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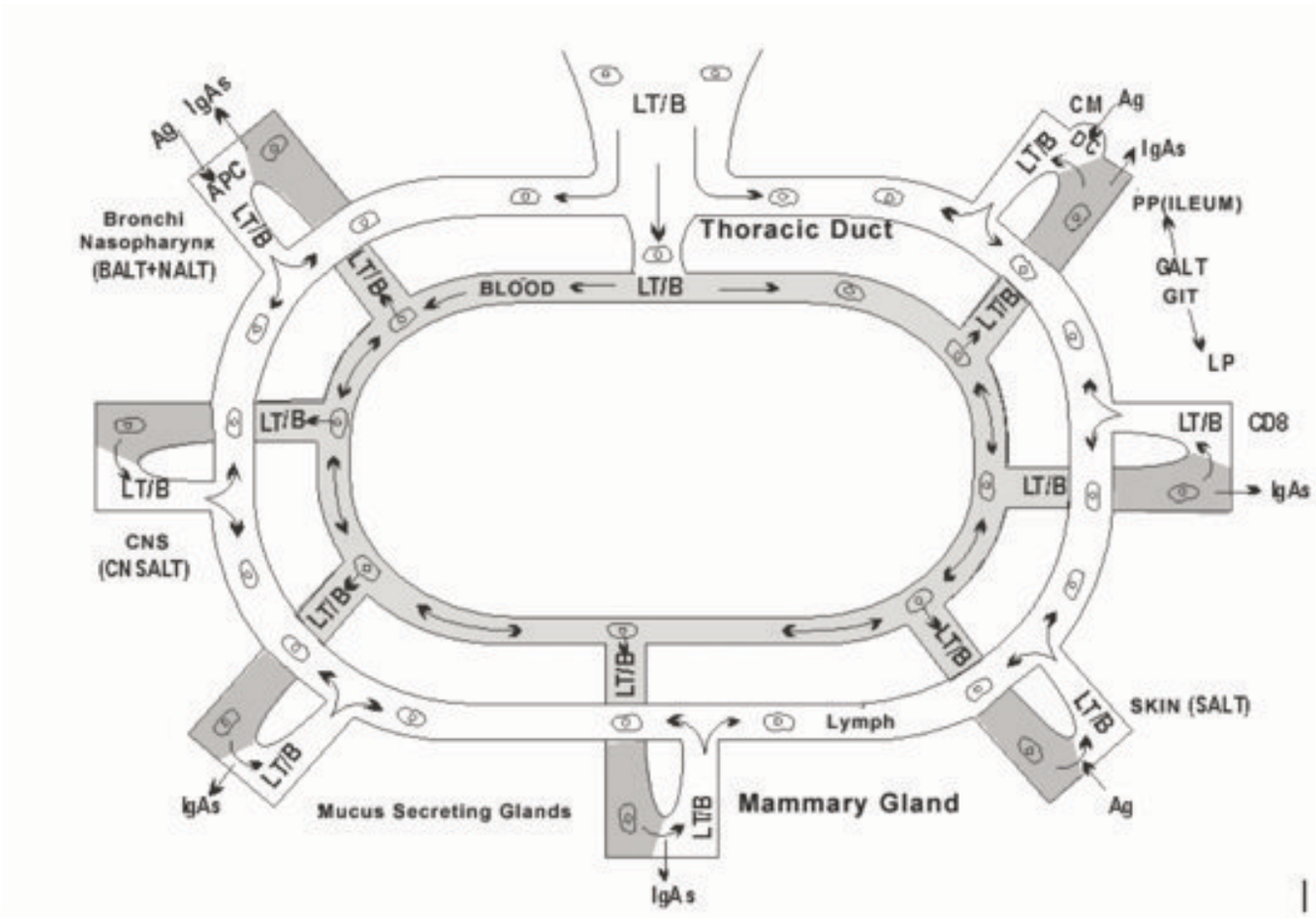
"IMMUNE STORM" AND PROBIOTICS: THE BETTER WAY TO PREVENT COVID-19 IN THE ELDERLY

IMMUNOLOGICAL ASPECTS AND FAILURES ON THE COVID19 TREATMENT



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CONTEÚDO

COMENTÁRIOS DO EDITOR

Com o advento da pandemia de Coronavirus todas as revistas médicas do Mundo dedicaram 2020 para publicar artigos sobre o tema. JFA tem a satisfação de apresentar neste primeiro semestre da 2020 artigos sobre o tema escritos por nosso editor chefe.

The new coronavirus

The new coronavirus, commonly known as the SARS-nCov-2 is a simple strain RNA with positive polarity (ssRNA+). The disease caused by this new virus is known as COVID19. Both virus and disease are known as "coronavirus" by the public.

