Medical and Research Publications
International Open Access

Conceptual Review Article **Journal of MAR Pulmonology (Volume 3 Issue 5)**

Discovery of the Mechanism of COVID-19, SIRS and SEPSIS, Defense and Treatment.

Mast cells and Histamine Storm an Overlooked Aspects in COVID-19 and in Ventilated Patients Potential Role of Antihistamine.

MA Magdalena Filcek[1*], MD Mayank Vats[2], MD Anna Skrzyniarz-Plutecka[3]

1*. Specialist Neuro-architecture, Master of Interior Architecture, pilot of hot air balloons, innovator of many patented projects: Vinci Power Nap® - Dream's Space® and the Balonodrom Project©. Poland

2. Senior Specialist - Interventional Pulmonologist, Pulmonologist, Intensivist & Sleep Physician at Rashid Hospital and Dubai hospital. UAE

3. Head of Anesthesiology and Intensive Care Department, Masovian Oncology Hospital, Wieliszew, Warsaw University Maria Sklodowska-Curie, Specialist in Anesthesiology and Intensive Care and with experience in Infectious Diseases. Poland

Consultant : PhD Ewa Aplas - specialist molecular genetic, biotechnology. Poland

Consultant : MD, PhD Mirosław Mastej - specialist histamine and HIT. Poland

Consultant : MSc Pharm Andrzej Kotarski - specialist pharmacy. Poland

Consultant : PhD Agata Kolodziejczyk - specialist biomimetics, Director of Scientific Projects Analog Astronaut Training Center. Poland

Consultant: MD, PhD Grzegorz Gogolewski - specialist in internal diseases and emergency medicine - Clinic of Emergency Medicine and Cathedral and the Clinic Internal Medicine and Allergology AM in Wroclaw. Poland

Corresponding Author: Magdalena Filcek - Specialist Neuro-architecture, Master of Interior Architecture, pilot of hot air balloons, innovator of many patented projects: Vinci Power Nap® - Dream's Space® and the Balonodrom Project©. Poland

Received Date: September 20, 2021

Published date: October 01, 2021

Citation: Magdalena Filcek. "Discovery of the Mechanism of COVID19, SIRS and SEPSIS, Defense and Treatment. Mast cells and Histamine Storm an Overlooked Aspects in COVID19 and in Ventilated Patients Potential Role of Antihistamine." MAR Pulmonology 3.5

Abstract

The entire human population is waiting for a revolutionary discovery regarding the current pandemic. There is an urgent global need to identify therapies that will prevent SARS-CoV-2 infection and improve patient outcomes with COVID-19. Understanding the pathophysiology is a key research priority. In this article, we identify the mechanism and possible effective prevention with treatment of COVID-19 from the onset of the first symptoms to severe cases requiring ventilator assistance. We show a possible process that can lead to hyperimmune / systemic inflammatory response syndrome and what can trigger it this discovery led us to define preventive drugs with favorable safety profiles that could have significant benefits by becoming widely available for COVID-19 prevention and treatment options, saving many people around the world.

SARS-CoV-2 could act as one of environmental triggers for mast cells in lungs to release the storm of histamine which either directly or indirectly open the way for another triggers (cytokines, TNFa, IL-1, IL-6, etc), leading to inflammations and damages of many organs. Histamine by affecting the H1, H2, H3, H4 receptors, causes an allergic and pseudo-allergic reaction called histamine intolerance (HIT), considering also the relationship with the key genes.

Stimulation of this histamine H receptors, among others leads to: bronchospasm, cough, shortness of breath, in-crease in platelet aggregation, decrease in saturation, tachycardia, vasodilation and increase in their permeability, edema, diarrhea, hypotension, characteristic severe fatigue, fever, headache, neurological changes, as well as multi-organ changes including hyper inflammation in the lungs, intestines, heart, kidneys, liver. The above symptoms of a systemic inflammatory reaction are also observed in the developing COVID-19 and its multi-organ complications.

Moreover mast cells could be also activating under the influence of markedly low air temperature and dryness, as well as too high pressure/volume of air delivered by ventilator into the lungs of patients with COVID-19 - releasing again avalanche ejection of histamine from the granules, also cytokines, tryptase, etc.

There is a high probability that the symptoms of SIRS and SEPSIS as well as COVID-19, could be histamine storm with histamine intolerance symptoms, which, in its acute form, can lead to anaphylactic shock. The discovery of this mechanism could improve the health of millions of people by strategically disseminating the simple idea of histamine intolerance, the dose of antihistamines, selected enzymes, genes and the improvement of the use of mechanical ventilation.

Keywords: COVID-19, SARS-CoV-2, HIT, histamine, intolerance, antihistamines, DAO, HNMT, cytokines, tryptase, mast cells, SIRS, SEPSIS

Acronyms/Abbreviations:

ARDS - Acute respiratory distress syndrome

CFS - Chronic fatigue syndrome

COVID -19 - coronavirus disease 2019

COPD - Chronic obstructive pulmonary disease

CRH - Corticotropin releasing factor

DAO - Diamine Oxidase

EAA - Extrinsic Allergic Alveolitis

(Hypersensitivity Pneumonitis)

ECMO - Extra Corporeal Membrane Oxygenation

EIB - Exercise-Induced Bronchoconstriction

EVW - Extravascular water

HH - Heated Humidifier

HIT - Histamine Intolerance

HME - Heat Moisture Exchanger

HNMT - Histamine N-methyltransferase

ICU - Intensive Care Unit

SEPSIS - Specific reaction of the body to infection

SIBO - Small intestinal bacterial overgrowth

SIRS - Systemic inflammatory response syndrome

VAP - Ventilator associated pneumonia

Introduction

The COVID-19 pandemic, caused by the corona virus SARS-CoV-2, reached millions of the global population, and is associated with a high incidence of patients suffering from severe acute respiratory syndrome (SARS) which in turn places them at significant risk of death. The whole process starts with breathing difficulty or shortness of breath, with time „many of these patients require admission to an intensive care unit (ICU) and 80% of them require invasive mechanical ventilation" **[**1**][**2**][**3**]** and it has been linked to lasting damage to the lungs.

Early reports indicated „that those patients when ventilated are at high risk of nosocomial pneumonia, **[**4**]** and, especially, ventilator associated pneumonia (VAP)" **[**5**][**3**]** With time more serious conditions occur in COVID-19 patients, such as systemic inflammation, organ dysfunction and failure, so similar to the symptoms of SIRS or closely related to SEPSIS.

In this hypothesis we are showing that not only the cytokine storm but also histamine storm can make this systemic inflammation which occurs in patients also with COVID-19.

"The biological impact of histamine follow its interaction with four types histamine receptors, H1R, H2R, H3R, and H4R, all of which belong to the G protein coupled receptor family" **[**6**]**.

In response to various environmental/ physical/ allergic stimuli there is activation of a complex interaction between several inflammatory cells, including basophils, mast cells, lymphocytes, dendritic cells, neutrophils, and eosinophils" **[**7**][**8**]**.

"Among these, mast cell histamine is an axial player in stimulating the development of allergic related inflammatory diseases by regulating the maturation and activation of leukocytes and directing their migration to target sites where they cause chronic inflammation. Histamine also exerts a various other immune regulatory functions by modulating the functions of monocytes, T cells, macrophages, neutrophils, eosinophils, B cells, and dendritic cells" **[**6**]** leading to the immunoparalysis effects of critical illness very similar to SEPSIS **[**9**][**10**].**

The hypothesis is on the subject of activation of mast cells in lungs stimulated at the beginning by the virus, and then by too low air temperature delivered to the lungs from the ventilator, under the influence of which (and / or pressure caused by too high pressure / volume of air in the lungs) mast cells are activated, causing them to release large amounts of histamine, leading to problems with breathing, increased blood clotting, inflammation and too much cytokine release. Histamine in large amounts leads to histamine intolerance and damages many organs: lungs, heart, kidneys, peripheral nervous system, and many others very similar symptoms to COVID-19 (see the pictures below and the table at: **[**11**][**12**][**13**][**14**]**).

The severity of the COVID-19 disease and its symptoms in the respiratory system depends on the course of the immune response to the infection, often not the infection itself, but an excessive reaction to it causes the disease to progress to a severe form.

Excessive reactivity of the immune system or its failure may lead to disease progression to a severe state, serious tissue damage (not only in the respiratory system), thromboembolic events, and long-term consequences of COVID-19 disease and prolonged complications.

In this article we are showing that it is not only the cytokine storm but also histamine storm that can make this hyperimmune reaction and systemic inflammation which occurs in patients with COVID-19.

„New Study Estimates More Than 900,000 People Have Died Of COVID-19 In U.S. We have estimated to date that 6.9 million people have died from COVID-19 globally already" **[**15**]**. The analysis comes from researchers at the University of Washington's Institute for Health Metrics and Evaluation, who looked at excess mortality from March 2020 through May 3, 2021 **[**16**][**17**][**18**]**. The pandemic can result in an increased number of deaths from other causes for a number of reasons, including weakened healthcare systems, their capacity, and failing to treat other diseases.

The failure to predict the future course of the current pandemic has so far created many uncertainties related to the biological, epidemiological and clinical features of COVID-19, and we believe that with our hypothesis this can be changed.

The author found that the symptoms of COVID-19 SIRS, SEPSIS are similar as HIT that is why she recommends antihistamines and enzyme DAO neutralizing histamine as help to treat above diseases.

1.1 Background of discovery

The parents of the first author at the end of January 2021 had got COVID-19, both had pneumonia and got to hospital. Mother of the author recovered after 3 weeks, but her Father unfortunately got worse and was admitted to the pulmonary hospital. After one week he was put in coma together with a muscle relaxant and put under a ventilator.

The statistics showing a mortality rate of 88% of COVID-19 patients placed under ventilation in Poland were terrifying, and the media informed that it was partially due to too high mechanical pressure of air which damaged the lung alveoli.

The author started to search why it is like this to help her Father survive during mechanical ventilation. She was searching and learning everything about breathing, artificial respiration, mechanical ventilators, etc. She has found that the first idea of a ventilator was done by Leonardo da Vinci but the first working ventilator was an invention of Jean-François Pilatre de Rozier, made in the early 1880s,

the French great inventor and teacher of chemistry, and physics of gasses **[**19**]**, who became first pilot of hot air balloons in history of humankind.

Magdalena Filcek is also a pilot of hot air balloons and a scientist, inventor, she started to analyze how to lower the mechanical pressure and use the law of physics instead. As a pilot she knows the physics of gases and Charles Law, which allows balloons to fly.

She started to think about the lungs as balloons and tried to help to uplift them by warming the air. She asked doctor what is the temperature of air going to her Father's lungs from the ventilator, and got the information that the air has probably the „room temperature", that is around 20°C. From that she knows that it is 17°C below what is needed for lungs, for good oxygen CO2 exchange. She knows from physics that this level of temperature will not give correct humidity level needed for lungs as well.

Moreover, because of Charles Law, the pressure of this air temperature as being warmed up in the lungs will increase, causing damage. She wanted to know what damage can be done in lungs by too cold and too dry air so she pursued research in science articles. She have found that only 5 degree below what is needed leads to really big problems.

Moreover, she has read in science articles that there are a very large number of mast cells are in the human lungs which can be activated also by viruses, too low temperature as well as too high pressure, all of which lead to the release of a histamine storm.

When the author become aware of what this amount of histamine is doing in the body, she realized that the symptoms are very similar to COVID-19, SIRS and SEPSIS symptoms, and concluded that in this case the antihistamines should help to stop the development of disease. She consulted the details of this discovery with more than 50 doctors, pulmonologists, anesthesiologists, allergists, respirator technicians, physicists, geneticists, doctors from internal and emergency medicine. The hypothesis was sent to Dr. Mayank Vats, Senior Pulmonologist, Internist and Sleep Physician at Dubai hospital, to check if it is correct and if antihistamines are effective treatment for patients. Then she contacted Dr. Miroslaw Mastej specialist of histamine to consult this subject in her discovery and then with Dr. Anna Skrzyniarz-Plutecka to check the temperature of air from ventilators on the ICU and to consult the hypothesis regarding antihistamines and their role in patient treatment under anesthesia machines during operations. Above doctors were surprised by such great results after employing this discovery in the care plan.

The author made consultations also with Agata Kolodziejczyk the Director of Scientific Projects Analog Astronaut Training Center, during the looking for the possibility to create a device to warm and humidity the air going from respirator to her Father lungs, with available on market and easy to use elements (almost like during Apollo 13 mission).

The Father of the author was in coma under ventilation for 1,5 months and during this time every second day the author was calling the doctors to consult the next steps of discovery so the doctors could make some improvements for her Father treatments also with using antihistamines.

After 3 months, the Father of the author left hospital and is at home, breathing and talking by himself, engaging in rehabilitation for gut health and muscular strength to be able to walk again.

This traumatic situation probably will need the rehabilitation not only for his body and mind but also for the whole close family as the stress and anxiety was too hight for few months and can lead to PTSD.

2. Respirator and inflammatory response factors

In the physiological state, the pressure in the lungs is lower than outside, whereas in mechanical ventilation it is higher. „The ventilator blows air, the alveoli and entire lungs expand, fill with oxygen, then (after reaching a certain maximum value of the pressure of the pumped gas), it cuts off and the chest passively descends, exhales" says Dr. Katarzyna Kramek-Romanowska from the Institute of Biocybernetics and Biomedical Engineering of the Polish Academy of Sciences in Warsaw **[**20**]**. VAP occurs in more than 86% cases after connecting patients to the ventilator **[**3**]**. ”Patients with severe COVID-19 associated ARDS requiring ECMO had a very high late onset VAP rate” **[**3**]** based on research of the inflammatory factor analysis built on a case of an ICU patients with ventilator associated pneumonia **[**21**][**22**]**, which suggests that secondary pneumonia develops with time.

During the COVID-19 pandemic very often there were too many ventilators and too few specialists to operate them **[**23**]**. Without the right equipment at the right time, which cannot meet the physiological needs of the patient's body which is "put at great risk" **[**24**]**.

The invasive devices together with sedation are important reasons for breach of natural defense **[**25**]**.

2.1. Temperature of air in lungs

During spontaneous breathing „the temperature of the inhaled air increases during its passage through the upper airway, and at the level of the alveolar-capillary interface, it is at body temperature (37°C), with 100% relative humidity and 44mg/L absolute humidity" **[**26**][**27**]**. Oxygen from a wall installation or container is very cold due to expansion. The mixture of air flowing from the ventilator and flowing into the lungs may be at average "room" temperature of about 23 degrees Celsius (or even less depends on the temperature in the room). During endotracheal intubation the natural air ways are bypassed. Cold and dry gases are delivered to the patients but have to be heated and humidified as well **[**28**]**.

„Hypothermia is defined as core temperature of less than 36° centigrade” **[**29**].** ”Hypothermia has many complications namely increased perioperative blood loss due to impaired blood coagulation pathways,

altered drug metabolism, which leads to prolonged drug actions, delayed recovery and morbid cardiac events such as arrhythmias. Others are post operative shivering, prolonged hospital stay and patients' less satisfaction with surgical and anesthesia experience" [30]. Lastly, hypothermia results in impaired wound healing and susceptibility to wound infection [31]. Better postoperative outcomes are achieved when normothermia is maintained perioperatively" [32].

„In spite of overwhelming evidence demonstrating the reduced complications and costs associated with maintaining normothermia, it's been estimated that only 30 to 40 percent of surgical patients now receive some type of active perioperative warming. This is alarming in light of the frequency of inadvertent hypothermia. A recent study showed that without effective warming, as many as 90 percent of surgical patients will become hypothermic. In Europe, The United States and around the world, millions of patients continue to receive inadequate warming therapy or no warming at all - even though hypothermia has been called the most frequent, preventable complication of surgery. One U.S. physician has described maintaining normothermia this way: "There are few, if any, anesthetic interventions that have been proven to so markedly improve the outcome of surgery with so little effort, risk, and cost, making this a nearly ideal area for performance measurement and improvement" [33][34][35].

2.2. Heated Humidifier (HH) & Heat Moisture Exchanger (HME)

Ventilators deliver the air mix in a given volume, pressure and time rate to the patient's lungs during mechanical breathing.

From our observations most of respirators do not have a HH or HME device, and patients get air into their lungs without heating and humidifying [36] (which is not used due to the often given excuse which is the possibility of bacterial proliferation), the reason of this could be that some of those devices are disposable and should be exchanged but they are not. If the filters are not changed every 7 days or more frequently, there is a risk of bacterial contamination [37]. It should be noted that COVID-19 patients are kept long term under ventilators (weeks or even months).

For economic reasons many hospitals use the HME (which doesn't heat the air to a good temperature anyway) or do not use any devices to heat and humidify the air [38], but regular filters only.

There is little science research regarding the heated humidifiers for mechanically ventilated adults and children compared to heat and moisture exchangers [39] questioning if HME device are really doing what they are supposed to do [40] checking its efficiency of airway in anesthetized humans [41].

"Commonly used methods of humidifying inhaled gases include heated humidifiers (HH), heat and moisture exchangers (HME) and hygroscopic condenser humidifiers.

- HH - Heated humidifiers provide warm, saturated gas at the artificial airway" [42] but „HHs without a heated wire have been associated with a higher risk of VAP" [43].

„In review of Cochrane Review [44][45] have been found no difference in the risk of VAP when HMEs or HHs were used, other reviews also reported no difference between HH and HME in the risk of artificial airway occlusion, pneumonia [46], mortality or length of ICU stay [43].

As with our findings, Siempos and colleagues found that HME reduced humidification costs [39][43].

- HME - Heat Moisture Exchanger may not prevent hypothermia and should not be used alone as it is not sufficient [47]. There are no studies of HMEs working at different range of humidity and temperature, all the measurements were done in "conditions laid down ISO 9360 (water bath temperature set at 37 °C, tidal volume 250–1000 ml)" [48][49][50][51][52][53].

As a conclusion only HHs, that can warm and moisturize the air properly are good solution to use with ventilators in treatment of the ICU patients.

2.3. The nasal function

The nose plays the main role as efficient heat and humidity exchanger, and it is the most used route by which the air enters the lungs [54][55][56].

"We normally breathe through the nose, which in 90% moisturizes and heats the air we breathe to 35-36°C degrees before it reaches the lungs" [57][58][59].

„The ability of the human nose to warm and humidify the respiratory air is important to maintaining the internal environment of the lungs, since ambient air is conditioned to nearly alveolar conditions (at body temperature and fully saturated with water vapor) upon reaching the nasopharynx" [57] „and the intrathoracic airways play little role in the conditioning process, even in frigid environments" [60][61][62].

Patients with a ventilator tube in the trachea cannot use their nose to heat and humidify the air so the temperature reaching the lungs directly can be much lower than required - even by 15 degrees below, if the room temperature is 20°C degrees [63].

In many cases the air could be too cold and too dry.

2.4. The impact and consequences of cold on the respiratory tract.

It is known from research that "patients with bronchial hyper responsiveness are at risk of bronchospasm from sudden inhalation of cold air due to changes in the internal balance of the lower respiratory tract. When the air temperature drops quickly without gradual adaptation, even with

changes as low as 2°-3°C, but especially with changes greater than 5°C, negative consequences for the respiratory system may occur and the patient is at risk of severe exacerbation of the disease and may find himself in a clinical condition characterized by an exacerbation of respiratory symptoms of chronic / obstructive (like asthma and COPD) within a few hours or days **[**64**]**.

Cold airway damage is caused not only by direct temperature effects but also by hyperventilation. Airway cooling is improved by increasing airflow in the airways. Breathing air at + 20°C at 15 l/min lowers the temperature of the trachea to 34°C, while breathing similar air at 100 l/min lowers this temperature to 31°C" **[**65**]**. „To understand the mechanisms of cold air provoked respiratory symptoms is essential for successful management of the symptoms" **[**66**]**.

„Current evidence indicates that the stimulus of airway cooling and/or drying is translated into airflow limitation via the generation of bronchoactive mediators, neural reflexes or hyperemia and edema that result in a net narrowing of the airway **[**67**][**68**]**. In addition, airway instability may occur, which could lead to airway closure and derecruitment of some airways" **[**69**]**.

„We conclude that the peripheral airways of asthmatic individuals with EIB are responsive to cool, dry air, and may play an important role in EIB" **[**70**][**71**]** and „that breathing dry air produces an acute reduction of extravascular water (EVW) of the loose connective tissue of the airways and an increase in the maximum response to histamine" **[**72**]**.

The above research shown that the low temperatures in our lungs causes bronchoconstriction which decreases the lungs' capacity.

2.5. Humidity of air the basics of physics

„Dry air from ventilators - peripheral airways responsiveness to cool, dry air - causes marked epithelial lesions and local inflammation" **[**73**]**.

Regarding the air humidity that is measured as the amount of water vapor in the air. „Maximum humidity is the maximum amount of water vapor contained in a given amount of air, and is strongly related to the air temperature. The higher the air temperature, the more water vapor can be in it. Exceeding the maximum humidity (e.g. as a result of air temperature drop) causes water vapor condensation" **[**74**][**75**]**.

The amount of water vapor in the air is limited and depends on the temperature of the mixture (humid air), as it is shown in „Air Properties: Temperature and Relative Humidity" **[**76**][**77**]**.

„Changes in relative humidity and temperature of the anesthetic gases were measured (…). It is concluded that the output of relative humidity and temperature in the circle system is not sufficient to

prevent broncho-epithelial damage. Ciliary beat automaticity appears to behave according to an all or nothing principle" **[**78**]**.

„With dry air we found widespread loss of the ciliae on scanning electron microscopy in 10 of 12 animals, associated with detachment or sloughing of the epithelium, subepithelial vascular congestion, edema, and cellular infiltration on light microscopy. Our data demonstrate that a short exposure of the trachea to dry air causes marked epithelial lesions and local inflammation" **[**79**][**80**][**81**][**82**]**. Too cold and too dry air from a ventilator together with too high air pressure can activate the mast cells, release a lot of histamine and cytokines inducing and participating in inflammatory processes that can lead to VAP - secondary pneumonia **[**83**]**.

Calcifications, adhesions and scarring, "burns" in the lungs can be the result high mechanical pressure as well as too low temperature and dryness of the air supplied can damage the alveoli, and dry the lungs from the inside.

From the observation of doctors: Even though patients with COVID-19 are symptomatic with dyspnea, initial x-rays often show no opacification. Blood, however, note marked increase of cytokines, which leads the doctors can notice that the VAP develops with time.

3. Mast cells:

Mast cells (known as masticates or labrocytes) are type of white blood cells produced in the bone marrow, being a part of the immune system. They are located all over the body but the highest numbers of mast cells are located in places constituting the main gateway to infection - where the body meets the environment: the skin, lungs (directly in the epithelium lining of the respiratory system) and urinary and gastrointestinal tract (in the intestines), connective tissue, mucous membranes and around the nerves. Also they can be found in the heart, as well as in the immediate vicinity of blood and lymph vessels, and their number in these places is very high. This may indicate that mast cells are among the first cells to recognize an invading pathogen" **[**84**]** can be classified as "rapid reaction forces" playing a significant role during the processes of defense mechanisms.

Mast cells are the first to respond to protect body from germs and infections and are referred to as „the starting factor in the inflammatory process" **[**85**].** They have ability to phagocytosis and have up to a thousand basophilic granules in which released the substances during the inflammatory reactions and tissue structure **[**86**][**87**]**.

Mast cells are the major producer of histamine in the body and are a type of innate immune cells involved in the body's defense against biological , chemical and physical factors. In response to „the factor attack" they can react violently, releasing the contents of their granules: histamine, tryptase, heparin, prostaglandin D2, leukotrienes and other clinically relevant mediators, with a strong effect. Mast cells

play an important role in specific and innate immunity as well as in allergic inflammation associated with IgE. On their surface is the FcεRI receptor that binds IgE antibodies [88]. When a mastocyte comes into contact with an allergen or are activated by factor, it releases histamine, which affects other neighboring and distant cells [89].

During severe allergic or pseudo allergic reactions, substances secreted in large amounts by mast cells cause systemic symptoms, multiorgan inflammatory response syndrome, including anaphylactic shock" [90][91].

They also contain proteases (e.g. tryptase or chymase), due to the presence of proteolytic enzymes, they can be divided into 2 subpopulations: "tryptase only (MCT) cells and cells that have both tryptase and chymase (MCTC) proteases. MCTs are found in the alveolar wall of the lungs, while MCTCs are found in the skin, blood vessels, and the intestinal submucosa" [92].

Many new studies shown participation of mast cells not only in allergic reactions, but also in the innate and acquired immune responses, in inflammatory processes [85][93] in the formation of blood vessels and the development of neoplasms (including the hematopoietic system) [94]. They can also cause mastocytosis causes a wide range of symptoms, which can vary depending on the type of mastocytosis (cutaneous, systemic or aggressive (ASM) [95][96][97]). The symptoms of the systemic mastocytosis are very similar to COVID-19 [98].

Mast cells produce metalloproteinases substances that cause inflammation, joint problems breaking down collagen, skin problems, unsealing the intestinal mucosa and the blood brain barrier [99]. „Also the role of mast cells in autoimmune diseases has been described, including in systemic lupus erythematosus and rheumatoid arthritis and anti tumor activity (e.g. secreting TNF α)" [87].

„The allergic response to innocuous antigens reflects the pathophysiological aspects of a defensive immune response whose physiological role is to protect against helminthic parasites. It is triggered by antigen binding to IgE antibodies bound to the high affinity IgE receptor FcεRI on mast cells. Mast cells are strategically distributed beneath the mucosal surfaces of the body and in connective tissue. Antigen crosslinking the IgE on their surface causes them to release large amounts of inflammatory mediators. The resulting inflammation can be divided into early events, characterized by short-lived mediators such as histamine, and later events that involve leukotrienes, cytokines, and chemokines, which recruit and activate eosinophils and basophils. The late phase of this response can evolve into chronic inflammation, characterized by the presence of effector T cells and eosinophils, which is most clearly seen in chronic allergic asthma" [100].

