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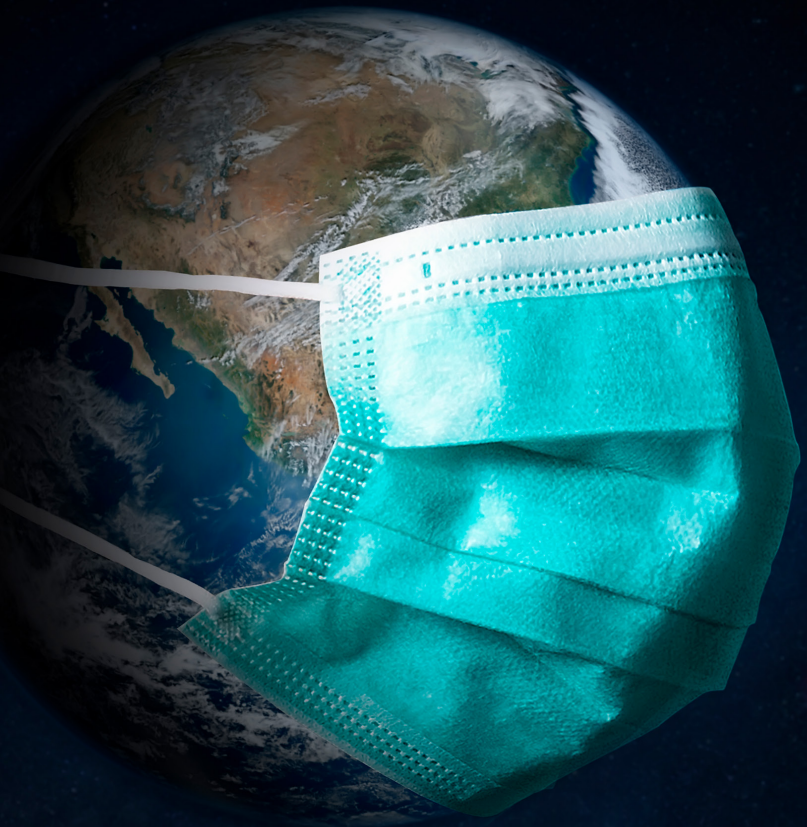

COVID-19 no Brasil:
Os Múltiplos Olhares da Ciência para Compreensão e Formas de Enfrentamento

4

Luís Paulo Souza e Souza
(Organizador)

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COVID-19 no Brasil os múltiplos olhares da ciência para compreensão e formas de enfrentamento 4

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APRESENTAÇÃO

O ano de 2020 iniciou marcado pela pandemia da COVID-19 [*Coronavirus Disease 2019*], cujo agente etiológico é o SARS-CoV-2. Desde a gripe espanhola, em meados de 1918, o mundo não vivia uma crise sanitária tão séria que impactasse profundamente todos os segmentos da sociedade. O SARS-CoV-2 trouxe múltiplos desafios, pois pouco se sabia sobre suas formas de propagação e ações no corpo humano, demandando intenso trabalho de Pesquisadores(as) na busca de alternativas para conter a propagação do vírus e de formas de tratamento dos casos.

No Brasil, a doença tem se apresentado de forma desfavorável, com elevadas taxas de contaminação e de mortalidade, colocando o país entre os mais atingidos. Em todas as regiões, populações têm sido acometidas, repercutindo impactos sociais, sanitários, econômicos e políticos. Por se tratar de uma doença nova, as lacunas de informação e conhecimento ainda são grandes, sendo que as evidências que vão sendo atualizadas quase que diariamente, a partir dos resultados das pesquisas. Por isso, as produções científicas são cruciais para melhor compreender a doença e seus efeitos, permitindo que se pense em soluções e formas para enfrentamento da pandemia, pautando-se na cientificidade. Reconhece-se que a COVID-19 é um evento complexo e que soluções mágicas não surgirão com um simples "*estalar de dedos*", contudo, mesmo diante desta complexidade e com os cortes de verbas e ataques de movimentos obscurantistas, os(as) Cientistas e as universidades brasileiras têm se destacado neste momento tão delicado ao desenvolverem desde pesquisas clínicas, epidemiológicas e teóricas, até ações humanitária à população.