Estimates show that each infected person propagates the SARS-nCoV-2 infection to other 1.4 to 3.9 people when the community is not immune and no preventive measure has been issued.

The new coronavirus has a singular particularity in his action mechanism that differs from other classic coronavirus like SARS and MERS, that is the production of a protein that has the property of inhibiting the host's immune response, mainly the innate immunity.

As the coronavirus acts with its immune blocking property, its pathogenic action is out of control. It starts to replicate indefinitely and generates immune disease in the host, by suppressing its immune response. Without the innate response present, the host resorts to the adaptive immune response, also suppressed.

After that the coronavirus disease spread all over the human body. Mainly the lungs are all ways affected. The major question today is the lack of a specific therapy directed at immunological failures caused by SARS-nCoV-2, presented by patients with COVID19.

The main objective of this paper is to call attention to the mistakes in the treatment of COVID 19.

COVID-19 and deaths

The statistics of the incidence of the infection, diseases and deaths related the COVID-19 all over the word, among human, are clear to shown the evident conclusion that children are protected against the COVID-19 infections, with an incidence of the disease in less than 2% with no deaths. On the other hand the infection in adults has a expressive incidence with deaths ranging from 4% in the sixties, increasing to 18% over the eight decade of life.

The better tree explanations to this evident situation are: 1- the clear state of immunization and the state of immune alert among the children, 2- the constant stimulaton of the children microbiota, and 3- the state of immunosenescence among the adults, specialty over the sixth decade of life.

The scope of this article is to prevent this state of loss of immune response and the loss of CD8, acting Apresentação 2020 n2preventively with constant and preventive provocation to the immune system of the adults, with a “immune storm” using all the vaccines against to the preventable infectious diseases and with the use of probiotics.

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Original Article

“IMMUNE STORM” AND PROBIOTICS: THE BETTER WAY TO PREVENT COVID-19 IN THE ELDERLY

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Introduction

The statistics of the incidence of the infection, diseases and deaths related the COVID-19 all over the word, among human, are clear to shown the evident conclusion that children are protected against the COVID-19 infections, with an incidence of the disease in less than 2% with no deaths. On the other hand the infection in adults has a expressive incidence with deaths ranging from 4% in the sixties, increasing to 18% over the eight decade of life.

The better tree explanations to this evident situation are: 1- the clear state of immunization and the state of immune alert among the children, 2- the constant stimulaton of the children microbiota, and 3- the state of immunosenescence among the adults, specialty over the sixth decade of life.

Material and clinical evidence of adult immunization in Brazil

The statistics in China and all over the countries, among the COVID-19 prevalence point to the numbers of more than 95% among adults and less than 5% among children and adolescents. Taking the number of deaths among all humans the prevalence of deaths is ranging from more than 18% over 80 years of life, ranging around 7% among adults in the in the seventies, over 5% in the sixties, with a clear decline in incidence until zero in children.

Over the decades the clear situation of immune response among adults show that at the third decade of life the adults start to have infectious diseases like Hepatitis A, Hepatitis B, Measles, Mumps, Yellow Fever, Influenza, Diphtheria, Pneumococcal Disease, HPV, Herpes Zoster and others less prevalent.

The low adherence of adults and the elderly to immunizations for diseases to which they are susceptible and which are immunopreventable, in addition to the risk of damaging their own health, are potential sources of the spread of viruses and bacteria in those age groups.

It is also worth noting the financial and social impact resulting from hospitalizations, loss of productivity and absences from work, for example. A study published in the journal Annals of Medicine in 2018 estimated that morbidity from vaccine-preventable diseases cost the United States about $ 9 billion each year. (1.2)

Occurrence of vaccine-preventable diseases in Brazil among adults and the elderly.

MEASLES: a disease extinct among us until a few years ago, which represented an oversight and one of the causes of decreased immunization against it, therefore appears as a health problem among us, after the cases that occur migrate from Venezuela. Until January last year, 10,302 cases had been confirmed - about 95% (9,724) in Amazonas – with 12 deaths in the national territory. In Amazonas, the available data points out that among 15 to 29 years old group, are responsible for 46% of the cases. Currently, 10 states in Brazil have active circulation of the measles virus. (3,4)

YELLOW FEVER: In 1980, Brazil started successive outbreaks of wild yellow fever, which increased since 2016. From 2016 to 2018, we had 2,155 cases and 745 deaths and the most affected states were Minas Gerais, São Paulo, Rio de Janeiro and Espírito Santo. The age distribution of the records shows that the prevalence was higher among adults between 41 and 55 years old (age group with lower vaccination coverage), with a predominance of males. (5 a 7)