Apart of above mast cells are also involved with vital functions in the body: by taking part in wound healing with forming new blood vessels, bone growth and secretion of gastric acid.

3.1. Factors of activation of mast cells leading to inflammation.

„Demonstration of the synthesis and release of numerous cytokines and serine proteases by these cells resulted in reconsidering and qualifying mast cells to the circle of important pathogenetic links of many inflammatory diseases" **[**92**]**.

"The inflammatory process can be called a complex, dynamic and ordered sequence of sequences occurring in the tissues in response to the damaging factor. Inflammation aims to limit the action, destroy and remove the causal stimulus, and repair the resulting damage. This process can be classified as chronic or acute depending on the strength and duration of the stimulus on the tissue" **[**86**]**.

It is caused by the mast cells suddenly releasing excessive amounts of histamine, usually after exposed to some triggers.

„Mast cell activation can be triggered by both immunological and non-immunological means. The first route can take place in two ways: in a mechanism dependent and independent of IgE antibodies. However, many non-specific stimuli can also trigger the release of its mediators from the cell" **[**92**]**.

The following list includes the most common triggers of anaphylaxis and mastocytosis can be divided into:

1.Biological (bacteria, viruses, fungi, protozoa, exotoxins, endo-toxins, action of proteins and toxins produced by bacteria, live and killed bacteria).

2. Chemical (turpentine, acids, bases, toxins, drugs:(amphotericin B, quinine, ibuprofen, aspirin, antibiotics), anesthetics (lignocaine, tetracaine, procaine, morphine, codeine, etomidate, thiopental, succinylcholine, enflurane, isoflurane), paraben, preservatives, insect bites or stings and their venoms.

3. Physical (cold, heat, exercise, heat, overheating, cold, irritation, sun, fatigue, physical exertion, pressure, vibration, mechanical, ionizing radiation, magnetic field, ultrasonic waves).

Also: alcohol (specially red wine), certain foods (cheese, shellfish, spices), emotional factors such as stress and excitement, viral and bacterial infections (cold or flu), allergens (of any kind)" **[**101**]**, „the cilia or cell walls with bacterial antigens" **[**86**]**.

„In addition, skin, tonsil and intestinal mast cells can be activated by: substance P, vasoactive intestinal peptide (VIP), components of the complement C5a, C3a, somatostatin, morphine, major basic protein (MBP), platelet activating factor (PAF), platelet factor 4 (PF4 platelet factor 4), very low density lipids (VLDL very low density lipoprotein)" **[**92**]**.

When mast cells are activated, they secrete mediators. „The release of mediators takes place in three stages:

I. Within 5 minutes after activation, the per formed mediators contained in the cytoplasmic grains are secreted proteoglycans, enzymes, biogenic amines and cytokines (histamine, heparin/chondroitine sulfate, neutral proteinases (tryptase, chymase, carbocsypeptidase), acidic hydrolases, metaloproteinases (MMP-9, MMP-2, MMP-3), elastase, katepsin-G, ki-ninogenase, cytokins (TNF-α, bFGF, VEGF, TGF-beta, NGL, IL-3, -4, -5, -6, -6, -8).

II. In 30 minutes after activation, secondary mediators resulting from the metabolism of membrane li-pids are released prostaglandins, leukotrienes (LT), thromboxanes (TX) and platelet activating factor (PAF), (PGD2, PGE2, LTB4, LTD4, TXA2, PAFPGD2, PGE2, LTB4, LTD4, TXA2, PAF).

III. In 6 hours after activation, de novo synthesized cytokines are secreted, including chemokines (IL-1 alfa, IL-1 beta, IL-2, IL-3, IL-4, -5, -6, -9, -10, -12, -13, -16, -18, TNF, GM-CSF, INF gamma, PDGF, SCF, MIP-1 alfa, MIP-1 beta, MIP-2 alfa, MIP-2 beta, MIP-3 alfa, MCP-1, MCP-3, MCP-4, RANTES, limfotactine, eotaxin)" **[**86**]**.

„Also tryptase - an enzyme secreted by mast cells, influences vasodilation, and chymase together with tryptase and vascular endothelial growth factor (VEGF) increase their permeability. IL-1 beta, -3, -5, -8, tumor growth factor (TGF beta), TNF, PGD2, PAF and tryptase are chemoattractants of neutrophils and IL-1, -8 and TNF also stimulate them activity.

An important information is the fact that mast cell degranulation leads to the secretion of all performed mediators, so the release of one substance from this group also proves the secretion of the remaining ones" **[**86**]**.

Summing up, in the process of developing inflammatory reactions, including allergic reactions, sub-stances secreted by mast cells (degranulation) may cause systemic symptoms, including anaphylactic shock - a type of sudden, severe systemic allergic or non-allergic reaction which may be fatal **[**87**][**102**]**.

3.2. Mast cells in the lungs

Recent study shows that there are many mast cells in the lungs **[**6**][**103**][**104**]**, they are also found in the bronchi of healthy individuals and patients with asthma **[**105**][**106**]**. Electron microscopy and BAL determination of mast cell mediators confirmed the degranulation of these cells in asthma **[**107**][**108**]** as well as chronic obstructive pulmonary disease, respiratory infections and lung fibrosis **[**103**]**. „Mast cells contribute to the fibrosis processes by producing hyaluronic acid and intensify the growth of collagen fibers thanks to the effects of heparin. Mast cells also activate fibro blasts through tryptase, which stimulates the synthesis of their template ribonucleic acid (mRNA). Thanks to these mechanisms, mast cells can contribute to tissue repair and collagen synthesis (in the lungs could produce a hydrogel that significantly inhibits gas exchange in bronchoalveolar spaces) and fibrosis" **[**86**]**.

Mast cells participate in the defense against respiratory infections **[**89**]**. „Pathogenic roles include immunomodulatory, proinflammatory and profibrotic activities. Another complicating factor is the notorious mast cell heterogeneity, where each anatomical compartment of the lung harbors site specific mast cell populations" **[**103**]**.

„In addition to the release of autacoid mediators, airway mast cells are an important source of neutral proteases, especially tryptase, which have various effects on proteins, including the ability to activate receptors" **[**109**]**, for example the histamine receptors (including H1), which are numerous in the lungs **[**110**]**. „The massive amounts of vasoactive mediators and proteases that are released by PCMC within minutes should greatly facilitate the subsequent constitution of an inflammatory infiltrate. One may therefore speculate that serosal type mast cells function as promoters rather than as effectors of inflammation in allergies and autoimmune diseases" **[**111**]**.

„The pulmonary pathological findings associated with COVID-19 seems to result from the release of multiple proinflammatory cytokines, especially inter leukin (IL)-6, that can damage the lungs **[**112**]**.

„A key source of such cytokines and chemokines is the mast cells, which are ubiquitous in the body, especially the lungs, and are critical for allergic and pulmonary diseases. In fact, activated mast cells were recently detected in the lungs of deceased patients with COVID-19 and were linked to pulmonary edema, inflammation, and thromboses" **[**113**][**114**]**.

There were found many amounts of „mast cell tryptase and histamine concentrations in bronchoalveolar lavage (BAL) from patients with interstitial lung disease" **[**115**]** this shows its important role in the pathogenesis of hypersensitivity pneumonitis **[**116**][**117**]**.

„With an ever present abundance and vast multi-functional capacity, mast cells are most probably involved in most, if not all, types of inflammatory conditions of the respiratory tract" **[**103**]**.

3.3. Activation of mast cells in the lungs

„There are mast cells, which in response to various environmental stimuli **[**7**][**118**]** produce a plethora of inflammatory mediators, such as histamine, cytokines, chemokines, eicosanoids and reactive oxygen species **[**119**][**120**]**.

„The direct signal for their degranulation (degranulation is a rapid release to the outside of the granularity content) is, inter alia, the reaction of the antigen with IgE antibodies on the surface of the mast cell membrane. The signal inducing degranulation may also be the binding of microbial patterns by other receptors (including TLRs), as well as often not taken into account physical factors. Factors that can activate mast cells also in the lungs are:

1. Physics factors: temperature: too cold / hot air, pressure, vibration, magnetic field, ultrasonic waves

2. Chemical/ biological factors: pH difference, ion difference, toxic substance,

3. Biological: bacteria, virus (like SARS-Cov-2) etc." [121][86][122][123][124][125].

Considering carefully the above first two physical factors that can activate mast cells during patient invasive ventilation: Does cold and dry or warm and humid air matter in tidal volumes and pressure?

- COLD: the air that goes directly through the tube into the patient's lungs may be too cold and too dry, because the oxygen, which is compressed in cylinders when it comes out of the conduit "from the wall" expands according to the laws of physics. In many cases active heating and humidification devices are not used together with the ventilator [126]. The airways inside the thorax are forced to deliver the substantial amount of thermal energy required to bring the inspiration fully saturated at internal temperature.

Regarding human lungs: „Jogging is very difficult in the winter compared to summer. Because, at low temperatures our lungs shrink which decrease the human lungs' capacity" [127].

More over there is observation that by cooling down the collected blood in the test tube in vitro the aggregation of platelets occurs [128].

- PRESSURE: the air coming out from the ventilator can cause too much air pressure in the lungs due to its volume in relation to its temperature and humidity. This could occur because of two reasons:

1. Cold and dry air, at approx. 20 °C, in the volume determined by the ventilator, it is heated in the lungs to 37 °C and according to Charles's law [77] an isochoric transformation takes place: as the temperature of a constant volume of gases increases the pressure increases as well. "At a constant pressure, the volume of a given mass of an ideal gas is directly proportional to the absolute temperature" [129]. In simple way: when the temperature increases pressure or volume also increases.

2. Additionally, very often the tidal volume of air supplied is calculated at 5-7ml/per kilogram of the patient (very often on the total body weight, which is very bad because overweight patients do not have larger lungs) [130] [131][132][133][134].

In results: calculating tidal volume from lean body mass could be appropriate for a temperature of 37 °C but this is a completely wrong calculation for cold and dry gases because the calculated lung gas volume will increase according to Charles's law [127] inside the lung causing internal damage alveoli [135][136].

„There is a difference between the physiological state, when the pressure in the lungs is lower than that of the outside, and mechanical ventilation, when it is higher. The lungs may be damaged if the air pressure is not selected properly or if the pressure is too high. It's not about an explosion. Man is not a balloon. Alveoli can lose the elastic property that allows them to return to their original shape. For

example, it may damage the epithelium, cause inflammation, release interstitial fluid, and in extreme cases, "flood" the lungs and completely lose the ability to gas exchange." „Reducing the diameter of the bronchi makes the air unable to over come the increased resistance, and although the ventilator maintains the same initially set pressure, the oxygenation index drops" **[**20**]**.

"Mechanical Ventilation induces injury of the lungs at high volumes and pressures that can damage the lungs causing their swelling or aggravating existing swelling. This is because the alveoli of the lungs are overstretched. In patients with ARDS, ventilation at tidal volumes lower than conventionally used is recommended" **[**137**]**.

The situation described above can not only damage the alveoli but can also activate the destruction of the mast cell membrane releasing stored cytokines and histamine, thereby causing an avalanche of other symptoms that doctors already know and are powerless against them at the moment.

„The massive amounts of vasoactive mediators and proteases that are released by PCMC within minutes should greatly facilitate the subsequent constitution of an inflammatory infiltrate. One may therefore speculate that serosal-type mast cells function as promoters rather than as effectors of inflammation in allergies and autoimmune diseases" **[**88**]**. There have been found „mast cell tryptase and histamine concentrations in bronchoalveolar lavage from patients with interstitial lung disease" **[**115**]**.

In response to inhalation of various antigens of organic (e.g. fungi, bacteria, animal proteins) or chemical (e.g. diisocyanates, acid anhydrides, copper sulphide) origin an inflammatory disease that develops like: hypersensitivity pneumonitis (Extrinsic Allergic Alveolitis) **[**138**]** which could be also caused by fungal infections from species of Aspergillus, given to a wide variety of diseases **[**139**][**140**]**. "Exposure to low temperatures often causes allergic responses or urticaria. Similarly, menthol, a common food additive is also known to cause urticaria, asthma, and rhinitis. Furthermore, menthol, a TRPM8 agonist, induced the dose dependent release of histamine from RBL-2H3 cells. When TRPM8 transcripts were reduced by siRNA (small interfering RNA), menthol and cold - induced Ca(2+) influx and histamine release were significantly reduced. TRPM8 mediates the menthol and cold induced allergic responses of mast cells, and suggest that TRPM8 antagonists be viewed as potential treatments for cold and menthol-induced allergies" **[**141**]**. There is an undeniable role of mast cells in the pathogenesis of hypersensitivity pneumonitis **[**142**][**116**]**. Chronic nature of this disease is also brings diagnostic problems as it can resemble a lot of other lung conditions such as pneumonia and bronchitis **[**143**]**.

Initially, the activator of mast cells may be the COVID-19 virus, then cytokines and histamine are released, causing first symptoms of dyspnea **[**87**]** then the inflammatory response which develops "allergic" symptoms, pneumonia and other symptoms similar to COVID-19 symptoms.

3.4. Angiogenesis from mast cells in lungs

Mast cells and their role in immunity and cancer angiogenesis (the process of the formation of capillary/ blood vessels), occurs in embryonic development, also in the post-fetal life (both as a physiological and pathological process) [149]. "The granules of these cells are located within the endothelial cells of blood vessels and stimulate their proliferation. Histamine participates in this process through both its receptors H1 and H2. Heparin causes vessel formation in vitro, while TNF-alpha both inhibits and stimulates angiogenesis" [86].

Mast cells are also responsible for and take part in angiogenesis in lungs (regarding the author's hypothesis): in the wound healing phases from damage of the endometrial and alveoli, marked epithelial lesions, local inflammation, platelet aggregation (increased blood clotting by histamine), endometrial regeneration (following damage by cold and dry air and inflammation). Angiogenesis can be observed also during regulation of ion metabolism [144][145].

"Research has shown that what sets COVID-19 lung pathobiology apart from influenza virus infection is equally severe is angiogenesis" [146].

3.5. Blood clotting and thrombosis

Difficulty breathing or shallow breathing may be silent symptoms of thrombosis. They may be a symptom of a pulmonary embolism. Mast cell deficiency causing the lack of the histamine release prevents DVT (deep vein thrombosis) [147]. Mast cells exacerbate DVT [148], "likely through endothelial activation and Weibel Palade body release, which is, at least in part, mediated by histamine. Because mast cells do not directly contribute to normal hemostasis, they can be considered potential targets for prevention of DVT in humans" [147]. "Antihistamine may play a key role in inhibiting the activation of coagulation cascade in CU" [149] "because the levels of coagulant factors trend toward recovery after antihistamine administration [150][151] and gives new hope to prevent dangerous blood clots which are found in the legs [152].

There is also connection of releasing histamine, thrombosis and affected energy ATP in platelets.

Because platelets have mitochondria therefore undergo the Krebs cycle and oxygen phosphorylation.

As in other cells, adenosine triphosphate (ATP) constitutes the majority of the adenine nucleotide in the metabolic pool. The ATP in this pool is the energy source needed to maintain cellular function.

In addition to the energy necessary for proper homeostasis, platelets consume a large amount of it during aggregation and release reactions. In addition to ATP, the dense granules contain the essential

adenosine diphosphate (ADP), Ca ++, magnesium ions and serotonin, which substances are released outside during the release reaction (degranulation).

Platelets clump together after in vitro activation of platelets, what can lead in vivo to the disseminated intravascular coagulation from the platelet's serotonin. In addition to vascular damage associated with inflammatory diseases, some inflammatory cytokines (especially PAF) cause aggregation of platelets.

The pathogenesis of thrombosis can include endothelial activation or damage, disturbances in blood flow (turbulence or stagnation), changes in coagulation factors, fibrinolytic factors or their inhibitors, and activation of platelets. The consumption of clotting factors and platelets during the formation of these clots causes a tendency to bleed.

Vitamin K is necessary for the carboxylation reaction, which results in the formation of the active forms of clotting factors: II, VII, IX and X., that is why coagulation disorders are dependent on vitamin K deficiency **[**153**]**. Referring to thrombosis, it is worth looking at serpins that control a number of biological processes, such as clotting or inflammation **[**154**]**. „Coagulation is accelerated by an external electric or magnetic field, by mechanical pressure, e.g. ultrasonic field, mixing and centrifugation. Coagulation caused by mechanical external factors is called assisted coagulation. In turn, the coagulation caused by the Brownian motion itself is the so called perikinetic coagulation" **[**155**]**. Warfarin is an antagonists of vit.K, it is used medicinally as anticoagulant but vit. C (ascorbic acid) make possible warfarin resistance **[**156**]**.

3.6. Mast cell and tryptase

Tryptase is a serine proteinase derived from the secretory granules found in mast cells and is used as a marker of mast cell activation **[**157**]**.

"Recent years have brought a lot of new research and information on the role of tryptase and other serine proteases and their influence on the PAR-2 receptor (proteinase-activated receptor). Four types of PAR receptors have been identified (PAR − 1, PAR − 2, PAR − 3 and PAR − 4) and belong to the family of G protein related receptors.

The presence of the PAR-2 receptor has been demonstrated in epithelial, endothelial and smooth muscle tissues, which play an important physiological role in the regulation of many biological systems, including: cardiovascular, digestive, respiratory, peripheral nervous system of the skin, kidneys and secretory glands. The presence of active tryptase in tissues may cause: increased bronchial hypersensitivity to histamine, stimulation of fibroblasts to increase collagen production, stimulation of epithelial cells to produce pro inflammatory cytokines, activation of the vascular neoplasm process, biodegradation of fibrinogen and kininogen, degradation of extracellular compounds such as VIP,

peptide with calcitonin gene (CGRP - calcytonine gene relatedpeptide), 72 kDa gelatinase, fibronectin, prostromelysin, increased expression of intercellular adhesion molecul 1 (ICAM 1 inter cellular adhesion molecule 1) of epithelial cells, induction of mRNA expression. a growth factor for smooth muscle cells, fibroblasts and epithelial cells, stimulating the production of IL-8 during allergic inflammation and increasing the expression of vascular cell adhesion molecule (VCAM-1).

Reactivation of tryptase in the endosomes of cells facilitates the process of antigen uptake by cells capable of this. The ability of tryptase to directly activate other cells and the ability to cleave peptide hormones and activate proenzymes suggest its participation not only in immediate allergic reactions or mastocytosis, but also in inflammatory, degenerative and neoplastic processes and in the wound healing process.

The most sensitive and specific is the simultaneous determination of serum tryptase and histamine. The biological half-life of tryptase is 1.5–2.5 hours. It is an important marker of systemic anaphylaxis, reaching the highest serum concentration 15–120 minutes after the onset of clinical symptoms. Increased serum levels as a result of anaphylactic shock are observed up to 3 days after death. In systemic, less turbulent allergic reactions, increased levels of tryptase in the blood are noticed after 1-6 hours. after exposure to the allergen, while an increased concentration of histamine under the same conditions is detected after just 15 min.

The levels of histamine and tryptase in the serum were also measured in patients hypersensitive to aspirin, patients with bronchial asthma and allergic rhinitis. In these patients, severe or moderate bronchospastic reactions with skin and / or gastrointestinal symptoms have been observed after aspirin challenge; they had a significantly increased concentration of tryptase (51–400 × 10–6 g / l). This enzyme is a selective indicator of clinical symptoms of aspirin challenge.

Relatively high concentrations of tryptase were also found in bronchial lavage in people with bronchial asthma, with interstitial lung diseases, in nasal lavage in people with allergic rhinitis and in synovial fluid, in people with arthritis, in serum in acute appendicitis, in hyperpyrexia, in cases of cutaneous allergic reactions, but no increase in serum concentrations has been shown in cases of local allergic reactions.

To date, no in vivo inhibitor of human tryptase has been detected. Instead, a strong synthetic inhibitor, gabexate, has been developed. It is a small molecule serine protease inhibitor that has over 100 times more potent action on human tryptase than on other serine proteases, such as thrombin and trypsin. Another, equally selective blocker is natamostat. Due to the important role of mast cells and their mediators in the pathogenesis of many inflammatory and allergic diseases, the use of protease inhibitors, including tryptase inhibitors, may prove beneficial in therapy. Despite promising experiences, tryptase inhibitors have not yet moved beyond the research stage" **[**92**]**.

Considering also the symptoms of allergic and pseudo-allergic reactions that are symptoms of mast cell activation, it would be advisable to check serum histamine and tryptase levels in people suffering from COVID-19, HIT, SIRS and SEPSA.

4. The role and difference of histamine and bradykinin.

4.1. Bradykinin kinin

Studies in anaphylaxis suggests that there is co-existence of mast cell activation and release of bradykinin. „It was shown that excessive mast cell activation during anaphylaxis initiates contact activation, resulting in bradykinin release" **[**158**]**.

„The peptide, bradykinin, has cardiovascular effects similar to those of histamine and plays prominent roles in inflammation and nociception" **[**159**]**.

Bradykinin is a tissue hormon, which during inflammation, tissue damage and allergic reactions is released locally from mast cells and basophils, is also involved in inflammatory development. It increases the permeability of capillaries, which results in local swelling, warmth and redness, which are classic symptoms of an inflammatory reaction. Bradykinin also irritates the nerve endings, causing a burning pain that informs about a disturbance of functions in a given area and dilates blood vessels (skin, striated muscles, kidneys, brain, viscera, coronary vessels, etc.) by paralysis of smooth muscles in the walls of the vessels, which causes, among others, the effect of a decrease in blood pressure (due to an increase in the volume of the vascular bed). Contracts the smooth muscles of other organs (than vessels), e.g. bronchus, uterus. Researches shown that bradykinin increases the release of catecholamines from the adrenal glands also may be significant in gout, inflammatory bowel disease, rheumatoid arthritis, asthma or disseminated intravascular coagulation with beneficial effects for example in the heart, kidney, and circulation with antithrombotic effect **[**159**][**160**][**161**]**.

„Bradykinin administered directly to the hippocampus has been shown to interfere with short-term but not long-term memory fixation via B1 receptors, bradykinin may impair memory, e.g. in the course of post traumatic, inflammatory and neurodegenerative changes. It is worth mentioning that any of the three common symptoms of BMS (pain, dysgeusia, and salivation disorders) can be caused by bradykinin. Changes in the conformation of bradykinin and oligomerization due to metal imbalances (copper and zinc) result in a loss of the pro inflammatory properties of bradykinin. The excess of copper ions, more than zinc ions, affects the signal transmission through the B1 and B2 receptors" **[**162**]**.

Bradykinin is inactivated (degradated) by angiotensin converting enzyme (ACE, which functions are balanced by its homologue ACE2 **[**163**]**) in the lungs and kidneys **[**164**]** and inhibition of the ACE enzyme leads to an increase in bradykinin levels; increased bradykinin sensitizes somatosensory fibers and thus causes hyperalgesia, and is also believed to be the cause of dry cough.

„ACE and ACE2 also have intimate roles with the plasma kallikrein kinin system (KKS), a hormonal pathway that modulates the intrinsic blood coagulation system, endothelial cell growth and angiogenesis. The KKS consists of plasma and tissue kallikreins, plasma high (HK) and low (LK) molecular weight kinino-gens, their derivative kinin peptides, including bradykinin (BK) and des Arg9-BK, and two G-protein coupled bradykinin receptors (B2R and B1R)" **[**163**]**. „Bradykinin may mediate this via local release of histamine and proinflammatory peptides (e.g: substance P, neuropeptide Y)" **[**165**][**166**]**. In particular with regard to allodynia, which is a clinical feature of many painful conditions such as neuropathies, complex regional pain syndrome, post-herpetic neuralgia, fibromyalgia and migraine, bradykinin has been shown to sensitize TRPV1 receptors (whose function is to detect and regulate body temperature) by lowering thus the temperature threshold at which they activate, thereby possibly contributing to the above described soreness **[**167**]**.

"Bradykinin is a potent stimulator of the formation of nitric oxide by the vascular endothelium. It also stimulates formation of prostacyclins" **[**168**][**169**]**. Researches proposed bradykinin as an explanation for many COVID-19 symptoms for example: dry coughs, myalgia, headaches, nausea, vomiting, diarrhea, anorexia, decreased cognitive function, fatigue, arrhythmia and sudden cardiac death **[**170**]**.

But also another study has been shown that bradykinin induced bronchoconstriction is blocked by anticholinergic agents but not by antihistamines or cyclooxygenase inhibitors **[**159**]**, what is opposite to the observed in cases introduced in this article where antihistamines are stoped development of COVID-19 symptoms. Together with bradykinin antithrombotic effect which is again opposite to commonly thrombosis effect, the author infer that the mechanism which causing the symptoms of COVID-19 is the activation of mast cells and the histamine storm with bradykinin activations symptoms co-existing.

4.2. Histamine autacoid:

Histamine is produced in mast cells in the body, apart from mast cells, histamine is also produced by other cells of our body: immune, nervous, stomach walls and platelets. This biogenic amine is formed from the amino acid histidine, also have been found in the food **[**171**]**. It is a major mediator in inflammation, and anaphylaxis response, allergic respiratory disease, gastric acid secretion, as well as „also plays a role in neuro-transmission in brain" **[**172**]**, as histamine containing neurons control both homeostatic and higher brain functions, including regulation of the sleep-wake cycle, and falling asleep (excess histamine can lead to insomnia) **[**173**]**. circadian and feeding rhythms, immunity, learning, memory, drinking, body temperature **[**174**]**.

