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Review Article

Evaluation of Immune Response, Comorbidities and Immunomodulation in SARS-CoV2 Pandemic

Gerardo T López Pérez[1]*, María de Lourdes Patricia Ramírez Sandoval[2] and Mayra S Torres Altamirano[3]

[1]Allergist-Infectologist-Pediatrician, Head of Allergy Service, National Institute Of Pediatrics, Titular Member of the Mexican Academy of Pediatrics and Member of Mexican College of Pediatricians Specialists in Clinical Immunology and Allergy; Mexican College of Clinical Immunology and Allergy and European Academy of Allergy and Clinical Immunology, México

[2]Pediatrician and Infectologist, Medical Staff Member at General Hospital Z-32 IMSS, Titular Member of the Mexican Academy of Pediatrics and Mexican Association of Pediatric Infectology: Member of the Mexican Association of Infectology and Clinical Microbiology, México

[3]Pediatric Dentistry, Medical Director of Asistencia Pediatrica Integral, México

***Corresponding Author**: Gerardo T López Pérez, Allergist-Infectologist-Pediatrician, Head of Allergy Service, National Institute Of Pediatrics, Titular Member of the Mexican Academy of Pediatrics and Member of Mexican College of Pediatricians Specialists in Clinical Immunology and Allergy; Mexican College of Clinical Immunology and Allergy and European Academy of Allergy and Clinical Immunology, México.

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Abstract

SARS-CoV2 can be originate from bats or unknown intermediate hosts and cross the species barrier toward humans. Virus-host interactions affect the entry and viral replication. Virus genome encodes four essential structural proteins, the glycoprotein spike, the small envelope protein, protein arrays and nucleocapsid protein. The S glycoprotein of SARS-CoV2 binds to receptors on the host cell enzyme, angiotensin-converting enzyme 2 (ACE2), which is a critical step for the entry of viruses, it is expressed more in men than in women probably by the estradiol and testosterone that can influence in a different way the activity of ACE.

It is considered a viremia phase when the virus can pass from the salivary glands and mucous membranes, in special nose and larynx, to lungs and other organs with the same receptors as heart, liver and even to the central nervous system. It can get intestines, which may explain why is detected SARS-CoV-2 in feces for up to 30 days from the start of the infection.

Risk factors of the host are key to viral pathogenesis and the most recognized are an immunosuppressed status, old age, systemic arterial hypertension, diabetes mellitus or chronic lung diseases. When the immune system is inefficient to effectively control the virus in the acute phase may evolve to a serious or critical condition.

The timely and accurate diagnosis of infection by SARS-CoV2 is the cornerstone of efforts to provide adequate treatment to patients, limiting the spread of the virus and ultimately, eliminating the presence of the virus in humanity.

It is essential to know that treatment has several aspects, the first is during the acute and critical phase of the disease, where the life of the patient is involved and the other, is the stage in which his/her clinical condition is mild and is where it really is to recommend only isolation. However, this is something you should consider because some evolve to seriousness; this should be avoid because it implies serious health and quality life impairment with an increase of contagion. It has been suggested the use of immunostimulants, known as biological response modifiers, whose effectiveness has been demonstrated in other type of acute and recurrent viral respiratory infections.

Keywords: *SARS-CoV2; Immune Response in COVID-19; Risk Factors to Covid-19; Treatment; Immunomodulation in Covid-19; Pidotimod*

Introduction

The World Health Organization declared COVID-19 as a pandemic on 11 March 2020. However, from the beginning of December 2019 and until 30 April 2020, according to the Johns Hopkins University at world level has been notified, 3,196,664 people infected and

227,705 have died. At the top of this list of infected are USA with 1,040,488 cases, Spain with 236, 809, Italy with 203,591 and France with 166,543, in México there are 17,799 cases, and in Italy 27,682 deaths, Spain 24,275, United Kingdom 26,097 and New York 18,076, México until now has 1,732 deaths.

Human immune system is a perfect system that combines a whole range of cells and mediators to provide protective immunity against microbes (viruses, bacteria, fungi, parasites, etc). Its intervention is with early reactions known as innate immunity and subsequent responses, called adaptive immunity; both are very important for the defense against intracellular germs such as SARS-COV2 that originates the COVID-19.

Many properties of the immune system are fundamental for its normal functions. Among them are: the specificity against different antigens, the ability to rapidly expand the clones of lymphocytes specific for the antigen, specialized responses against different microbes, the maintenance of homeostasis and the ability to discriminate between foreign and own antigens.

The elimination of the antigens often requires the participation of a number of effector cells. The CD4 T helper lymphocytes aid the macrophages to eliminate ingested microbes and to B-lymphocytes to produce antibodies. Cytotoxic T lymphocytes (CTL CD8) cause the lysis of the cells that contain intracellular microorganisms with which eliminate the reservoirs of the infection. The antibodies, products of B-lymphocytes, neutralize the infectivity of microbes and promote its elimination by phagocytes and by the activation of the complement system. All these functions are carried out in an immunologically normal patient but not in a patient with comorbidities in contact with the coronavirus as in elderly, children under 5 years old, pregnancy and patients with any primary or secondary immunodeficiency, as is the case of HIV/AIDS. And of course, in those with diabetes mellitus, metabolic syndrome, obesity, immunosuppression, and in the case of infection by SARS-CoV2, also in the masculine gender.

Pathogeny

SARS-CoV2 could originate from bats or unknown intermediate hosts and cross the species barrier toward humans. Virus-host interactions affect the entry and viral replication. Within the viral factors, SARS-CoV2 is a positive coronavirus wrapped with single stranded RNA (ssRNA). Two-thirds of the viral RNA encode 16 non-structured proteins. The remaining part of the viral genome encodes four essential structural proteins, the spike glycoprotein (S), the small envelope protein (E) and the protein arrays (M), and nucleocapsid protein (N), and several accessory proteins. The S glycoprotein of SARS-CoV2 binds to receptors of the host cell enzyme, angiotensin-converting enzyme 2 (ACE2), which is a critical step for the virus entry. It has been identified the activator molecule that facilitates the invagination of the membrane for the endocytosis of SARS-CoV2 is the transmembrane protease cellular serine type 2 (TMPRSS2) (Figure 1).

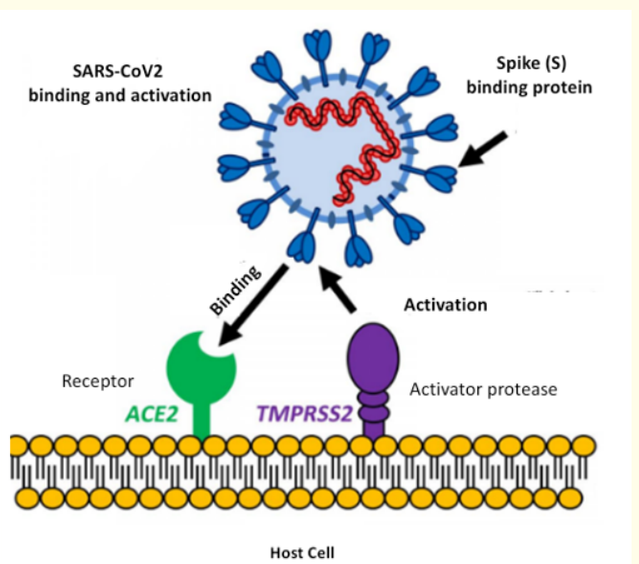

Figure 1: *SARS.CoV2 binding and activation. (Modified from German primate center. Preventing Spread of SARS Coronavirus-2 in Humans. Göttingen infection researches identify potential drug March 6th, 2020 https://www.labmanager.com/news/preventing-spread-of-sars-coronavirus-2-in-humans-21942).*

As all infectious process, it is essential the interaction of the new agent SARS-CoV2, the immune response of the host supported by its health status or comorbidities and the environment (Figure 2).