HEPATITIS A: Of the 165,000 cases of hepatitis A, registered as occurring in Brazil, in the last 20 years, 20% occurred in individuals over 20 years of age. In comparison with the incidence in children under 10 years old, with 54% of cases, the participation of adults is still small. However, in 2017 the most affected group was people aged 20 to 39 years. The majority are men, who contracted the virus sexually. What is alarming about the statistics and what calls our attention is the increase in incidence in this age group, growing 14 times in just one year. What cannot be overlooked is that more than 70% of deaths from Hepatitis A occur among adults. These data are leading us to have to take vigorous vaccination actions in these adults after adolescence. (8)

HEPATITIS B: Also in the last 20 years we have had high numbers of Hepatitis B cases, totaling 218,000 cases. It draws our attention that adults are responsible for 91% of cases with more than 200,000 notifications. Among adults, the incidence prevails after the age of 20, with the majority of those notified aged between 35 and 39 years, with a male prevalence and respective incidence between 38.3% and 54.4% of the total. During the period, the detection rate of Hepatitis B fell in the range of 0 to 34 years old, remained the same in the range of 35 to 39 years old and increased from 40 years old, with emphasis on those over 60 years old. Hepatitis B killed 14,000 patients in this period. Although there is no specific vaccine against hepatitis D, deaths were also considered preventable, since the virus only affects people infected with hepatitis B, an immune preventable disease. (9)

DIPHTHERIA: Vaccination brought down the incidence of diphtheria in Brazil to the point that many doctors have not even seen the disease in the past 20 years, with only about 100 cases reported. Of these 33 cases occurred in 2010, in an outbreak in State of Maranhão, with 10 deaths. We must keep our diphtheria vaccination schemes up to date due to recent outbreaks in other surrounding countries, where more than 300 deaths have occurred. The Ministry of Health recommends vaccination against diphtheria with the adult type pair every ten years, from the age of 14. (10 a 12)

INFLUENZA: The influenza that occurred in the United States, in the 2017-2018 outbreaks, reached about 11 million people, who needed hospitalization with the record of 80,000 deaths. As in other occasions, those over 65 were the main victims, concentrating 70% of hospitalizations and 90% of deaths. The predominant strain was a variant of A (H3N2), not included in the vaccine for the Northern Hemisphere.

In Brazil, at the same time, in 2018, we had hospitalizations for influenza in almost 7,000 cases with “severe acute respiratory syndrome” (SARS), almost twice as much as in 2017. Of the 1,381 registered deaths, the majority (76.4 %) occurred in people with some risk factor, the most common being: age over 60 years (55.1%), patients with chronic cardiovascular disease (31.6%) and patients with chronic lung diseases (24.6%). (13,14)

It is worrying that in view of the need for annual vaccination, the uncertainty about circulating serotypes, the fact that universal vaccines do not yet exist and the cyclical nature of the appearance of mutations in viruses, we cannot rule out the occurrence of pandemics of this disease in the future.

PNEUMOCOCCAL DISEASE: The World Health Organization (WHO) estimates that 1.6 million people of all age groups die each year from pneumococcal disease. In the United States, the estimate is that 900,000 people contract pneumococcal pneumonia every year and that 400,000 require hospitalization. Of these, 5% to 7% die - lethality is higher in the elderly. (15,16)

In Brazil, there was an important drop in invasive pneumococcal disease (IPD) among children under 5 years after the introduction of the 10-valent pneumococcal conjugate vaccine (PCV10). However, different from the expected collective immunity protecting other age groups, in addition to those vaccinated, there was no decrease in the occurrence of IPD among adults and an increase in the incidence among the elderly was observed. (17 a 21)

MUMPS: Mumps is not compulsory to report, so it is not possible to know precisely the real impact of the disease. However, there are reports of increased incidence in federal units, in all regions of the country, in the last 5 years, with the registration of about 40,000 reported cases. (22 a 27)

In Brazil from 2011 to 2014, about 20,000 cases of pertussis were reported. There were about 10,000 cases in children under 1 year, with 87% of cases in children under 6 months of age. Lethality follows the same pattern: in the period, 98.7% of deaths were in children under 1 year, of which 97% were less than 2 months old, a range in which there is still no indication of the first dose of the vaccine. Since 2015, pertussis cases have decreased. As for the incidence, the fall was from 4.2 / 100,000 inhabitants in 2014 to 0.9 / 100,000 inhabitants in 2017. (28 a30)

In adults, Bordetella pertussis infection is asymptomatic in most cases, which explains the low incidence of the disease in this age group. However, adults are the main source of infection for the child, especially those under 1 year old, who have not yet completed the vaccination schedule against the disease. The main strategy to preserve them in this period of greatest risk is the vaccination of pregnant women after 20 weeks of pregnancy, a conduct that allows maternal antibodies to be transferred via the transplacental route and protect the baby in the first three months of life. Vaccination of older children, adolescents and adults living with children less than 1 year also contributes to reducing the threat to the baby, since the source of the infection is at home about 75% of the time.