Reconhecendo que, para entender a pandemia e seus impactos reais e imaginários no Brasil, devemos partir de uma perspectiva realista e contextualizada, buscando referências conceituais, metodológicas e práticas, surge a proposta deste livro. A obra está dividida em diversos volumes, elencando-se resultados de investigações de diversas áreas, trazendo uma compreensão ampliada da doença a partir de dimensões que envolvem alterações moleculares e celulares de replicação do vírus; lesões metabólicas que afetam órgãos e sistemas corporais; quadros sintomáticos; alternativas terapêuticas; efeitos biopsicossociais nas populações afetadas; análise das relações das sociedades nas esferas culturais e simbólicas.

Destaca-se que esta obra não esgota a discussão da temática [e nem foi pensada com esta intenção], contudo, avança ao permitir que os conhecimentos aqui apresentados possam se somar às informações já existentes sobre a doença. Este material é uma rica produção, com dados produzidos por diversos(as) Pesquisadores(as) de regiões diferentes do Brasil.

Sabemos o quão importante é a divulgação científica e, por isso, é preciso evidenciar a qualidade da estrutura da Atena Editora, que oferece uma plataforma consolidada e confiável para os(as) Pesquisadores(as) divulgarem suas pesquisas e para que os(as)

leitores(as) tenham acesso facilitado à obra, trazendo esclarecimentos de questões importantes para avançarmos no enfrentamento da COVID-19 no país.

Luís Paulo Souza e Souza

SUMÁRIO

CAPÍTULO 18

HISTORICAL OVERVIEW OF SARS-COV-2 INFECTION AND THE INFLUENCE OF ACE INHIBITORS, ARBS, IBUPROFEN AND CORTICOIDS

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ABSTRACT: The SARS-CoV-2 was first identified in China and later spread to several continents. The worldwide concern is the high transmissibility of the virus due to the form of contagion being interpersonal, through nasal and oral aerossolby coughing, sneezing, or speaking, besides they can be deposited on objects and remain for hours or days. The objective is to report an update of the literature data on COVID-2019 and the use of drugs such as ibuprofen, corticosteroids, and ACE inhibitors. Descriptive exploratory literature review. Success in controlling spread depends primarily on public health measures, informing and preventing transmission, such as contact isolation. Clinical manifestations range from common cold to severe pneumonia. The main symptoms are fever, unproductive cough, and dyspnea. The elderly, those with comorbidities and immunosuppressed are at risk for complications. The SARS-CoV-2 uses the angiotensin-converting enzyme (ACE) present in endothelium, lungs, and kidneys to bind to the target cells. ACE inhibitors or ARBs increase ACE enzyme expression. ECA2 expressed on the superficial spikes of the virus can be amplified by ibuprofen. Corticosteroids can stop or slowing the progression of infections, but immunosuppression

and hyperglycemia increase mortality. It is not recommended to interrupt ACE inhibitors due to the benefits. As a symptomatic treatment, other anti-inflammatory drugs should be used replacing ibuprofen and patients using corticoids for indication should not have their use suspended, but their initiation should be discouraged.
keywords: Infecções por Coronavirus; Ibuprofeno; Sistema Renina-Angiotensina; Angiotensina II; Corticosteroides.
KEYWORDS: Coronavirus infections; Ibuprofen; Renin-Angiotensin System; Angiotensin II; Corticosteroids.

RESUMO: O SARS-CoV-2 foi identificado pela primeira vez em 2019 na China e, posteriormente, se disseminou para os vários continentes. A preocupação mundial é a alta transmissibilidade do vírus devido à forma de contágio ser interpessoal, por meio de aerossol nasal e oral, provenientes da tosse, fala e espirro, além de ser depositado em objetos e permanecer por horas ou dias. O objetivo foi relatar uma atualização dos dados da literatura sobre o COVID-2019 e o uso de drogas como ibuprofeno, corticosteróides e inibidores da ECA. Revisão descritiva da literatura exploratória. O sucesso no controle da disseminação depende principalmente de medidas de saúde pública, informando e impedindo a transmissão, como o isolamento de contatos. As manifestações clínicas variam de resfriado comum a pneumonia grave. Os principais sintomas são febre, tosse improdutiva e dispnéia. Os idosos, aqueles com comorbidades e imunossuprimidos estão em risco de complicações. O SARS-CoV-2 usa a enzima conversora de angiotensina (ECA) presente no endotélio, pulmões e rins para se ligar às células-alvo. Inibidores da ECA ou BRA aumentam a expressão da enzima da ECA. O ECA2 expresso nos picos superficiais do vírus pode ser amplificado pelo ibuprofeno. Os corticosteróides podem parar ou retardar a progressão das infecções, mas a imunossupressão e a hiperglicemia aumentam a mortalidade. Não é recomendado interromper os inibidores da ECA devido aos benefícios. Como tratamento sintomático, outros medicamentos anti-inflamatórios devem ser utilizados em substituição ao ibuprofeno e os pacientes em uso de corticóide para indicação não devem ter seu uso suspenso.
PALAVRAS - CHAVE: Infecções por Coronavirus; Ibuprofeno; Sistema Renina-Angiotensina; Angiotensina II; Corticosteroides.