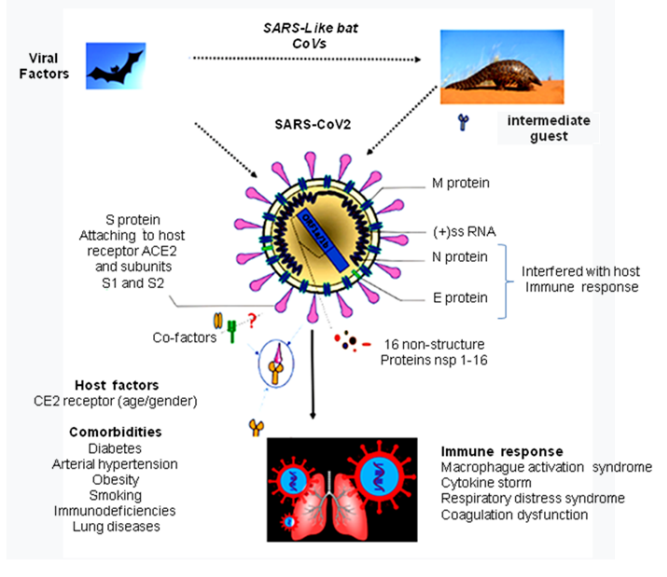

Figure 2: *Viral and host factors that influence the pathogenesis of SARS-CoV2. (Modified from Guo Y., et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the Status. Military Medical Research (2020) /:11 https://doi.org/10.1186/s40779-020-00240-0).*

The expression of ACE2 is increased in patients with type 1 or type 2 diabetes, treated with ACE inhibitors and angiotensin II receptor blockers type 1 (ARBs). In those treated with ACE inhibitors and ARB, it results in a positive regulation of ACE2, which also increases with thiazolidinediones and ibuprofen. Thus, the increase in the expression of ACE2 would facilitate the SARS-CoV2 infection (https://doi.org/10.1016/S2213-2600(20)30116-8 1). Emphasizing the importance that has the receptor of the angiotensin-converting enzyme 2 (ACE2), which varies its expression according to age. It increases its expression as a child grows older, being greater at 17 years and, in addition, is expressed more in men than in women. Then, it is considered that estradiol and testosterone can influence in a different way ACE activity, this explains the impairment of SARS-CoV and SARS-CoV2 in certain population groups. It can be considered that the evolution of the patients experiments the following clinical phases:

1. The viremia phase, where the virus can pass the mucous membranes, especially the nasal and larynx, enters the lungs through airways. The most common symptoms are fever and cough (doi:10.1056/NEJMoa2002032). Acute phase or pneumonia, where the virus would attack in addition to lungs other target organs, heart and kidney, which express receptor for angiotensin-converting enzyme 2 (ACE2) [1].

2. In this phase, it may lose control of the viral clearance and fall into an immune catastrophe that aggravates the clinical picture and determines the death. Virus can also reach the digestive tract, which explains some of the symptoms and why in feces is detected SARS-CoV2 for up to 30 days [2].

3. There is a recovery phase, where the immune function is effective in the acute phase (pneumonia phase) (Figure 3).

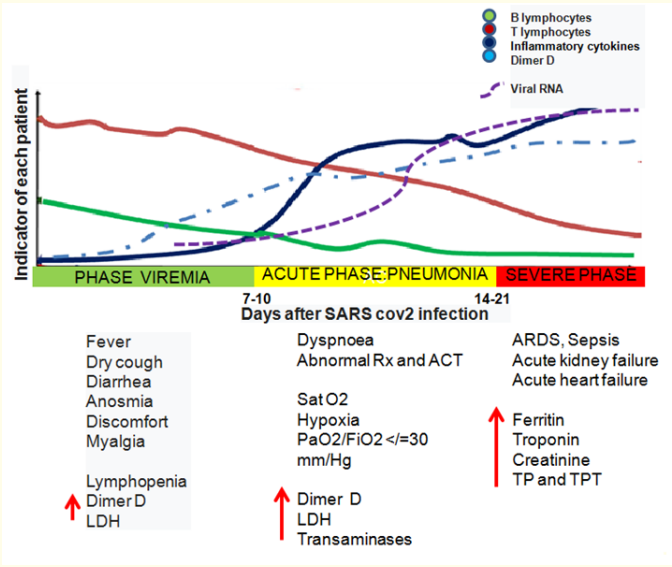

Figure 3: *Pathogenesis of COVID-19. Correlation between clinical phases of the infection and immunological and clinical markers (modified from Ling Lin, Lianfeng Lu, Wei Cao and Taisheng Li (2020) Hypothesis for potential pathogenesis of SARS-CoV2 infection - a review of immune changes in patients with viral pneumonia, Emerging Microbes and Infections, 9:1, 727-732, DOI: 10.1080/22221751.2020.1746199).*

The patient with a immunosuppressed status as old age or combined with other diseases such as systemic arterial hypertension, diabetes or chronic lung diseases, his/her immune system cannot effectively control the virus in the acute phase (pneumonia phase) and evolves to a serious or critical condition. The appearance of symptoms of acute respiratory distress syndrome (ARDS) is approximately 8 days. Then, complications may include ARDS in 29%, anemia in 15%, acute heart failure in 12%, secondary infection 10%, and death in 15%.

Virus initiates a second attack, causing the patient's condition worsens around 7 to 14 days after the start. Leukopenia and lymphopenia in early stage of the disease are data of poor prognosis. It is also associated with poor prognosis a significant increase of IL-6 (doi:10.110 1/2020.02.10.20021832). Non-survivors had higher levels of neutrophils, D-dimer, blood urea nitrogen and creatinine than survivors [3].

Oral mucosa in the infection by COVID-19

Salivary glands are involved in the pathogenic process. In a previous study on SARS-CoV, their epithelium cells became infected, because they have high expression of ACE2 still with more expression than lung epithelium, which suggests that the salivary glands could be potential target organs for COVID-19. In addition, ARN in SARS-CoV can be detected in saliva before pulmonary lesions appear. This may explain the presence of asymptomatic infections. The positive rate of COVID-19 in patient's saliva can reach 91.7%. These infected cells could be an important source of virus in saliva, particularly in the early stages of infection. This observation has significant implications for understanding the respiratory transmission of SARS-CoV and possibly, in SARS-CoV2, which is fundamental to the development of effective strategies for diagnosis, prevention and therapy [4] (Figure 4).

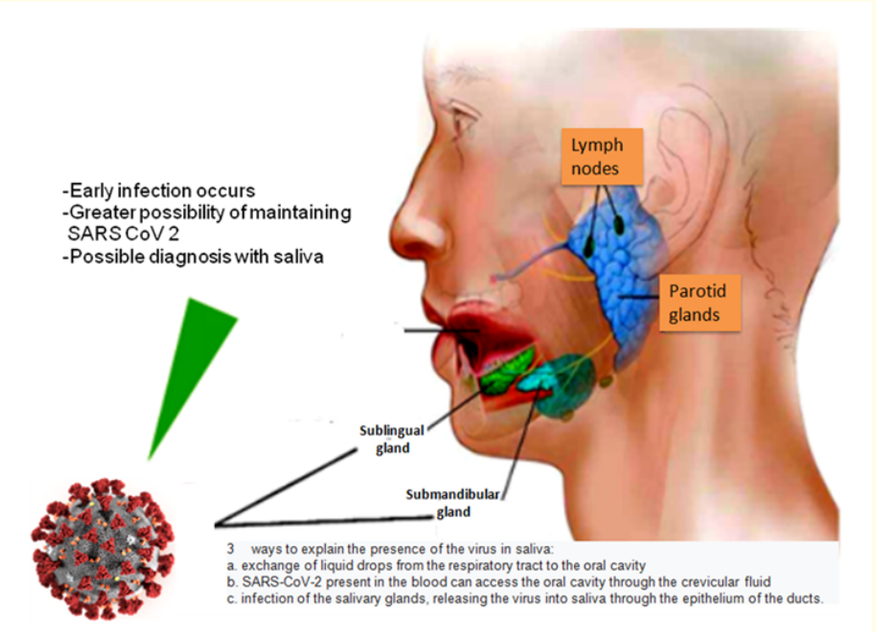

Figure 4: *SARS-Cov19 and interaction in salivary glands.*

Pulmonary pathology

Pulmonary lesions in cases of SARS show a nonspecific inflammatory response, which plays an important role throughout the course of the disease. It is characterized by edema and cellular infiltration, also, severe exfoliation of alveolar epithelial cells, alveolar widening, infiltration and hyperplasia, damage to pulmonary interstitial arteriolar walls, damage to alveolar septa, and organized infiltration of alveolar space and finally, necrosis [5] (Figure 5). In addition to the direct damage caused by the binding of alveolar pneumocytes to ACE2 and the internalization of the virus for replication, there is an acute lung lesion through angiotensin-converting enzyme (ACE) that converts angiotensin I (AT I) in angiotensin II (AT II). AT II binds to angiotensin II receptor 1a (AT1aR), causing tissue damage and pulmonary edema, or binds to angiotensin II receptor 2 (ATR2) reducing tissue damage. ACE2 inactivates AT II, generating angiotensin 1-7 (AT 1-7) [6].