The milder evolution among adults, however, does not mean that they are completely free from complications, especially the elderly, such as: weight loss (33%), urinary incontinence (28%), syncope (6%), rib fractures due to cough (4%) and pneumonia (2%). The hospitalization rate varies from 1% to 4% and deaths are rare. (31)

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HPV: About 5% of new annual cancer detections worldwide are attributed to HPV. The virus is responsible for more than 99% of cases of cervical cancer - a disease that annually affects about 20,000 Brazilian women and kills another 5,000 - and for malignant tumors in the anus (91% of the total), penis (63 %), vagina (75%), oropharynx (72%) and vulva (69%). In addition, HPV is responsible for about 20,000 cases of genital warts annually in the country. (32 a 34)

Countries that have implemented the vaccine in the public system have already reaped important results. In England, where girls aged 12 to 18 have been vaccinated since 2008, there has been a reduction in the occurrence of HPV infection and genital warts in about 75% of cases. In Australia, where it has been offered since 2006 for girls aged 9 to 26 and for boys aged 9 to 13, there has been a 59% reduction in the diagnosis of genital warts in women since 2013; 48% drop in the incidence of high-grade cervical lesions (risk of progressing to cancer) in girls under 18 and 88% reduction in oral HPV infection rates. Although the priority worldwide is the vaccination of adolescents and young people, adult men and women can also benefit from vaccination, with a reduced risk of new infections, reinfections and recurrence of pre-existing injuries. (35)

HERPES ZOSTER: Herpes zoster manifests itself in people previously infected with the varicella zoster virus, which, after causing chickenpox, remains latent and can be reactivated in situations of low immunity, including immunosenescence. The serum prevalence for the virus is similar across the planet: from 95 to 98% in adults. In the United States, the CDC estimates that approximately 30% of individuals will develop shingles at some point in life, with an incidence curve linked to advancing age, especially after age 60. From the age of 85, one in two people will develop the disease. The most frequent complication of herpes zoster is post-herpetic neuralgia (PHN), which occurs in 18% to 30% of cases, particularly in those over 60 years of age. (36,37)

The chicken pox virus can plague us more than once. This virus is able to reactivate with advancing age and cause a painful attack, as an Herpes Zoster. The projection is that more people will suffer from it after the age of 60, according to an analysis published in the journal BMC Geriatrics. The rate of people affected by the problem is expected to grow from 2.35 to 3.74% per year until 2030, as shown by scientists who evaluated data from Australia, Japan and the United States.

TUBERCULOSIS: Tuberculosis is a disease present throughout the national territory, with an alarming incidence in some municipalities in our Brazil.

BCG is a preventive immunization, performed at birth, with the objective of preventing severe forms of tuberculosis, such as tuberculous meningitis, pulmonary tuberculosis and systemic forms of tuberculosis.

BCG administration is made by a single dose, with intradermal injection, in children weighing 2 kg or more.

The immune response caused by BCG activates cellular immunity with increased circulation of lymphocytes of the CD8 system. This knowledge makes BCG another weapon of immunological

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activation in patients in the state of immunosenescence and in need of activation of the immune system of CD8 response.

Importance of dendritic cells, our microbiome and CD8 lymphocytes in oral tolerance

The fundamental participation of dendritic cells

Oral tolerance begins with the migration of dendritic cells coupled to antigens, favoring the production of growth transforming factors of T lymphocytes, for their differentiation into a regulatory cell, the regulatory T cell, whose main function is to promote throughout the immune system and thus systemic oral tolerance throughout the body.

This state of permanent production of regulatory T cells depends on the arrival of new antigens and new activation of dendritic cells. Thus, for each antigen, new production of regulatory T cells, subsequently generating expansion and more specific oral antigen tolerance. Thus, we maintain an increasing amount of regulatory T cells in the intestines for all antigens that presented to dendritic cells.

One of the basic functions of dendritic cells is the natural uptake of antigens of any kind, which cross the M cell membrane and enter from the intestinal lumen into the internal environment. This antigen capture aims at two complementary actions. The first is to produce regulatory T lymphocytes, which inhibit the allergic response to the absorbed antigens. The other function is to produce an immune response to the absorbed antigen in order to eliminate it, with the production of specific antibodies.