Histamine works through histamine receptors i.e. proteins located on the outer membrane of most of the cells.. As many as 4 types of receptors have been discovered so far (H1R, H2R, H3R and H4R) Different on various cells **[**175**]**. „It can be said that one histamine key opens 4 types of locks, and the

locks them selves are located in different organs doors to different chambers. Hence the variety of symptoms caused by just one histamine!" [89].

The multiple effects on the respiratory tract and the other organs action of histamine is based on the stimulation of the H1, H2, H3 and H4 receptors:

„The H1 receptors are daily in lungs, mediate bronchoconstriction, vasoconstriction and dilation, micro-vascular shunt and activation of sensory nerves, (are expressed in many cells, including mast cells, and are involved in Type 1 hypersensitivity reactions).

The H2 receptors in some species they mediate vasodilation and mucus secretion. The H2 receptor is highly expressed in gastric tissues, stimulating gastric acid secretion and mediating gastrointestinal motility, food intake and (are involved in Th1 lymphocyte cytokine production).

The H3 receptors modulate nociception, is expressed mainly in the central nervous system and to a lesser extent in the peripheral nervous system, where it controls the release of various neurotransmitters, (are mainly involved in blood-brain barrier function).

The H4 receptors is abundant in bone marrow and white blood cells, where it regulates mast cell chemotaxis, (are highly expressed on mast cells where their stimulation exacerbates histamine and cytokine generation)" [6][110][173][176][177][178][179]. „Both H1R and H4R have important roles in the progression and modulation of histamine mediated allergic diseases" [6][110].

However, it should be remembered that histamine and its action are usually beneficial for our body. Its excess is harmful. "Too much histamine can cause allergy symptoms even if there has not been contact with the allergen. One of the reasons is too low amount of the enzyme that degrades histamine (diamine oxidase – DAO), deficiency caused by substances that reduce its activity fluconazole, cephalosporins, propafenone, alcohol or caused by the course of digestive system diseases, e.g. chronic intestinal inflammation, infectious diseases, irritable bowel syndrome, Hepatitis A virus (Hep A or HAV) as an RNA virus [180], under the influence of prolonged stress or excessive physical exertion or the imbalance between the intake of histamine from food or otherwise released from mast cells. Hence, histamine is broken down with a delay, enters the bloodstream and causes allergic-like symptoms: headache, migraine, itchy skin, utricaria, rash, red patches of skin, palpitations, tachycardia, abdominal pain, abdominal distention, nausea, bowel cramps, arthritis, etc., while „histamine is absorbed through the intestinal wall into the blood and lymph and is transported to different places in the body, causing severe disease symptoms" [181].

Histamine excessively released from mast cells can leads to multi organ inflammation.

The storm of histamine can lead to serious complications like **(Pic.1)**:

Bronchospasm

Increased blood clotting

Tachycardia

Expansion of blood vessels

Increased permeability of the capillary vessels

Adrenaline release

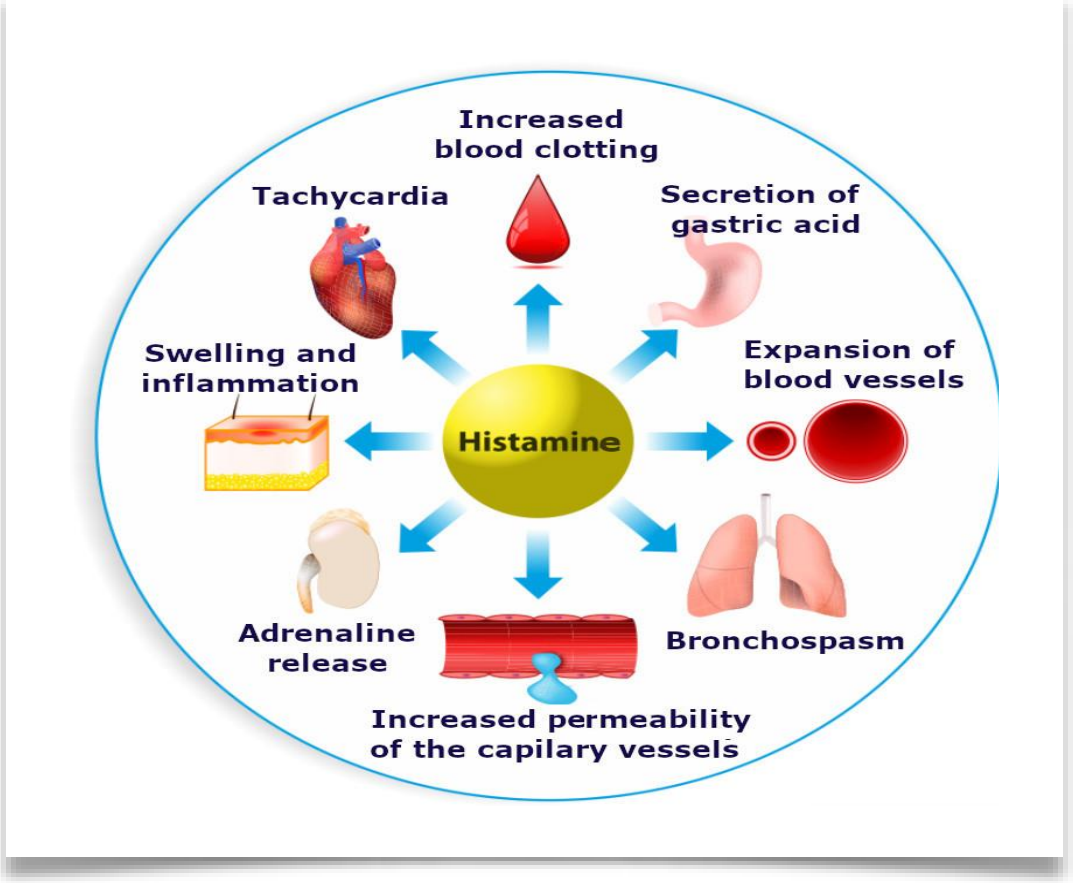
Secretion of gastric acid

Swelling and inflammation

Headache, etc.

Slows down the flow of blood and lymph and increases the permeability of the vessel walls to water **[**181**].**

"There is a close relationship between histamine and IL-6. Histamine has been shown to induce exocytosis and IL-6 production in human pulmonary macrophages by interacting with H1R10 as well as inducing IL-6 production in human endothelial cells **[**183**][**184**]**. „Histamine-induced production of interleukin IL-6 and IL-8 by human coronary artery endothelial cells is enhanced by endotoxin and tumor necrosis factor-alpha" **[**185**]**.



Pic.1. Histamine impact. Infographic source **[**182**]**.

Moreover, histamine seems to be a "paracrine regulator of T-cells, in COVID-19" **[**186**]** and be involved in inhibition of the local immune response against cancer **[**187**]**. Increased levels of IL-6 have been reported in various neoplastic conditions, and in most disease models.

Antihistamines may be involved in the regulation of cytokines such as IL-6 due to the role of histamine as a mediator of inflammation in nasal fibroblasts **[**184**][**188**]**.

Within minutes, two enzymes involved in the metabolism of histamine can break it down by: diamine oxidase (DAO) in the extracellular space (e.g. in the blood, and intestinal wall) and histamine N-methyltransferase (HNMT) which is involved in metabolism of the persistently present intracellular primarily endogenous histamine.

4.3. Histamine secretions and Histamine receptors in the lungs.

Scientists in researches confirmed that mast cells are principal sources of airway and serum histamine, contributes to inflammation in mycoplasma pneumonia **[**189**]**.

According to principal investigator George Caughey, MD, chief of pulmonary/critical care medicine at the San Francisco VA Medical Center and Mr. Caughey prof. of medicine at the University of California, San Francisco, the lung neutrophils can produce histamine in significant quantities, the result could mean that "histamine acts as a link between airway infections and asthma and bronchitis, which are associated with allergy. In both, we observe inflammation—swelling, blood vessel leak, and muscle contraction that narrows the airway" **[**190**][**191**]**.

„In vitro, mycoplasma directly stimulated histamine production by naive neutrophils and strongly up-regulated mRNA encoding histidine decarboxylase, the rate limiting enzyme in histamine synthesis. In vivo, treatment with antihistamines pyrilamine or cimetidine decreased lung weight and severity of pneumonia and tracheobronchitis in infected mice. These findings suggest that neutrophils, provoked by mycoplasma, greatly expand their capacity to synthesize histamine, thereby contributing to lung and airway inflammation" **[**189**]**.

4.4. The role of histamine and histamine receptors in mast cells mediated allergy, neurogenic inflammation and hyperimmune response

"Histamine also exerts various other immune regulatory functions by modulating the functions of monocytes T cells, macrophages, neutrophils, eosinophils, B cells, and dendritic cells. The biological impact of histamine follows their interaction with four types histamine receptors H1-4R all of which belong to the G protein coupled receptor family"**[**192**][**193**][**194**][**195**][**196**][**197**]**.

„Histamine plays a key role in the complex physiopathological mechanism known as neurogenic inflammation, its four receptors contribution to this condition, with particular focus on nociceptive pain, neurogenic inflammation in the skin, airways and interstitial cystitis" **[**198**]**.

"The term 'neurogenic inflammation' has been adopted to describe the local release of inflammatory mediators, such as substance P and calcitonin gene related peptide, from neurons. Once released, these neuropeptides induce the release of histamine from adjacent mast cells. In turn, histamine evokes the release of substance P and calcitonin gene-related peptide; thus, a bidirectional link between histamine and neuropeptides in neurogenic inflammation is established" **[**198**]**.

„One plausible chain of events leading up to a hyperimmune response could involve early viral triggering of macrophage activation, followed by T helper cell stimulation, in turn leading to cytokine release, stimulation of macrophages, neutrophils, and monocytes, in conjunction with B cell and plasma cell activation, and antibody production **[**199**]**. Toxic shock, macrophage activation syndrome, and secondary haemophagocytic lymphohistiocytosis, may be explained by immunological activation and dysregulation of similar inflammatory pathways **[**200**]**. In each of these syndromes, a cytokine storm leads to failure of multiple organs" **[**201**] [**202**][**203**][**204**]**.

4.5. Histamine via female hormones, axis HPA, CRH and its the role of the gut

„There is an interconnection in the body between histamine, estrogen, progesterone and cortisol in regards to systemic functionality. It can also be stated that an endogenous imbalance in these substances can cause or contribute too many reproductive or non-reproductive issues. Animal data has demonstrated that cellular histamine concentrations in ovarian and uterine mast cells varies across the menstrual cycle, and the activation of mast cells within endometrial tissue is most significant during the premenstrual phase following the decrease in progesterone and estradiol" **[**205**][**206**][**207**][**208**][**209**][**210**][**211**][**212**][**213**][**214**]**.

„The course of platelet-leukocyte aggregates formation during the menstrual cycle followed the course of estrogen levels, strongly suggesting direct effects of estrogen on platelet-leukocyte interaction" **[**295**]**.

„Corticotropin-releasing hormone (CRH; previously known as corticotropin-releasing factor) is the central regulator of the hypothalamic-pituitary-adrenal (HPA) axis, which is the main organizer of the body's response to stress **[**216**][**217**][**218**][**219**]**.The hypothalamic-pituitary-adrenal (HPA) hormonal response to stress results in mast cell degranulation and consequently elevated levels of histamine" **[**205**]**.

"Stress induces the hypothalamic production and release of CRH, which together with related urocortin (URC) peptides regulate behavioral, autonomic, endocrine, reproductive, cardiovascular, gastrointestinal and metabolic functions both on the central and on the peripheral levels **[**220**][**221**]**. It is also accepted that peripheral CRH and related peptides have predominantly proinflammatory functions, **[**222**][**223**]** this way differ from central immunosuppressive activity **[**217**][**224**][**225**][**226**][**227**][**228**]**.

Also „the immunological form of communication between the gut and the CNS is formed by cytokines, the concentration of which is influenced by the state of the gut microbiome. It has been confirmed that intestinal bacteria can both reduce the levels of pro-inflammatory cytokines: TNF-alpha, IFN-gamma, IL-6, and modulate the levels of anti-inflammatory cytokines, eg. IL-10 **[**229**]**. Cytokines can directly influence the CNS, e.g. by penetration through regions permeable to some of them in the blood-brain barrier, with the help of specific transporters or by activation of afferent nerve fibers, eg vagus nerve" **[**230**][**231**]**.

The cascade of inflammatory mediators, including TNF-α, IL-1 and IL-6, increase tissue resistance to insulin. In case of preexisting diabetes, further intensification insulin resistance may aggravate diabetes **[**232**]**.

5. Histamine intolerance HIT & Mast Cell Activation Syndrome (MCAS)

Just 4 years after the word "allergy" was invented, histamine was discovered by Dr. Pirquet, and in 1932 its role in anaphylactic shock, the worst form of allergy, was explained. „Meanwhile, it turned out that the mere consumption of histamine or its increased level in our digestive tract causes the same symptoms as a true allergy to a specific allergen. This, still underestimated, in my opinion, discovery may turn out to be a break through in the approach to the treatment of patients with food hypersensitivity and intolerance" **[**89**][**233**]**.

Not only allergies (IgE reactions) but also drugs, medical conditions, nutritional deficiencies, DAO deficiency, SIBO, leaky gut, and histamine rich foods, the environmental and physical triggers (like cold, pressure, vibrations) can lead to the disequilibrium of accumulated histamine and no capacity for its degradation leads to histamine intolerance **[**171**]**.

„The concept of histamine intolerance HIT, assumes that someone does not have to be allergic to any allergen, but has too much histamine in the body for various reasons and feels the symptoms exactly like allergies, or even stronger ones."

„Despite the similarities in symptoms, the difference in biological mechanisms between allergy and HIT turns out to be extremely important in practice. There is no need to be the allergen in histamine intolerance this is the most important thing, and there is no have to be the entire chain of the immune system's erroneous response to an allergen. However, a huge amount of histamine molecules appears in our body, usually quite suddenly and unexpectedly **[**89**]**. When the body does not break down histamine, and it leaks through the intestinal lining, it enters the bloodstream and flows with it, will cause an immune response and similar reactions in distant places **[**234**]**. A person's allergic response symptoms are likely to be more severe the more histamine they have accumulated in their bloodstream. „People with histamine intolerance tend to have a variety of symptoms that can make it difficult to determine the source" **[**235**]**.

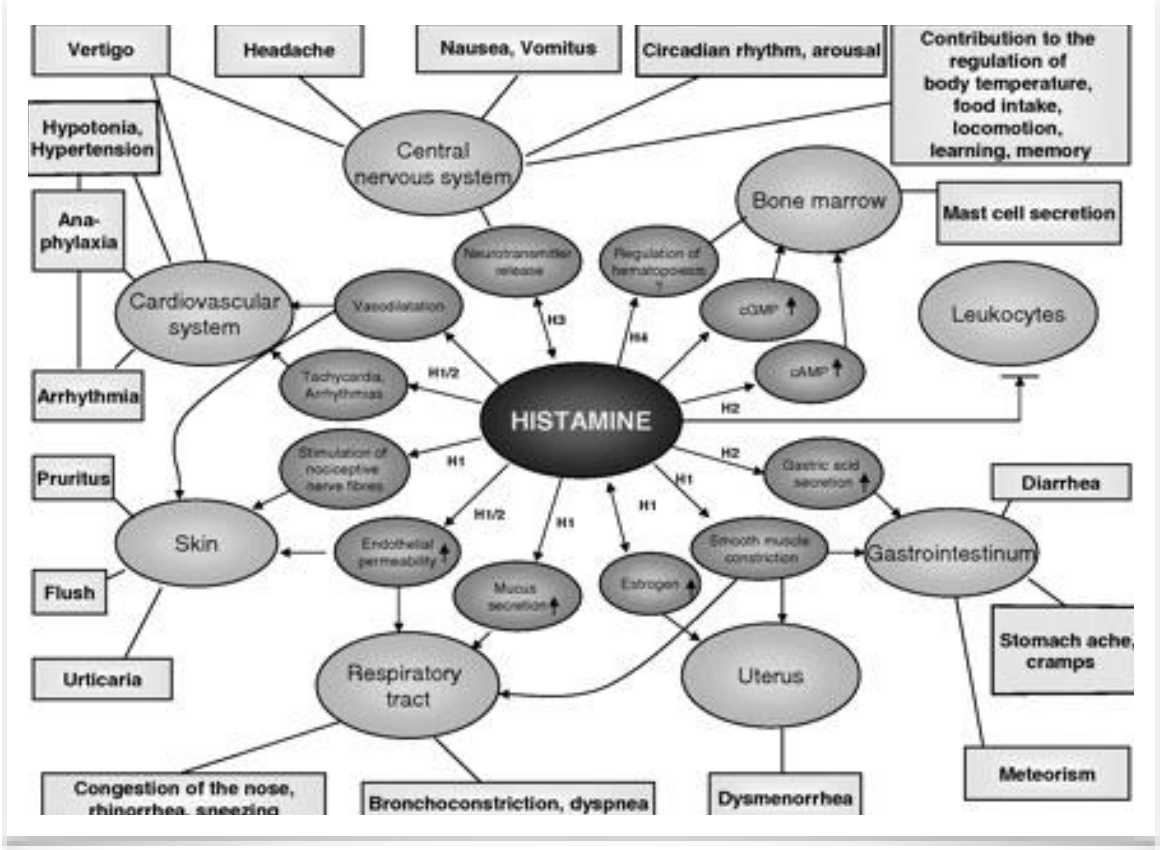
„Immune-mediated ('classic') histamine release involves mast cells and basophils, which degranulate stored histamine after antigen induced IgE antibodies bind to membrane receptors.

Non-immunological histamine release involves the degranulation of stored its from mast cells and basophils or the passive transport of histamine in non storing cells (enterochromaffin-like, histaminergic neurons, lymphocytes, monocytes, platelets, neutrophils, and gastric and dendritic cells, which produce histamine in response to specific stimulus (as opposed to storing it), which can be induced by endogenous (neuropeptides, cytokines, complement) or exogenous physical, chemical or alcohol, food,

medication factors **[**236**]**, where "biogenic amines including histamine are also produced by bacterial decarboxylation in food" **[**237**]**.

Some of the white blood cells with histamine in granulocytes circulate with the blood and lymph (basophil granulocytes), some of them (mast cells) wait in the mucosa of the respiratory tract, intestines, conjunctiva of the eyes, etc. If they comes into contact, even with a small amount of protein (allergen) or other activators, it releases histamine from its interior within a few seconds. A small chemical molecule that in turn acts on neighboring cells and also penetrates the blood going with it to other places in our body (also by histamine H1, H2, H3, H4 receptors). In fact, a billions of histamine molecules are release from a single mast cell. And there may be several dozen or even several hundred thousand mast cells themselves in the area where the allergen has penetrated or has been activated histamine release by physical triggers.

So we are dealing with a real local war and in other places where histamine has reached. This is how we could explain the symptoms in various organs" **[**13**][**181**][**238**][**239**]**. **(Pic.2).**



Pic.2. Histamine receptors impact. Pic.source: **[**13**]**

„The symptoms of histamine intolerance are similar to those of an allergy, and can include any of the following:

- Arrhythmia, or accelerated heart rate (tachycardia)

- Difficulty Breathing

- Nasal Congestion,

- Sneezing,

- Headaches

- Hypertension

- Fatigue

- Anxiety

- Hives

- Difficulty regulating body temperature

- Abdominal cramps

- Nausea, vomiting

- Tissue swelling

- Vertigo or dizziness

- Difficulty falling asleep

The real problem is possible excess of biogenic amines or „when their degradation is inhibited or disturbed in the body, then histamine is thought to cause multiple gastrointestinal symptoms. These may be accompanied by extra-intestinal symptoms including cardiovascular, respiratory and skin complaints" **[**240**][**241**]**.

In case of a histamine storm creating the cascade of next reactions, it can lead to a multi-organ systemic process, and even to anaphylactic shock" **[**181**][**238**]**.

HIT can occur by increasing levels of histamine, which may also be associated with a reduction in the effectiveness or abundance of diamine oxidase (DAO), the major enzyme that breaks down ingested histamine, or a decrease in the effectiveness or abundance of histamine-N-methyltransferase, or HNMT, an enzyme that helps break down histamine in cells.

"The histamine related mechanisms are associated with drug intake include inhibition (lowering) of DAO activity and histamine activity (muscle relaxants, narcotics, analgesics, local anesthetics, hypnotics, antihypertensives, antiarrhythmics, diuretics, antibiotics, antiemetic, bronchodilator, antiseptic, mucolytic, H2 antagonists, or inactivation of vitamin B6, antihypertensive, antibiotic, hormonal contraceptives)" **[**171**]**.

The low DAO enzyme status causes also SIBO (the bacteria in SIBO can degrade the DAO enzyme, plus they can also produce histamine themselves, so it's a double whammy), gluten intolerance, genetic mutations, intestinal conditions or injuries that compromise the gut lining and affect digestion, inflammation from Crohn's, bowel disease, ulcerative colitis, liver conditions, DAO is blocking by drinks: alcohol, energy drinks, tea and medications **[**238**]**.

Histamine Intolerance is connected also with „Mast Cell Activation Syndrome (MCAS) occurs when the mast cells are over-reactive and over-release inflammatory chemicals into the body. The mast cells regulate the immune system and are involved in allergies and anaphylactoid reactions. Mast cells are important in wound healing, immunity, and blood-brain barrier function" **[**242**]**, their abnormal growth and accumulation of mast cells leads to mastocytosis **[**243**][**123**][**124**][**125**]**.

5.1. Enzymes: DAO and HNMT

"The two major enzymes in the human body that reduce histamine are HNMT and DAO. HNMT works with histamine in our central nervous system while DAO works to break down histamine in the foods we consume.

DAO diamine oxidase is an enzyme produced by the kidneys, thymus and intestinal mucosa **[**244**][**245**][**246**]**. Study shows that the oral DAO supplementation improves symptoms, including GI, cardiovascular, respiratory and skin complaints in patients suffering from HIT" **[**241**]**.

A common cause for a secondary lack of DAO are inflammatory or degenerative bowel diseases, because more than 90 % of DAO is produced in the intestinal epithelium but also alcohol, toxins and drugs.

„Common factors that interfere with DAO and HNMT levels include significant proportion of widely used prescription drugs, for example: non-steroidal anti inflammatory drugs (ibuprofen, aspirin) painkillers (diclofenac, naproxen), antibiotics, analgesics, antispasmodics, diuretics, malaria drugs, tuberculosis medications, antidepressants, immune modulators, histamine (H2) blockers", deficiencies of vitamin B-6, vitamin C, copper, or zinc (since copper constitutes DAO's central atom and is hence vital for its performance" **[**247**]**), extreme or chronic stress, stressful situations, low oxygen state, injury or trauma, a rapid change in temperature and its extremes" **[**235**][**248**]**.

N-methyltransferase (HNMT) which is involved in metabolism (50-80%) of the persistently present intra-cellular primarily endogenous histamine, mainly in kidneys and liver, but also in bronchi, large intestine, ovary, prostate, spinal cord, spleen, trachea [171] and peripheral tissues [249]. In the case of flawed HNMT activity, the organs which are most affected are brain, liver and mucous membrane of bronchus" [250].

„Consequently, a lack of HNMT leads rather to chronic forms of HIT, often affecting the nervous system. Main symptoms would be unrest, myoclonic twitches, insomnia, fatigue, vertigo, and states of anxiety. In the case of flawed HNMT activity, the organs which are most affected are brain, liver and mucous membrane of bronchus" [247][251][252][253].

5.2. Important role of genes: AOC1, HDC, NOS2, TPSAB1, KIT, antibodies from plazma cells

Taken together, these data suggest that inhibition or under expression of NOS2 and AOC1 determines the susceptibility to get sick, increasing the risk of infection" [254].

„In the process of infection, two other genes can play a fundamental role: NOS2, which expresses inducible nitric oxide synthase (iNOS), and AOC1, which encodes diamine oxidase (DAO)" [255].

"Both also highlight in the small intestine and are involved in polyamine metabolism. These biogenic amines are important for viral replication, being enhanced when NOS2 and AOC1 genes are down-regulated. In addition, NOS2 shows a negative correlation with ACE2 (connected with bradykinine) and TMPRSS2, while non-degraded histamine by DAO can lead to an up-regulation of both genes on which the virus depends" [254].

5.2.1. AOC1 and HDC Gene

„Catalyzes the degradation of compounds such as putrescine, histamine, spermine, and spermidine, substances involved in allergic and immune responses, cell proliferation, tissue differentiation, tumor formation, and possibly apoptosis. Placental DAO is thought to play a role in the regulation of the female reproductive function" [256].

„Histidine decarboxylase is the only element in the histamine synthesis pathway that produces histamine in a onestep reaction. Histamine cannot be generated by any other known enzyme. HDC is therefore the major source of histamine in most mammals and eukaryotes. In humans, histidine decarboxylase is encoded by the HDC gen" [257].

5.2.2. NOS2 Gene

„This gene encodes a nitric oxide synthase which is expressed in liver and is inducible by a combination of lipopolysaccharide and certain cytokines" **[**258**]**.

„NO (nitric oxide) is also an effector molecule produced by mast cells that could be involved in the pathophysiology of enterocolitis, is able to potentiate mast cell cytotoxicity mediated by TNF-α " **[**259**]**.

"NO is an important cellular signaling molecule. It helps to modulate vascular tone, insulin secretion, airway tension and peristalsis, participates in the regulation of heart function and is involved in angiogenesis (growth of new blood vessels from existing once) and nervous development. May act as a reverse neurotransmitter. Nitric oxide is mediated in mammals by the calcium and calmodulin-controlled isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS). The inducible isoform, iNOS, involved in the immune response, binds calmodulin at physiologically relevant concentrations and produces NO as an immune defense mechanism because NO is an electron unpaired free radical. It is the direct cause of septic shock and may act in autoimmune diseases. NOS signaling is involved in the development and fertilization of vertebrates" **[**260**]**.