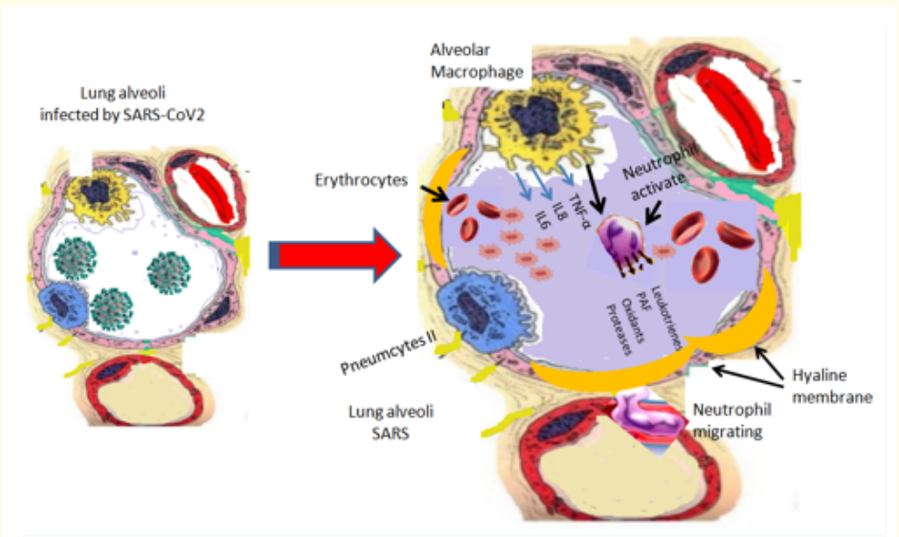

Figure 5: *Infection by SARS-CoV2 and severe alveolar inflammation.*

Brain impairment

It can lead to cerebral edema and cause death long before the establishment of the systemic homeostatic deregulation and present hyposmia, and in acute respiratory failure involve the olfactory bulb (Figure 6).

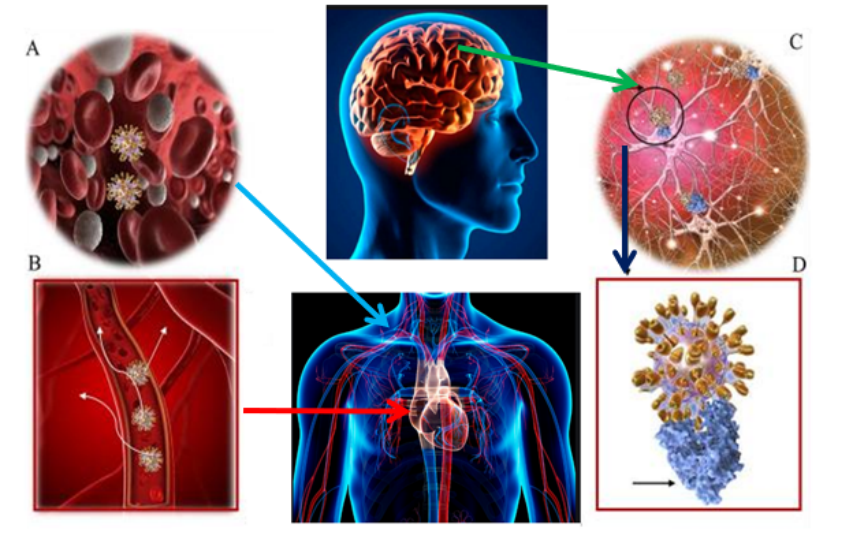

Figure 6: *Tissue distribution of ACE2 receptors in humans. The viremia (A) spread the virus COVID-19 throughout the body through the bloodstream (B). Neurotropism can occur through the circulation and/or superior nasal transcriptional pathway that allows COVID-19, which reaches the brain (C) binds to ACE2 receptors (D, blue). COVID-19 attacks lungs, heart, kidneys, intestines, brain and testes. Modified from Baig AM, Khalleg A., et al. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interactions and Proposed Neurotropic Mechanisms. ACS Chemical Neuroscience 2020 11 (7), 995-998 DOI: 10.1021/acschemneuro.0c00122.*

Impairment of the metabolism of Hem group of hemoglobin

Finally, it has been consider that ORF8 and the surface glycoprotein could bind the porphyrin, as well as, orf1ab, ORF10 and ORF3a proteins could coordinate the attack of Hem in the 1-beta chain of hemoglobin dissociating the iron to form porphyrin. This attack will cause less hemoglobin that can carry oxygen and carbon dioxide. The lung cells are unable to exchange carbon dioxide and oxygen with the consequent inflammation resulting finally in lung images of frosted glass. Thus, chloroquine could prevent orf1ab, ORF3a and ORF10 attack hem to form porphyrin and inhibit the binding of ORF8 and the surface glycoproteins to porphyrins, with the aim of alleviating the symptoms of shortness of breath.

On the other hand, favipiravir may inhibit that the envelope protein and the protein ORF7a bind to porphyrin, preventing that the virus enters host cells and trap free porphyrins [7].

Risk factors

To understand these changes it is necessary to outline the immune response of the infected individual, however, it is essential to consider the factors associated which unbalance it. Among them, it may include the following conditions.

Age

According to that reported in the point of origin of this pandemic, it can be observed that related to age, the majority of them were between 30 and 79 years old (87%), only 1% had 9 years old or less, 1% were between 10 and 19 years old and 3% had 80 years old or more. The overall rate of lethality (ORL) was 2.3% (1023 deaths among 44 672 confirmed cases). There were no deaths in the group of 9 years old or less, but in the cases of 70 to 79 years old had an ORL of 8.0% and in the cases of 80 years old and older was 14.8%. There were no reported deaths among mild and serious cases. ORL was 49.0% among the critical cases. This same raised among those with preexisting comorbid conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer. On the other hand, among the 44 672 cases, 1716 were healthcare workers (3.8%), 1080 of which were in Wuhan (63%). In general, the 14.8% of confirmed cases among healthcare workers were classified as serious or critical and 5 deaths were observed.

Most of the cases were classified as mild (81%; that is to say, not pneumonia and mild pneumonia). However, 14% were severe (i.e. dyspnea, breathing rate ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to the fraction of inspired oxygen < 300 and/or pulmonary infiltrates > 50% within 24 to 48 hours) and 5% were critical (i.e. respiratory failure, septic shock and/or dysfunction or multi-organ failure [8].

Diabetes and other chronic non-communicable diseases

In a meta-analysis of eight studies, were included 46,248 infected patients. The result showed that the most frequent clinical symptom was fever (91 ± 3, CI 95% 86 - 97%), followed by cough (67 ± 7, CI 95%, 59 - 76%), fatigue (51 ± 0, CI 95%, 34 - 68%) and dyspnea (30 ± 4, CI 95%, 21 - 40%). The prevalent comorbidities were systemic arterial hypertension (SAH) (17 ± 7, CI 95%, 14 - 22%) and diabetes mellitus (8 ± 6, CI 95%, 6 - 11%), followed by cardiovascular diseases (CVD) (5 ± 4, CI 95%, 4 - 7%) and chronic obstructive pulmonary disease (COPD) (2 ± 0, CI 95%, 1 - 3%). Compared to the non-serious patient, it was associated the participation of SAH, COPD and CVD (OR 2.36, CI 95%: 1.46 - 3.83), (OR 2.46, IC 95%: 1.76 - 3.44) and (OR 3.42, IC 95: 1.88 - 6.22), respectively. It was concluded that the prevalence of comorbidities in patients with COVID-19 infection, could be a risk factor for seriously ill patients in comparison with patients that are not impaired [9].