The participation of the microbiome

Within the intestinal lumen, in the distal portions of the digestive tract, we have a proportion of bacteria that in quantity are equivalent to the eukaryotic cells of our own organism. The intestinal microbiota has a great participation in the intestinal immune responses, being able to promote induction or depletion of the response of the regulatory T cells, thus influencing the oral tolerance. Thus, different compositions of the intestinal microbiota can affect oral tolerance. The more native and saprophytic, the better the compositions of our microbiome in the production of oral tolerance.

Our digestive tract has, in its lumen, a numerically high number of bacteria, in the order of 10 billion, per cubic centimeter of luminal content, which constitute our microbiome. These bacteria are in permanent contact with the intestinal mucosa, along the digestive tract, influencing the functions, not only of this mucosa, which represents the interface of contact with the microbiota, but influencing the functions of the digestive tract, especially in interactions with the immune and nervous system. This association is called immuno-neuro-microbiome interaction, with direct participation in the modulation of the tolerance system.

The participation of CD8 lymphocytes

Due to its direct action on the mucosa of the digestive tract, the microbiota has a direct influence on the production of CD8 lymphocytes and dendritic cells, which are fundamental in the immune response and in the generation of antigen and food tolerance.

The extremes of this interaction occur in newborns, considered “germ free”, where the enteric concentration of bacteria is low, resulting in the absence of stimulation for the generation of CD8 lymphocytes, dendritic cells and production of tolerance to antigens. In this age group, the regulatory T cells lymphocyte system is not established and the tolerance to antigens, such as food, is impaired.

Over time, the microbiota gradually multiplies, coinciding with the generation of CD8 lymphocytes, which now represent 15% of the lymphocytes in the enterocyte lamina propria and 85% of the intraepithelial lymphocytes. In special circumstances, due to luminal contamination or inflammation of the enteric mucosa, the exacerbation of the microbiota generates an excess of CD8 lymphocytes, a situation that is often established in children, due to environmental contamination, parasites or poor hygiene. This dysbiosis situation can be balanced with probiotics.

Another tolerance mechanism that can be related to CD8 cells, occurs after the antigens are attached to dendritic cells. These cells can induce anergy or deletion of CD8 T cells, specific antigens. This type of tolerance via CD8 is achieved via peripheral dendritic cells. Thus, we understand that our oral tolerance depends on a healthy microbiome and the generation of regulatory T lymphocytes, dependent on dendritic cells and CD8 lymphocytes.

Discussion

One real observation and a clinical evidence, for the explanation to these evident discrepancies in the statistics among COVID19 in children and adults is the “state of the art” of the immune responses among those two populations.

Since birth and early in life children are taking vaccines against all infectious diseases, including shots to prevent bacteria and virus diseases. At this moment of their lives children is under a tremendous “immune storm” with their immune system acting against all the possible preventable diseases. The numbers of shots of vaccines against those diseases are close to one hundred during infancy and childhood. We can call this a “immune storm”.

In children, due to environmental contamination, parasites or poor hygiene, a state of disbiosis in frequent, and this situation, the exacerbation of the microbiota, generates an excess of CD8 lymphocytes, a situation that is often established in children.

On the other hand the adult are losing their ability to prevent infectious diseases entering in the state of immunosenescence over the years. The Brazilian experience as previously mentioned shown as that at the third decade of life we start to have preventable diseases, situation that increase over the years. Especially over the sixties this state of immune loss are evident and the elderly are no more capable to prevent infectious diseases. At this age the memory to prevent preventable infectious diseases are almost zero.

This loss of immune activities can clearly explain the catastrophic situation of the absence of response in the adult life to coronavirus exposition. More the immunosenescence present, more the aggressively of the COVID-19.

Conclusion

To prevent this state of loss of immune response and the loss of CD8 we can act preventively with constant and preventive provocation to the immune system of the adults, with a “immune storm” using all the vaccines against to the preventable infectious diseases and with the use of probiotics.

We must start immunization early in adulthood, since the third decade of life, inducing all over the decades, the immune system to be alert against all the infectious diseases. We must create a state of

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“immune storm”, to prevent the immunessence present over the sixties years of life.

If you are over the sixties in the state of immunosenescence we argue you to take as soon as possible one shot of each one of the vaccines listed: influenza 4V; VPP23 (pneumococcus); dTpa-VIP (diphtheria, tetanus, pertussis with polio inactivated); Hepatitis A and B; ACWY (meningococcus); MMR (measles, mumps and rubeola) and Herpes Zoster, according with the Brazilian society of immunization for the elderly. In this special situation of the need of stimulation of CD8 we add BCG to the mentioned immunizations. (38)

Other fundamental treatment that can activate the CD8 is the use of large amounts of probiotics. We recommend daily doses of more than 20 billions of active lactobacillus and bifidobacterias as probiotics.