INTRODUCTION

In December 2019, the first cases of "pneumonia of unknown etiology" were registered in Wuhan city, China. [1] The patients manifested fever over 38ºC, pneumonia characteristic radiological examination findings, normal or reduced leukocyte count or lymphopenia, without a satisfactory response to 3 to 5-day administered antimicrobial therapy. [2] The seafood market exposure was identified as a common factor among patients with respiratory conditions. [3]

On December 31st, 2019, 59 suspect cases were transferred to a designated hospital where lower respiratory tract samples were collected (bronchoalveolar lavage) and on January 3rd, 2020, the new coronavirus (SARS-CoV-2) were identified and confirmed as a pathogen causing a set of acute respiratory conditions, now called as Coronavirus

Disease-19 (COVID-19). [4, 5, 6]

With an average incubation period of 4 days, great transmissibility of COVID-19 was identified, as a factor of great concern worldwide. A high level of interpersonal contagion has been identified from infected individuals, through droplets and aerosols from the mouth and nose during coughing, sneezing, or speaking, which can remain active and infectious on surfaces or objects for a period of 2 to 7 days. [1.7]. Consequently, in March 2020, the World Health Organization (WHO) characterized the disease as a pandemic. [8]

Although infection by the new coronavirus has a very wide clinical manifestation, ranging from a simple cold to severe pneumonia, this new virus has not yet fully clarified its spectrum. The main clinical symptoms are respiratory origins, such as dry cough and dyspnea, fever, myalgia, fatigue, shock, acute respiratory distress syndrome, acute or renal cardiac injury, secondary infection, and death. Laboratory tests commonly found in hospitalized patients include lymphocytopenia, thrombocytopenia, and leukopenia, elevated C-reactive protein, chest X-ray with signs of pneumonia [1,2,5, 9]

The diagnosis is made by collecting secretion from the lower respiratory tract, through sputum or bronchoalveolar lavage, and superior, through nasopharyngeal aspiration or oral swab [10] between the third and the seventh day after the onset of viral symptoms. The technique used for virus detection is through the polymerase chain reaction (RT-PCR - Reverse transcription-polymerase chain reaction) or positive serology for COVID-19. [11]

The disease due to COVID-19 infection is generally mild, especially for children and young adults. However, it can have a severe course in about 1 in 5 infected people in need of hospital care. [7] The median age of infected and clinically symptomatic patients who were diagnosed was 49 to 56 years.

The intensity of viral replication, associated with the development of lung injury due to the disease, contributes to making the group of patients with chronic diseases at higher risk, among them are the elderly, smokers, cardiovascular diseases, diabetes mellitus, chronic lung diseases, cancer and other diseases immunosuppressive drugs, and the consequent need for admission to the intensive care unit. [12] SARS-CoV-2 infection may contribute to the destabilization of cardiovascular diseases previously compensated by the increase in oxygen consumption generated by the disease. There seems to be a higher incidence of case reports in biologically male individuals. [13]

According to the American College of Cardiology (ACC), among patients hospitalized for COVID-19, 50% had chronic diseases and 40% had cardiovascular or cerebrovascular disease. [14]

In a study carried out with 41 hospitalized patients and with infection confirmed by laboratory tests with the new coronavirus in Wuhan, 49% of the patients were between 25 and 49 years old and 34% between 50 and 64 years old, with an average age of 49, 0 years. In this study, no child or adolescent was infected. Of the 41 patients, 32% were admitted to the ICU (Intensive Care Unit) because they needed a high-flow nasal cannula or higher-

level oxygen support measures to correct the hypoxemia. Most of the infected patients were male (73%); less than half had underlying diseases (32%), including diabetes (20%), hypertension (15%), and cardiovascular disease (15%). [4]