"NO is released as a result of the attachment of certain endogenous substances to their respective receptors, including histamine which acts through the H1 receptor. Nitric oxide produced by pulmonary leukocytes in bronchial asthma is a multidirectional molecule that participates in both physiological and pathological processes. Depending on the concentration, nitric oxide may be involved in neurotransmission, regulation of pressure and vascular permeability, as well as the body's immune response.

It is produced by many cells through the oxidation of L-arginine catalyzed by nitric oxide synthase (NOS)" **[**109**]**.

„NOS-2, also called inducible synthase nitric oxide (inducible nitric oxide synthase, iNOS) occurs in macrophages, smooth muscles, and fibroblasts and endothelial cells. He is responsible for the production of not nitric oxide involved in the immune response and taking part in intracellular destruction detoxification of microorganisms by macrophages. NOS-2 is induced either by cytokines produced during inflammatory reactions or immune and bacterial toxins. Occurs mainly in macrophages, but may be induced in vascular membranes, primarily in the case of septic shock in the course of which he is responsible for pressure drop due to excessive expansion of the act" **[**261**]**.

„Nitrous oxide inactivates the cobalamin form of vitamin B12, long-term use of large amounts of it can lead to symptoms of vitamin B12 deficiency (anemia and neuropathy), also can damage the bone marrow, and could have a negative effect on the ovaries and testicles" **[**262**][**263**][**264**]**.

5.2.3. TPSAB1 Gene

„Tryptases comprise a family of trypsin-like serine proteases, the peptidase family S1. Tryptases are enzymatically active only as heparin-stabilized tetramers, and they are resistant to all known endogenous proteinase inhibitors. Beta tryptases appear to be the main isoenzymes expressed in mast cells; whereas in basophils, alpha tryptases predominate.

Tryptases have been implicated as mediators in the pathogenesis of asthma and other allergic and inflammatory disorders" **[**265**]**.

"The rapid degradation of histamine, which is a well-known mediator causing allergy symptoms, makes it an impractical marker of mast cell activation, while tryptase remains stable and measurable for several hours. This persistence of tryptase makes it a useful tool for confirming the influence of mast cells on severe reactions such as anaphylaxis, indicates the possibility of mast cell disorders and is considered by the WHO to be the lesser diagnostic criterion for systemic mastocytosis. Tryptase is a marker of future severe allergic reactions, an increased baseline level of tryptase indicates the risk of anaphylactic reactions, also after administration of the vaccine during specific immunotherapy (desensitization)" **[**266**]**.

„Human genes that encode proteins with enzyme tryptase activity include: TPSAB1 =Typase alpha-1, TPSAB1 =Tryptase beta-1, TPSB2 = Tryptase beta-2, TPSD1 = Tryptase delta, TPSG1 = Tryptase gamma, PRSS22 = Tryptase epsilon" **[**267**][**268**][**269**][**270**]**.

„Tryptase in diagnostics it is marker and shows systemic mastocytosis, also it can show mutations of the KIT D816V gene with PCR tests" **[**184**][**271**][**272**][**273**]**. „Tobío et al. report that the mutant KIT D816V **[**274**]** receptor triggers the expression and release of IL-6 in cancerous mast cells. In many cases, KIT and / or IgE receptor activation may play a role in cytokine secretion **[**184**]**.

5.3. Plazma cells and antibodies

„The lifespan, class of antibodies produced, and the location that the plasma cell moves to also depends on signals, such as cytokines, received from the T cell during differentiation.

Differentiation through a T cell-independent antigen stimulation (stimulation of a B cell that does not require the involvement of a T cell) can happen anywhere in the body and results in short-lived cells that secrete IgM antibodies.

The T cell-dependent processes are subdivided into primary and secondary responses: a primary response (meaning that the T cell is present at the time of initial contact by the B cell with the antigen)

produces short-lived cells that remain in the extramedullary regions of lymph nodes; a secondary response produces longer-lived cells that produce IgG and IgA, and frequently travel to the bone marrow.

Plasma cells can only produce a single kind of antibody in a single class of immunoglobulin. In other words, every B cell is specific to a single antigen, but each cell can produce several thousand matching antibodies per second.

The current state of knowledge suggest that after the process of affinity maturation in germinal centers, plasma cells develop into one of two types of cells: short-lived plasma cells (SLPC) or long-lived plasma cells (LLPC). LLPC resides in the bone marrow for a long period of time and secrete antibodies, thus providing long-term protection. LLPC can maintain antibody production for decades or even for a lifetime of an individual.

LLPC can also be found, in lesser degree, in gut-associated lymphoid tissue (GALT), where they are producing IgA antibodies and providing mucosal immunity. There have been several molecules identified that support the survival of LLPC, such as IL-5, IL-6, TNF-α, stromal cell-derived factor-1α, and signaling via CD44.

LLPC secret high levels of IgG independently of B cells. LLPC in bone marrow are the main source of circulating IgG in humans.**[**20**]** Even though traditionally IgA production is associated with mucosal sites, some plasma cells in bone marrow also produces IgA. We can also find LLPC in bone marrow producing IgM" **[**275**][**276**][**277**][**278**]**.

6. SEPSIS, SIRS, could be a storm of histamine?

"SEPSIS and its treatment have confounded investigators for nearly 3,000 years, so far it has not been possible to establish its cause" **[**279**]**. The term SEPSIS comes from the word "rotten blood" **[**280**]**. Avicenna in the 11th century used the term "rotting of blood" for severe diseases associated with the purulent process **[**281**][**282**].**

Since 1991, the consensus definition of sepsis has been the 'systemic inflammatory response (SIRS) to a microbial infection" **[**279**]**.

"SIRS is a serious condition related to systemic inflammation, organ dysfunction, and organ failure. It is a subset of cytokine storm, in which there is abnormal regulation of various cytokines. SIRS is also closely related to sepsis, in which patients satisfy criteria for SIRS and have a suspected or proven infection" **[**283**][**284**][**10**][**285**][**286**][**287**]**.

„When two or more of these criteria are met with or without evidence of infection, patients may be diagnosed with SIRS:

- Tachypnoea (rapid breathing), spontaneous respiration rate greater than 20 per minute;

- Tachycardia (rapid heartbeat) heart rate over 90 beats per minute

- Body temperature below 36 °C or above 38 °C

- Blood leukocyte changes leukocytosis, leukopaenia or neutrophilia.

- Confusion,

- Edema

- Decreased urination,

- Metabolic acidosis (which may be accompanied by a faster breathing rate that leads to respiratory alkalosis),

- Low blood pressure due to decreased systemic vascular resistance, higher cardiac output,

- Disorders in blood-clotting that may lead to organ failure.

- PaCO2 below 4.3 kPa (32 mm Hg) in arterial blood gas testing

- Blood leukocyte count of less than 4,000 cells per mm^3 or greater than 12,000 cells per mm^3, or the presence of more than 10% of immature neutrophils.

Additionally, symptoms of a specific infection, such as meningitis, may be present: fever, vomiting, headache, stiff neck, photophobia, somnolence, arthralgia, seizures **[**286**][**288**]**.

In the absence or inadequate treatment, symptoms of failure of specific organs and systems appear with SEPSIS:

- Central nervous system - symptoms of encephalopathy, impaired consciousness,

- Vegetative symptoms;

- Respiratory system - acute respiratory distress syndrome (ARDS),

- Oxygenation index (PaO2 / FiO2) <250 mmHg (in the presence of other diseases of the respiratory system, the index is <200 mmHg);

- Circulatory system - initially features of hyperkinetic circulation, then acute circulatory failure, arterial hypotension (systolic blood pressure <90 mmHg or mean pressure <70 mmHg) persisting> 1 h with adequate hydration, or the need to administer vasopressors to maintain normal blood pressure is the so-called septic shock;

- Urinary system - acute renal failure, decrease in diuresis <0.5 ml/kg/h for two hours with normal hydration, serum creatinine above twice the upper limit of normal;

- Liver - acute liver failure, bilirubin> 3 upper limit of normal, jaundice, INR> 3.0;

- Digestive system - enteritis, acute pancreatitis, intestinal obstruction, peritonitis;

- Haematological disorders - disseminated intravascular coagulation (DIC) syndrome, thrombocyte count <100,000/µl, or drop below 50% of the three-day test value or 30% of the 24-hour value, lymphoma like changes, anemia; metabolic disorders - non-respiratory acidosis, lactates> 1.5 upper limit of normal, arterial blood pH <7.3, excess base (BE) <-5 mmol/l" **[**279**]**.

Note: Fever and an increased white blood cell count are features of the acute phase reaction, while an increased heart rate is often the initial sign of hemodynamic compromise.

An increased rate of breathing may be related to the increased metabolic stress due to infection and inflammation, but may also be an ominous sign of inadequate perfusion resulting in the onset of anaerobic cellular metabolism" **[**289**]**.

"In the development of these disorders, there is a vicious circle mechanism, consisting in the intensification of disturbances in the work of one system by the dysfunction of the other, which is itself adversely affected by the first (positive feedback).

In fact, it is a multi-system mechanism and the changes taking place are linked by a complex network of connections. The result is usually multiple organ failure syndrome and SEPSIS, often with fatal consequences. „Septic shock remains defined as a subset of sepsis in which the risk of mortality is substantially increased, and is characterized by hypotension that persists during volume resuscitation and requires the use of vasopressors, with in hospital mortality rates approaching 30–50%" **[**279**]**.

„Treatment of SEPSIS is a major clinical problem. It should be conducted in intensive care units where the patient can be adequately cared for. It is long lasting and requires large financial outlays. In the European Union, the annual cost of treatment is USD 6.7 billion, and in the United States - USD 17 billion **[**290**][**291**]** and is associated with high mortality **[**292**]**, which is approximately 16%, in severe SEPSIS 36%, and in septic shock - 58% **[**293**]**. The average duration of treatment is about 19 days **[**294**]**. In Western Europe and the United States, mortality is estimated at approximately 30% **[**294**]**. The highest incidence of SEPSIS is within the hospital, mainly in intensive care units" **[**295**]**.

„Currently, it is believed that the presence of bacteria in the blood is not necessary for the diagnosis of SEPSIS. Positive cultures are found only in 20–40% of acute SEPSIS, (40–70% in septic shock)" **[**296**]**.

„A systemic inflammatory reaction is triggered by the local spread of pathogenic antigens or toxins. Risk factors for SEPSIS include: intravenous punctures intravesical catheter drains, implanted dentures and

devices, mechanical ventilation of the lungs, parenteral nutrition, transfusion of blood and fluids the presence of bedsores and wounds" [295]. There is no specific laboratory marker for SEPSIS.

6.1. SEPSIS, COVID-19, HIT leads to multiple organ failure.

Hematological disturbances occurring during sepsis mainly include the syndrome of disseminated intravascular coagulation (DIC) [297][298]. It is manifested by an increase in clotting times, a decrease in the level of fibrinogen and platelets.

It is caused by the stimulation of the extrinsic coagulation system by cytokines and a malfunction of the anticoagulant mechanisms (antithrombin III, thrombomodulin). This leads to the formation of numerous small clots in the vessels, which further disturbs the transport and use of oxygen by the tissues. (SUCH AS IN COVID-19 AND HIT).

In the lungs, endothelial function is impaired as a result of infiltration by neutrophils, resulting in extravasation of the fluid into the interstitial tissue and into the alveoli. This leads to the development of acute respiratory distress syndrome (ARDS). (SUCH AS IN COVID-19 AND HIT).

The negative impact of the generalized infection on the liver results in hyperbilirubinemia and an increase in the level of transaminases.

Hypoxia of this organ resulting from sepsis leads to increased blood flow through the portal system. Symptoms of liver failure become apparent when hepatic blood flow is insufficient. (SUCH AS IN COVID-19 AND HIT).

In the kidneys, acute renal failure develops as a result of vascular dilatation and insufficient organ perfusion, as well as due to the action of various factors such as endothelin, thromboxane A2, neutrophils and coagulation factors. (SUCH AS IN COVID-19 AND HIT).

At the same time, as a result of the decrease in the level of glutamine within the gastrointestinal wall, its function and the possibility of the development of multi-organ failure are disturbed." (SUCH AS IN COVID-19 AND HIT) [295][279].

„Disseminated intravascular coagulation - DIC occurs at higher rates in people with bacterial SEPSIS (83%), severe trauma (31%)," [299][300] also occur s in COVID -19 [301].

The use of steroids in sepsis is controversial as we can read in "Systemic steroids in severe sepsis and septic shock" [302]. Studies do not give a clear picture as to whether and when glucocorticoids should be used and „steroids should no longer be recommended for patients with SEPSIS" [303]. The 2016 Surviving Sepsis Campaign recommends low dose hydrocortisone only if both intravenous fluids and vasopressors are not able to adequately treat septic shock [304][305][306][307].

Until now anaphylaxis was usually understand as allergic reactions to food, insect venom, medications, or latex, and septic shock was shown as another form of distributive shock also known as blood poisoning , but knowing that there is connection of sepsis and histamine [308], and mast call activation syndrome presenting as anaphylaxis [309], the author hypothesizes that sepsis could start with the storm of histamine leads to storm of cytokines, in this case the antihistamines could help in treatment, as outlined further.

"SEPSIS also involves effects on endothelial tissues and microcirculation, primary and secondary immune tissues, coagulation, parenchymal tissues and neurological disturbances that directly affect microglial cells and neurons" [279], the same like in intolerance of histamine.

Analyzing above symptoms the author is speculating and putting a hypothetic question: if EBOLA could be a bradykinin and cytokine storm? As in Disease Course of Zaire ebola virus Infection „levels of bradykinin gradually increased to concentrations approximately 7 fold higher than those in controls late in disease [310].

7. COVID-19 Symptoms and Complications

COVID-19 affects different people in different ways. Most infected people with positive PCR test for SARS-CoV-2 could be asymptomatic, the other will develop mild to moderate illness and recover without hospitalization, but there are millions of severe COVID-19 very often lead to death [311][312][313][314][315][316].

„Clinical description of COVID-19:

According to the CDC, the majority of SARS-CoV-2 infections are asymptomatic or mild.

Those that proceed to more severe forms present with:

- Fever (higher the 38°C or lower then 36°C),

- A non-productive dry cough that may result in

- Hemoptysis and

- Shortness of breath.

Other common symptoms are:

- Myalgia,

- Fatigue,

- Sore throat,

- Nausea,

- Vomiting,

- Diarrhea,

- Conjunctivitis,

- Anorexia, and

- Headache" **[**317**]**.

- „Reports from blood studies include leukopenia, eosinopenia, neutrophilia, elevated liver enzymes, C-reactive protein, and ferritin.

- Furthermore, autopsies have reported extensive hyaline membrane formation in the lungs of COVID-19 patients. Specifically, histological analysis of the lungs of a deceased COVID-19 patient showed organizing hyaline membranes in the early stages of alveolar lesions and prominent hyaline membranes in the exudative phase of diffuse alveolar damage. In a seperate post mortem study of lung tissue from COVID-19 patients, microscopic examination found 'numerous hyaline membranes without evidence of interstitial organization'. Furthermore, in another autopsy study of a COVID-19 patient, histological analysis found extensive hyaline membranes, which the authors interpreted as indicative of ARDS.

- Finally, a meta-analysis showed that there was a statistically significant 4.6 fold difference in lung weight of COVID-19 patients versus controls, which they conclude is consistent with the HA-hydrogel formation known to occur in ARDS.

- Although much focus has been on the lung due to the need for ventilator support of end-stage disease, COVID-19 also affects the intestine, liver, kidney, heart, brain, and eyes.

- Nearly one-fifth of hospitalized patients experience tachycardia and cardiac injury, many of whom have had no history of cardiovascular problems prior to infection. Responses include acute myocardial injury, myocarditis, and arrhythmias that may be due to viral infection directly, which is consistent with high expression of the SARS-CoV-2 receptor ACE2 in cardiac tissue.

- An important extension of the RAS in controlling cardiac contraction and blood pressure is the potent inotrope apelin (APLN), which acts as an NO dependent vasodilator when its receptor (APLNR) heterodimerizes with BDKRB1 APLN (98 fold), APLNR (3190 fold) and BDKRB1 (2945 fold) are all up-regulated in COVID-19 BAL. As with BK and ANG derived peptides, APLN is inactivated by Neprilysin (MME), which is significantly down regulated in the BAL samples from COVID-19 individuals (−16 fold). Therefore, increased APLN signaling can be added to the imbalanced RAS increased blood coagulation.

- In addition to cardiac dysfunction, neurological involvement in COVID-19 was revealed after an MRI assessment of COVID-19-positive patients with encephalopathy symptoms in France identified

enhancement in leptomeningeal spaces and bilateral frontotemporal hypoperfusion which are consistent with increased vascular permeabilization in the brain.

- Furthermore, earlier reports from China indicate high frequencies of dizziness, headache, as well as taste and smell impairment.

- The most recent reports from the United States and China indicate that 30–50% of COVID-19 patients experience adverse gastrointestinal symptoms.

- Direct infection by the virus and damage to the kidney was also observed, specifically in the proximal tubules. These latter two findings are not surprising given the higher expression of ACE2 in these tissues compared to tissues overall, which would facilitate infection by the virus.

- Finally, COVID-19 patients also frequently display skin rashes including 'covid-toe' that appear to be related to dysfunction of the underlying vasculature.)" **[**318**]**.

„Other less common symptoms are:

- Irritability,

- Confusion,

- Reduced consciousness (sometimes with seizures),

- Anxiety,

- Depression,

- Sleep disorders,

- More severe and rare neurological complications such as strokes, brain inflammation, delirium and nerve damage" **[**12**][**312**][**313**][**314**][**315**]**.

„Many patients who either recovered from or had mild symptoms after COVID-19 exhibit diffuse, multi-organ symptoms months after the infection prompting the Centers for Disease Control and Prevention to name it adult multisystem inflammatory syndrome. These symptoms include malaise, myalgias, chest tightness, brain fog, and other neuropsychiatric symptoms that are quite similar to those presented by patients diagnosed as having mast cell activation syndrome (MCAS)" **[**319**][**320**]**.

7.1. Multisystem inflammatory syndrome in children and COVID-19

„Multisystem inflammatory syndrome in children (MISC) can rapidly lead to medical emergencies such as insufficient blood flow around the body (a condition known as shock) **[**321**]**. Failure of one or more

organs can occur as a result [322][234]. „All affected children have persistent fever. Other clinical features vary. The first symptoms often include:

- Acute abdominal pain with diarrhea or vomiting,

- Muscle pain and general tiredness are frequent,

- Low blood pressure is also common,

- Pink eye, rashes, enlarged lymph nodes, swollen hands and feet, "strawberry tongue",

- Various mental disturbances are possible,

- Cytokine storm may take place, in which the child's innate immune system stages an excessive and uncontrolled inflammatory response,

- Heart failure is common,

- Clinical complications can include damage to the heart muscle,

- Respiratory distress,

- Acute kidney injury,

- Increased blood coagulation,

- Coronary artery abnormalities can develop (ranging from dilatation to aneurysms)" [323][324].

COVID-19 is very similar to to multi systemic inflammatory response syndrome (SIRS, MIS-C), Kawasaki disease, SEPSIS and to INTOLERANCE OF HISTAMINE, what is leading to the hypothesis that probably the symptoms of above diseases could be cause by the storm of histamine.

7.2. Phases of inflammatory development

7.2.1. Definition

The inflammatory process can be called a complex, dynamic and orderly sequence of sequences occurring in the tissues (activating mast cells to release histamine and other substances) in response to the damaging factor. The damaging factors can be divided into: 1. Physical (mechanical, temperature, ionizing radiation, magnetic field, ultrasonic waves). 2. Chemical (turpentine, acids, bases). 3.Biological (bacteria, viruses, fungi, protozoa, exotoxins, endotoxins). Inflammation is aimed at limiting the action, destroying and removing the causal stimulus, and repairing the resulting damage. This process can be divided into chronic or acute depending on the strength and duration of the stimulus action on the

tissue. A moderate inflammatory reaction is beneficial for the organism, as it leads to the removal of necrotic products, the excretion of exotoxins and endotoxins along with the exudate, and the formation of a line separating the inflammatory focus due to the superiority of repair processes over destruction processes" **[**86**]**.

7.2.2. Acute phase reaction

„The acute phase reaction of inflammation is called sudden and immediate changes in damaged tissues and systemic symptoms of the inflammatory process: increased body temperature, pain, water and electrolyte disturbances, acute phase protein secretion (CRP), neutrophilia. The main mediators of inflammation are low molecular weight proteins called cytokines. Within the tissues, it manifests itself in changes in the microcirculation the lumen of the blood vessels widens and blood flows to the inflamed area. Venous vasoconstriction slows blood flow, which increases hydro static pressure and results in the formation of small wall clots and platelet aggregation in the damaged endothelium. As a result of the increase in vascular permeability, the exudative fluid penetrates into the tissues causing swelling, which forms the so-called absorbent blockage.

The cells of the immune system are responsible for the phagocytosis of microorganisms, antigen-antibody complexes and intracellular digestion. Thanks to proteolytic enzymes, they cause dissolution of thrombotic necrosis and histolytic necrosis - separation of dead tissue. The consequence of the intensification of inflammatory processes is the activation of fibrinolysis and coagulation processes. Fibrinogen penetrates into the extravascular space and forms the so-called fibrin blockade. The task of both blocks fibrin and lymphatic is to limit the inflammatory process. Completion of repair processes is associated with the removal of dead tissues and revascularization of damaged tissues. During this phase of inflammation, it is reduced, the damaging factor is removed and the organism's homeostasis is restored" **[**86**]**.

7.2.3. Chronic inflammation

„Chronic inflammation, on the other hand, is often the decline in the acute phase, where the process does not proceed so rapidly, but the tissues are not healed due to the continuous unremoved action of the damaging stimulus of less intensity than in the acute phase or the insufficient regenerative capacity of the organism. Primarily chronic inflammations also occur, when the damaging stimulus acts with little force over a long period of time. The acute phase of inflammation is characterized by strong symptoms such as malaise, a feeling of breakdown. They are usually accompanied by low grade fever or pain, and physical examination often shows swelling, redness, tissue warmth and dysfunction. On the other hand, the chronic phase is characterized by less severe symptoms or their complete absence, while

the symptoms are often nonspecific and generally unpleasant for the patient, therefore chronic inflammations in dentistry are most often detected accidentally on radiographs (which is often the case in the case of granulomas and cysts) or when the process causes significant tissue destruction, noticeable to the patient, or is exacerbated" **[**86**]**.

Inflammatory response causing „degeneration numbers of white blood cells (dead leukocytes from the body's immune response (mostly neutrophils which were used in the fight), dead or living bacteria (or other microorganisms), and tissue debris" **[**325**]**, leads to formatting platelet-leukocyte aggregates, which is increased in several inflammatory and thrombotic conditions **[**326**]**. „Mast cell-derived histamine appears to mediate at least part of the leukocyte endothelial cell adhesion and platelet-leukocyte aggregation by engaging H1-receptors on endothelial cells and platelets to increase the expression" **[**327**]**.

„The defenses in sepsis are dependent on mast cells that produce tumor necrosis factor alpha (TNF-α), which in turn attracts and activates neutrophils to the site of infection" **[**328**]**.

SEPSIS results from the host hyper inflammatory response to infection „is often associated with homeostatic changes ranging from subclinical activation of blood coagulation (hypercoagulability), which may contribute to localized venous thromboembolism, to acute disseminated intravascular coagulation (DIC), characterized by widespread microvascular thrombosis and subsequent consumption of platelets and coagulation proteins, eventually causing bleeding manifestations.

The ensuing microvascular thrombosis and ischemia are thought to contribute to tissue injury and multiple organ dysfunction syndrome" **[**329**]** „causing multiple organ failure and high mortality" **[**330**]**.

"SEPSIS caused by gram negative bacteria and that caused by gram positive bacteria often manifest similar clinical features" **[**330**][**331**][**332**]**.

7.3. Typical syndromes for nonspecific factors

„Experiments on rats show that if the organism is severely damaged by acute nonspecific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.

This syndrome develops in three stages: during the first stage, 6–48 hours after the initial injury, one observes rapid decrease in size of the thymus, spleen, lymph glands, and liver; disappearance of fat tissue; edema formation, especially in the thymus and loose retroperitoneal connective tissue; accumulation of pleural and peritoneal transudate; loss of muscular tone; fall of body temperature;

formation of acute erosions in the digestive tract, particularly in the stomach, small intestine, and appendix; loss of cortical lipoids and chromaffin substance from the adrenals; and sometimes hyperemia of the skin, exophthalmos, increased lachrymation and salivation. In particularly severe cases, focal necrosis of the liver and dense clouding of the crystalline lens are observed.

In the second stage, beginning 48 hours after the injury, the adrenals are greatly enlarged but regain their lipoid granules, while the medullary chromaffin cells show vacuolization; the edema begins to disappear; numerous basophiles appear in the pituitary; the thyroid shows a tendency towards hyperplasia (more marked in the guinea pig); general body growth ceases and the gonads become atrophic; in lactating animals, milk secretion stops. It would seem that the anterior pituitary ceases production of growth and gonadotropic hormones and prolactin in favor of increased elaboration of thyrotropic and adrenotropic principles, which may be regarded as more urgently needed in such emergencies.

If the treatment be continued with relatively small doses of the drug or relatively slight injuries, the animals will build up such resistance that in the later part of the second stage the appearance and function of their organs returns practically to normal; but with further continued treatment, after a period of one to three months (depending on the severity of the damaging agent), the animals lose their resistance and succumb with symptoms similar to those seen in the first stage, this phase of exhaustion being regarded as the third stage of the syndrome.

