j.imbio.2020.152001

[76] Knierman, M.D., Gelfanova, V., Zlatniski, N.A., Mullen, J.H., Siegel, R.W. and Konrad, R.J. (2021) Severe SARS-CoV-2 Infection Treated with the Mannose Binding Lectin Associated Serine Protease 2 (MASP2) Inhibitor Narsoplimab. *Journal of Allergy and Infectious Diseases*, **2**, 24-28.

[77] Bumiller-Bini, V., De Freitas Oliveira-Toré, C., Carvalho, T.M., Kretzschmar, G.C., Gonçalves, L.B., *et al.* (2021) MASPs at the Crossroad between the Complement and

the Coagulation Cascades—The Case for COVID-19 (2021). *Genetics and Molecular Biology*, **44**, Article ID: e20200199.
https://doi.org/10.1590/1678-4685-gmb-2020-0199

[78] Gralinskia, L.E., Sheahana, T.P., Morrison, T.E., Menacherya, V.D., Jensen, K., *et al.* (2018) Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. *Host-Microbe Biology*, **9**, Article No. e01753-18.
https://doi.org/10.1128/mBio.01753-18

[79] Biryukov, S. and Stoute, J.A. (2014) Complement Activation in Malaria: Friend or Foe? *Trends in Molecular Medicine*, **20**, 293-301.
https://doi.org/10.1016/j.molmed.2014.01.001

[80] Elhadad, S., Chapin, J., Copertino, D., van Besien, K., Ahamed, J. and Laurence, J. (2021) MASP2 Levels Are Elevated in Thrombotic Microangiopathies: Association with Microvascular Endothelial Cell Injury and Suppression by Anti-MASP2 Antibody Narsoplimab. *Clinical and Experimental Immunology*, **203**, 96-104.
https://doi.org/10.1111/cei.13497

[81] Magro, C., Mulvey, J.J., Berlin, D., Harp, J., Baxter-Stoltzfus, A., Laurence, J., *et al.* (2020) Complement Associated Microvascular Injury and Thrombosis in the Pathogenesis of Severe COVID-19 Infection: A Report of Five Cases. *The Journal of Laboratory and Clinical Medicine*, **220**, 1-13.
https://doi.org/10.1016/j.trsl.2020.04.007

[82] Eriksson, O., Hultström, M., Persson, B., Lipcsey, M., Ekdahl, K.N., *et al.* (2020) Mannose-Binding Lectin Is Associated with Thrombosis and Coagulopathy in Critically Ill COVID-19 Patients. *Thrombosis and Haemostasis*, **120**, 1720-1724.
https://doi.org/10.1055/s-0040-1715835

[83] US Government Clinical Trials (2020). (CBDRA60) to Prevent Or Reduce Symptoms of COVID-19 and Prevention of Post-Acute Sequelae of SARS-CoV-2 Infection PASC. https://www.clinicaltrials.gov/ct2/show/NCT04777981

[84] Barre, A., van Damme, E.J.M., Simplicien, M., Le Poder, S., Klonjkowski, B., *et al.* (2021) Mannose-Specific Lectins from Plants, Fungi, Algae and Cyanobacteria, as Potential Blockers for SARS-CoV, MERS-CoV and SARSCoV-2 (COVID-19) Coronaviruses: Biomedical Perspectives. *Cells*, **10**, Article No. 1619.
https://doi.org/10.3390/cells10071619

[85] Ogata, A.F., Cheng, C., Desjardins, M., Senussi, Y., Sherman, A.C., *et al.* (2021) Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of MRNA-1273 Vaccine Recipients. *Clinical Infectious Diseases*, Article No. ciab465. https://doi.org/10.1093/cid/ciab465

[86] Japanese Government (n.d.) SARS-CoV-2 MRNA Vaccine (BNT162, PF-07302048). In: *Pfizer Report*, Japanese Government, Tokyo, 6.
https://www.docdroid.net/xq0Z8B0/pfizer-Reportjapanesegovernmentpdf#page=16

[87] Out of Mind (2021, August 22).
https://www.oom2.com/t76590-Shocking-New-Study-Reveals-Covid-Vaccines-Do-Permanent-Damage-To-62-Of-Recipients

[88] Gupta, A., Sardar, P., Cash, M.E., Milani, R.V. and Lavie, C.J. (2021) Covid-19 Vaccine-Induced Thrombosis and Thrombocytopenia—A Commentary on an Important and Practical Clinical Dilemma. *Progress in Cardiovascular Diseases*, **67**, 105-107.
https://doi.org/10.1016/j.pcad.2021.05.001