Another study with 138 laboratory-confirmed patients with COVID-19 showed that 64 (46.4%) had one or more coexisting medical conditions. Hypertension, diabetes, and cardiovascular disease were the most common coexisting conditions. [5]

Patients over 60 years old, with comorbidities such as diabetes and heart disease and children at perinatal age, are the group most likely to develop Acute Respiratory Failure Syndrome, and consequently, need treatment in the ICU. [15]

The COVID-19 pandemic has resulted, so far, in more deaths compared to the sum of both, Severe Acute Respiratory Syndrome (SARS) of 2002, originating in China and spreading worldwide with more than 8,000 infected and about 800 deaths, and the Middle East Respiratory Syndrome (MERS) 2012 [16], originating in Saudi Arabia spread to the Middle East, Europe, and Africa with 2,266 cases and 804 deaths from WHO. [17.18]

The use of antihypertensive drugs, especially angiotensin-converting enzyme inhibitors (ACE inhibitors) and specific angiotensin blockers (BRAs), as well as drugs with anti-inflammatory power such as ibuprofen and glucocorticoids, have been widely discussed in the current world scenario, since they are widely used drugs and, several times, for the treatment of pathologies in which their suspensions can be very harmful to sick individuals. As a result, knowing what is in the recent literature about the use of these drugs and their possible interactions with COVID-19 is of great relevance for clinical practice.

Thus, the objective of the present study is to evaluate the influence of drugs such as ACE inhibitors, ARBs, ibuprofen, and corticosteroids on coronavirus infection, responsible for the current pandemic.

METHODS

This is an exploratory-descriptive study reviewed the literature with articles selected from MEDLINE US National Library of Medicine / National Institutes of Health MedLine (PubMed / NIH), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Health Sciences (LILACS) - Latin American and Caribbean Health Information Center / Pan American Health Organization / World Health Organization (Regional Library of Medicine / BIREME / PAHO / WHO) and USE Library System (SIBI-USP) published between 1995 and 2020 in English, Portuguese and Spanish languages. The following descriptors were used for the search: Coronavirus infections; Ibuprofen; Renin-Angiotensin system; Angiotensin II; Corticosteroids. Fifty-three publications were viewed.

LITERATURE REVIEW

In different historical moments, other viral pandemic disseminations by respiratory

ways in humans demonstrated high mortality rates by cardiovascular complications, supplanting all the other causes, including pneumonia and other respiratory outcomes. SARS and MERS caused myocarditis and promptly progressing heart failure, evidencing the heart diseases' development potential, including acute coronary event by rupture of atherosclerotic plaque and acute myocardial infarct. [19.20]

Analysis of interactions between the virus and its receptors generates predictive data for the new infection based on prior knowledge of other strains. Current studies have shown the presence interaction between the SARS-CoV, responsible for the 2002 outbreak, and the SARS-CoV-2 related to the surface protein receptor connection: several research lines demonstrated infection by SARS-CoV is determined by the affinity between the viral surface protein and host ACE2 connecting, initially, in the fixing step. The specific amino acids in positions 442, 472, 479, 480, and 487 intensify the viral connection to ACE2. When all fragments that favor ACE2 are combined with the viral surface protein, the virus enters the human cell. Of the 14 fragments contained in the SARS-CoV viral surface, 9 are completely maintained and 4 are partially maintained in SARS-CoV-2, determining similarity in contamination form. The evolutive relation between SARS-CoV is well established and both viruses use the ACE2 receptor to infect lung host cells. [20] It is worth noting, however, that the SARS-CoV-2 receptor binding domain has a greater affinity for ACE2 compared to SARS-CoV. [21]

The COVID-19 infection has its main origin in the respiratory tract, possibly causing acute respiratory infections, although there are also reports of the gastrointestinal tract, related to the inhibition of ACE (angiotensin-converting enzyme). [22] Coronaviruses are single tape RNA viruses, which have a protein anchored in their envelope that first performs a connection to the receptor to the host cell, right after the interaction, occurs the fusion of the cell membranes. This connection occurs through a mandatory domain receiver (RDB), which has a central structure, the receptor-binding motif (RBM), which recognizes the ACE receptor in the host, attaching itself to its external surface. [23]