Patients with dyspnea were 6.6 times more likely to be admitted to the ICU (CI 95%: 4.28 to 10.0) compared with those without dyspnea. Although COPD was relatively rare, even in ICU patients, was by far the strongest predictive comorbidity for admission to the ICU (by 17.8%, CI 95%, 6.56 - 48.2). Those with CVD and hypertension were 4.4 (CI 95%, 2.64 - 7.47) and 3.7 (CI 95%, 2.22 - 5.99) times more likely to have an admission in the ICU, respectively, compared with patients without comorbidity [10]. Chronic disease share several standard features with infectious disorders, such as pro-inflammatory state and the attenuation of innate immune response. For example, diabetes occurs in part because the accumulation of innate immune cells activated in the metabolic tissues leads to the release of inflammatory mediators, especially, IL-1β and TNF-α, which promotes the systemic resistance to insulin and damage to β-cells. In addition, metabolic disorders can lead to low levels of the immune function by affecting the function of macrophages and lymphocytes, which can make individuals more susceptible to complications of the disease.

Pollution

Air pollution is well known as one of the most important causes of airways inflammation. In models of mice exposed for three months to particles of ≤ 2.5 μm in diameter (PM2.5), increased IL-4, TNF-α in lung and serum and transforming growth factor (TGF)-β1, as well as leukocytes and macrophages.

In humans: both PM2.5 and PM10 lead to systemic inflammation with an overexpression of PDGF, VEGF, TNF-α, IL-1 and IL-6, even in non-smoking young healthy subjects.

It has been observed that the alveolar macrophages (AM), exposed *in vitro* to PM10, significantly increased the levels of IL-1β, IL-6, IL-8 and TNF-α, which underlines the role of AM in the cleanliness of particles and the activation of the immune response. There is a high correlation between nitrogen dioxide (NO_2) with induction of hyper-expression of IL-6, both being responsible for an inflammatory state even in a pediatric population.

Among the other most common contaminants, the ozone (O_3) and sulfur dioxide (SO_2) also have a role in the induction of inflammation of the respiratory and systemic system, particularly through IL-8, IL-17 and TNF-α.

With this, the lethality observed in Lombardy and Emilia Romagna, during this Pandemic of Covid 19, it was around 12% while in the rest of Italy was approximately 4.5%. Also, Northern Italy was identified as one of the most polluted areas in Europe in terms of smog and air pollution, due to its climatic and geographical conditions, which cause the stagnation of pollutants [11].

Based on this direct and evident correlation between high level of lethality and atmospheric pollution, the overreaching question addressed from this paper is: are communities living in polluted area such as Mexico City, among other Italian, more predisposed to die of Covid-19 due to their health status?

Smoking

Smoking history is in patients with cancer a risk. Tobacco use significantly increases gene expression of angiotensin-converting enzyme 2, the binding receptor for SARS-CoV2 of severe acute respiratory syndrome, which may explain the high susceptibility to COVID-19 in smokers. In addition, has been identified cigarette smoking as the main cause of chronic obstructive pulmonary disease as an independent risk factor for severe cases of COVID-19 [12].

Cancer

The risk for cancer patients facing this infection is generally insufficient to issue a conclusion. It has been observed that the development of cancer is generally associated to a dull immune status characterized by immunosuppressive cytokines overexpressed, suppressed induction of pro-inflammatory response and danger signals, besides of maturation of dendritic cells impaired and improved functional immunosuppression of the populations of leukocytes, which is contradictory with the events that result in severely ill patients with COVID-19 [13].

HIV/AIDS

While people living with HIV who are treated with a normal count of CD4 T cells and a suppressed viral load may not have an increased risk of serious illness, many people living with HIV have other conditions that increase their risk. It must assumed that the immune suppression, indicated by a low count of CDA T cells (< 200/μl), or those that do not receive antiretroviral treatment; it is also associated with an increased risk for a more severe disease. For patients with low CDA counts (< 200/ml), or that experiment a decrease in CD4 during an infection by COVID-19, it is necessary to take measures for opportunistic infections [14].

Rheumatic diseases

Patients with rheumatic diseases, is known have an increased risk of infection attributed to the activity of the disease, comorbidities, immunosuppressive therapy, etc. WHO promotes that general population take some basic protection measures against COVID-19 and other respiratory viruses. According to the clinical information published until now on the new and previous outbreaks caused by coronavirus (SARS and MERS), there is not overwhelming evidence that patients with rheumatic diseases have an increased risk

compared with other comorbidities. Although, it is necessary that more information arise on this outbreak before a firm conclusion can be reached doi:10.1136/ annrheumdis-2020-217322.

In a recent study, chloroquine and hydroxychloroquine widely used in rheumatic patients, showed potent *in vitro* antiviral effect in a COVID-19 assay by increasing endosomal pH that is required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors, adding its well-known immunomodulatory action. Chloroquine is being considered to be included in the next version guidelines for the prevention, diagnosis and treatment of pneumonia caused by COVID-19, issued by the National Health Commission of the People's Republic of China [15].

Pregnancy

There are also unanswered questions specific to pregnant women, such as whether they are more severely affected? and whether intrauterine transmission occurs? Although guidelines for pregnant women from the American College of Obstetricians and Gynecologists and the Centers of Disease Control and Prevention have been rapidly developed based on the best available evidence, additional information is required to inform key decisions, such as temporarily separate infected mothers and their newborns, and whether it is safe for infected women to breastfeed [16].

Pediatric patients

Pediatric age has been considered without high risk of severity or complications (doi.org/10.1111/apa.15270).

Children infected by SARS-CoV2 have represented around 2% of the cases diagnosed in China [17], 1.2% of the cases in Italy [18] and 5% of the positive COVID-19 cases in the United States [19]. These low numbers match data in SARS epidemic in 2003, when 6.9% of positive cases were children, but fortunately none died.

Observing less impairment in the pediatric age, was suggested that the angiotensin-converting enzyme (ACE) 2, receptor of S protein of SARS-CoV2, in children has less expression than in adults.

The review of the greatest number of positive cases of COVID-19 was in China with 72,314 subjects, and approximately 2% of the 44,672 confirmed cases were children aged 0 - 19 years. Of these, 0.9% were under the age of 10 years at the time of diagnosis. There were 965 total deaths (2.2%) but only one child died in the 10 to 19 year age group [20].

Italian data reported that only 1.2% of 22512 were children and in fact, no deaths had been recorded below the age of 30 years in Italy [21]. In a report of 4226 cases detected in the United States, 5% were children. They constituted less than 1% of all hospitalizations. Of 123, only were admitted to the hospital between1.6% to 2.5%, none needed intensive care and not reported any deaths [22].

With regard to comorbidities of pediatric patients, it was noted that three (1.8%) of 171 patients required intensive care and all had underlying disease. They reported the death of a child of 10 months with intussusception and multi-organ failure. Although those admitted to the hospital between January and February 26, 149 (87.1%) had been discharged before 8 March 2020 [23].

In another report, there was one case with bilateral hydronephrosis with renal calculus, one was undergoing chemotherapy for leukemia, and another had intussusceptions (doi.org/10.1016/j. jinf.2020.02.024). In 398 pediatric patients, most of the children recovered in 1 to 2 weeks [24]. By the moment, data are scarce on the clinical characteristics of children with cancer infected by this virus, although it is suggested an increased risk of COVID-19 in adults with cancer (doi.org/10.1016/S1470-2045(20)30205-9).

Although of the 4226 reported patients with COVID-19 in USA until 16 March 2020, there were no deaths, it is suggested to take into account the history of congenital or acquired disease, as might occur in pneumopathies and asthma, since the 10% of children suffer from

them.

Obesity

The disproportionate impact of H1N1 flu and now COVID-19 in patients with obesity and severe obesity is not surprising given the impact of obesity in lung. Obesity is associated with a decrease in expiratory reserve volume, functional capacity and compliance of the respiratory system. In patients with increased abdominal obesity, lung function is further committed to patients in supine position by the decline in diaphragmatic excursion, which makes it difficult ventilation. In addition, the increased inflammatory cytokines associated with obesity can contribute to increase the morbidity associated with obesity in infections by COVID-19 [25].

Adipose tissue expresses ACE2. The general activation of the renin angiotensin system of the angiotensin-converting enzyme (ACE)/ angiotensin II/type 1 angiotensin 2 receptor (AT1R) plays an important role in the pathophysiology of obesity and visceral adiposity-related cardiac risk. The interaction between ACE2-RAS system, adipose tissue and risk for COVID 19 in obese patients.

Dipeptidyl peptidase 4 (DPP-4) has been identified as a receptor of MERS CoV. This enzyme is expressed in diabetes and obesity. Blocking of DPP-4 increases secretion of glucagon-like peptide 1 that further allows improving the sensitivity to insulin in tissues and improves the metabolism of glucose. Inhibition of the enzymatic activity of DPP-4 inhibits the activity of T lymphocytes and their secretion of interleukins 6 and 10. The production of adipokines interferes with the proper chemotaxis and macrophage activity, this would mean that DPP4 could be a target site for therapeutic. On the other hand, production of adiponectin increases the production of IL6 pro-inflammatory cytokines (Figure 7).