We consider the first stage to be the expression of a general alarm of the organism when suddenly confronted with a critical situation, and therefore term it the “general alarm reaction.” Since the syndrome as a whole seems to represent a generalized effort of the organism to adapt itself to new conditions, it might be termed the “general adaptation syndrome.” It might be compared to other general defense reactions such as inflammation or the formation of immune bodies. The symptoms of the alarm reaction are very similar to those of histamine toxicosis or of surgical or anaphylactic shock; it is therefore not unlikely that an essential part in the initiation of the syndrome is the liberation of large quantities of histamine or some similar substance, which may be released from the tissues either mechanically in surgical injury, or by other means in other cases.

It seems to us that more or less pronounced forms of this three stage reaction represent the usual response of the organism to stimuli such as temperature changes, drugs, muscular exercise, etc., to which habituation or inurement can occur” **[**333**]**.

8. Antihistamines

„A whole group of antihistamines have been produced. One of the mainstays in the treatment of allergy symptoms. Despite different chemical and commercial names, they work in a very similar way - preventing histamine from reaching its H receptor. Antihistamines are not the only drugs we use in allergies. We also have anti-leukotriene drugs that have nothing to do with histamine" [89][181]. „Histamine, Bradykinin, and Their Antagonists" [159].

Doctors observed a milder course of COVID-19 in patients with various manifestations of atopic disease, allergic rhinitis or bronchial asthma, who were treated with local anti-inflammatory drugs (glucocorticoids) for these diseases. Recent reports suggest that asthmatics / allergy sufferers who take antihistamines either have no or much milder COVID-19 symptoms [334][335][336].

Perhaps the initial dyspnea may begin with activation of mast cells, allergic alveolitis (AZPP) and the phenomenon (reaction) of Arthus [337] and if no antihistamine drug is administered it usually leads to severe dyspnea and connecting the patient to a ventilator thereby releasing "sequential doses of histamine". Meanwhile other reports indicate a lower-than-expected representation of patients with asthma and COVID-19 is consistent with this idea [338][339][340].

Analysis of medical records of over 200,000 release made it clear that popularly used antihistamines not only heal but also prevent from spreading the corona-virus. This is to be confirmed by randomized human clinical trials. According to epidemiological data, taking these drugs with ingredient diphenhydramine was associated with a lower likelihood of contracting the coronavirus. "We found that these particular drugs showed direct antiviral activity against SARS-CoV-2 during a laboratory experiment," said Dr. David A. Ostrov, immunologist, associate professor at UF College of Medicine's, one of the authors of the discovery. For now, the mechanism by which certain antihistamines exert their antiviral activity is unclear. "Just because antihistamines do inhibit the coronavirus in laboratory tests, doesn't mean they will actively inhibit it in humans, but they can," added Dr. Ostrov" [179]. „We found that usage of select antihistamines, including diphenhydramine, hydroxyzine and azelastine was associated with reduced incidence of SARS-CoV-2 positivity in a large population, antiviral activity by clemastine, cloperastine, and astemizole in vitro implicate specific antihistamines as repurposing candidates for prevention and treatment of SARS-CoV-2 infection. These three drugs exhibited direct antiviral activity in vitro. (.....) Although mechanisms by which specific antihistamines exert antiviral effects is not clear" on the date: 29 January 2021 [341].

„Approved drugs, such as clemastine and cloperastine, were also shown to inhibit SARS-CoV-2 in Vero cells potently" [342]. "H1 receptor blockade could suppress the release of interferon gamma and may be effective in suppressing inflammation caused by the SARS-CoV-2 infection" [343].

Also another studies shown that histamine receptor antagonists reduce long COVID-19 symptoms **[**344**][**345**]** and inhibit the overproduction of cytokines in cells of the gastrointestinal tract infected with SARS-CoV-2 **[**346**]**.

Author of this paper went on to uncover of the mechanisms connected with activation of mast cells and releasing histamine could give the answer why the antihistamines are working. Growing evidence also shows that various RNA viral infections could be inhibited by H1 receptor antagonists **[**347**][**348**][**349**][**350**]**. „Emerging evidence has reported that H1 receptor antagonists show significant promise as anti-SARS-CoV-2 medications" **[**351**]**.

Also important is to know that antihistamine may play a key role in inhibiting the activation of coagulation cascade in CU" **[**352**][**353**]**.

Pharmacologist A.Kotarski adds informations about the possible available in pharmacy antagonist for histamine receptors:

"Despite the discovery of four histamine H1-H4 receptors, which are responsible for the effects of histamine, drugs that act on the H1 and H2 receptors are currently used to treat symptoms caused by histamine release.

H2 receptor antagonists:

The H2 receptor is responsible for the production of gastric juice dependent on the histamine mechanism. The active substance currently used is famotidine, which is an antagonist of this receptor. Other substances such as cimetidine and ranitidine are not used. The H2 receptor antagonists are displaced by proton pump inhibitors which are more effective in inhibiting hydrochloric acid secretion.

H1 receptor antagonists:

The H1 receptor stimulation leads to contraction of smooth muscles, vasodilation and subsequent decrease in pressure, increased mucus secretion on the mucous membranes and an increase in the tone of the parasympathetic system. Histamine is a mediator of the allergic inflammation reaction. It is responsible for the formation of allergic hay fever, conjunctivitis and urticaria, both of an allergic and non allergic basis, when the causative factor of skin symptoms are products with histamine or with the ability to release it.

The H1 receptor antagonists act by reversibly and competitively binding to the H1 receptor, thereby canceling out and reversing the effects of histamine. However, medicines containing these active substances do not inhibit the symptoms of an allergic reaction caused by other mediators. The H1 receptor antagonists are divided into three generations in **(Table.1)**.:

Generation	Active substances	Application
I	Hydroxyzyna, clemastine, ketotifen, promethazine, dimenhydrinate	Rapid allergic reactions parenteral. Skin diseases aggravated by stress, as well as those with severe itching. Central nervous system depressant effect in these ailments. Certain centrally acting and cholinolytic antihistamines used to inhibit symptoms associated with labyrinth damage.
II	Cetirizine, loratadine, azelastine, astemizole, rupatadine, fexofenadine, desloratadine, levocetirizine, bilastine.	As above, without CNS depressant and cholinolytic activity. They are not administered parenterally.
III	No substances meet the criteria, although sometimes the newest of the second generation are placed in this category.	No uses due to lack of active substances in this category.

Table.1. The active substance of antihistamines."

Dr M.Mastej recommendations: „Sometimes the allergic reaction is very severe and we have to reach for the strongest drugs that suppress the immune system, i.e. steroids, although they also do not work causally. Unfortunately, in the case of histamine intolerance, neither anti-leukotriene drugs nor steroids have any use, because they do not work through histamine".

Histamine is one of the first triggers of the cytokine storm. Its release from mastocytes or other immunocompetent cells e.g. during viral infection further stimulates different types of white blood cells (leukocytes) and macrophages, dendritic cells etc. located in tissues all over the body, including pulmonary area (bronchi, alveoli), lymphatic nodes in mediastinum, pleura, intestines, brain, skin, vessel walls etc.

Therefore, following the author Magdalena Filcek hypothesis, it seems very rationale to STOP (block) histamine receptors in the entire organism, just to diminish cytokine storm from the beginning. As we know SARS-CoV2 infection in some patients causes mild symptoms (probably a mild cytokine release) or severe and life threatening symptoms where the cytokine storm likely is greatly exaggerated and it's not the virus itself that kills but our immune over reaction destroys lungs in consequence. „Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19" **[**354**]**.

I recommend not only H1 (histamine type 1) receptors to be blocked but also H2, H3 and H4. Of course it is well known that H1 receptors are involved in allergy and inflammation, which "naturally leads doctors' thinking" to block H1 receptors in COVID-19, but there are many reasonable arguments to also use H2 blockers, and / or non-selective all H receptors blockers. That would mean additional or even mandatory intravenous administration in patients under ventilation (life supporting machines) and remaining in a pharmacologically induced coma."

It is reasonable to measure the level of DAO in blood and if is lower add the supplementation of DAO enzyme.

8.1. Dosage of Antihistamines, DAO and other

Dr Mirosław Mastej recommendations:

- „H1 selective blockers of choice could be: levocetirizine 5 to even 20 mg (at starting dose), per os, and desloratadine 5 to 20 mg (at starting dose).

- H2 selective blockers can be : famotidine 40 mg MINIMUM, but 80 or 120 mg as starting dose may be required. Please pay attention that famotidine in doses above 80 mg is losing its H2 selectivity and blocks H1 receptors as well! That makes this drug a first line treatment in the beginning of symptoms not to allow the cytokine storm from developing.

- Also CLEMASTINE , the only I.V. (or I.M.) non selective histamine blocker is worth of consideration when the patient can not swallow tablets. 2 to 8 mg daily in I.V, infusion should block both H1, H2 as well as H3 and H4. Pay attention that H3 and 4 are mainly located in the brain and are involved in sleep regulation. Probably the blockade of H3 and H4 receptors will be beneficial in COVID-19 patients due to some SEDATIVE effects of CLEMASTINE.

/Hydroxyzine I.M. is some alternative to Clemastine when parenteral H-blockers administration is not possible, but hydroxyzine is not allowed intravenously!/.

In summary, my recommendation as a medical doctor working and studying "histamine" for more than 30 years (not only in immunology or infectious diseases) would be:

1/ Give orally levocetirizine (5 mg) OR desloratadine (5 mg) PLUS 80 mg of famotidine (in little children half the dose, i.e. 40 mg) to all PCR positive COVID-19 patients as soon as possible.

2/ Include intravenous infusion of CLEMASTINE in all patients who can not take oral Histamine receptor blockers. Continue infusion until resolution.

Dr Mastej additional comment is as follows:

The main first line tool in our bodies to destroy virions (any kind) is nitric oxide free radicals, produced in neutrophiles. (see details in term: oxidative burst in neutrophiles). The NO production is possible only when L-arginine amino acid is available for those white cells. And of course the bone marrow must be able to produce neutrophiles themselves.

To fulfill both conditions the organism of COVID-19 patients must be nourished with:

1/ Iron and vitamin C (both mandatory for bone marrow neutrophiles proliferation)

2/ Larginine, which is essential source of NO (and oxidative burst) in neutrophiles."

„In humans, Amantadine is involved in the antihistamine effect of loratadine H1-antihistamine action" **[**371**].**

8.2. DAO and vitamines:

Diamine oxidase supplementation improves symptoms in patients with histamine intolerance **[**241**]**, therefore, the oral supplementation of commercially available DAO food supplements, has been suggested as a treatment of histamine intolerance **[**355**]**. „Study shows that the oral DAO supplementation improves symptoms, including gastro intestinal, cardiovascular, respiratory and skin complaints in patients suffering from HIT" **[**241**]**, which are taken several hours before the planned consumption of foods suspected of high histamine content.

"Vitamin C and B6, D3 are also helpful increasing the activity of the naturally produced enzyme DAO in the intestines" **[**181**]**. Vitamin D3 contributes to mast cell stabilization and its regulatory axis **[**368**]**.

Additionally, important is to keep the vitamin B12 on good level as nitrous oxide depletes vitamin B12 levels, what can cause serious neurotoxicity if the user has preexisting vitamin B12 deficiency **[**356**][**357**][**358**]**.

"Clostridium difficile toxin A (Tx-A) mediates secretion and inflammation in experimental enterocolitis. Significant increases in leukocyte adherenceand emigration (LAE) and albumin leakage were noted within 15-30 min of Tx-A exposure. These responses were accompanied by mast cell degranulation and the formation of platelet leukocyte aggregates. The mast cell stabilizer, lodoxamide, an H1- (but not an H2-) receptor antagonist, and diamine oxidase (histaminase) were also effective in reducing the LAE and albuminleakage elicited by Tx-A **[**327**][**328**][**359**][**360**]**.

"There are also several substances used as drugs that inhibit their degranulation by stabilizing the cell membrane of mast cells. These include disodium cromoglycate or nedocromil. Therefore, such

preparations inhibit the biological activity of histamine in a nonspecific manner and independent of its direct effect on individual receptors" **[**361**]**.

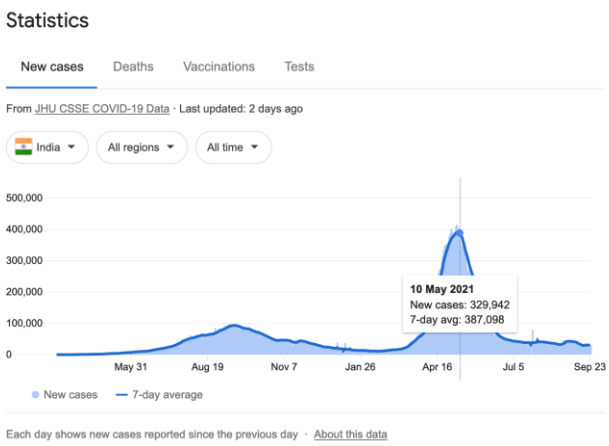
9. Cases of using antihistamines on patients with COVID-19 and patients after COVID-19 on ICU: Materials and methods

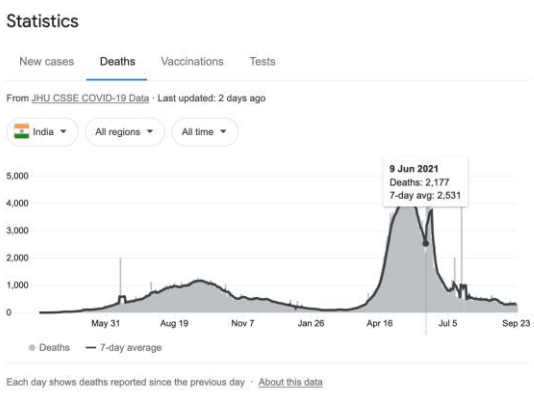
9.1. Dr Mayank Vats Interventional Pulmonologist, Adult Pulmonologist, Intensivist and Sleep Physician in Rashid Hospital in Dubai

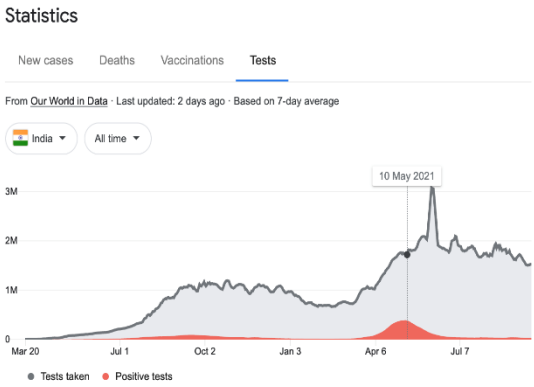
As per personal communication/ telephonic discussion, antihistamines primarily levocetirizine and cetirizine has been used quite often in the management of COVID-19 patients especially in moderate to sick hospitalized patients requiring high flow oxygen and or mechanical ventilation and it helped significantly for the suppression of cough, symptoms of dyspnea and breathlessness and throat symptoms with significant symptomatic relief to the patients and hence justifying the role of histamine in the pathophysiology of COVID-19 and which responded well to antihistaminic medicines.

Although there are no double blinded randomized controlled trial of the effects of antihistaminic in COVID-19 patient but our vast clinical experience on the large numbers of COVID-19 patients in suggest that definitely histamine mechanism plays a significant role in the COVID-19 related complex pathophysiology and we recommend to conduct double blinded multi center trials to establish the role of antihistamines in the management of COVID-19 patients to offer a safe and cost effective solution to break the chain of COVID-19 pathophysiology and help patients.

The Government of India, following the informations from the authors of this article, during the top level of pandemia, **on the 4th of May 2021** included the antihistamines (Levocitrizine 5 mg) to official protocol for COVID-19 treatment, helping to reduce the numbers of cases.







(Table.2.) The charts from Google Statistics regarding the COVID-19 new cases and deaths in India, after the introduction of the Levocetirizine in the Indian national COVID-19 treatment protocol the numbers of cases reduced exponentially, although it can't be attributable only to Levocetirizine, as many other factors we also operating simultaneously but this show that Levocetirizine helped a lot.

9.2. Dr Anna Skrzyniarz-Plutecka Head of Anesthesiology and Intensive Care Department, Masovian Oncology Hospital in Wieliszew

The measure of the temperature of the air on **(Pic. 3.)**:

1. The temperature of air in the room is 23,6°C (for this temperature 100% humidity is 21,22 mg/L), which should be noted: would be markedly lower with air conditioning.

2. The temperature of oxygen going out from „the wall" is 23,6°C (for this temperature 100% humidity is 21,22 mg/L)

3. The temperature giving to patient from respirator with 60% of oxygen is 26,9°C (for this temperature 100% humidity is 25,54 mg/L)

4. The temperature of air which should be given to the lungs is 37°C (for this temperature 100% humidity is 44mg/L)

Pic. 3. One of example of temperature or air going from respirator to patients' lungs on ICU.

9.2.1. The ICU clinical case report of a patient with pulmonary edema as a result of histamine shock

Introduction

A 44-year-old patient without load was qualified for general anesthesia for ENT surgery septoconcho-plastics at the beginning of May 2021. She had a history of headaches and periodically migraine - relieved by painkillers, the state after appendectomy years ago. She denies allergies. In physical examination without deviations, weight - 56 kg, height 152 cm, BMI - 24 kg/m2, life parameters normal. In the laboratory tests performed before the operation without any deviations, the ECG was normal.

The course of anesthesia and surgery

At 5:30PM the patient is admitted to the operating theater in a general stable condition. In the hours 5:40–6:40PM the course of anesthesia and the operation were correct. After anesthesia, awake,

extubated, conscious with verbal-logical contact, life parameters normal (BP–140/90 mmHg, HR–89/min, 100%). After a few minutes, trismus, skin with a bluish-gray color, decrease in SpO2 to 30%, HR–50/min. 10 mg of Midanium I.V., 100 mg of Skoline I.V. were administered and the patient was re-intubated. A pink foamy discharge was aspirated from the endotracheal tube, indicating pulmonary edema. Subject symmetrical pupils, equal, with the correct reaction to light, auscultation revealed crackling over the entire pulmonary fields. At 6:50PM 100 mg of Hydrocortisone I.V., 100 mg of Furosemide I.V. was administered with no effect. The patient with respiratory insufficiency, mechanically ventilated, and with limited circulatory efficiency was transferred to the Intensive Care Unit.

Course and treatment in the ICU

On admission to the ICU, the patient was still respiratory insufficient, mechanically ventilated, sedation with I.V, Dexmedetomidine infusion and pain treatment with Paracetamol and Metamizol in I.V. fractionated doses. She was cardiovascularly unstable–norepinephrine infusion with a small flow of 0.08-0.32 mg/h I.V. was needed, which was disconnected after 3 hours. In the arterial blood gas analysis performed 40 minutes after the incident has occurred symptoms of acidosis (pH-7.26, BE-(-3.1) mmol/l) revealed, increased CO2 partial pressure of 55.9 mmHg and decreased O2 partial pressure of 50.5 mmHg and increased level of D dimers 1010 ng/ml with the norm to 500 ng/dl, APTT was shortened to 21.6s with the norm 25.4-36.9s. At 7:20PM due to the patient's serious condition and suspected histamine shock, 6 mg of Clemastinum I.V, and 5 mg of morphine were administered I.V. (then, in the next 2 days of stay, she received Clemastinum in a dose of 2 mg I.V. daily). At 8:00PM the patient was transported to the computed tomography unit for CT examination of the head and chest. In the CT of the head there were no signs of intracerebral and pericerebral bleeding, shaded nasal passages and partially the posterior nostrils are described (state after laryngological surgery and tamponade). In CT of the chesta trace of fluid in the right pleural, no features of fluid in the left pleural, scattered inflammatory thickenings are visible in both lungs mainly around the bronchovascular bundles with the formation of consolidation in the segment 2 of the right lung with a wide base adjoining the fissure. Less severity of lesions in segment 2 of the left lung, in segment 6 bilaterally dorsally. Few areas of ground glass opacities. The area and distribution of lesions is not typical of COVID-19 inflammation. In the performed echocardiography no obvious signs of ischemia, EF–65%, no contractility disorders, no signs of fluid in the pericardial sac.

At 8:20PM, one hour after the administration of anti histamine drugs, the patient's clinical condition improved, auscultationally normal vesicular murmur, without additional pathological murmurs. In control tests, arterial blood gas analysis was normal, the level of cardiac enzymes was normal (normal CK-MB, normal troponin T). On the next day at 6:30AM the patient was awake, extubated, her breathing was efficient with oxygen supplementation through the mask. From 1:00PM own breathing without oxygen supplementation. Follow-up studies showed a transient increase in the total number of

leukocytes especially in the neutrophil and monocyte class, and a decreased level of lymphocytes. In the control chest X-ray in the lower parts of both lungs and in the periaphragmatic residual, slight parenchyma densities. In the completed interview from the patient in Nov 2020, a previous infection of the upper and lower respiratory tract (the COVID-19 test was not collected), and small parenchymal densities were described on a chest X-ray.

Due to the very good condition of the patient, on the next day she was transferred to the surgical unit and discharged home with the recommendation to take the antihistamine drug for 5 days and to get the chest X-ray in 4-6 weeks.

Comment

At the end of April 2021, I spoke with Ms Magdalena Filcek, the author of the hypothesis regarding the histamine reaction in COVID-19, SIRS and SEPSIS, and after connecting patients to a ventilator. I believe that it included many accurate observations in the matter of the effect of ventilator air temperature on lung mast cells and the "histamine and cytokine" storm they release. After analyzing the above hypothesis, antihistamines were used in the described situation, based on the patient's clinical picture and the lack of response to the administration of steroids and diuretics. In my opinion, the clinical course and the patient's condition prove the correctness of the above concept.

9.2.2. The ICU clinical case report of a patient with numerous internal diseases and the prophylactic use of antihistamines

Introduction

A 56-year-old patient qualified for general anesthesia for surgery to remove the right salivary gland tumor in May 2021. History of arterial hypertension treated with several antihypertensive drugs, type 2 diabetes treated with oral medicines, bronchial asthma-treated with inhalation and oral steroids, reactive arthritis and obesity. Allergies of aspirin, non-steroidal anti-inflammatory drug (NSAIDs), metamizole and inhalant allergy (dust, pollen of grasses and trees). The patient additionally states that he was in the emergency room many times over several years due to severe an aphylaxis and worsening of bronchial asthma due to inhalant allergy and taking painkillers (NSAIDs). He had a mild COVID-19 infection in February 2021 general weakness was the dominant symptom. In the physical examination, the following abnormalities included: significant abdominal obesity, multiple purulent papular skin eruptions on the arms, chest and back area, weight - 103 kg, height 178 cm, BMI - 32.5 kg/m2, life parameters: BP-160/90 mmHg, HR-70/min, SpO2 94-95%. In the laboratory tests per-formed before the operation, glucose - 186 mg/dl, otherwise without significant deviations, the ECG was normal.

The course of anesthesia and surgery

At 3:00PM, the patient was admitted to the operating theater in a general stable condition. Life parameters without significant deviations: BP-155/58 mmHg, HR-80 /min, SpO2 93-94%. 15 minutes before induction of general anesthesia, patient was administered prophylactically 6 mg of Clemastinum I.V. The course of anesthesia and surgery were without complications. I.V, steroids, which are standard in this type of ENT procedures, were not administered. Patient awake and extubated without any signs of respiratory hypersensitivity. Parameters after the operation: BP-130/80 mmHg, HR-70 /min and SpO2 97%.

Comment

At the end of April 2021, I spoke with Ms Magdalena Filcek, the author of the hypothesis regarding the histamine reaction in COVID-19 and after connecting patients to a ventilator. I believe that it included many accurate observations in the matter of the effect of ventilator air temperature on lung mast cells and the "histamine and cytokine" storm they release. After analyzing the above hypothesis, and on the basis of the patient's clinical picture, I decided to use prophylactic intravenous antihistamines in the above described case. In my opinion, due to the patient's medical history, blocking the histamine receptors protected him from perioperative respiratory complications, which proves the correctness of the above concept. Such an action also had a preventive effect on the swelling of tissues in the operated area, which often occurs in this type of surgery. Usually in such situations I.V. steroids are used with little effect. In the case described above, their use was not necessary, because despite the 3-hour procedure, there was no significant swelling. In my opinion, this individualized clinical approach contributed to a faster recovery of the patient and shortened his stay in the hospital.

9.3. Discussion

Surgical treatment causes a high frequency of peri operative complications, especially complications related to the respiratory system, posing a threat to health and life **[**362**]**. It is important to reconsider the muscle relaxation and mechanically recruiting lung maneuvers - due to too much of pressure needed to open the lungs by lifting the muscles and ribs against gravity which could lead to activation of mast cells in the lungs.

In the procedure of checking how many hospitals use a heater and humidifier (up to 37 °C and 100% humidity), and how many hospitals use "bare" ventilators without heated respiratory systems - it is VERY IMPORTANT to check what is the temperature and humidity of the air which is going to the patient's lungs from the ventilator, and to check if hospitals are using HH or HME, as there is "the effect of heat and moisture exchanger and gas flow on humidity and temperature in a circle anesthetic system" **[**363**]**. Moreover, it is very important to be aware of warming up blood and fluids which are given to patients, because:

"Infusion of 1L of fluid at 21 °C can lower the patient's temperature by 0.25 °C. The infusion of thawed blood products at a temperature of 4 °C has an even greater impact on lowering the temperature" **[**364**]** also cold blood and fluids can activate the mast cells in the body to release storm of histamine and cytokines.

In any cases it is advisable to giving antihistamines throughout the whole process of treatment, before, during mechanical ventilations, operations and afterwards.