The angiotensin-converting enzyme (ACE) and its counterpart ECA2, belongs to the ACE2 family of dipeptidyl carboxypeptidases, however, they have two opposite physiological functions. ACE cleaves angiotensin I to generate angiotensin II (the peptide that binds and activates AT1 to constrict the blood vessel and thereby raising blood pressure), whereas ECA2, inactivates angiotensin II by generating angiotensin 1-7 (which has function vasodilator through activation of its Mas receptor). It thus acts as a negative body renin-angiotensin regulator. [21]

The protein similarity between the SARS-CoV-2 and SARS-CoV viruses is 76 - 78%. Thus, the sequence equality between the viral surface proteins suggests the possible compatibility between the same receptor. The viral protein surface fragments correspond to amino acids. The 493 fragment of SARS-CoV-2 corresponds to the 479 fragment of SARS-CoV and both represent asparagine, which removes the unfavorable interaction and

improves viral connection to human ACE2. Besides that, SARS-CoV-2 Gln493 is compatible with hotspot-31, suggesting that the coronavirus can recognize ACE2 and infect human cells. Fragment 487 corresponds to threonine, which strengthens structural stability and also leads to favorable interaction with ACE2, improving the viral connection to man, configuring a critical function in transmission. [23]

Fragments 455, 486, and 494 correspond to leucine, phenylalanine, and serine, respectively, and assist in the binding of the viral protein with the angiotensin II converting enzyme, although the binding is not as intense as the fragments mentioned above. Among them, phenylalanine (Phe486) is the strongest and most favorable interaction, facilitating the recognition of human cells. It is important to point out that structural analysis warns of a greater capacity for infection from the mutation of fragment 501 of SARS-CoV-2 (487 - SARS-CoV), increasing the chances of contamination of patients, who must be well monitored in the face of infectious condition. [23]

Use of Renin-Angiotensin-Aldosterone System Inhibitors

The renin-angiotensin-aldosterone system (RASA) is capable of contributing significantly to hydro electrolytic homeostasis, blood pressure (BP) control, regulation of metabolic processes, and modulation of the growth and cell proliferation of various tissues, being involved in several physiological or pathophysiological processes. Its main components are renin, angiotensinogen, ECA, ECA2, angiotensins, and the receptors that mediate their actions. [24]

SRAA acts especially on arterial regulation, having its main actions performed by angiotensin II, vasopressor peptide, and growth factor activity in the cardiovascular system. This is formed by the hepatic angiotensinogen cleavage by an enzyme cascade initiated by renin, which is mainly renal in synthesis, which converts it to angiotensin I. [25] This conversion occurs when there is a drop in blood pressure, which leads to cleavage of the pro-renin in juxtaglomerular cells, with consequent release of renin. [26] Then, due to the action of ACE, Angiotensin I catalyzes into Angiotensin II, mainly through the passage of blood in the lungs, intestine, kidneys, and blood vessels, where ACE is expressed by endothelial cells. [27]

During the short stay of Angiotensin II in the blood, it works by raising blood pressure through direct vasoconstriction of the arterioles, generating an increase in peripheral vascular resistance, in addition to reducing the levels of renal excretion of water and sodium, which configures the ability to promote slower and longer-lasting effects of pressure increase [26], enhanced by the reduction of aldosterone secretion (secondarily increasing sodium and water retention) and the activation of the sympathetic nervous system that releases catecholamines. By inhibiting ACE, the transformation of angiotensin I into angiotensin II is inhibited, inhibiting all its effects. Also, ACE degrades bradykinin, a potent endogenous vasodilator, and natriuretic substance; consequently, the inhibition of this enzyme enhances

the effects of this peptide. [28]

The ACE2 ectoenzyme is opposed to ECA's actions. In this sense, even though ECA2 is homologous to ACE, ACE inhibitors and ARBs are not able to inhibit their activity, on the contrary: both ACE inhibitors and ARBs seem to increase ECA2 expression. [29]

ACE inhibitors are important antihypertensives that act by preventing the transformation of angiotensin I into II in the blood and tissues, being effective in the treatment of arterial hypertension in hyperemic patients. [27] Currently, these drugs are widely used not only in the treatment of high blood pressure but in other cardiovascular diseases (or associated with them) such as heart failure; myocardial infarction; type 2 diabetes; kidney failure, and diabetic nephropathy. [30]