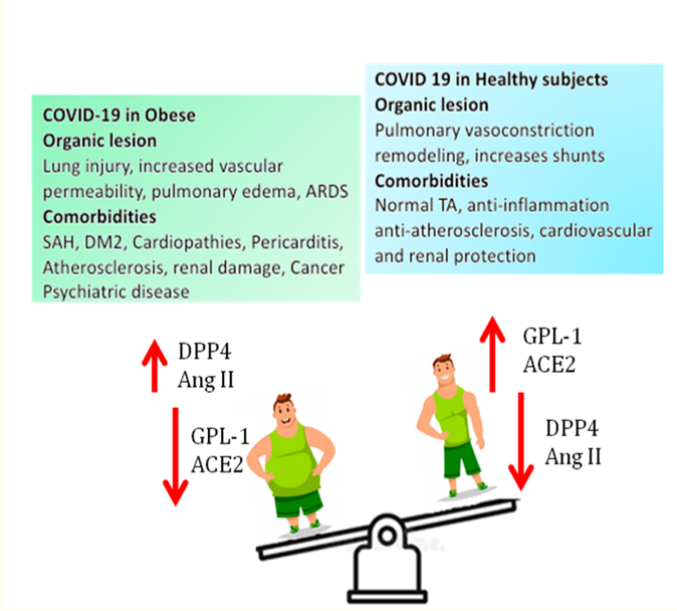

Figure 7: *Obesity and Covid-19. Modified from Malavazos A., et al. Targeting the adipose tissue in Covid-19, doi: 10.1002/by.22844.*

Immune response to SARS-CoV2 infection

Non-specific immune response

Taking as a model the infection caused by SARS-CoV and that shares a 79% similarity with SARS-Cov2, can have some interesting data to understand the clinical picture and design intervention strategies.

This virus has the possibility to infect the human being through binding Spike glycoprotein (S) of SARS-CoV2 and the receptor of the angiotensin-converting enzyme 2 (ACE2). The systematic detection of β-CoV receptors showed that human cells expressing ACE2 promote the entrance of SARS-CoV2, it is known that binding S protein and ACE2 it is10 to 20 times greater than that observed with SARS-CoV-2 [26]. The genomic ribonucleic acid (RNA), included RNA of double chain (RNAdc) of SARS COV within the cell, acts as Pathogen-Associated Molecular Pattern (PAMPs) that are recognized by the Recognition Receptor Pattern (RRPs) of the endosomal RNA in which the receptors type Toll (TLR3 and TLR7) and RIG-1/MDA5 stand out. This event of recognition leads to the activation of the signaling cascade starring the nuclear enhancing factor of kappa light chains of B cells activated (NF-kB) and Interferon Regulator Factor 3 (IFR3). In nuclei this transcription factors induce the expression of IFN (interferon) type I and other pro-inflammatory cytokines. These initial responses comprise the first line of defense against viral infection at the site of entry [27]. Is highly probable that SARS-CoV2 uses similar strategies to modulate the host innate immune response, especially in the type I IFN damping response. In SARS disease, were diagnosed approximately 25% with Acute Respiratory Distress Syndrome (ARDS) and the mortality rate exceed 50% [28]. The advance age of more than 65 years gave an unfavorable prognosis reaching a mortality of 50%. IFN not only acts to control viral infections, but also to program adaptive immune response. In patients with serious disease, there were aberrant responses to IFN observed, from the stimulated genes with interferon (ISG) and even some cytokines in comparison with healthy individuals [29]. SARS-CoV2 induced belatedly type I IFN, causing loss of viral control in an early phase of infection until 48 hours after the infection, conditioning the appearance of pulmonary edema, severe hypoxia and accumulation of inflammatory cells in lungs; it has been observed progression of late phase fibrosis of ARDS, systemic inflammatory responses and multi-organic failure. According to progression of ARDS, the principal target of infection by SARS-CoV2 are ciliated epithelium cells of the airways and type II alveolar pneumocytes [30]. ARDS is also associated to inflammatory cytokines induction, including IL-1, IL-6, IL-8, CXCL-10 and TNFα, many of which are highly expressed in lungs of patients with SARS [31].

T cells immune response

MERS-CoV and SARS-CoV are beta-coronavirus that can cause fatal infection in the lower respiratory tract with extrapulmonary manifestations [32].

The T lymphocytes, CD4+ T, and CD8+ T particularly, play a significantly antiviral role equilibrating the combat against pathogens with risk of developing autoimmunity or overwhelming inflammation [33].

The CD4+ T promote the production of specific virus antibodies by activating B Cells, T-dependents. The CD8 T lymphocytes are cytotoxic and can kill virus infected cells; these represent approximately 80% of all inflammatory infiltrative cells in the pulmonary interstitium of patients infected with SARS-CoV and they play a vital role in the elimination of coronavirus in the infected cells, inducing serious immune lesions [34].

Interstitial pneumonitis mediated by the immune system and delayed elimination of SARS-CoV of the lungs results from exhaustion of lung recruitment of CD4+ T lymphocytes and production of neutralizing antibodies [35].

The CD8 + T cell fall do not affect or delays the viral replication at the time of the infection with SARS-CoV [36].

On the other hand, the helper T cells produce pro-inflammatory cytokines through signaling path of NF-kB; thus, IL-17 cytokines recruit monocytes and neutrophils at the site of the infection with inflammation and activation of further cytokines and chemokines cascades, such as IL-1, IL-6, IL-8, IL-21, TNF -β and MCP-1 [37].

In infection by MERS-CoV induction of apoptosis by intrinsic and extrinsic pathways of T cells is observed. The results of the current investigation show that the response of the T cells to S protein and other structural proteins (including M and N proteins) is sustained and persistent. This provides evidence to the design of a vaccine against SARS composed of viral proteins, that can induce dominant, effective and of long-term memory cell responses against virus.

Antibody immune response

In a study in 173 patients with infection by SARS-CoV2, it was observed that the seroconversion rate and the antibodies level increased rapidly during the first two weeks, the cumulative seropositivity rate reach the 50% in day 11 and 100% in day 39. The total antibodies seroconversion time, IgM and IgG consistently appeared ($p < 0.05$) with a mean of a day of seroconversion at 11, 12 and 14 days, respectively.

Due to the lack of blood samples recollected of patients in a later stage of the disease, it is unknown how long can last the antibodies. Therefore, it was concluded that even in the first stages of the disease within 1 week, some patients with undetectable RNA could be examined by the antibody test. The combination of PCR and antibodies tests increase significantly the sensitivity to detect patients ($p < 0,001$). These findings indicate that the serologic test is an important complement to the detection of RNA during the course of the disease.

The timely and accurate diagnosis of the infection by SARS-CoV2 is the cornerstone of the efforts to provide adequate treatment to patients, limit the spread of the virus and as a last instance, and eliminate the presence of the virus in humanity. Nowadays, the viral RNA detection based real time Polymerase Chain Reaction (RT-PCR) is almost the only way to confirm the diagnosis of infection by SARS-CoV2, however, epidemiologically linked cases to the exposure to the SARS-CoV2 and typical pulmonary imaging findings were negative for RNA in samples of the upper respiratory tract. The sensitivity of RT-PCR depends of several factors, such as sample types, the different stages of the infection in patients, the ability of recollection of samples and the quality and test consistency of PCR that are used. This can lead to a noticeably delay of the early diagnosis and generate a serious problem to provide timely treatment of vital support and especially a preventive quarantine [38].

In other study, in this pandemic, levels of IgM and IgG were evaluated and it was found that, from a total of 34 hospitalized patients within week 3 after the onset of symptoms, all patients were positive to IgM and IgG; in week 4, all results for IgM and IgG were positive, although the IgM decreased while IgG continue rising. However, in week 5, all patients were positive for IgM, while 2 patients (16.7%) had negative results for IgM. The IgM level continue decreasing and the IgG levels continued until the end of the 7 weeks, where 2 patients (33.3%) had negative results for IgM.

The detection and the specific antibodies profile against SARS-CoV2 will provide valuable information for rapid detection of suspects, help the diagnosis and evaluate the on going disease (Figure 8).