[89] Arepally, G.M. (2017) Heparin-Induced Thrombocytopenia. *Blood*, **129**, 2864-2872.
https://doi.org/10.1182/blood-2016-11-709873

[90] Warkentin, T.E. and Dager, W.E. (2005) Chapter 24. Heparin-Induced Thrombo-

cytopenia. In: Garg, H.G., Linhardt, R.J. and Hales, C.A., Eds., *Chemistry and Biology of Heparin and Heparan Sulfate*, Elsevier Science, Amsterdam, 673-697. https://doi.org/10.1016/B978-008044859-6/50025-3

[91] Clausen, T.M., Sandoval, D.R., Spliid, C.B., Ward, A.B., Carlin, A.F., *et al.* (2020) SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. *Cell*, **183**, 1043-1057.E15. https://doi.org/10.1016/j.cell.2020.09.033

[92] Scully, M., Singh, D., Lown, R., Poles, A.K., Solomon, T., *et al.* (2021) Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 NCoV-19 Vaccination. *New England Journal of Medicine*, **384**, 2202-2211. https://doi.org/10.1056/NEJMoa2105385

[93] Comer, S.P., Cullivan, S., Szklanna, P.B., Weiss, L., Cullen, S., *et al.* (2021) COVID-19 Induces a Hyperactive Phenotype in Circulating Platelets. *PLoS Biology*, **19**, Article ID: E3001109. https://doi.org/10.1371/journal.pbio.3001109

[94] Saburova, O.A., Butina, T.Yu., Ryumin, A.M., Mikhailova, E.A. and Sobchak, D.M. (2020) Immunological Criteria for Predicting Severe and Complicated Forms of Chickenpox. *Sovremennye Tehnologii V Medicine*, **12**, 48-54. https://doi.org/10.17691/stm2020.12.4.06

[95] Elsaie, M.L., Youssef, E.A. and Nada, H.A. (2020) Herpes Zoster Might Be an Indicator for Latent COVID 19 Infection. *Dermatologic Therapy*, **33**, Article ID: e13666. https://doi.org/10.1111/dth.13666

[96] van Dam, C.S., Lede, I., Schaar, J., Al-Dulaimy, M., Rösken, R. and Smits, M. (2021) Herpes Zoster after COVID Vaccination. *International Journal of Infectious Diseases*, **111**, 169-171. https://doi.org/10.1016/j.ijid.2021.08.048

[97] Channa, L., Torre, K. and Rothe, M. (2021) Herpes Zoster Reactivation after MRNA-1273 (Moderna) SARS-CoV-2 Vaccination. *American Academy of Dermatology*, **15**, 60-61. https://doi.org/10.1016/j.jdcr.2021.05.042

[98] Shah, S., Baral, B., Chamlagain, R., Murarka, H., Adhikari, Y.R., *et al.* (2021) Reactivation of Herpes Zoster after Vaccination with an Inactivated Vaccine: A Case Report from Nepal. *Clinical Case Reports*, **9**, Article ID: e05188. https://doi.org/10.1002/ccr3.5188

[99] Steain, M., Sutherland, J.P., Rodriguez, M., Cunningham, A.L., Barry Slobedman, B., *et al.* (2014) Analysis of T Cell Responses during Active Varicella-Zoster Virus Reactivation in Human Ganglia. *Journal of Virology*, **88**, 2704-2716.

[100] Serrano-Villar, S., Sainz, T., Lee, S.A., Hunt, P.W., Sinclair, E., Barbara, L., *et al.* (2014) HIV-Infected Individuals with Low CD4/CD8 Ratio Despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality. *PLoS Pathogens*, **10**, Article ID: e1004078. https://doi.org/10.1371/journal.ppat.1004078

[101] Ostroumov, D., Fekete-Drimusz, N., Saborowski, M., Kühnel, F. and Woller, N. (2018) CD4 and CD8 T Lymphocyte Interplay in Controlling Tumor Growth. *Cellular and Molecular Life Sciences*, **75**, 689-713. https://doi.org/10.1007/s00018-017-2686-7

[102] Knutti, N., Huber, O. and Friedrich, K. (2019) CD147 (EMMPRIN) Controls Malignant Properties of Breast Cancer Cells by Interdependent Signaling of WNT and JAK/STAT Pathways. *Molecular and Cellular Biochemistry*, **451**, 197-209. https://doi.org/10.1007/s11010-018-3406-9

[103] Chen, Y., Xu, J., Wu, X., Yao, H., Yan, Z., Guo, T., *et al.* (2020) CD147 Regulates Antitumor $CD8^+$ T-Cell Responses to Facilitate Tumor-Immune Escape. *Cellular & Molecular Immunology*, **18**, 1995-2009. https://doi.org/10.1038/s41423-020-00570-y