As the ARBs are capable of acting on both systolic and diastolic pressure and promote pressure control making it impossible for angiotensin II to come into contact with AT1 receptors, preventing the action of blood pressure elevation by vasoconstriction and the release of aldosterone by the adrenals, which causes water retention. [31] The blockage of the AT1 receptor culminates in an increase of renin and angiotensin I and II in the blood and tissues, which leads to greater stimulation of AT2 and MAS receptors promoting vasodilation by increasing bradykinin and nitric oxide, natriuresis and inhibits cellular growth. In these conditions, the AT2 receptors receive a greater amount of connections and the MAS receptors are more stimulated by the increase in the angiotensin peptide. [32]

Therefore, it can be seen that the angiotensin-converting enzyme plays an important role in cardiovascular system pathologies. The expression of this enzyme is greater in patients with cardiovascular diseases such as hypertension and diabetes, [27] once the angiotensin-converting enzyme inhibition treatment increases the enzymatic expression.

SARS-CoV-2 appears to not only obtain initial entry through ECA2 but also to sub-regulate its activity, rendering the enzyme unable to exert protective effects on the organs. It has been postulated, but not proven, that the unshakable activity of angiotensin II may be partly responsible for organ damage in Covid-19. Negative regulation of ACE2 activity in the lungs facilitates the initial infiltration of neutrophils and may result in unopposed angiotensin II accumulation and local activation of RAAS. Deregulated ACE2 can also attenuate cardioprotection in the context of myocardial impairment and abnormal pulmonary hemodynamics in Covid-19. Myocardial injury markers are elevated during Covid-19 disease and increase rapidly with clinical deterioration and premature death. [33.34]

The lower activity of ACE results in increased expression of this enzyme, which favors viral infection and increases the risk of severe forms, [35] playing a fundamental role in the disease caused by coronavirus and other types of viruses, such as influenza; the coronaviruses that cause severe acute respiratory syndrome use ECA2, present in the endothelium, lungs, and kidneys, to bind to the target cells, allowing greater exposure and predisposition of patients with cardiovascular pathologies to SARS-CoV-2 contamination. [14] In addition, specific amino acids have been identified that enhance viral binding to

ECA2 between the new coronavirus and human receptors, however, these are less efficient compared to SARS-CoV binding affinity. [23.36]

After a study inducing myocardial infarction in rats, it was found that ARBs increase cardiac expression of ACE2 three times after chronic treatment (28 days). Besides, it can be seen that losartan positively regulates renal ECA2 expression and that higher levels of ECA2 in the urine have been observed in patients with hypertension treated with olmesartan. Such data thus suggest that chronic AT1 blockade results in positive regulation of ACE2 in rats and humans. [21]

Under epidemiological parameters, new research shows that pre-existing cardiovascular disease increases the risk of COVID-19 infection: 15% of hospitalized patients had hypertension, and 15% also had a cardiovascular disease in Wuhan, China, at the outbreak of cases in January 2020. Also, among patients who developed severe conditions, such as coronavirus pneumonia, 40% developed associated cerebrovascular disease. Thus, it is concluded that patients with cardiovascular risk should be more monitored than those who do not have cardiovascular pathologies. [14]

However, these drugs should not be discontinued. In addition to the lack of proven clinical evidence on the use of ACEI / BRA in complications or fatal conditions caused by COVID19, its benefits cannot be disregarded. These drugs not only reduce symptoms but alter the natural history of the disease, reducing mortality from arterial hypertension and the occurrence of serious outcomes, such as stroke and acute myocardial infarction, in addition to being able to change prognosis, decrease the risk of decompensation and delaying the decline in renal function in patients with nephropathies. [37]

There is a clear potential for damage related to the withdrawal of RAAS inhibitors in patients in stable condition, and Covid-19 is particularly severe in patients with underlying cardiovascular diseases and, in many of these patients, active myocardial injury, myocardial stress, and cardiomyopathy develop during the disease. Therefore, until additional data is available, RAAS inhibitors should be continued in patients in stable conditions who are at risk. [33.38]

It is also worth noting that some studies point to the possibility that ARBs may provide some protection against severe lung injury, as observed in animal tests. [39] Many studies on SARS-CoV, probably also relevant to the current epidemic, suggest that binding of the coronavirus surface protein to ECA2 leads to negative regulation of ECA2 production, that is, decreases its production. Consequently, there is excessive production of angiotensin, since the body understands that there is a lack of this due to the low conversion resulting from the lower amount of ACE2. The excess of circulating angiotensin, in turn, stimulates the greater expression of the AT1 receptor, which contributes to lung injury since it generates increased pulmonary vascular permeability. Given the above, it can be seen that a higher expression of ACE2 could, paradoxically, protect infected individuals against acute lung injury