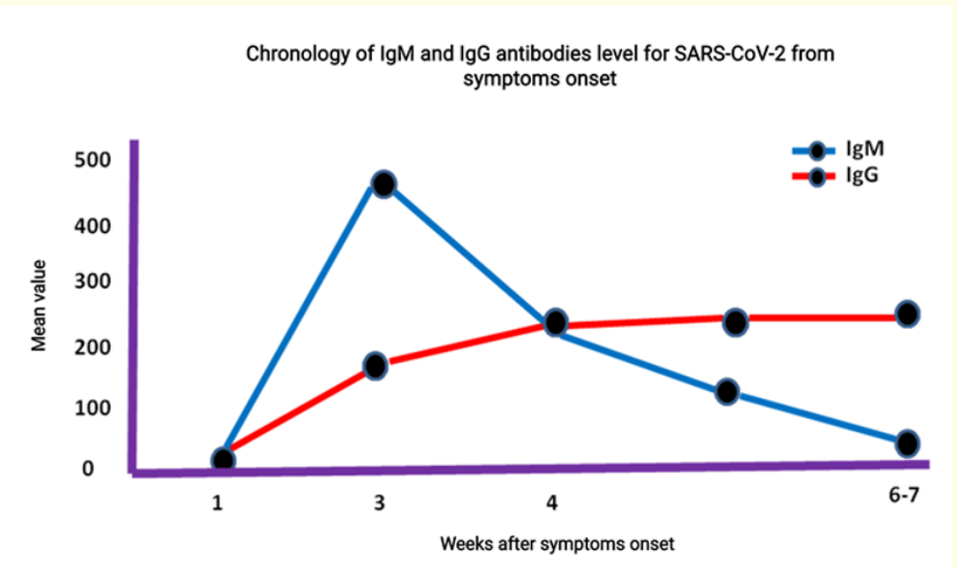

Figure 8: *Antibody response to SARS-CoV2. Modified from Xiao T, Gao Ch and Zhang S. Profile of Specific Antibodies to SARS-CoV2: The First Report, Journal of Infection (2020), doi: https://doi.org/10,1016/j.inf.2020.03.012).*

There is evidence that some cells do not have the usual ACE2 receptors in its surfaces that the viruses use to enter. However, can occur the infection by other type of coronavirus, producing ineffective neutralizing antiviral antibodies. These can facilitate entry of the virus to the host cells leading to greater ineffectiveness, mechanism known as ADE (Antibody Dependent Enhancement) or facilitation of the infection by antibodies. Previously infectious strains could have been human coronavirus that cause the common cold (229E) [39] or several strains of bat coronavirus or by SARS-CoV that shares approximately an homology of 79% [40].

The availability of neutralizing antibodies against SARS-CoV2 will offer benefits to the control of the current pandemic and it is a high priority. However, there is a reference of a patient who died of SARS, and that showed strong responses to neutralizing antibodies (Nab) and pulmonary pro-inflammatory accumulation, suggesting that Nab intervened in it (Figure 9) [41].

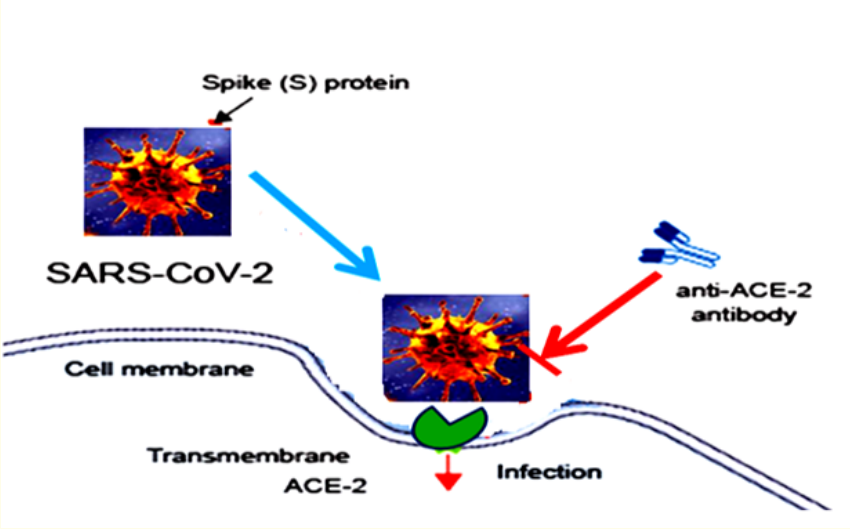

Figure 9: *Neutralizing antibodies against SARS-CoV2. Interaction of the Spike Protein and the cellular receptor for the fusion of the membrane and the entry in the target cell. The monoclonal antibodies vs Spike Protein could inhibit binding of the virus to its receptor. (Modified from Shanmugaraj B., et al. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19) Asian Pac J Allergy Immunol 2020;38:10-18 DOI 10.12932/AP-200220-0773).*

Cytokines Storm in the macrophage activation syndrome (MAS) secondary to the infection by SARS-CoV2

The Macrophage Activation Syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome little known, which is characterized by a fulminant and fatal hypercytokinemia with multi-organ failure. It triggers more frequently from viral infections and occurs in 3 · 7 - 4 · 3% of sepsis cases. It is clinically characterized by constant fever, cytopenia and hyperferritnemia; lung involvement (ARDS included) occurs in approximately 50% leading to pulmonary edema and liver, heart and kidney damage. These symptoms are associated with a Cytokines Storm manifesting elevated serum levels of IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM -CSF, IFNγ, TNFα, IP10, MCP1, MIP1A and MIP1B. The most severely ill patients have even higher levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A and TNFα [42].

COVID-19 infection with MAS, was related to the sustained elevation of IL-6 and IL-1. Clinical and laboratory parameters in MAS/ sHLH phenotype are similar to the primary hemophagocytic lymphohistiocytosis (HLH), but the latter is invariable autosomal recessive, occurs in childhood and is typically due to mutations that affects the cytotoxic T cells NK y CD8 + function. The laboratory parameters

that include very high reactive protein C (PCR) and hyperferritnemia, are key to SAM/HLH diagnosis and are elevated in COVID-19 with pneumonia. Other characteristics, as coagulopathy and abnormal liver function, may be evident, suggesting an overlap with SAM/HLH. The disseminated intravascular coagulation (DIC) associated with MAS/HLH, presents elevation of the D-dimer that could represent an extension of this new hyperinflammatory lung immunopathology virus induced to the adjacent microcirculation with extensive secondary fibrinolytic activation. Therefore, COVID-19 could be associated with extensive pulmonary micro thrombosis instead of DIC, which generally occurs in advanced MAS. A characteristic feature of the primary HLH but not of MAS/sHLH is a deficient NK function, which is also reported in the infection by COVID-19, but by different mechanisms. It is currently unclear if elevated levels of IL-6 are harmful or beneficial in pneumonia by COVID-19. In experimental model systems, IL-6 can suppress or facilitate viral replication, considerations about therapy anti-IL-6 are key. The early use of strategies of antiretroviral therapy to reduce viral load is crucial to prevent the relative immunosuppression that could be contributing to the development of MAS. Patients with pneumonia by COVID-19 not only have serological markers associated with the development of SAM, including hyperferritnemia and altered liver function tests with coagulopathy, but also the preliminary tests demonstrate evidence of efficacy for blocking anti-IL-6R with tocilizumab.

Hypercytokinemia, which includes IL6, is associated to the infection by SARS-CoV2 and it can be found, in MAS and sepsis. The viral or bacterial coinfections increase systemic responses to cytokines (Figure 10).