[104] Zheng, H. and Gong, B. (2017) CD147 Expression Was Positively Linked to Aggres-

siveness and Worse Prognosis of Gastric Cancer: A Meta and Bioinformatics Analysis. *Oncotarget*, **8**, 90358-90370. https://doi.org/10.18632/oncotarget.20089

[105] Nabeshima, K., Iwasaki, H., Koga, K., Hojo, H., Suzumiya, J., *et al.* (2006) Emmprin (Basigin/CD147): Matrix Metalloproteinase Modulator and Multifunctional Cell Recognition Molecule That Plays a Critical Role in Cancer Progression. *Pathology International*, **56**, 359-367. https://doi.org/10.1111/j.1440-1827.2006.01972.x

[106] Global Research (2021, September) Diagnostic Lab Certified Pathologist Reports 20 Times Increase of Cancer in Vaccinated Patients. https://www.globalresearch.ca/owner-Diagnostic-Labreports-20-Timesincrease-Cancer-Vaccinated-Patients/5756399

[107] Henderson, L.A., Hoyt, K.J., Lee, P.Y., Rao, D.A., Jonsson, A.H., *et al.* (2020) Th17 Reprogramming of T Cells in Systemic Juvenile Idiopathic Arthritis. *JCI Insight*, **5**, Article ID: e132508. https://doi.org/10.1172/jci.insight.132508

[108] De Zuani, M., Lazničková, P., Tomašková, V., Dvončová, M., Forte, G., *et al.* (2021) High CD4-To-CD8 Ratio Identifies an At-Risk Population Susceptible to Lethal COVID-19. *Scandinavian Journal of Immunology*, Early View, Article ID: e13125. https://doi.org/10.1111/sji.13125

[109] Ngono, A.E., Syed, T., Nguyen, X.V., Regla-Navamercylia, J.A., Tono, S., *et al.* (2020) $CD8^+$ T Cells Mediate Protection Against Zika Virus Induced by an NS3-Based Vaccine. *Science Advances*, **6**, Article ID: eabb2154. https://doi.org/10.1126/sciadv.abb2154

[110] Kulkarni R. (2020) Antibody-Dependent Enhancement of Viral Infections. In: Bramhachari, P., Ed., *Dynamics of Immune Activation in Viral Diseases*, Springer, Singapore, 9-41. https://doi.org/10.1007/978-981-15-1045-8_2

[111] Zellweger, R.M., Eddy, W.E., Tang, W.W., Miller, R. and Shresta, S. (2014) CD8+ T Cells Prevent Antigen-Induced Antibody-Dependent Enhancement of Dengue Disease in Mice. *The Journal of Immunology*, **193**, 4117-4124. https://doi.org/10.4049/jimmunol.1401597

[112] Yahi, N., Chahinian, H. and Fantini, J. (2021) Infection-Enhancing Anti-SARS-CoV-2 Antibodies Recognize Both the Original Wuhan/D614G Strain and Delta Variants. A Potential Risk for Mass Vaccination? *Journal of Infection*, **83**, 607-635. https://doi.org/10.1016/j.jinf.2021.08.010

[113] Tanioka, H., Tanioka, S. and Kaga, K. (2021) Ivermectin for River Blindness and Malaria Why COVID-19 Is Not So Spread in Africa: How Does Ivermectin Affect It? MedRxiv 2021.03.26.21254377. https://doi.org/10.1101/2021.03.26.21254377

[114] Scheim, D. (2020) Ivermectin for COVID-19 Treatment: Clinical Response at Quasi-Threshold Doses via Hypothesized Alleviation of CD147-Mediated Vascular Occlusion. https://doi.org/10.2139/ssrn.3636557

[115] Haslam, S.M., Houston, K.M., Harnett, W., Reason, A.J. and Morris, H.R. (1999) Structural Studies of N-Glycans of Filarial Parasites. Conservation of Phosphorylcholine-Substituted Glycans among Species and Discovery of Novel Chito-Oligomers. *Journal of Biological Chemistry*, **274**, 20953-20960. https://doi.org/10.1074/jbc.274.30.20953

[116] Coste, I., Gauchat, J.F., Wilson, A., Izui, S., Jeannin, P., *et al.* (2001) Unavailability of CD147 Leads to Selective Erythrocyte Trapping in the Spleen. *Blood*, **97**, 3984-3988. https://doi.org/10.1182/blood.V97.12.3984