This can be explained by some mechanisms: the blockage of excessive AT1 activation

mediated by angiotensin caused by a viral infection, preventing the exacerbated increase in pulmonary vascular permeability; the regulation of ECA2, which reduces the production of angiotensin by ACE and thereby increases the production of the vasodilator angiotensin [21]; the anti-fibrotic function of ACE2 in Severe Acute Respiratory Syndrome, caused by desquamation of pneumocytes and destruction of the hyaline membrane, resulting from the pulmonary action of COVID-19. [39]

Thus, the use of losartan can be protective in the face of this complication, despite the need for proof by tests on live animals. [39] It is noteworthy that, although calcium channel blockers do not reduce the mortality of patients with heart failure and coronary artery disease (CAD), they can be an alternative to the treatment of hypertension and cardiovascular diseases, since this class of drug does not demonstrate ECA2 performance. [27]

Use of Ibuprofen

Regarding anti-inflammatory activity, ibuprofen and corticosteroids are widely used drugs that have important consequences concerning its use in COVID-19 patients.

Ibuprofen is a drug of the nonsteroidal anti-inflammatory group (NSAID) used to treat pain, fever, and inflammation. They act by competitively inhibiting arachidonic acid by the active center of enzymes cyclooxygenases 1 and 2, thus avoiding the consequent formation of pro-inflammatory mediators by this route. [40].

When there is a harmful stimulus to the tissue, whether chemical, physical, or biological, there is the release of several inflammatory mediators, such as prostaglandins, histamine, serotonin, and other peptides, such as angiotensin, substance P and bradykinin. Besides, the harmful process triggers tissue acidosis, with the production of potassium and hydrogen ions. [41]

This acute inflammatory reaction causes morphological and vascular changes and promotes the formation of cellular infiltrate at the site of the injury. Besides this release of inflammatory mediators, there is direct cellular injury by the release of intracellular enzymes and activates the complement system. All of these changes lead to selective sensitization by algic substances (mainly prostaglandins, serotonin, and bradykinin). [41]

Prostaglandin is the most important inflammatory substance, the main ones being I2, E1 and E2, generating not only pain, but fever, since they act on the hypothalamus, increasing body temperature, and the local inflammatory stimulus itself, by increased neutrophil chemotaxis to the site of inflammation. The great mediator of the formation of the inflammatory substances cited is the enzyme cycloxygenase (COX). Thus, anti-inflammatory substances act as central and peripheral enzyme inhibitors of COX, and therefore they prevent and considerably reduce the release of these substances. Ibuprofen, in particular, as well as other drugs such as paracetamol and dipyrone, has greater power to inhibit the release of Prostaglandin E, being more effective as antipyretics, since this prostaglandin is

the main modulator of body temperature. [41]

This drug is classified as a non-selective COX inhibitor, inhibiting both constitutional COX-1 and COX-2, induced only by the inflammatory process and by IL1, IL2, and TNFα interleukins. Because it also inhibits COX 1, responsible for the production of constitutional prostaglandins that participate in the secretion of gastric mucus to protect gastric cells and thus presents an increased risk of gastrointestinal side effects, it is a drug with reversible effect. [41]

This medicine, as well as ACE inhibitors and ARBs, also increase ACE2 levels, since angiotensin is one of the substances released when tissue injury occurs. Thus, its use is reported to increase the risk of serious infection. [41]

There is no evidence of interactions or side effects, but its use is believed to facilitate infection, since ACE2, expressed in the superficial spicules of the virus, can be amplified by Ibuprofen. [27]

Non-steroidal anti-inflammatory drugs (NSAIDs), including Ibuprofen, prolong the duration of acute inflammatory diseases, especially respiratory ones. Due to the inhibitory effect on cyclooxygenases, there is less recruitment of polymorphonuclear cells and inhibition of the synthesis of lipoxins and resolvins, generating a sluggish immune system and perpetuated infection [42].

Ibuprofen and other anti-inflammatory drugs also cause exacerbation of serious pathologies, such as acute myocardial infarction, in addition to complications such as cerebrovascular [43] and nephrotoxic events. NSAIDs have also been associated with complicated pneumonia and pleural effusion. Specifically in SARS-CoV-2 infection, anti-inflammatories exacerbate the activity of the water and sodium regulatory enzyme in the body, in addition to contributing to the development of pneumonia [44]. Due to the similarity between COVID-19 and SARS - CoV - 2, it is believed that there is the same effect in both diseases.