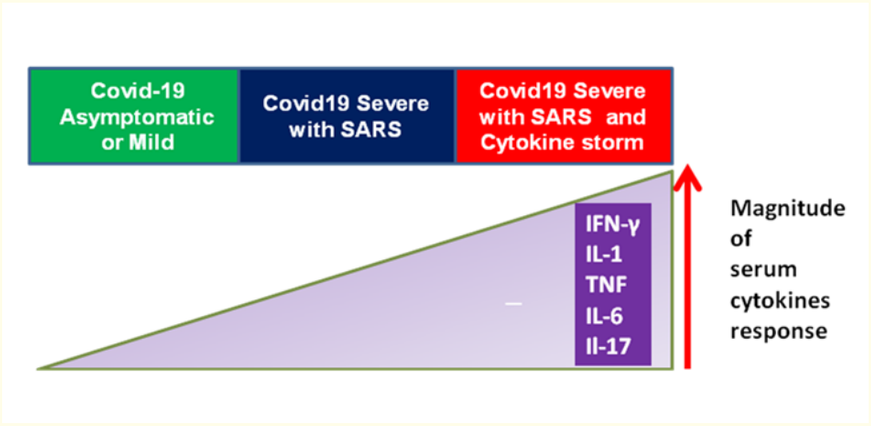

Figure 10: *Hypercytokinetic overlaps between ARDS and MAS (modified from Dennis McGonagle., et al. Autoimmunity Reviews, https:// doi.org/10.1016/j.autrev.2020.102537).*

On the other hand, TH17 and TH1 cells participation, which express TNFα and produce IL-17, has wide pro-inflammatory effects because they induce: a) G-CSF cytokines (responsible for granulopoiesis and neutrophil recruitment), IL-1β, IL-6, TNFα (they cause systemic inflammatory symptoms, including fever); b) KC chemokines, MIP2A, IL-8, IP10, MIP3A (attracting and recruiting immune infiltrators); and arrays metalloproteinases (involved in tissue damage and remodeling) [43] (Figure 11).

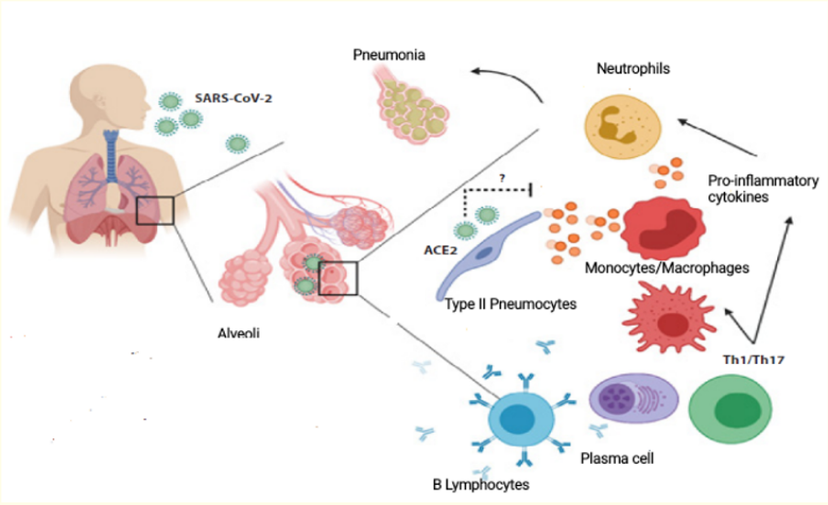

Figure 11: *Pathophysiology of the interaction of SARS-CoV2, lung damage and immune response- The IFN type I response delayed or suppressed during initial infection. Viral replication triggers hyperinflammatory conditions. Infllux of activated and inflammatory neutrophils. Monocytes/ macrophages. And induced Th1/Th17 response (modified of Eakachai Prompetchara E, Ketloy E, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian PAC J Allergy Immunol DOI 10.12932/AP-200220-0772).*

In summary, in pathophysiology of MAS it is noted uncontrolled proliferation of T cells and excessive activation of macrophages and hypersecretion of pro-inflammatory cytokines, IL-1β, IL-6, IFN and tumor necrosis factor α (TNFα). Along with the uncontrolled macrophage response, pathological activation of thrombin is found in these patients, showing multiple thrombotic episodes that go from peripheral ischemia, pulmonary thromboembolism to disseminated intravascular coagulation (DIC) (Figure 12).

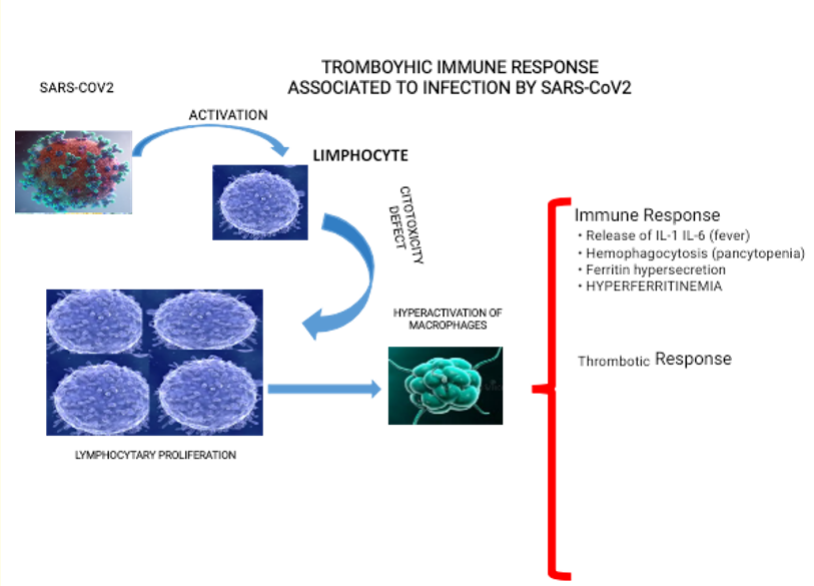

Figure 12: *Immune Thrombotic Response Associated to Covid-19 Modified from (RITAC) Gauna M https://fundacionio.com/wp-content/uploads/2020/04/Si%CC%81ndrome-RITAC.pdf.*

Treatment

The world has experienced the outbreak of MERS-CoV, SARS-CoV and now SARS-CoV2. All of these emerge in a periodic and unpredictable way, they spread quickly and induce serious infectious diseases, become a continuous threat to human health. This is especially true when there are no vaccines or medications approved for the treatment of CoV infections. Although a universal vaccine broadly protective is considered the maximum protection against the spread of the virus, the development of a vaccine can take a long time.

Effective therapeutic measures have been proposed using the knowledge of the innate immune response. Targeted immunotherapy is a good alternative to some antivirals that have narrow treatment windows and are easily found with the drug resistance.

Control of cytokines production and inflammatory response is important, since they are responsible for the accumulation of cells and fluids. This strategy is very challenging since still there is not site of the immune response that can be specifically inhibited without compromising the beneficial defense of the host. Notable achievements have been reached in the analysis of damaging and protective mechanisms. For example, completely block of a proximal event in the immune response, another is the activation of pathogen recognition receptors (PRR) related to the response of interferon but it seems incautious considering its role in the regulation of the host defense. It is probably a most viable objective, to control the production of oxygen free radicals, the NET formation, or of IL-1, IL-4, IL-6, IL-8 e IL-21 (Figure 13).

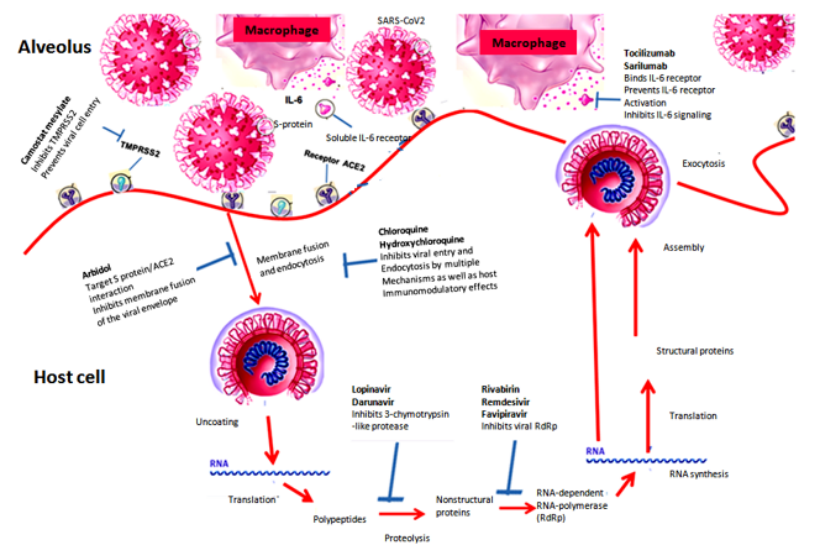

Figure 13: *Opportunity for therapeutic intervention based on the response of the host immune system induced by virus and the viral processing within the target cells. Modified by Sanders JM, Monogue ML, Jodlowski TZ Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. JAMA Published online on April 13, 2020. Doi:10.1001/jama.2020.6019.*

Recommendations in epidemics

The recommendations of good clinical practices indicate that in the epidemics the best way of treating serious respiratory infections is to control de source of infection, provide an early diagnose, report, isolate, generate support treatments and timely publish epidemic information to avoid unnecessary panic. With regard to people, it is recommended a good personal hygiene, an adjusted mask when prescribed and avoid crowded places to prevent infections in this case by SARS-CoV2.