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Original Article

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Introduction

The new coronovirus, commonly known as the SARS-nCov-2 is a simple strain RNA with positive polarity (ssRNA+). The disease caused by this new virus is known as COVID19. Both virus and disease are known as "coronavirus" by the public. (1)

The virus has a great affinity with the angiotensin-converting enzyme 2 receptors (ACE2), which are present in the surface of human pneumocytes, adhering to them and using as part of its penetration mechanism. The SARS-nCoV-2 can also use the basigina protein to penetrate in host cells. (2,3)

The main transmission mechanism of the SARS-nCoV-2 are by droplets produced by the respiratory system of the infected, which are expelled as cough or sneeze within a radius of up to 1.8 meters. Another possible transmission is the indirect contact with contaminated surfaces. (4)

Preliminary investigations suggest that the coronavirus may remain active in plastic and steel for up to three days, while not resisting more than one day on cardboard surfaces and four hours over copper. Viral RNA has also been observed in feces of infected patients. (5,6)

Bats are also the most likely the natural reservoir for the SARS-nCoV-2, although some differences between both bat coronavirus and human SARS-nCoV-2 suggest that humans were infected by an intermediary host. (7)

On January 12, 2020 Wuhan, China, five SARS-nCoV-2 genomes were isolated. On January 30 forty two SARS-nCoV-2 different genomes were known. A phylogenetics analysis of these samples reveal up to seven different mutations on a common predecessor, which indicates that the first human infection occured between November or December of 2019. This month we already have 410 publicly available SARS-nCoV-2 genomes. (8,9)

The oldest case of known human infection dates to November 17, 2019. Later on the virus spread itself to all chinese provinces and furthermore to all continents, being confirmed that transmission between humans has ocurred everywhere worldwide. On January 30, 3020, the World Health Organization declared COVID19 an international public health emergency and on March 11 a pandemic with more than 100 thousand deaths around the World. (10 a 13)

Estimates show that each infected person propagates the SARS-nCoV-2 infection to other 1.4 to 3.9 people when the community is not immune and no preventive measure has been issued. (14,15)

The SARS-nCoV-2 has a singular particularity in his action mechanism that differs from other classic SARS CoV and MERS CoV that is the production of a non-structuring protein (nsp1). This gives it the property of inhibiting the host's immune response, mainly the innate immunity. This fact results from one of the characteristics of COVID19 patients which is the observed occurance of precariousness in non-especific immune response and the already known natural lymphopenia and neutrophilia. Mostly because the immune system is being inhibited by the viral action.(16)

When inspired, the coronavirus adheres to the ACE2 specific cell receptor and, through endocytes, enters the pneumocytes, located on the surface of the alveoli, at the lung/respiratory tree interface. Inside the pneumocyte cytoplasm it remains inside the endosome, until it breaks its membrane and releases itself into the cell in its cytoplasm, like an "innate messenger" RNA virus. Then it completes its life cycle. It directly produces its proteins that translate viral replication, using its RNA as a template. Thus, more identical viruses appear in the internal cellular environment. They migrate into the endoplasmic reticulum and then acquire another endosomal vesicle and migrate out of the cell to infect new cells. Due to their aggressiveness, they end up destroying the pneumocytes that line our alveoli and continue with intense viral proliferation and attacking the adjacent pneumocytes. (17-20)

What draws attention in anatomo-pathological findings are the rarefaction of lymphocytes in inflammatory lesions. This lymphocytic hypoplasia characterizes a state of systemic depletion of the immune system. This is explained by the immune-pathological findings described below. (21-25)

Immuno-pathological evidence

As the coronavirus acts with its immune blocking property, its pathogenic action is out of control. It starts to replicate indefinitely and generates immune disease in the host, by suppressing its immune response. Without the innate response present, the host resorts to the adaptive immune response, also suppressed. (16)

The endogenous protein synthesized by the virus in infected cells activates the T CD8 + cells specific to the virus, through the main pathway of the histocompatibility complex 1 (MHC 1), promoting proliferation and differentiation so that the T CD8 + cells reach their maximum cytotoxicity capacity. With the participation of NK cells, the action of cytotoxic CD8s tend to kill pneumocytes. Perforin participates in this action, which when puncturing the pneumocytes leads to cell death and also granzyme participates with specific activity of programming the pneumocyte apoptosis. (26,27)

T CD4 + cells can also differentiate into different types of Th after interacting with the antigen presentation, made by antigen presenting cells, such as dendritic cells, in the presence of MHC 1. This perfect presentation allows the T CD4 lymphocyte to recognize the viral-antigenic peptide , thus initiating the process of humoral immune response. Among Th, Th1 stands out, which can recruit and activate macrophages to induce them to phagocytize viruses and produce a late inflammatory response. (26,28)