Unintentional Hypothermia: with an incidence of <36 °C may affect 50% to 90% of patients and has been defined as the most common preventable surgical complication. One American physician described maintaining normothermia this way: "There are few, if any, anesthetic interventions that have been proven to significantly improve surgery outcomes with so little effort, risk and cost that makes it an almost perfect area for measurements and improvements" **[**365**]**.

Active patient warming has been recommended as an infection-prevention step by healthcare authorities around the world. In fact, forced air warming has been specifically recommended as a warming modality in SSI-reduction guidelines issued by the U.S. Institute for Healthcare Improvement, the UK National Institute for Health and Clinical Excellence, the Scottish Patient Safety Alliance, the Canadian Patient Safety Institute, and the Australian Commission for Safety and Quality in Health Care. In 2009, forced-air warming was included as an active warming modality in the U.S. Centers for Medicare and Medicaid Services SCIP Infection 10 quality measure **[**364**]**.

„Due to a different cause of histamine intolerance, slightly different drugs will be used than in the case of allergies. If symptoms are present, an antihistamine doses and the oral administration of the DAO enzyme should be given. In severe cases, it may be necessary also to administer a steroid" **[**181**]** (which unfortunately have sides effects).

A recent report from observations in many countries shows a lower than expected representation of asthma and allergy patients with COVID-19 who took medications containing antihistamines as active substances, which is consistent and supports the presented finding **[**338**][**341**][**350**]**. Considering the potential benefits of antihistamines in the respiratory symptoms with cough, breathing difficulties and throat symptoms, and after seeing the clinical benefits of antihistamines in COVID-19 patients, we retrospectively conceptualize possibilities of histamin storm as a part of complex pathophysiology of COVID-19 patients and we found good results.

It seems that mechanisms that trigger autoimmune/autoinflammatory responses in SIRS, SEPSIS, HIT, children with PMIS and adults with severe COVID-19 (including the induction of high concentrations of IL-6) are similar **[**366**][**367**]**. It will be worth to search deeper to check how this discovery of the mechanism can help find solutions for prevent or treat other illnesses like for example: cancer,

Parkinson, Alzheimer **[**369**]**, Ebola, HCV, HIV, flu and many more, also considering „mast cell activation disease, its concise practical guide for diagnostic workup and therapeutic options" **[**370**]**.

10. Conclusion

This discovery of COVID-19 mechanism can help with defense and treatment, is a rediscovery of gas physics in mechanical ventilation, mast cells in lungs and the histamine with antihistamines. The symptoms of COVID-19, SIRS and SEPSIS could be the histamine intolerance symptoms - following the mechanism: the histamine storm, which leads to failure of multiple organs in the body, is unleashed from mast cells triggered at the beginning by COVID-19, causing breathing problems. After that mast cells are extensively activated to release next doses of histamine by particularly cold, dry air from ventilator providing also regarding to the Charles Law - too much volume or pressure into the patient's lungs.

Mast cells could contribute to the pathogenesis of COVID-19 and multi-organ inflammatory syndromes also occurring in HIT, SIRS and SEPSIS through the release of mediators taking part in proinflammatory, thrombogenicity or fibrotic process. SARS-CoV-2 could act as an environmental, an external trigger for mast cells, somehow opening the way to another trigger like histamine, possibly causing a chain of events that lead to a hyperimmune response. This life-threatening dysfunction to a dysregulated response to infection is very often far from of infection site. Difference between allergies and Histamine Intolerance called "Pseudo-Allergy" is that allergies are an IgE mediated histamine response to an allergen and the Histamine Intolerance is the body's toxic response due to the excessive accumulation of exogenous or endogenous histamine, causing so many problems, virtually in every area of the body, which also plays a key role in the complex physiopathological mechanism known as neurogenic inflammation.

The reason could be an inability of the body to efficiently neutralize too much of released histamine.

Hence, it is reasonable to consider inhibition of histamine at least for prophylaxis with enzymes DAO supplementation and with antihistamines (for example: antagonists for H1 of II generation) from the first onset of COVID-19 dyspnea symptoms also for symptomatic treatment of patients diagnosed as having COVID-19, HIT, SIRS and SEPSIS symptoms and in whole process of mechanical ventilator treatment on ICU, where also is recommended adding the HH device to respirator (36-37°C of air with 100% of humidity).

First cases that verified Magdalena Filcek discovery were done in UAE, Poland and India - they showed that antihistamines have beneficial effects for symptomatic treatment during the COVID-19 pandemic or as adjuvant therapy for severe of COVID-19 with chronic multi-organ symptoms also with regular patients before and after operation on ICU. The Government of India, following the informations from

authors of this article during the top of pandemia included the antihistamines (Levocitrizine 5 mg) to official protocol for COVID-19 treatment, helping to reduce the numbers of cases and deaths. **(Table.2)**

The above evidence together indicates that H1 receptor antagonists represents a promising tool to provide novel therapies in the current situation, because this is an intolerance to too much of histamine released from mast cells in the body, not an allergy. The antihistamines already have the clinical studies for blockage of histamine receptors, they have no side effects and are available over the counter.

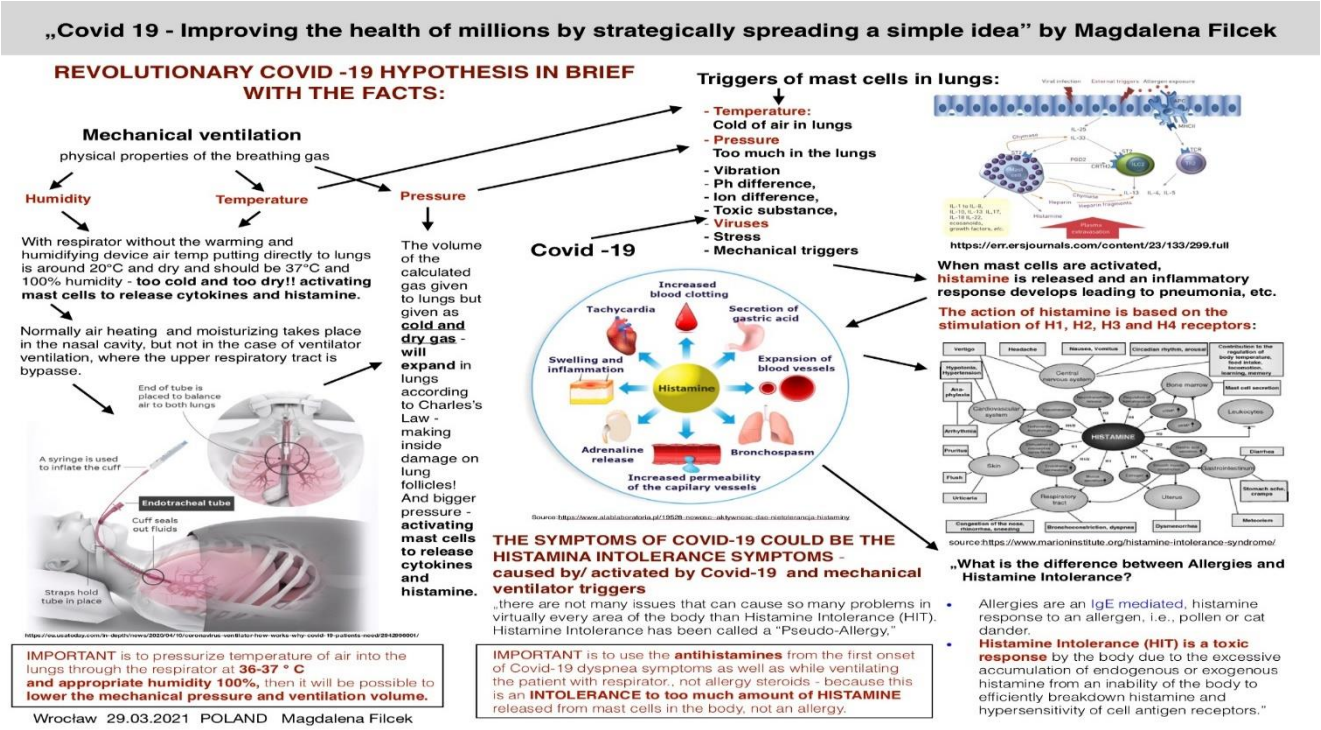
Better understanding of mast cell heterogeneity and histamine actions, which are involved probably in all types of inflammatory conditions of the respiratory tract, at the microenvironmental level and their additional physical triggers, could lead to new revolutionary strategies of treatment for allergic and nonallergic respiratory diseases.

COVID-19 as an invisible spreading infection, makes humankind look forward for a medical agent that is highly safe, and which can be used by a wide range of patients antagonists for H1 receptors has a natural role suppressing a number of inflammatory activities, that is why they can improve patients outcomes, also in reducing lung inflammation induced by histamine, those make them the answer for mitigation the histamine excess inflammatory response of COVID-19. **(Pic.4).**

Repurposing drugs is a viable strategy in the current context that can significantly reduce drug development times and aid in a rapid response also to a new virus version epidemic. Histamine H1 receptor antagonists have been reported to have a broad spectrum of antiviral activity.

In summary, antihistamines can: reduce the number of hospitalizations of patients with COVID-19 as well as their connection to a ventilator, reduce the number of VAP and possible deaths from COVID-19, SEPSIS and other diseases, and inhibit the progression of disease from the first symptoms.

Additional work is needed to relate our findings to the clinical studies to determine of specific antihistamines and its dosages to check which are the most effectiveness for COVID-19 patients and also on ICU - to help millions of people globally.



Pic.4. Iconographic of the discovered mechanism of pathophysiology of COVID-19. The author of infographic is Magdalena Filcek with assistance of Ewa Aplas for the main schema.

Reference

[1**]** Goyal P, Choi J.J, Pinheiro L.C, et al. „Clinical Characteristics of Covid-19 in New York City." N Engl J Med. 2020;382(24):23722374. doi:10.1056/NEJMc2010419

[2**]** Grasselli G, Zangrillo A, Zanella A, et al. „Baseline Characteristics and Outcomes of 1591 Patients Infected With SARSCoV2 Admitted to ICUs of the Lombardy Region, Italy" **[**published correction appears in JAMA. 2021 May 25;325(20):2120**]**. JAMA. 2020;323(16):15741581. doi:10.1001/jama.2020.5394

[3**]** Maes, M., Higginson, E., PereiraDias, J. et al. „Ventilatorassociated pneumonia in critically ill patients with COVID-19". Crit Care 25, 25 (2021). https://doi.org/10.1186/s13054021034605

[4**]** Vincent JL, Sakr Y, Singer M, et al. "Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017." JAMA. 2020;323(15):14781487. doi:10.1001/jama.2020.2717

[5**]** Zhou F, Yu T, Du R, et al. „Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." Lancet. 2020;395:1054–62

[6**]** B.T.Elden et al. „The Role of Histamine and Histamine Receptors in Mast CellMediated Allergy and Inflammation: The Hunt for New Therapeutic Targets" 13 August 2018. Front. Immunol. | https://doi.org/10.3389/fimmu.2018.01873

[7**]** Rothenberg M.E. „Eosinophilia." N Engl J Med. 1998;338(22):15921600. doi:10.1056/NEJM199805283382206

[8**]** Kay A.B. „Allergy and allergic diseases. First of two parts." N Engl J Med. 2001;344(1):3037. doi:10.1056/NEJM200101043440106

[9**]** Conway Morris A, Datta D, ShankarHari M, et al. „Cellsurface signatures of immune dysfunction riskstratify critically ill patients: INFECT study." Intensive Care Med. 2018;44(5):627635. doi:10.1007/s0013401852470

[10**]** American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864874.

[11**]** Branco ACCC, Yoshikawa FSY, Pietrobon AJ, Sato MN. „Role of Histamine in Modulating the Immune Response and Inflammation." Mediators Inflamm. 2018;2018:9524075. Published 2018 Aug 27. doi:10.1155/2018/9524075

[12**]** Götz M. „Pseudoallergien sind Histaminintoleranzen **[**Pseudoallergies are due to histamine intolerance**]**." Wien Med Wochenschr. 1996;146(15):426430.

[13**]** Dr. D. Jernigan „Histamine Intolerance; The Cause of Hundreds of Symptoms" https://www.marioninstitute.org/histamineintolerancesyndrome/

[14**]** Sinanović O, Muftić M, Sinanović S. „COVID-19 Pandemia: Neuropsychiatric Comorbidity and Consequences." Psychiatr Danub. 2020;32(2):236244. doi:10.24869/psyd.2020.236

[15**]** „Insights from IHME's latest COVID-19 model update" http://www.healthdata.org/covid/video/insightsihmeslatestCovid-19modelrun

[16**]** Sulivan B., "New Study Estimates More Than 900,000 People Have Died Of COVID-19 In U.S." May 6, 2021 https://www.npr.org/sections/coronavirusliveupdates/2021/05/06/994287048/newstudyestimates morethan900000peoplehavediedofCovid-19inus

[17**]** Woolf SH, Chapman DA, Sabo RT, Zimmerman EB. „Excess Deaths From COVID-19 and Other Causes in the US, March 1, 2020, to January 2, 2021." JAMA. 2021;325(17):1786–1789. doi:10.1001/jama.2021.5199

[18**]** Ritchie H, OrtizOspina E, Beltekian D et al. (2020) "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' **[**Online Resource**]**

[19**]** Lynn M.R., „ModernDay Icarus: JeanFrançois Pilâtre de Rozier" http://ultimatehistoryproject.com/jeanfrancoispilatrederoziermoderndayicarus.html,

[20**]** Stanek Misiąg E. „Oddech z respiratora" 21.12.2020 https://www.mp.pl/pacjent/pulmonologia/wywiady/255472,oddechzrespiratora

[21**]** Krzeminska S.,Borodzicz A., Arendarczyk M.„Inflammatory factor analysis based on a case of an ICU patients with ventilator associated pneumonia" © Evereth Publishing, 2018 Pielegniarswto w anestezjologii I intensywnej opiece 2018;4(1):2533

http://evereth.home.pl/archiwumpdf/PAIO/2018/1/5.pdf

[22**]** Herbert G. "Study: 88% of coronavirus patients on ventilators died in NY" Apr 23, 2020

https://www.syracuse.com/coronavirus/2020/04/study88ofcoronaviruspatientsonventilatorsdiedinny.html

[23**]** „Now the U.S. Has Lots of Ventilators, but Too Few Specialists to Operate Them"

https://www.nytimes.com/2020/11/22/health/Covidventilatorsstockpile.html

[24**]** Bergin T. "The U.S. has spent billions stockpiling ventilators, but many won't save critically ill COVID-19 patients" December 2, 2020

https://www.reuters.com/article/ushealthcoronavirusventilatorsinsigh idUSKBN28C1N6

[25**]** ÁlvarezLerma F, PalomarMartínez M, SánchezGarcía M, et al. „Prevention of VentilatorAssociated Pneumonia: The Multimodal Approach of the Spanish ICU "Pneumonia Zero" Program." Crit Care Med. 2018;46(2):181188. doi:10.1097/CCM.0000000000002736

[26**]** Plotnikow GA, Accoce M, Navarro E, Tiribelli N. „Humidification and heating of inhaled gas in patients with artificial airway. A narrative review." Acondicionamiento del gas inhalado en pacientes con vía aérea artificial. Revisión narrativa. Rev Bras Ter Intensiva. 2018;30(1):8697.

[27**]** Tobi M. „Principles and practice of mechanical ventilation. 2nd edition." New York: McGraw Hill; 2006. pp. 1109–1115

[28**]** Bickler PE, Sessler DI. „Efficiency of airway heat and moisture exchangers in anaesthetized humans." Anaesth Anal. 1990;71:189–200

[29**]** Allan KG, Wilson IA. „Oxford Handbook of Anaesthesia. Second Edition." New York: Oxford University Press Inc.; 2006. pp. 524–525

[30**]** Sessler DI. „Complications and treatment of mild hypothermia." Anesthesiology. 2001;336:1730–1737

[31**]** Frank SM. „Consequences of hypothermia." Curr Anaesth Crit Care . 2001;12:79–86

[32**]** Insler SR, Sessler DI. „Perioperative thermoregulation and temperature monitoring." Anesthesiol Clin. 2006;24:823–837

[33**]** Young V, Watson M. „Prevention of Perioperative Hypothermia in Plastic Surgery." Aesthetic Surgery J. 2006

[34**]** Sessler, DI. „Perioperative Heat Balance." Anesth. 2000;92

[35**]** Sessler DI. "Current concepts: Mild Perioperative Hypothermia." New Engl J Med. 1997; 336(24)

[36**]** Drager products https://www.draeger.com/pl_pl/Products/BreathingCircuitsHeated#benefit**][**7 https://www.draeger.com/pl_pl/Products/BreathingCircuitsHeated#mediagallery

[37**]** Luyt, CE., Sahnoun, T., Gautier, M. et al. „Ventilatorassociated pneumonia in patients with SARSCoV2associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study." Ann. Intensive Care 10, 158 (2020). https://doi.org/10.1186/s13613020007754

[38**]** Solomita M, Palmer LB, Daroowalla F, et al. „Humidification and secretion volume in mechanically ventilated patients." Respir Care. 2009;54(10):13291335

[39**]** Gillies D, Todd DA, Foster JP, Batuwitage BT. „Heat and moisture exchangers versus heated humidifiers for mechanically ventilated adults and children." Cochrane Database Syst Rev. 2017;9(9):CD004711. Published 2017 Sep 14. doi:10.1002/14651858.CD004711.pub3

[40**]** Lemmens HJ, BrockUtne JG. „Heat and moisture exchange devices: are they doing what they are supposed to do?." Anesth Analg. 2004;98(2):. doi:10.1213/01.ane.0000096560.96727.37

[41**]** Bickler PE, Sessler DI. "Efficiency of airway heat and moisture exchangers in anesthetized humans." Anesth Analg. 1990;71(4):415418

[42**]** Broach DS, Durbin GC. „A randomized, controlled, clinical Trial of a Chemically Reactive Heated Humidifier." Respir Care. 2001;46:37–42

[43**]** Siempos II, Vardakas KZ, Kopterides P, Falagas ME. „Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials." Critical Care Medicine 2007;35(12):2843-51

[44**]** Kelly M, Gillies D, Todd DA, Lockwood C. "Heated humidification versus heat and moisture exchangers for ventilated adults and children. Anesthesia and Analgesia „2010;111(4):1072

[45**]** Geiseler J., Fresenius J., Karg O. (2012) Active Versus Passive Humidification: Efficiency Comparison Between the Methods. In: Esquinas A. (eds) Humidification in the Intensive Care Unit. Springer, Berlin, Heidelberg.

[46**]** Bench S. „Humidification in the long-term ventilated patient; a systematic review." Intensive and Critical Care Nursing 2003;19:75-84. **[**PUBMED: 12706733

[47**]** Anaegbu N, Olatosi O, Tobi K. „Effectiveness of heat moisture exchangers (hmes) in preventing perioperative hypothermia among adult patients undergoing abdominal surgery under general endotracheal anaesthesia." J West Afr Coll Surg. 2013;3(3):1632

[48**]** Eckerbom B, Lindholm CE. „Laboratory evaluation of heat and moisture exchangers. Assessment of the Draft International Standard (ISO/DIS 9360) in practice." Acta Anaesthesiol Scand. 1990;34(4):291295. doi:10.1111/j.13996576.1990.tb03088.x

[49**]** Cigada M, Elena A, Solca M, et al. "The efficiency of twelve heat and moisture exchangers: an invitro evaluation." Intensive Care World 1990; 7: 98– 101

[50**]** Branson R, Davis J. ‚Evaluation of 21 passive humidifiers according to the ISO 9360 standard: moisture output, dead space and flow resistance." Respiratory Care 1996; 41: 736– 43

[51**]** Campbell R.S, Davis K., Johannigman J., Branson R. „The effects of passive humidifier dead space on respiratory variables in paralyzed and spontaneously breathing patients" March 2000 Respiratory Care 45(3):30612

[52**]** Lellouche F. Thesis: optimisation de l'humidification des gaz au cours de la ventilation mechanique. Paris: Universitè XllVal de Marne, 20072008

[53**]** Chandler M. „Measurement of heat and moisture exchanger efficiency" 12 August 2013 https://doi.org/10.1111/anae.12368

[53**]** Pertuze J, Watson A, Pride NB. „Maximum airflow through the nose in humans." J Appl Physiol (1985). 1991;70(3):13691376. doi:10.1152/jappl.1991.70.3.1369

[54**]** Proctor, D. F., and D. L. „Swift.Temperature and water vaporadjustment." In:Respiratory Defense Mechanisms,edited by J. D.Brain, D. F. Proctor, and L. M. Reid. New York: Dekker, 1977, p.95–125

[55**]** Niinimaa V, Cole P, Mintz S, Shephard RJ. „The switching point from nasal to oronasal breathing."

Respir Physiol. 1980;42(1):6171. doi 10.1016/00345687(80)901048

[57**]** Betlejewski S, Betlejewski A. „Wpływ aerodynamiki przepływu powietrza przez nos na fizjologie nosa **[**The influence of nasal flow aerodynamics on the nasal physiology**]**." Otolaryngol Pol. 2008;62(3):321325. doi:10.1016/S00306657(08)702634

https://doczz.pl/doc/3714665/wplywaerodynamikiprzeplywupowietrzaprzeznosnafizjo...

[58**]** Keck T, Leiacker R, Riechelmann H, Rettinger G. „Temperature profile in the nasal cavity." The Laryngoscope. 2000 Apr;110(4):651654. DOI: 10.1097/00005537200004000000021.

[59**]** „Cold Air and Colds" https://www.drgreene.com/qaarticles/coldaircolds

[60**]** Cole P. „Recordings of Respiratory Air Temperature" „The Journal of Laryngology & Otology. 1954;68(5):295307. doi:10.1017/S0022215100049690

[61**]** Jones AS, Lancer JM, Stevens JC, Beckingham E. „Nasal resistance to airflow (its measurement, reproducibility and normal parameters)." J Laryngol Otol. 1987;101(8):800808. doi:10.1017/s0022215100102762

[62**]** Webb P. „Air temperatures in respiratory tracts of resing subjects in cold." J Appl Physiol. 1951;4(5):378382. doi:10.1152/jappl.1951.4.5.378

[63**]** Plotnikow GA, Accoce M, Navarro E, Tiribelli N. Humidification and heating of inhaled gas in patients with artificial airway. A narrative review. Acondicionamiento del gas inhalado en pacientes con vía aérea artificial. Revisión narrativa. Rev Bras Ter Intensiva. 2018;30(1):8697. doi:10.5935/0103507x.20180015

[64**]** D'Amato M, Molino A, Calabrese G, Cecchi L, AnnesiMaesano I, D'Amato G. „The impact of cold on the respiratory tract and its consequences to respiratory health." Clin Transl Allergy. 2018;8:20. Published 2018 May 30. doi:10.1186/s1360101802089

[65**]** D'Amato, M., Molino, A., Calabrese, G. et al. „The impact of cold on the respiratory tract and its consequences to respiratory health." Clin Transl Allergy 8, 20 (2018). https://doi.org/10.1186/s1360101802089

[66**]** Koskela H.O. „Cold airprovoked respiratory symptoms: the mechanisms and management." 2007 International Journal of Circumpolar Health, 66:2, 91100, DOI:10.3402/ijch.v66i2.18237

[67**]** Anderson S.D, Daviskas E, Smith CM. „Exerciseinduced asthma: a difference in opinion regarding the stimulus" Allergy Proc. 1989;10(3):215226. doi:10.2500/108854189778960054

[68**]** McFadden E.R Jr, Gilbert IA. „Exerciseinduced asthma." N Engl J Med. 1994;330(19):13621367. doi:10.1056/NEJM199405123301907

[69**]** Kaminsky D.A, Bates JH, Irvin CG. „Effects of cool, dry air stimulation on peripheral lung mechanics in asthma." Am J Respir Crit Care Med. 2000;162(1):179186. doi:10.1164/ajrccm.162.1.9806079

[70**]** Kaminsky D.A, Irvin C.G, Gurka D.A, et al. „Peripheral airways responsiveness to cool, dry air in normal and asthmatic individuals." Am J Respir Crit Care Med. 1995;152(6 Pt 1):17841790. doi:10.1164/ajrccm.152.6.8520737

[71**]** Koskela H.O. „Cold airprovoked respiratory symptoms: the mechanisms and management." Int J Circumpolar Health. 2007;66(2):91100. doi:10.3402/ijch.v66i2.18237

[72**]** Van Oostdam J.C, Walker D.C, Knudson K, Dirks P, Dahlby R.W, Hogg J.C. Effect of breathing dry air on structure and function of airways. J Appl Physiol (1985). 1986;61(1):312317. doi:10.1152/jappl.1986.61.1.312

[73**]** Barbet J.P, Chauveau M, Labbé S, Lockhart A. „Breathing dry air causes acute epithelial damage and inflammation of the guinea pig trachea." J Appl Physiol (1985). 1988;64(5):18511857. doi:10.1152/jappl.1988.64.5.185

[74**]** "Humidity" https://science.jrank.org/pages/3420/Humidity.html

[75**]** "How Temperature & Humidity are Related" https://sciencing.com/temperatureampamphumidityrelated7245642.html

[76**]** Shelton D.P. „Air Properties: Temperatureand Relative Humidity" https://extensionpublications.unl.edu/assets/pdf/g1849.pdf

[77**]** „Termodynamika – cwiczenia „Wstep teoretyczny do cwiczen z przedmiotu Termodynamika oraz Teoria Maszyn Cieplnych" http://fluid.itcmp.pwr.wroc.pl/~pblasiak/TABLICE_WZORY/Termodynamika_TEORIA.pdf

[78**]** Anger C, van Bömmel T, Phadanaanek S, et al. „Das Verhalten von relativer Luftfeuchtigkeit und Temperatur im Inspirationsteil des DrägerKreissystems und deren Einfluss auf die Funktion des Flimmerepithels **[**Characteristics of the relative humidity and temperature in the inspiratory part of the Dräger circle system and their influence on the function of the ciliary epithelium**]**." Anasth Intensivther Notfallmed. 1990;25(1):107111.