In addition to all the measures adopted with respect to WHO recommendations, it should be mandatory strengthen the immune system both people unaffected by viral infection, as a first-line prevention measure, and people affected, to prevent the appearance of complications.

This strategy must be adopted, specially in fragile subjects, like elderly people, due to the "immunosenescence" and those with possible comorbidities. In recent years, the use of immunostimulant drugs constantly increased obtaining today more importance and visibility to prevent the appearance and to reduce the length of airways.

Theoretical basis to assess the use of an immunostimulant (Pidotimod) in COVID-19

Pidotimod is a synthetic dipeptide molecule (3-1-pyroglutamyl-1-thiazolidine-4-carboxylic acid) provided with immunomodulatory activity that affects innate and adaptive immune responses.

Studies in different areas have shown the benefits of Pidotimod, including its use in hepatitis C, genital HPV infection, Henoch-Schönlein purpura, nephrotic syndrome, and immunosuppressed individuals such as children and the elderly [44].

By stimulating the immune cells that act on the adaptive and innate immunity, it improves the clinical conditions of the patients [44].

Its effectiveness has been observed in children between 2 and 14 years old, during acute pictures of infection, since after its use, they reduce the duration of fever, the need for antibiotic treatment, hospitalization, absence from school, time of recovery and relapse rate [45].

Effect on innate immunity

The recognition of Pathogen-Associated Molecular Pattern (PAMP) through Toll-like Receptors (TLR) results in the activation for NF-kB, which controls DNA transcription in response to diverse stimuli, including viral and bacterial infections. NF-kB activation leads to internalization and phagocytosis of bound pathogens, such as viruses. Upregulates the HLA-DR expression and CD83, CD88 co-stimulants surface markers.

By promoting the maturation of epithelial dendritic cells (DC), allows the release of pro-inflammatory mediators such as TNF-α, activation of virgin T lymphocytes with proliferation and polarization towards Th1 phenotype. It also improves the cytotoxic activity of natural killer (NK) cells and the phagocytic activity of neutrophils [44].

Adaptive immunity effect

Improve secretion of IFN-y and other Th1 cytokines as IL12 through which Th1 mediates inflammatory reactions. The increase in Th1 cytokines not only would improve capabilities of the immune system to fight viral infections, but also have a protective role against the development of atopy; there was also found that pidotimod downregulates the expression of CD30 in cells bounded to Th2 cells [44].

On the other hand, it has been shown to promote greater production of secretory IgA at the nasopharyngeal and salivary levels (sIgA) in children with respiratory tract infections due to the direct effect on lymphocytes. This property would be very useful since the onset of coronavirus infection is in the pharynx and salivary glands [45].

Viral infections

The most common causes of respiratory tract infections have a viral origin, especially human rinovirus (HRV), adenovirus, parainfluenza virus, respiratory syncytial virus (RSV), enterovirus, human metapneumovirus, and Coronavirus, in addition to the influenza virus.

Viruses tend to cause a direct invasion of the epithelial cell in the respiratory tract using various receptors, such as the intercellular adhesion molecule (ICAM)-1 in HRV, for obtaining access to human cells; it stimulates the production of inflammatory pro-cytokines including IL8, IL6, MCP-1 (a chemokine that recruits monocytes), which leads to the generation of inflammatory response; necrosis of cells infected by the host; decrease ciliary clearance and increase mucous secretions causing an increment in the severity of the disease, mortality and morbidity with progression, such as pneumonia.

On the other hand, the host immune system tends to control viral infections by the apoptosis induction of infected cells, using different mechanisms including: increase secretion of alpha-TNF; stimulation of natural killer cells (NK) to secret perforin, and stimulation of macrophages and neutrophils; to produce reactive oxygen species that cause oxidation of the proteins, lipids and DNA of the infected host cell, leading to death [46].

It increases the expression of a molecule that functions as identifier of molecular patterns associated to TLR2 pathogens without increasing ICAM or IL8 levels, thus playing a protective role in the decrease of susceptibility to HRV infection and other viruses, generated by the neutrophils-mediated damage in the airways surface [47].

It is also able to overregulate NLRP12, which is a protective molecule against abnormal inflammatory response induced by virus [48].

Lower respiratory tract infections

In pneumonic pictures, it was observed that it induced the effectiveness of the immune system by stimulating some proteins, such as lactoferrin, cathepsin G, myeloperoxidase, which are known to be provided with a potent antibacterial. It was associated with reduced production of alpha-TNF, a pro-inflammatory cytokine whose excess production is known as a negative prognostic factor in Community Acquired Pneumonia (CAP). Finally, the finding that Pidotimod increases the expression of CD80 and CD86 in DC, confirming its role in triggering the adaptive immunity response [49] and increasing secretion of TNFα e IL12. It was found that, also determines a long-term improvement in the activity of the immune system, upregulating CCL3, CXCL1, CXCL2, IL-18, IL-1b, IL-6, IL-8, NFkB1 and NLRP3 gene expression involved in inflammation and chemotaxis, in addition to genes involved in antimicrobial activity (for example, AMPc, lactoferrin, cathepsin G and myeloperoxidase), reducing this way the risk of early recurrences during CAP [50].

Furthermore, it significantly reduces the period of cough and fever and improves the serum immunoglobulin levels (IgG, IgA or IgM) and the T lymphocytes subtypes (CD3+, CD4+) (Figure 14).

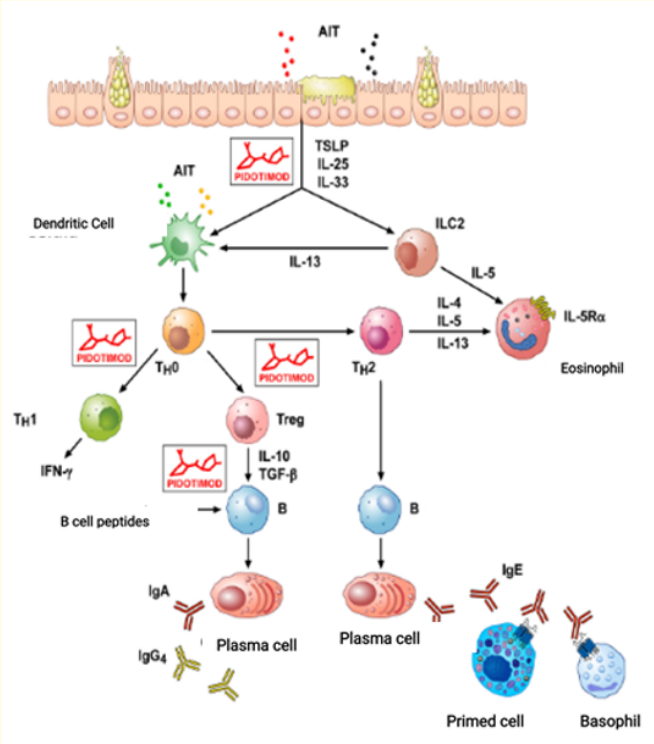

Figure 14: *The main mechanisms of action of pidotimod, in both levels of innate and adaptive immunity. Taken from Puggioni F, Alves-Correia M, Mohamed M., et al. Immunostimulants in respiratory diseases: focus on Pidotimod. Multidisciplinary Respiratory Medicine 2019; 14:31*

Conclusion

With the advent of this new coronavirus known as SARS-CoV2 and which, is the producer of Covid-19 Pandemic, it has generated in humanity a wild use of epidemiological resources to contain it. However, this will be impossible if we do not know the risk factors of the population that is most infected and the conditions of the immune response that precipitated as a response to it. In such a way that the pharma-immunological measures taken by populations and individuals, will be ineffective in the lack of integrating of all this information. Behavior has been changing as it affects various populations, initially having a very low fatality rate in China but when arriving to America it has increased, this is obviously due to the population characteristics and the set of comorbidities on this side of the world. The nutritional aspect, pollution and smoking, promote a very bad evolution facing this virus, therefore, this should make us look back at humanity as a whole, and especially the population belonging to this hemisphere must already change their lifestyle in a convincing manner, seeking to bring down the comorbidities that expose the population to death before any new pandemic.

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