With the activation of the humoral response, T lymphocytes inform B lymphocytes of the need for the production of specific antibodies against the attacking viruses. With that the antibodies produced by the B lymphocytes, specific of the humoral response against the viral antigen, can specifically neutralize the virus to block the infection. (26,29)

Still the specific immune response is the key factor in completing the elimination of the virus. (30) If the immune system cannot produce a strong specific response, capable of eliminating viruses, it, due to failure of the host's immune system, will continue to strengthen the nonspecific inflammatory response. This removal will be done inefficiently and disastrously. This will not only prevent the virus from being effectively removed, but also extend the lesion and infection to a large area of tissue. Hypoxic ischemia and even necrosis will lead to an uncontrolled inflammatory response and will trigger a storm of inflammatory cytokines. (28)

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The specific immune response requires a certain time for the elimination of the virus, which does not occur due to the delayed immune response, characteristic of the immune response to the coronavirus. This delay causes, after only 96 hours of the viral infection, full multiplication within the cells of the lung parenchyma, with evident rarefaction of cells of the specific immune response, the lymphocytes. (31)

It is observed that all patients with the coronavirus have characteristic lymphopenia and neutrophilia, as do T CD4 + cells and T CD8 + cells also significantly reduced in peripheral blood. These findings conflict with those found in classical viruses in which the innate response presents lymphocytosis with neutropenia and normal specific immune activation, with rapid recruitment of T CD8 cells to the injured sites. (32)

On the other hand, in infected tissue, Th17 T CD4 + cells, which have a pro-inflammatory role, are increased, while a temporary increase occurs with highly cytotoxic T CD8 + cells, which suggests a tendency to produce inflammatory cytokine storms, which aggravated tissue damage. (30)

During COVID19, we observed that the level of IL-6 in critically ill patients is significantly higher than that of patients with mild disease. The opposite behavior is observed with the levels of T CD4 + cells, T CD8 + cells and NK cells, which are lower in critically ill and in elderly patients, than the levels observed in patients with mild disease and younger, suggesting that critically ill patients, at any age , may have immunosuppression. (31)

Therefore, for a long period of time after infection, we can rely only on increasing the nonspecific inflammatory response to resist the invasion and spread of the virus, resulting in an increased risk of macrophage and cytokine storms, complication of serious diseases and a higher mortality rate. . The change in response from mild to severe in patients with COVID-19 may be caused by a storm of macrophages and cytokines, caused by the inefficiency of the specific immune response. (31)

With the onset of the inflammatory storm, we observed an exaggerated macrophage action, giving rise to what we call Macrophage Activation Syndrome, where it is observed: 1- uncontrolled proliferation of T cells; 2- excessive activation of macrophages; 3- hypersecretion of pro-inflammatory cytokines, interleukins IL-1β, IL-6, interferon and tumor necrosis factor α (TNFα). (33)

It was observed that the new coronavirus can replicate in large quantities (34), rapidly activating T CD4 + cells, proliferating and differentiating Th1 cells that start to secrete pro-inflammatory cytokines such as IL-6, gamma interferon and colony stimulating factor granulocytes and macrophages (GM-CSF). GM-CSF can also activate monocytes to further release IL-6 and other factors, leading to the formation of a cytokine storm. Released by T lymphocytes and monocytes may be the key link in the COVID-19-induced cytokine storm, causing the patient's condition to evolve into Severe Acute Respiratory Syndrome, until death. (34)

Therefore, IL-6 and GM-CSF released by T lymphocytes and monocytes may be the key link in the cytokine storm induced by COVID-19. Mononuclear cells, like nonspecific immune cells, suggest that the mechanism of COVID-19 triggering cytokines may be closely related to the destruction of the specific and inate immune balance of the immune response. (33-37)

Clinical and pathological evidence

It is worth mentioning that several studies have shown that the average age of severe cases of COVID-19

infection is higher than that of mild cases (66 and 51 years respectively) and is more likely to be accompanied by other basic diseases (72.2% and 37 , 3% respectively). The average time for diagnosis is also longer (8d and 4d respectively). (38)

These findings suggest that the elderly are unable to complete their specific immune response or require long-term induction to develop this effective immune response due to the degeneration of their immune response function. As time goes by, only the innate answer remains. In the innate response, we run the risk resulting from macrophage and cytokine activation and the consequent inflammatory storm. (26)

A complicating factor of the immune response in the elderly is that they naturally tend to have a reduction in CD8 lymphocytes, especially in situations of stress, a natural occurrence in infections, of any nature, especially an alarm situation such as COVID19 infection. Depression so common in the elderly is another factor that inhibits CD8. At this age, COVID19 is more severe than at any other age. (26)