[117] Balaban, D.V., Popp, A., Lungu, A.M., Costache, R.S., Anca, I.A., *et al.* (2025) Ratio of Spleen Diameter to Red Blood Cell Distribution Width. *Medicine*, **94**, Article No. e726. https://doi.org/10.1097/MD.0000000000000726

[118] Pouladzadeh, M., Safdarian, M., Choghakabodi, P.M., Amini, F. and Sokooti, A. (2021) Validation of Red Cell Distribution Width as a COVID-19 Severity Screening Tool. *Future Science OA*, **7**, 7. https://doi.org/10.2144/fsoa-2020-0199

[119] Foy, B.H., Phil, D., Carlson, J.C.T., Reinertsen, E., *et al.* (2020) Association of Red Blood Cell Distribution Width with Mortality Risk in Hospitalized Adults with SARSCoV-2 Infection. *JAMA Network Open*, **3**, Article ID: e2022058. https://doi.org/10.1001/jamanetworkopen.2020.22058

[120] Srivastava, K., Cockburn, I.A., Swaim, A.M., Sullivan, D., Zavala, F., *et al.* (2008) Platelet Factor 4 Mediates Inflammation in Cerebral Malaria. *Cell Host and Microbe*, **4**, 179-187. https://doi.org/10.1016/j.chom.2008.07.003

[121] Campbell, R.A., Boilard, E. and Rondina, M.T. (2020) Is There a Role for the ACE2 Receptor in SARS-CoV-2 Interactions with Platelets? *Journal of Thrombosis and Haemostasis*, **19**, 46-50. https://doi.org/10.1111/jth.15156

[122] Yu, H.H., Qin, C., Chen, M., Wang, W. and Tian, D.S. (2020) D-Dimer Level Is Associated with the Severity of COVID-19. *Thrombosis Research*, **195**, 219-225. https://doi.org/10.1016/j.thromres.2020.07.047

[123] Zong, X., Gu, Y., Yu, H., Li, Z. and Wang, Y. (2021) Thrombocytopenia Is Associated with COVID-19 Severity and Outcome: An Updated Meta-Analysis of 5637 Patients with Multiple Outcomes. *Laboratory Medicine*, **52**, 10-15. https://doi.org/10.1093/labmed/lmaa067

[124] Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.Q., *et al.* (2020) Lymphopenia Predicts Disease Severity of COVID-19: A Descriptive and Predictive Study. *Signal Transduction and Targeted Therapy*, **5**, Article No. 33. https://doi.org/10.1038/s41392-020-0148-4

[125] Huang, I. and Pranata, R. (2020) Lymphopenia in Severe Coronavirus Disease-2019 (COVID-19): Systematic Review and Meta-Analysis. *Journal of Intensive Care*, **8**, Article No. 36. https://doi.org/10.1186/s40560-020-00453-4

[126] Meltzer, E., Keller, S., Shmuel, S. and Schwartza, E. (2019) D-Dimer Levels in Non-Immune Travelers with Malaria. *Travel Medicine and Infectious Disease*, **27**, 104-106. https://doi.org/10.1016/j.tmaid.2018.05.004

[127] Kalungi, A., Kinyanda, E., Akena, D.H., Kaleebu, P. and Bisangwa, I.M. (2021) Less Severe Cases of COVID-19 in Sub-Saharan Africa: Could Coinfection or a Recent History of Plasmodium Falciparum Infection Be Protective? *Frontiers in Immunology*, **18**, Article ID: 565625. https://doi.org/10.3389/fimmu.2021.565625

[128] Kusi, K.A., Frimpong, A., Partey, F.D., Lamptey, H., Amoah, L.E. and Ofori, M.F. (2021) High Infectious Disease Burden as a Basis for the Observed High Frequency of Asymptomatic SARS-CoV-2 Infections in Sub-Saharan Africa. *AAS Open Research*, **4**, 2. https://doi.org/10.12688/aasopenres.13196.2

[129] Crump, A. and Omura, S. (2011) Ivermectin, 'Wonder Drug' from Japan: The Human Use Perspective. *Proceedings of the Japan Academy, Series B*, **87**, 13-28. https://doi.org/10.2183/pjab.87.13

[130] Pöltl, G., Kerner, D., Paschinger, K. and Wilson, I.B.H. (2007) N-Glycans of the Porcine Nematode Parasite *Ascaris suum* Are Modified with Phosphorylcholine and Core Fucose Residues. *The FEBS Journal*, **274**, 714-726. https://doi.org/10.1111/j.1742-4658.2006.05615.x