[79**]** Barbet JP, Chauveau M, Labbé S, Lockhart A. „Breathing dry air causes acute epithelial damage and inflammation of the guinea pig trachea." J Appl Physiol (1985). 1988;64(5):18511857. doi:10.1152/jappl.1988.64.5.1851

[80**]** „Weather and Your Lungs" February 16, 2016 https://www.lung.org/blog/weatherandyourlungs

[81**]** "Why You Need a Humidifier/ Effects of Dry Air and Low Humidity" October 13, 2017 https://www.servicechampions.net/blog/needhumidifiereffectsdryairlowhumidity/

[82**]** Davis R.E., Rossier C.E., Enfield K.B.„The Impact of Weather on Influenza and Pneumonia Mortality in New York City, 1975–2002: A Retrospective Study" 28 March, 2012 https://doi.org/10.1371/journal.pone.0034091

[83**]** Bonten MJ, Froon AH, Gaillard CA, et al. The systemic inflammatory response in the development of ventilatorassociated pneumonia. Am J Respir Crit Care Med. 1997;156(4 Pt 1):11051113. doi:10.1164/ajrccm.156.4.9610002

[84**]** Niedzwiedzka P., Deptula W. „The role of mast cells in immunity." http://www.medycynawet.edu.pl/images/stories/pdf/pdf2008/112008/20081112911294.pdf

[85**]** St John AL, Abraham SN. „Innate immunity and its regulation by mast cells." J Immunol. 2013;190(9):44584463. doi:10.4049/jimmunol.1203420

[86**]** Renkielska D. Gdanski Uniwersytet Medyczny „Komorki tuczne w przewleklych zmianach okolowierzcholkowych szczek" 2014 https://pbc.gda.pl/Content/44697/doktorat%20RENKIELSKA%20Dorota.pdf

[87**]** Kopec-Szlezak J. „Mast cells and their role in immunity and cancer" J. Transf. Med. 2015; 8: 49–59 https://journals.viamedica.pl/journal_of_transfusion_medicine/article/view/42497/30229

[88**]** Malbec O., Roget K., Schiffer C., Iannascoli B., Dumas A.R., Arock M. and Daëron M. „Peritoneal CellDerived Mast Cells: An In Vitro Model of Mature SerosalType Mouse Mast Cells" J Immunol May 15, 2007, 178 (10) 64656475; DOI: https://doi.org/10.4049/jimmunol.178.10.6465

[89**]** Mastej M. „To może być HIT !!!" 10 January 2017 https://hipoalergiczni.pl/mozebychit/

[90**]** University of Gdansk „Mastocytoza: choroba mastocytów (komórek tucznych)" https://alergologia.gumed.edu.pl/10481.html

[91**]** Romantowski J, Górska A, Lange M, Nedoszytko B, Gruchała, „How to diagnose mast cell activation syndrome: practical considerations." Pol Arch Intern Med. 2020;130(4):317323. doi:10.20452/pamw.15212

[92**]** Gogolewski G., Wolanczyk-Medrala A., Medrala W., The Participation of Tryptase in the Pathogenesis of Allergic and Inflammatory Diseases" Cathedral and the Clinic Internal Medicine and Allergology AM Adv Clin Exp Med 2006, 15, 5, 905–909

[93**]** Taylor ML, Metcalfe DD. „Mast cells in allergy and host defense." Allergy Asthma Proc. 2001;22(3):115119. doi:10.2500/108854101778148764

[94**]** Metz M, Grimbaldeston MA, Nakae S, Piliponsky AM, Tsai M, Galli SJ. „Mast cells in the promotion and limitation of chronic inflammation." Immunol Rev. 2007;217:304328. doi:10.1111/j.1600065X.2007.00520.x

[95**]** Frieri M. „Mast Cell Activation Syndrome." Clin Rev Allergy Immunol. 2018;54(3):353365. doi:10.1007/s1201601584876

[96**]** Cimolai N. „Comparing histamine intolerance and nonclonal mast cell activation syndrome." Intest Res. 2020;18(1):134135. doi:10.5217/ir.2019.00087

[97**]** Valent P. „Mast cell activation syndromes: definition and classification" 15 February 2013 https://doi.org/10.1111/all.12126

[98**]** B.A.Lawrence „Presentation, diagnosis, and management of mast cell activation syndrome" Medicine Hematology, Oncology, Transplant 1 April 2013 , ISBN 9781626181663 Symptoms Mastocytosis https://www.nhs.uk/conditions/mastocytosis/symptoms/

[99**]** Metcalfe DD, Baram D, Mekori YA. „Mast cells. Physiol Rev." 1997;77(4):10331079. doi:10.1152/physrev.1997.77.4.1033

[100**]** „Immunobiology: The Immune System in Health and Disease. 5th edition." https://www.ncbi.nlm.nih.gov/books/NBK27112/

[101**]** Metcalfe DD, Kaliner M, Donlon MA. The mast cell. Crit Rev Immunol. 1981;3(1):2374.

[102**]** Franco C.B., Chen C.C. Drukker M. Weissmann I.L. Galli S.J. Distinguishing Mast Cell and Granulocyte Differentiation at the SingleCell Level https://doi.org/10.1016/j.stem.2010.02.013

[103**]** Eriefalt J.S. „Mast cells in human airways: the culprit?" European Respiratory Review 2014 23: 299307; DOI: 10.1183/09059180.00005014

[104**]** American Academy of Allergy, Asthma & Immunology „Mast Cell Activation Syndrome (MCAS)" https://www.aaaai.org/conditionsandtreatments/relatedconditions/mcas

[105**]** Bradley BL, Azzawi M, Jacobson M, et al. „Eosinophils, Tlymphocytes, mast cells, neutrophils, and macrophages in bronchial biopsy specimens from atopic subjects with asthma: comparison with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness." J Allergy Clin Immunol. 1991;88(4):661674. doi:10.1016/00916749(91)90160p

[106**]** Djukanović R, Wilson JW, Britten KM, et al. Quantitation of mast cells and eosinophils in the bronchial mucosa of symptomatic atopic asthmatics and healthy control subjects using immunohistochemistry. Am Rev Respir Dis. 1990;142(4):863871. doi:10.1164/ajrccm/142.4.863

[107**]** Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skintest reactivity to allergens. N Engl J Med. 1989;320(5):271277. doi:10.1056/NEJM198902023200502

[108**]** Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. Am Rev Respir Dis. 1985;131(4):599606. doi:10.1164/arrd.1985.131.4.599

[109**]** BienkowskaHaba M. „Nitric oxide produced by pulmonary leukocytes in bronchial asthma" 13 Dec 2005 Issue: Postepy Hig Med Dosw 2005; 59 (0) GICID: 01.3001.0000.3701

[110**]** Barnes PJ. „Histamine receptors in the lung." Agents Actions Suppl. 1991;33:103122. doi:10.1007/9783034873093_9

[111**]** Malbec O, Roget K, Schiffer C, et al. Peritoneal cellderived mast cells: an in vitro model of mature serosaltype mouse mast cells. J Immunol. 2007;178(10):64656475. doi:10.4049/jimmunol.178.10.6465

[112**]** Theoharides TC. „COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. „Biofactors. 2020;46(3):306308. doi:10.1002/biof.1633

[113**]** Motta Junior JDS, Miggiolaro AFRDS, Nagashima S, et al. „Mast Cells in Alveolar Septa of COVID-19 Patients: A Pathogenic Pathway That May Link Interstitial Edema to Immunothrombosis." Front Immunol. 2020;11:574862. Published 2020 Sep 18. doi:10.3389/fimmu.2020.574862

[114**]** Theoharides TC. „Potential association of mast cells with coronavirus disease 2019." Ann Allergy Asthma Immunol. 2021;126(3):217218. doi:10.1016/j.anai.2020.11.003

[115**]** Walls AF, Bennett AR, Godfrey RC, Holgate ST, Church MK. „Mast cell tryptase and histamine concentrations in bronchoalveolar lavage fluid from patients with interstitial lung disease." Clin Sci (Lond). 1991;81(2):183188. doi:10.1042/cs0810183

[116**]** Soler P, Nioche S, Valeyre D, et al. „Role of mast cells in the pathogenesis of hypersensitivity pneumonitis. „Thorax. 1987;42(8):565572. doi:10.1136/thx.42.8.565

[117**]** Lee J. University of Colorado Denver „Hypersensitivity Pneumonitis" (Extrinsic Allergic Alveolitis) Jun 2021 https://www.msdmanuals.com/professional/pulmonarydisorders/interstitiallungdiseases/hypersensitivitypneumonitis

[118**]** Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med. 2001;344(1):3037. doi:10.1056/NEJM200101043440106

[119**]** Gordon JR, Galli SJ. Mast cells as a source of both preformed and immunologically inducible TNFalpha/cachectin. Nature. 1990;346(6281):274276. doi:10.1038/346274a0

[120**]** Young JD, Liu CC, Butler G, Cohn ZA, Galli SJ. Identification, purification, and characterization of a mast cellassociated cytolytic factor related to tumor necrosis factor. Proc Natl Acad Sci U S A. 1987;84(24):91759179. doi:10.1073/pnas.84.24.9175

[121**]** D.K. Cavanah, T.B. Casale: Histamine. W: The Mast Cell in Health and Disease. M.A. Kaliner, D.D. Metcalfe (red.). T. 62. Marcel Dekker, Inc., 1993, s. 321–342, seria: Lung Biology in Health and Desease. ISBN 9780824787325.

[122**]** "Symptoms and Triggers of Mast Cell Activation"

https://tmsforacure.org/symptoms/symptomsandtriggersofmastcellactivation/

[123**]** „Symptoms and Triggers of Mast Cell Activation"

https://mastocytosis.org.au/mastcellsexplained/signssymptomstriggers/symptomsandtriggersofmastcellactivation/

[124**]** Frieri M, Patel R, Celestin J. Mast cell activation syndrome: a review. Curr Allergy Asthma Rep. 2013;13(1):2732. doi:10.1007/s118820120322z

[125**]** „Mastocytozy skórne” https://www.mp.pl/pacjent/dermatologia/choroby/chorobyskory/73421,mastocytozy

[126**]** Wallin, M., Hedenstierna, G. Tidal volumes: cold and dry or warm and humid, does it matter?. J Clin Monit Comput 34, 871–873 (2020). https://doi.org/10.1007/s10877019004167

[127**]** https://www.youtube.com/watch?v=pO__fc6pWfI

[128**]** Mazur J. Agregacja płytek krwi – co to jest, jakie są objawy i jakie leki hamują agregację trombocytów? 31 Jan 2018 https://wylecz.to/chorobykrwi/agregacjaplytekkrwicotojestjakiesaobjawyijakielekihamujaagregacjetrombocytow/

[129**]** Podstawowe prawa gazowe http://www.uwm.edu.pl/kopits/dokumenty/rach3.pdf

Jackson C. D. „How are tidal volumes and rates determined in mechanical ventilation?” 15 Sep 2020

[131**]** https://en.wikipedia.org/wiki/Tidal_volume**]**

[132**]** Ricard J.D. „Are We Really Reducing Tidal Volume—And Should We?”

[133**]** Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilatorinduced lung injury. Crit Care Med. 1993;21(1):131143. doi:10.1097/00003246199301000000024

[134**]** Barbosa N.L., Ribeiro dos Santos G., Serra D.S. „Effects of increasing tidal volume on the mechanics of the mechanics of the respiratory system of healthy rats." December 2017

[135**]** Bardoczky GI, Yernault JC, Houben JJ, d'Hollander AA. Large tidal volume ventilation does not improve oxygenation in morbidly obese patients during anesthesia. Anesth Analg. 1995;81(2):385388. doi:10.1097/00000539199508000000030

[136**]** Chiumello D., Colombo A., Algieri I., Cressoni M., Quintel M., Gattinoni L., "Effect of body mass index in acute respiratory distress syndrome" https://doi.org/10.1093/bja/aev378

[137**]** Fan E., Brodie D., Slutsky A.S. „Acute Respiratory Distress SyndromeAdvances in Diagnosis and Treatment" 20 February 2018 JAMA. 2018;319(7):698710. doi:10.1001/jama.2017.21907

[138**]** Lewandowska K. „Alergiczne zapalenie pęcherzyków płucnych. Extrinsic allergic alveolitis (hypersensitivity pneumonitis)" Borgis Postępy Nauk Medycznych 4/2011, s. 274285

[139**]** Kradin R.L. Mark E.J. „The Pathology of Pulmonary Disorders Due to Aspergillus spp" 01 April 2008 Arch Pathol Lab Med (2008) 132 (4): 606–614. https://doi.org/10.5858/2008132606TPOPDD

[140**]** Barnes PD, Marr KA. Aspergillosis: spectrum of disease, diagnosis, and treatment. Infect Dis Clin North Am. 2006;20(3):545vi. doi:10.1016/j.idc.2006.06.001

[141**]** Cho Y, Jang Y, Yang YD, Lee CH, Lee Y, Oh U. TRPM8 mediates cold and menthol allergies associated with mast cell activation. Cell Calcium. 2010;48(4):202208. doi:10.1016/j.ceca.2010.09.001

[142**]** Soler P, Nioche S, Valeyre D, et al. Role of mast cells in the pathogenesis of hypersensitivity pneumonitis. Thorax. 1987;42(8):565572. doi:10.1136/thx.42.8.565

[143**]** Nowicki J, Murray MT. Bronchitis and Pneumonia. Textbook of Natural Medicine. 2020;11961201.e1. doi:10.1016/B9780323430449.001552

[144**]** Santulli G., „Angiogenesis: Insights from a Systematic Overview" https://novapublishers.com/shop/angiogenesisinsightsfromasystematicoverview/

[145**]** Birbrair A, Zhang T, Wang ZM, Messi ML, Mintz A, Delbono O (January 2015). "Pericytes at the intersection between tissue regeneration and pathology". Clinical Science. 128 (2): 81–93. doi:10.1042/CS20140278. PMC 4200531. PMID 25236972

[146**]** „How COVID-19 damages the lungs. A team of EUbacked researchers has compared the lungs of coronavirus victims and patients dead from influenzaassociated respiratory failure." 20 July 2020 https://cordis.europa.eu/article/id/421597howCovid-19damagesthelungs

[147**]** Ponomaryov T, Payne H, Fabritz L, Wagner DD, Brill A. Mast Cells Granular Contents Are Crucial for Deep Vein Thrombosis in Mice. Circ Res. 2017;121(8):941950. doi:10.1161/CIRCRESAHA.117.311185

[148**]** Budnik I, Brill A. Immune Factors in Deep Vein Thrombosis Initiation. Trends Immunol. 2018;39(8):610623. doi:10.1016/j.it.2018.04.010

[149**]** Cirino G, Cicala C, Bucci MR, Sorrentino L, Maraganore JM, Stone SR. Thrombin functions as an inflammatory mediator through activation of its receptor. J Exp Med 1996;183:8217

[150**]** Zhu H, Liang B, Li R, Li J, Lin L, Ma S, et al. Activation of coagulation, anticoagulation, fibrinolysis and the complement system in patients with urticaria. Asian Pac J Allergy Immunol 2013;31:4350

[151**]** „Features of antihistamineresistant chronic urticaria and chronic urticaria during exacerbation" https://www.eijd.org/article.asp?issn=00195154;year=2015;volume=60;issue=3;spage=323;epage=323;aulast=Huilan

[152**]** University of Birmingham. "New hope to prevent dangerous blood clots found in the legs." ScienceDaily. ScienceDaily, 3 August 2017. www.sciencedaily.com/releases/2017/08/170803135051.htm

[153**]** „Badanie hemostazy: osoczowy układ krzepnięcia i zaburzenia dotyczące płytek krwi" https://edraurban.pl/ssl/booksamplefile/diagnostykalaboratoryjnawweterynarii/pdf/093_110_r06_veterinarylabmed.pdf

[154**]** Stein PE, Carrell RW. What do dysfunctional serpins tell us about molecular mobility and disease?. „Nature Structural Biology". 2 (2), s. 96–113, 1995. DOI: 10.1038/nsb029596. PMID: 7749926.

[155**]** Selecki A., Gradon L., „Podstawowe procesy przemyslu chemicznego" Wyd. NaukowoTechniczne 1985 http://bcpw.bg.pw.edu.pl/Content/7296/gradon_selecki_sgpp.pdf

[156**]** Feezor RJ, Oberholzer C, Baker HV, et al. Molecular characterization of the acute inflammatory response to infections with gramnegative versus grampositive bacteria. Infect Immun. 2003;71(10):58035813. doi:10.1128/IAI.71.10.58035813.2003

[157**]** Payne V, Kam PC. „Mast cell tryptase: a review of its physiology and clinical significance." Anaesthesia. 2004;59(7):695703. doi:10.1111/j.13652044.2004.03757.x

[158**]** Hofman Z.L.M., van den Elzen M., Kuijpers J., de Maat S., Hack C.E., Knulst A.C., Rockmann H., Maas C. „Evidence for bradykinin release in chronic spontaneous urticaria" 03 January 2020 https://doi.org/10.1111/cea.13558

[159**]** Goodman and Gilman Manual of Pharmacology and Therapeutics Section IV „Inflammation, Immunomodulation, and Hematopoiesis" chapter 32 Skidgel R.A., Kaplan A.P., Erdös E.G., „Histamine, Bradykinin, and Their Antagonists" https://doctorlib.info/pharmacology/manual/33.html

[160**]** Konieczny G. PosadzyMalaczynska A., Tykarski A., „Działania niepożądane inhibitorów konwertazyangiotensyny" Katedra i Klinika Hipertensjologii, Angiologii i Chorób Wewnętrznych Akademii Medycznej im. Karola Marcinkowskiego w Poznaniu, Choroby Serca i Naczyń 2006, tom 3, nr 3, 140–148

[161**]**
https://podyplomie.pl/medycyna/35773,napadyobrzekuzagrazajacegozarcieszympodejrzewamywroszeniaobrzeknaczynioruchowy
https://podyplomie.pl/medycyna/35773,napadyobrzekuzagrazajacegozarcieszympodejrzewamywroszeniaobrzeknaczynioruchowy

[162**]** Naletova I, Nicoletti VG, Milardi D, Pietropaolo A, Grasso G. Copper, differently from zinc, affects the conformation, oligomerization state and activity of bradykinin. Metallomics. 2016;8(8):750761. doi:10.1039/c6mt00067c

[163**]** Chung MK, Karnik S, Saef J, et al. SARSCoV2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy. EBioMedicine. 2020;58:102907. doi:10.1016/j.ebiom.2020.102907

[164**]** Qadri F, Bader M. Kinin B1 receptors as a therapeutic target for inflammation. Expert Opin Ther Targets. 2018;22(1):3144. doi:10.1080/14728222.2018.1409724**]**

[165**]** Mukae S, Aoki S, Itoh S, Iwata T, Ueda H, Katagiri T. Bradykinin B(2) receptor gene polymorphism is associated with angiotensinconverting enzyme inhibitorrelated cough. Hypertension. 2000;36(1):127131. doi:10.1161/01.hyp.36.1.127

[166**]** Karlberg BE. Cough and inhibition of the reninangiotensin system. J Hypertens Suppl. 1993;11(3):S49S52.

[167**]** Mathivanan S, Devesa I, Changeux JP, FerrerMontiel A. Bradykinin Induces TRPV1 Exocytotic Recruitment in Peptidergic Nociceptors. Front Pharmacol. 2016;7:178. Published 2016 Jun 23. doi:10.3389/fphar.2016.00178

[168**]** "Histamine and Bradykinin" Cardiovascular Physiology Concepts 04 June 2007 https://www.cvphysiology.com/Blood%20Flow/BF014

[169**]** Histamine & bradykinin" Technology, Health & Medicine 01 April 2012 https://www.slideshare.net/ankit_2408/histaminebradykinin

[170**]** Garvin MR, Alvarez C, Miller JI, et al. A mechanistic model and therapeutic interventions for COVID-19 involving a RASmediated bradykinin storm. Elife. 2020;9:e59177. Published 2020 Jul 7. doi:10.7554/eLife.59177

[171**]** Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr. 2007;85(5):11851196. doi:10.1093/ajcn/85.5.1185

[172**]** Nuutinen S., Panula P. (2010) Histamine in Neurotransmission and Brain Diseases. In: Thurmond R.L. (eds) Histamine in Inflammation. Advances in Experimental Medicine and Biology, vol 709. Springer, Boston, MA. https://doi.org/10.1007/9781441980564_10

[173**]** Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev. 2008;88(3):11831241. doi:10.1152/physrev.00043.2007

[174**]** Ladero V., CallesEnriquez M., Fernandez M and Alvarez M.A., " Toxicological Effects of Dietary Biogenic Amines", Current Nutrition & Food Science 2010; 6(2) . https://doi.org/10.2174/157340110791233256

[175**]** Cataldi M, Borriello F, Granata F, Annunziato L, Marone G. „Histamine receptors and antihistamines: from discovery to clinical applications." Chem Immunol Allergy. 2014;100:214226. doi:10.1159/000358740

[176**]** Shamburek, R.D.; Schubert, M.L. Control of gastric acid secretion. Histamine H2receptor antagonists and H+K(+)ATPaseinhibitors.Gastroenterol. Clin. N. Am.1992,21, 527–550

[177**]** A Esbenshade, T.; E Browman, K.; Bitner, R.S.; Strakhova, M.; Cowart, M.D.; Brioni, J.D. The histamine H3 receptor: An attractivetarget for the treatment of cognitive disorders.Br. J. Pharmacol.2008,154, 1166–1181**]**.

[178**]** Thurmond, R.L.; Gelfand, E.W.; Dunford, P.J. The role of histamine H1 and H4 receptors in allergic inflammation: The search fornew antihistamines.Nat. Rev. Drug Discov.2008,7, 41–53

[179**]** „Antihistamines effective against COVID-19? The results of the laboratory tests confirm this." https://www.hellozdrowie.pl/lekiprzeciwhistaminoweskutecznewwalcezCovid-19wynikitestowlaboratoryjnychtopotwierdzaja/

[180**]** "Hepatitis A virus IgG Ab **[**Units/volume**]** in Serum by Radioimmunoassay (RIA)" https://loinc.org/51805/

[181**]** Mastej M. „Jak odroznic nietolerancje histaminy od alergii?" 18 June 2017 https://hipoalergiczni.pl/jakodroznicnietolerancjehistaminyodalergii/

[182**]** „Badanie diaminoksydazy w surowicy" https://www.alablaboratoria.pl/19528nowoscaktywnoscdaonietolerancjahistaminy

[183**]** Park IH, Um JY, Cho JS, Lee SH, Lee SH, Lee HM. Histamine Promotes the Release of Interleukin6 via the H1R/p38 and NFκB Pathways in Nasal Fibroblasts. Allergy Asthma Immunol Res. 2014;6(6):567572. doi:10.4168/aair.2014.6.6.567

[184**]** Valent P., „KIT D816V and the cytokine storm in mastocytosis: production and role of interleukin6" Haematologica Vol. 105 No. 1 (2020): January, 2020 https://doi.org/10.3324/haematol.2019.234864

[185**]** Li Y, Chi L, Stechschulte DJ, Dileepan KN. Histamineinduced production of interleukin6 and interleukin8 by human coronary artery endothelial cells is enhanced by endotoxin and tumor necrosis factoralpha. Microvasc Res. 2001;61(3):253262. doi:10.1006/mvre.2001.2304

[186**]** Sinha D.S. "Antihistamines might be effective in longCOVID". NewsMedical. 16 July 2021. https://www.newsmedical.net/news/20210608/AntihistaminesmightbeeffectiveinlongCOVID.aspx

[187**]** Masini E, Fabbroni V, Giannini L, et al. Histamine and histidine decarboxylase upregulation in colorectal cancer: correlation with tumor stage. Inflamm Res. 2005;54 Suppl 1:S80S81. doi:10.1007/s0001100404373

[188**]** Park IH, Um JY, Cho JS, Lee SH, Lee SH, Lee HM. Histamine Promotes the Release of Interleukin6 via the H1R/p38 and NFκB Pathways in Nasal Fibroblasts. Allergy Asthma Immunol Res. 2014;6(6):567572. doi:10.4168/aair.2014.6.6.567

[189**]** Xu X, Zhang D, Zhang H, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. J Exp Med. 2006;203(13):29072917. doi:10.1084/jem.20061232

[190**]** Tokar S.„White blood cells in lung produce histamine seen in allergies" 12 January 2007

[191**]** https://www.ucsf.edu/news/2007/01/5526/whitebloodcellslungproducehistamineseenallergies

[192**]** Thurmond RL, Desai PJ, Dunford PJ, FungLeung WP, Hofstra CL, Jiang W, et al. A potent and selective histamine H4 receptor antagonist with antiinflammatory properties. J Pharmacol Exp Ther (2004) 309:404–13. doi:10.1124/jpet.103.061754

[193**]** Parsons ME, Ganellin CR. Histamine and its receptors. Br J Pharmacol (2006) 147(Suppl 1):S127–35. doi:10.1038/sj.bjp.0706440

[194**]** O'Sullivan MP, Tyner JW, Holtzman MJ. Apoptosis in the airways: another balancing act in the epithelial program. Am J Respir Cell Mol Biol (2003) 29:3–7. doi:10.1165/rcmb.F273

[195**]** Jutel M, Blaser K, Akdis CA. Histamine in allergic inflammation and immune modulation. Int Arch Allergy Immunol (2005) 137:82–92. doi:10.1159/000085108

[196**]** Akdis CA, Simons FE. Histamine receptors are hot in immunopharmacology. Eur J Pharmacol (2006) 533:69–76. doi:10.1016/j.ejphar.2005.12.044

[197**]** Packard KA, Khan MM. Effects of histamine on Th1/Th2 cytokine balance. Int Immunopharmacol (2003) 3:909–20. doi:10.1016/S15675769(02)002357

[198**]** Rosa AC, Fantozzi R. The role of histamine in neurogenic inflammation. Br J Pharmacol. 2013;170(1):3845. doi:10.1111/bph.12266

[199**]** Lu X, Zhang L, Du H, et al. „SARSCoV2 Infection in Children." N Engl J Med. 2020;382(17):16631665. doi:10.1056/NEJMc2005073

[200**]** Tanner T, Wahezi DM. "Hyperinflammation and the utility of immunomodulatory medications in children with COVID-19. Paediatric Respiratory Reviews." 2020 Sep;35:8187. DOI: 10.1016/j.prrv.2020.07.003.