The same phenomenon of reduced immunity is observed in the presence of immunosenescence, which starts in men at around 40 years of age and is well established after 60 years of age. Over the years this abnormality of immune response increases, reaching its maximum expression after 80 years. The state of immunosenescence is characterized by the absence of immune response activity due to disuse. In other words, the immune system over time ceases to be stimulated and its reactivation will be slow. (39)

This is the reverse of what occurs in children, who from birth have permanent stimuli to the immune system due to the new proteins of the diet and numerous doses of vaccines they receive throughout childhood, reaching more than 100 vaccine applications in the first 10 years of life. We can say that this "immuno-storm" keeps the immune system on alert and with its immune defense cells, in constant activity. (39)

In addition, it is known that all newborns are born Th2, evolving to Th1, with the breastfeeding and maturation of their microbiota. After the first year of life, they start to react with the Th1 cellular system prevailing over the Th2 of humoral immunity. The constant aggressions to the digestive tract increase the levels of CD8, stimulated by the enteric microbiome. At this age, coronavirus infection is extremely rare and there are no cases of COVID19. (26)

Over time, already in the third decade of life, we began to observe that diseases such as hepatitis A, hepatitis B and many others start to occur due to the lack of specific immunization, as they are preventable diseases by vaccination. In the following decades this problem worsens and due to lack of vaccination, diseases such as diphtheria, herpes zoster, yellow fever, measles, HPV and others occur. The lack of immunological stimuli ends up characterizing the state of immunosenescence, the more severe the older the age. (39)

CD8 depletion: the source of the problem

It follows from everything that has been said that we have a problem resulting from the immune disorder, which has so far been unsolved: immunological depletion and especially that of T CD8 cells.

On one hand, we have an ssRNS + coronavirus which, in its specific actions on the host, inhibits its immune response, maintains its replication, produces lymphopenia and reduces T CD8 cells, activates and delays the innate response and triggers the entire pathological cascade of COVID19 disease.

On the other hand, we have a host that, due to age and its immunosenescence, already has immunological problems that are characterized by depletion of T CD8 lymphocytes and low capacity to respond to immune and infectious aggressions.

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Both situations, by the coronavirus and by the host, are competing resulting in immune depletion and the lack of T CD8 cells, the basis of the cellular immune response process. With the failure of the cellular immune response, COVID19 establishes itself in a catastrophic manner.

It is a well-known fact that COVID19 is rare in childhood, where Th1 cellular immune responses prevail, with permanent activation of T CD8-mediated immune responses. It is also common knowledge that COVID19 is frequent and severe in the elderly, where immune responses by the same CD8 lymphocytes are lacking.

Therapeutic misconceptions and their solutions

Lack of a specific therapy directed at immunological failures caused by SARS-nCoV-2, presented by patients with COVID19, where the deficiencies of innate and acquired responses prevail, with fundamental deficiency, of the cellular immune response, due to the lack of T CD8 lymphocytes. (26,42)

Adequate response: this answer rests on the knowledge of the behavior of the children's immune responses, where COVID19 is rare. In these children, CD8 is permanently activated by an active microbiota and an immune system in constant activity, by permanent immunizations throughout childhood. Applying this knowledge to adults, we actively propose to administration of high doses of probiotics, especially for the elderly, starting this therapy as early as possible. At the same time, we need to get the elderly out of their immunosenescence state. One measure is necessary for this: active immunization. The "immuno-storm" will quickly update immunizations that have been neglected in adulthood, starting with BCG and administering all vaccines that have not been updated in recent decades. With these two measures, we allow the elderly to have their immune system on alert and producing T CD8 cells.

CONCLUSION

All therapies to date have not any effect because it is not direct to reactivate the immune response, inhibited by the coronavirus, since it establishes itself as a viral infection. It results in severe pneumonia, as the lung is the “shock organ”.

From the findings demonstrated by the immune-pathological and clinical evidence, we observed that this infection is rare in childhood and frequent and severe in the elderly. As for the structured immune responses on the presence of T CD8 cells, we know that children react to infections with elevated CD8 and the elderly with CD8 deficiency.

We are waiting for the answers presented as a therapy that anticipates the failure of CD8 and thus the coronavirus would not have a fertile ground to establish itself, as is the case with children who do not have COVID19.

This response would be based on an immuno-storm from the age of 20, along with aggressive therapy with probiotics. In the current elderly, at risk of contracting coronavirus, we must also propose an emergency immuno-storm, associated with high doses of probiotics. For what begins at age 20 is preventive. We believe that BCG and other vaccines could activate the T CD8 cells of the elderly and thus prevent COVID19. Research is essential to prove these responses based on consolidated evidences.

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