[131] Mogire, R.M., Mutua, A., Kimita, W., Kamau, A., Bejon, P., *et al.* (2020) Prevalence of Vitamin D Deficiency in Africa: A Systematic Review and Meta-Analysis. *Lancet*, **8**, E134-E142. https://doi.org/10.1016/S2214-109X(19)30457-7

[132] Lima-Costa, M.F., Mambrini, J.V.M., De Souza-Junior, P.R.B., Bof de Andrade, F.,

Peixoto, S.V., Vidigal, C.M., *et al.* (2020) Nationwide Vitamin D Status in Older Brazilian Adults and Its Determinants: The Brazilian Longitudinal Study of Aging (ELSI). *Scientific Reports*, **10**, Article No. 13521. https://doi.org/10.1038/s41598-020-70329-y

[133] Aparna, P., Muthathal, S., Nongkynrih, B. and Gupta, S.K. (2018) Vitamin D Deficiency in India. *Journal of Family Medicine and Primary Care*, **7**, 324-330.

[134] Scott, D.W., Chen, J., Chacko, B.K., Traylor Jr., J.G., Orr, A.W. and Patel. R.P. (2012) Role of Endothelial N-Glycan Mannose Residues in Monocyte Recruitment during Atherogenesis. *Arteriosclerosis*, *Thrombosis*, and *Vascular Biology*, **32**, e51-e59. https://doi.org/10.1161/ATVBAHA.112.253203

[135] Wang, C., Jin, R., Zhu, X., Yan, J. and Li, G. (2015) Function of CD147 in Atherosclerosis and Atherothrombosis. *Journal of Cardiovascular Translational Research*, **8**, 59-66. https://doi.org/10.1007/s12265-015-9608-6

[136] Bilezikian, J.P., Bikle, D., Hewison, M., Lazaretti-Castro, M., Formenti, A.M, *et al.* (2020) Vitamin D and COVID-19. *European Journal of Endocrinology*, **183**, R133-R147. https://doi.org/10.1530/EJE-20-0665

[137] Chambers, E.S., Vukmanovic-Stejic, M., Turner, C.T., Shih, B.B., Trahair, H., *et al.* (2021) Vitamin D3 Replacement Enhances Antigen-Specific Immunity in Older Adults. *Immunotherapy Advances*, **1**, Article No. ltaa008. https://doi.org/10.1093/immadv/ltaa008

[138] Mercola, J., Grant, W.B. and Wagner, C.L. (2020) Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. *Nutrients*, **12**, Article No. 3361. https://doi.org/10.3390/nu12113361

[139] Campi, I., Gennari, L., Merlotti, D., Mingiano, C., Frosali, A., Giovanelli, L., *et al.* (2021) Vitamin D and COVID-19 Severity and Related Mortality: A Prospective Study in Italy. *BMC Infectious Diseases*, **21**, Article No. 566. https://doi.org/10.1186/s12879-021-06281-7

[140] CDC (Centers for Disease Control and Prevention) (n.d.) Influenza (Flu). https://www.cdc.gov/flu/about/burden/index.html

[141] Martineau, A.R., Jolliffe, D.A., Hooper, R.L., Greenberg, L., Aloia, J.F., Bergman, P., *et al.* (2017) Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data. *BMJ*, **356**, Article No. i6583. https://doi.org/10.1136/bmj.i6583

[142] Vázquez-Lorente, H., Herrera-Quintana, L., Molina-López, J., Gamarra-Morales, Y., López-González, B., *et al.* (2020) Response of Vitamin D after Magnesium Intervention in a Postmenopausal Population from the Province of Granada, Spain. *Nutrients*, **12**, Article No. 2283. https://doi.org/10.3390/nu12082283

[143] Frieri, M. and Ashok, V. (2011) Vitamin D Deficiency as a Risk Factor for Allergic Disorders and Immune Mechanisms. *Allergy and Asthma Proceedings*, **32**, 438-444. https://doi.org/10.2500/aap.2011.32.3485

[144] Ma, J.G., Wu, G.J., Xiao, H.L., Xiao, Y.M. and Zha, L. (2021) Vitamin D Has an Effect on Airway Inflammation and Th17/Treg Balance in Asthmatic Mice. *Kaohsiung Journal of Medical Sciences*, **37**, 1113-1121. https://doi.org/10.1002/kjm2.12441

[145] Pender, M.P. (2012) $CD8^+$ T-Cell Deficiency, Epstein-Barr Virus Infection, Vitamin D Deficiency, and Steps to Autoimmunity: A Unifying Hypothesis. *Autoimmune Diseases*, **2012**, Article ID: 189096. https://doi.org/10.1155/2012/189096