Although there is no specific evidence for the use of Ibuprofen and other NSAIDs in patients affected by COVID-19, observational data suggest that the use of NSAIDs can be harmful to the patient due to the effects mentioned above. Paracetamol, on the other hand, had fewer side effects and greater resolution in acute respiratory diseases, being, therefore, the advisable drug for these cases. [45] Thus, WHO initially recommended not to use this drug for the symptomatological treatment of COVID-19 infection. However, other anti-inflammatory drugs such as dipyrone and paracetamol may be alternatives until further studies are carried out. [46.47]

Use of Corticosteroids

Glucocorticoids are synthetic substances that simulate the effect of the cortisol hormone. The drug, free in plasma or interstitial fluid, penetrates the cell and binds to the cytoplasmic receptor, where it interacts with the receptor complex + HSP 90 to be transported

to the nucleus. After binding, it dissociates from HSP 90 and the receptor-ligand complex is actively transported to the nucleus, where it interacts with DNA, like most hormones. [41] Then, changes occur in the transcription of certain genes, inhibiting some and stimulating others, inducing the synthesis of anti-inflammatory proteins and other proteins that act on systemic metabolism. [48]

One of the important effects of this class of drugs is its anti-inflammatory and immunosuppressive capacity, radically reducing the manifestations of inflammation through deep COX inhibition effects and on the concentration, distribution, function, and chemotaxis of peripheral leukocytes, in addition to suppressive effects on inflammatory chemokines and other lipid and glycolipid mediators of inflammation. [41]

The immunosuppressive activity of these drugs is important for stopping or slowing the progression of pneumonia and is effective in the treatment of respiratory distress syndrome. In addition to playing an anti-inflammatory role to reduce systemic inflammation, decrease exudative fluid in lung tissue, promote absorption and prevent further diffuse alveolar damage, which can alleviate hypoxemia and effectively protect the lung to prevent the progression of respiratory failure. It can also induce a decrease in body temperature and help relieve symptoms of hyperthermia. [49]

Regardless of the benefits associated with the use of corticosteroids, complications induced by treatment, such as secondary infection (fungi and bacteria) and hyperglycemia should be valued. Current studies, although inconclusive, suggest increased mortality and secondary infection rates in influenza, decreased clearance of SARS-CoV and MERS-COV, and complications of therapy with corticosteroids. [50.51]

The use of corticosteroids was considered a therapeutic option for other coronaviruses in addition to COVID-19. In SARS, hydrocortisone was used in a group of patients without comorbidities or evidence of respiratory failure and recent onset of symptoms by SARS-CoV. There was evidence of the widening of the viral replication phase, with detectable RNA in the plasma at 12 days for those who used hydrocortisone versus 8 days for the placebo. [52]

In MERS-CoV, hydrocortisone was used in patients considered critical and the persistence of detectable viral RNA in plasma was also observed. Corticosteroid therapy was not associated with higher mortality, but most studies obtained inconclusive results as to the degree of recommendation for its use, with a small percentage of studies as unsatisfactory results.[53]

CONCLUSIONS

The SARS-CoV infection is determined by the affinity between the host's viral surface protein and ACE2, the highest affinity being the SARS-CoV-2 receptor binding by ACE2 compared to SARS-CoV. Given the previously established benefits of ACE inhibitors and

ARBs, so far there has been no recommendation for discontinuation due to the absence of data proving superiority in their discontinuation, and effective follow-up of these patients is oriented.

Among the non-steroidal anti-inflammatory drugs, the use of Ibuprofen should be replaced by others to relieve pain or inflammation by increasing ACE2 levels due to the release of angiotensin in tissue injury. There is no evidence of interactions or side effects, but its use is believed to facilitate infection, since ACE2, expressed in the superficial spicules of the virus, can be increased by Ibuprofen.

The use of corticoids should not be immediately suspended in patients with clinical indications but should be discouraged as initial therapy and/or in those without clinical indications that justify its usage. Treatment-induced complications such as secondary infection (fungi and bacteria) and hyperglycemia should be valued. Studies suggest increased mortality and secondary infection rates in influenza, SARS-CoV, and MERS-CoV.

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