[201**]** McCrindle BW, Rowley AH, Newburger JW, et al. (2017). "Diagnosis, treatment, and longterm management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association". Circulation. 135 (17): e927–e999.

[202**]** https://en.wikipedia.org/wiki/Multisystem_inflammatory_syndrome_in_children

[203**]** Radia T., Williams N., Agrawal P., Harman K., Weale J., Cook J., Gupta A. „Multisystem inflammatory syndrome in children & adolescents (MISC): A systematic review of clinical features and presentation" https://doi.org/10.1016/j.prrv.2020.08.001Get rights and content

[204**]** Gustine JN, Jones D. Immunopathology of Hyperinflammation in COVID-19. Am J Pathol. 2021;191(1):417. doi:10.1016/j.ajpath.2020.08.009

[205**]** "The relationship between histamine, oestrogen, progesterone and cortisol" FX Medicine https://www.fxmedicine.com.au/blogpost/relationshipbetweenhistamineoestrogenprogesteroneandcortisol

[206**]** Zierau O, Zenglussen AC, Jensen F. Role of female sex hormones, estradiol and progesterone, in mast cell behavior. Frontiers in Immunology 2012;3:doi:10.3389/fimmu.2012.00169.

[207**]** Loewendorf AI, Matynia A, Saribekyan H, et al. Roads less travelled: sexual dimorphism and mast cell contributions to migraine pathology. Front Immunol 2016;7:140.

[208**]** Theoharides TC, Stewart JM. Genitourinary mast cells and survival. Transl Androl Urol 2015;4(5):579586

[209**]** Fogel WA. Diamine oxidase (DAO) and female sex hormones. Agents Actions 1986;18(1):4445.

[210**]** Sessa A, Desiderio MA, Perin A. Oestrogenic regulation of diamine oxidase activity in rat uterus. Agents Actions 1990;29(34):162166.

[211**]** Reed BG, Carr BR. The normal menstrual cycle and the control of ovulation. Endotext 2015. Viewed 19 August 2018,

[212**]** Lee SK, Kim CJ, Kim DJ, et al. Immune cells in the female reproductive tract. Immune News 2015;15(1):1626

[213**]** Clifton VL, Crompton R, Read MA, et al. Microvascular effects of corticotropinreleasing hormone in human skin vary in relation to estrogen concentration during the menstrual cycle. J Endocrinol 2005;186:6976.

[214**]** Zayachkivska O, Musiol A. Histaminecortisol correlations: new link of multifactorial regulation of inflammation. Conference: University Hospital Centre and Grenoble Institute of Neurosciences Grenoble, France. Viewed 11 August 2018

[215**]** Rosin C, Brunner M, Lehr S, Quehenberger P, Panzer S. The formation of plateletleukocyte aggregates varies during the menstrual cycle. Platelets. 2006;17(1):6166. doi:10.1080/09537100500227021

[216**]** Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41residue ovine hypothalamic peptide that stimulates secretion of corticotropin and betaendorphin. Science. 1981;213(4514):13941397. doi:10.1126/science.6267699

[217**]** Chrousos GP. The hypothalamicpituitaryadrenal axis and immunemediated inflammation. N Engl J Med. 1995;332(20):13511362. doi:10.1056/NEJM199505183322008

[218**]** Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis **[**published correction appears in JAMA 1992 Jul 8;268(2):200**]**. JAMA. 1992;267(9):12441252.

[219**]** Rivier C, Vale W. Modulation of stressinduced ACTH release by corticotropinreleasing factor, catecholamines and vasopressin. Nature. 1983;305(5932):325327. doi:10.1038/305325a0

[220**]** Hillhouse EW, Grammatopoulos DK. The molecular mechanisms underlying the regulation of the biological activity of corticotropinreleasing hormone receptors: implications for physiology and pathophysiology. Endocr Rev. 2006;27(3):260286. doi:10.1210/er.20050034

[221**]** Fekete EM, Zorrilla EP. Physiology, pharmacology, and therapeutic relevance of urocortins in mammals: ancient CRF paralogs. Front Neuroendocrinol. 2007;28(1):127. doi:10.1016/j.yfrne.2006.09.002

[222**]** Karalis K, Sano H, Redwine J, Listwak S, Wilder RL, Chrousos GP. Autocrine or paracrine inflammatory actions of corticotropinreleasing hormone in vivo. Science. 1991;254(5030):421423. doi:10.1126/science.1925600

[223**]** Theoharides TC, Donelan JM, Papadopoulou N, Cao J, Kempuraj D, Conti P. Mast cells as targets of corticotropinreleasing factor and related peptides. Trends Pharmacol Sci. 2004;25(11):563568. doi:10.1016/j.tips.2004.09.007

[224**]** Slominski A, Zbytek B, Zmijewski M, et al. Corticotropin releasing hormone and the skin. Front Biosci. 2006;11:22302248. Published 2006 Sep 1. doi:10.2741/1966

[225**]** Zbytek B, Pfeffer LM, Slominski AT. Corticotropinreleasing hormone stimulates NFkappaB in human epidermal keratinocytes. J Endocrinol. 2004;181(3):R1R7. doi:10.1677/joe.0.181r001

[226**]** Zbytek B, Pfeffer LM, Slominski AT. CRH inhibits NFkappa B signaling in human melanocytes. Peptides. 2006;27(12):32763283. doi:10.1016/j.peptides.2006.07.017

[227**]** Slominski A., Wortsman J., Linton E., Pisarchik A., Zbytek B. (2003) The skin as a model for the immunodulatory effects of corticotropinreleasing hormone. In: Schäfer M., Stein C. (eds) Mind over Matter Regulation of Peripheral Inflammation by the CNS. Progress in Inflammation Research. Birkhäuser, Basel. https://doi.org/10.1007/9783034880398_10

[228**]** Slominski A. On the role of the corticotropinreleasing hormone signalling system in the aetiology of inflammatory skin disorders. Br J Dermatol. 2009;160(2):229232. doi:10.1111/j.13652133.2008.08958.x

[229**]** Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008;43(2):164174. doi:10.1016/j.jpsychires.2008.03.009

[230**]** Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav Immun. 2007;21(4):374383. doi:10.1016/j.bbi.2007.01.010

[231**]** KarakulaJuchnowicz H., Dzikowski M., Pelczarska A., Dzikowska I., Juchnowicz D.,„The braingut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia" http://www.psychiatriapolska.pl/uploads/onlinefirst/KarakulaJuchnowicz_PsychiatrPolOnlineFirstNr28.pdf

[232**]** Banerjee S., Mukherjee G.G., Singh J., Zargar A.H., „Critical Issues and Diabetes" https://books.google.pl/books?id=A9q4BwAAQBAJ&printsec=frontcover&hl=pl#v=onepage&q&f=false

[233**]** ComasBasté O, SánchezPérez S, VecianaNogués MT, LatorreMoratalla M, VidalCarou MDC. Histamine Intolerance: The Current State of the Art. Biomolecules. 2020;10(8):1181. Published 2020 Aug 14. doi:10.3390/biom10081181

[234**]** Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. World J Hematol 2014; 3(1): 117

[235**]** Huizen J.,16, 2021 „Which foods are high in histamine?" 16 April 2021 https://www.medicalnewstoday.com/articles/322543

[236**]** Marrion G. "The relationship between histamine, oestrogen, progesterone and cortisol" FX Medicine 09/17/2018

[237**]** Doeun D, Davaatseren M, Chung MS. Biogenic amines in foods. Food Sci Biotechnol. 2017;26(6):14631474. Published 2017 Dec 13. doi:10.1007/s1006801702393

[238**]** "All you need to know about histamine intolerance" https://justfortummies.co.uk/allyouneedtoknowabouthistamineintolerance/

[239**]** https://www.alablaboratoria.pl/19708nagraniezwebinariumnietolerancjahistaminyhitdowiedzsiejakrozpoznacijakpostepowaczpacjentemhit

[240**]** Schnedl, W. J., Schenk, M., Lackner, S., Enko, D., Mangge, H., & Forster, F. (2019). Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. Food science and biotechnology, 28(6), 17791784

[241**]** Schnedl WJ, Schenk M, Lackner S, Enko D, Mangge H, Forster F. Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. Food Sci Biotechnol. 2019;28(6):17791784. Published 2019 May 24. doi:10.1007/s10068019006273

[242**]** Marcos L.G.,„Allergologia et Immunopathologia "https://www.elsevier.es/enrevistaallergologiaetimmunopathologia105articulohistaminehistamineintoxicationintoleranceS0301054615000932

[243**]** Wernersson, S., Pejler, G. „Mast cell secretory granules: armed for battle." Nat Rev Immunol 14, 478–494 (2014). https://doi.org/10.1038/nri3690

[244**]** Schnedl, W.J., Schenk, M., Lackner, S. et al. Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. Food Sci Biotechnol 28, 1779–1784 (2019). https://doi.org/10.1007/s10068019006273

[245**]** Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol. 2007;35(4):495516. doi:10.1080/01926230701320337

[246**]** Jones BL, Kearns GL. Histamine: new thoughts about a familiar mediator. Clin Pharmacol Ther. 2011;89(2):189197. doi:10.1038/clpt.2010.256

[247**]** "Histamine Intolerance" IMD Institut fur Medizinische Diagnostik BerlinPotsdam GbR

[248**]** Kacik J., Wawrzyniak A., Rakowska M., Kalicki B. „Symptoms of pseudoallergy and histamine metabolism disorders" Pediatr Med Rodz 2016, 12 (3), p. 234–241 DOI: 10.15557/PiMR.2016.0023

[249**]** Yoshikawa T, Nakamura T, Yanai K. Histamine NMethyltransferase in the Brain. Int J Mol Sci. 2019;20(3):737. Published 2019 Feb 10. doi:10.3390/ijms20030737

[250**]** „HNMT histamine Nmethyltransferase" 8Jul2021 https://www.ncbi.nlm.nih.gov/gene/3176

[251**]** https://en.wikipedia.org/wiki/Histamine_Nmethyltransferase

[252**]** JiménezJiménez FJ, AlonsoNavarro H, GarcíaMartín E, Agúndez JAG. Thr105Ile (rs11558538) polymorphism in the histamine Nmethyltransferase (HNMT) gene and risk for Parkinson disease: A PRISMAcompliant systematic review and metaanalysis. Medicine (Baltimore). 2016;95(27):e4147. doi:10.1097/MD.0000000000004147

[253**]** Laura Maintz, Natalija Novak, Histamine and histamine intolerance, The American Journal of Clinical Nutrition, Volume 85, Issue 5, May 2007, Pages 1185–1196, https://doi.org/10.1093/ajcn/85.5.1185

[254**]** Macías A.M., „The Intestinal Perspective of COVID-19: NOS2 and AOC1 Genes as Epidemiological Factors, and a Homeopathic Approach to their Functional Improvement" 2020; 33(03): 196221 DOI: 10.1055/s00401715601

https://www.thiemeconnect.de/products/ejournals/abstract/10.1055/s00401715601?device=mobile&innerWidth=980&offsetWidth=980

[255**]** Poręba R., Derkacz A., Poręba M., Andrzejak R. „Endothelial function in patients with cardiovascular diseases. Part I: humoral factors and assessment of endothelial function" https://core.ac.uk/download/pdf/268452921.pdf

[256**]** AOC1 Gene https://www.genecards.org/cgibin/carddisp.pl?gene=AOC1

[257**]** Moriguchi T., Takai J., „Histamine and histidine decarboxylase: Immunomodulatory functions and regulatory mechanisms" 12 May 2020 https://doi.org/10.1111/gtc.12774

[258**]** NOS2 nitric oxide synthase 2 Gene ID: 4843 https://www.ncbi.nlm.nih.gov/gene/4843

[259**]** Calderón GM, TorresLópez J, Lin TJ, et al. Effects of toxin A from Clostridium difficile on mast cell activation and survival. Infect Immun. 1998;66(6):27552761. doi:10.1128/IAI.66.6.27552761.1998

[260**]** Nr rejestracyjny: 2015/19/B/NZ7/03830; Kierownik projektu: dr hab. Leszek Marian Kalinowski https://projekty.ncn.gov.pl/opisy/312224pl.pdf

[261**]** Stojek E., Skoczyńska A., „The effect of lead on vascular endothelium" Medycyna Pracy 2003; 54 (1): 87—93 Z Katedry i Kliniki Chorób Wewnętrznych, Zawodowych i Nadciśnienia Tętniczego Akademii Medycznej we Wrocławiu http://www.imp.lodz.pl/upload/oficyna/artykuly/pdf/full/Sto130103.pdf

[262**]** Stockton L, Simonsen C, Seago S. Nitrous oxideinduced vitamin B12 deficiency. Proc (Bayl Univ Med Cent). 2017;30(2):171172. doi:10.1080/08998280.2017.11929571

[263**]** Kawata T, Tamiki A, Tashiro A, et al. Effect of vitamin B12deficiency on testicular tissue in rats fed by pairfeeding. Int J Vitam Nutr Res. 1997;67(1):1721.

[264**]** Proc (Bayl Univ Med Cent). 2017;30(2):171172. doi:10.1080/08998280.2017.11929571

[265**]** TPSAB1 tryptase alpha/beta 1 Gene ID: 7177 https://www.ncbi.nlm.nih.gov/gene/7177

[266**]** Tryptaza https://www.alablaboratoria.pl/badanie/8598/tryptaza

[267**]** https://pl.wikiqube.net/wiki/TPSB2

[268**]** PRSS22 Gene https://www.genecards.org/cgibin/carddisp.pl?gene=PRSS22

[269**]** Huang C, Li L, Krilis SA, et al. Human tryptases alpha and beta/II are functionally distinct due, in part, to a single amino acid difference in one of the surface loops that forms the substratebinding cleft. J Biol Chem. 1999;274(28):1967019676. doi:10.1074/jbc.274.28.19670

[270**]** Caughey GH, Raymond WW, Blount JL, et al. Characterization of human gammatryptases, novel members of the chromosome 16p mast cell tryptase and prostasin gene families. J Immunol. 2000;164(12):65666575. doi:10.4049/jimmunol.164.12.6566

[271**]** Schwartz LB, Min HK, Ren S, et al. Tryptase precursors are preferentially and spontaneously released, whereas mature tryptase is retained by HMC1 cells, MonoMac6 cells, and human skinderived mast cells. J Immunol. 2003;170(11):56675673. doi:10.4049/jimmunol.170.11.5667

[272**]** Ide H, Itoh H, Tomita M, et al. cDNA sequencing and expression of rat mast cell tryptase. J Biochem. 1995;118(1):210215. doi:10.1093/oxfordjournals.jbchem.a124880

[273**]** HaeKi Min, Naotomo Kambe, Schwartz L.B. „Human mouse mast cell protease 7–like tryptase genes are pseudogenes" February 2001 https://doi.org/10.1067/mai.2001.112130

[274**]** Proprietary Name: KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM) https://www.accessdata.fda.gov/cdrh_docs/pdf14/H140006C.pdf

[275**]** Slifka MK, Matloubian M, Ahmed R. Bone marrow is a major site of longterm antibody production after acute viral infection. J Virol. 1995;69(3):18951902. doi:10.1128/JVI.69.3.18951902.1995

[276**]** Rawstron A.C. „Immunophenotyping of Plasma Cells" 01 May 2006 https://doi.org/10.1002/0471142956.cy0623s36

[277**]** Mei HE, Yoshida T, Sime W, et al. Bloodborne human plasma cells in steady state are derived from mucosal immune responses. Blood. 2009;113(11):24612469. doi:10.1182/blood200804153544

[278**]** Bohannon C, Powers R, Satyabhama L, et al. Longlived antigeninduced IgM plasma cells demonstrate somatic mutations and contribute to longterm protection **[**published correction appears in Nat Commun. 2016 Aug 16;7:12687. Lee, Francis EunHyung **[**Lee, Frances EunHyung**]]**. Nat Commun. 2016;7:11826. Published 2016 Jun 7. doi:10.1038/ncomms11826

[279**]** Hotchkiss, R., Moldawer, L., Opal, S. et al. Sepsis and septic shock. Nat Rev Dis Primers 2, 16045 (2016). https://doi.org/10.1038/nrdp.2016.45

[280**]** Funk DJ, Parrillo JE, Kumar A. Sepsis and septic shock: a history. Crit Care Clin. 2009;25(1):83viii. doi:10.1016/j.ccc.2008.12.003

[281**]** Vincent JL, Abraham E. The last 100 years of sepsis. Am J Respir Crit Care Med. 2006;173(3):256263. doi:10.1164/rccm.2005101604OE

[282**]** Zehava L.NoahMD Noah Z.L., „The History of Sepsis Management Over the Last 30 Years"

Clinical Pediatric Emergency Medicine Volume 15, Issue 2, June 2014, Pages 116119

[283**]** „Systemic inflammatory response syndrome"

https://www.ebi.ac.uk/ols/ontologies/efo/terms?iri=http%3A%2F%2Fwww.ebi.ac.uk%2Fefo%2FEFO_1001478&viewMode=All&siblings=false

[284**]** Parsons M. Cytokine storm in the pediatric oncology patient. J Pediatr Oncol Nurs. 2010;27(5):253258. doi:10.1177/1043454210368533

[285**]** Matthew J. Griffee, Matthias J. Merkel, Mark A. Warner; Irwin and Rippe's Intensive Care Medicine, 6th Edition.. Anesthesiology 2008; 108:968–969 doi: https://doi.org/10.1097/ALN.0b013e31816bbdf4

[286**]** Marino, Paul L. (1998). The ICU book. Baltimore: Williams & Wilkins. ISBN 0683055658.**[**9 Tsiotou AG, Sakorafas GH, Anagnostopoulos G, Bramis J (March 2005). "Septic shock; current pathogenetic concepts from a clinical perspective". Medical Science Monitor. 11 (3): RA76–85. PMID 15735579

[287**]** Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis3). JAMA. 2016;315(8):801–810. doi:10.1001/jama.2016.0287

[288**]** Rippe, James M.; Irwin, Richard S.; Cerra, Frank B (1999). Irwin and Rippe's intensive care medicine. Philadelphia: LippincottRaven.

[289**]** Devaji Rao S., Devaji Rao K. „Essentials of Surgery for Dental" Students EBook

[290**]** Grażyna Ciechomska. Groźne oblicze postępu. „Gazeta Lekarska". 01, 2002

[291**]** Cheney C.„New Data on Sepsis Prevalence and Costs 'Astonished' DHHS Researchers." February 2020
https://www.healthleadersmedia.com/clinicalcare/newdatasepsisprevalenceandcostsastonisheddhhsresearchers

[292**]** Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med. 1998;26(12):20782086. doi:10.1097/00003246199812000000045

[293**]** Szczeklik A. : Choroby wewnętrzne. Kraków: Medycyna Praktyczna, 2005, s. t. II, 2068. ISBN 8374300698

[294**]** Dane from Polską Grupą Roboczą ds. Sepsy przy Polskim Towarzystwie Anestezjologii i Intensywnej Terapii https://web.archive.org/web/20100810023400/http://sepsa.pl/

[295**]** https://pl.wikipedia.org/wiki/Sepsa

[296**]** A.S. Fauci, E. Braunwald, K.J. Isselbacher, J.D. Wilson, J.B. Martin, D.L. Kasper, S.L. Hauser, D.L. Longo (red.), Interna Harrisona, Lublin, Wydawnictwo Czelej Sp. z o.o., s. 1151, t. II, 2001, ISBN 8388063413

[297**]** Papageorgiou C., Jourdi G., Adjambri E., Walborn A., Patel P., Fareed J., Elalamy I., Hoppensteadt D., Gerotziafas G.T. „Disseminated Intravascular Coagulation: An Update on Pathogenesis, Diagnosis, and Therapeutic Strategies" 8 Oct 2018 doi: 10.1177/1076029618806424

[298**]** Iba, T., Watanabe, E., Umemura, Y. et al. Sepsisassociated disseminated intravascular coagulation and its differential diagnoses. j intensive care 7, 32 (2019). https://doi.org/10.1186/s405600190387z

[299**]** Levi M.M., Nagalla S. „Disseminated Intravascular Coagulation (DIC) Updated: Dec 06, 2020 https://emedicine.medscape.com/article/199627overview

[300**]** Make J.L. „Disseminated Intravascular Coagulation (DIC)" Jan 2020Jan 2020

https://www.merckmanuals.com/enca/professional/hematologyandoncology/coagulationdisorders/disseminatedintravascularcoagulationdic

[301**]** COVID-19 and Coagulopathy: Frequently Asked Questions 29 January 2021 https://www.hematology.org/Covid-19/Covid-19andcoagulopathy

[302**]** Patel GP, Balk RA. Systemic steroids in severe sepsis and septic shock. Am J Respir Crit Care Med. 2012;185(2):133139. doi:10.1164/rccm.2010111897CI

[303**]** Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with metaanalysis and trial sequential analysis. Intensive Care Med. 2015;41(7):12201234. doi:10.1007/s0013401538996

[304**]** Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304377. doi:10.1007/s0013401746836

[305**]** Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. Cochrane Database Syst Rev. 2019;12(12):CD002243. Published 2019 Dec 6. doi:10.1002/14651858.CD002243.pub4

[306**]** Fang F, Zhang Y, Tang J, et al. Association of Corticosteroid Treatment With Outcomes in Adult Patients With Sepsis: A Systematic Review and Metaanalysis. JAMA Intern Med. 2019;179(2):213223. doi:10.1001/jamainternmed.2018.5849

[307**]** Ni YN, Liu YM, et al. (September 2019). "Can corticosteroids reduce the mortality of patients with severe sepsis? A systematic review and metaanalysis". The American Journal of Emergency Medicine. 37 (9): 1657–64. doi:10.1016/j.ajem.2018.11.040. PMID 30522935

[308**]** AdibConquy M, Cavaillon JM. Stress molecules in sepsis and systemic inflammatory response syndrome. FEBS Lett. 2007;581(19):37233733. doi:10.1016/j.febslet.2007.03.074

[309**]** C.Akin, D.D. Metcalfe „Mastocytosis and mast cell activation syndromes presenting as anaphylaxis". In: Castells MC, editor. Anaphylaxis and hypersensitivity reactions. New York: Humana Press; 2011. p. 24556. http://dx.doi.org/10.1007/9781603279512_15

[310**]** Robert W. Cross, Karla A. Fenton, Joan B. Geisbert, Chad E. Mire, Thomas W. Geisbert, Modeling the Disease Course of Zaire ebolavirus Infection in the Outbred Guinea Pig, The Journal of Infectious Diseases, Volume 212, Issue suppl_2, October 2015, Pages S305–S315, https://doi.org/10.1093/infdis/jiv237

[311**]** Yang, L., Xie, X., Tu, Z. et al. The signal pathways and treatment of cytokine storm in COVID-19. Sig Transduct Target Ther 6, 255 (2021). https://doi.org/10.1038/s41392021006790

[312**]** COVID Overview Common Symptoms https://covidprotocols.org/en/chapters/covidoverview/

[313**]** Coronavirus disease (COVID-19)

https://www.who.int/emergencies/diseases/novelcoronavirus2019/questionandanswershub/qadetail/coronavirusdiseaseCovid-19#:~:text=symptoms

[314**]** Berlin D.A., Gulick R.M., Martinez F.J. „Severe Covid-19" The New England Journal of Medicine (Thapnyeoa)

[315**]** Shahri M.K., Niazkar H.R., Rad F., „COVID-19 and hematology findings based on the current evidences: A puzzle with many missing pieces." (lymphopenia) 02 Dec 2020

[316**]** LopezLeon S., WegmanOstrosky T., Perelman C.,Sepulveda R., Rebelled P.A., Cuapio A., Villapol S., „More than 50 Longterm effects of COVID-19: a systematic review and metaanalysis" 30 Jan 2021 10.1101/2021.01.27.21250617

[317**]** „Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)" CDC Centers for Disease Control and Prevention and 16 Feb 2021 cdc.gov/coronavirus/2019ncov/hcp/clinicalguidancemanagementpatients.html

[318**]** Garvin MR, Alvarez C, Miller JI, et al. A mechanistic model and therapeutic interventions for COVID-19 involving a RASmediated bradykinin storm. Elife. 2020;9:e59177. Published 2020 Jul 7. doi:10.7554/eLife.59177

[319**]** Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. J Allergy Clin Immunol. 2010;126(6):1099104.e4. doi:10.1016/j.jaci.2010.08.035

[320**]** Theoharides TC. Potential association of mast cells with coronavirus disease 2019. Ann Allergy Asthma Immunol. 2021;126(3):217218. doi:10.1016/j.anai.2020.11.003

[321**]** Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020;26:100527. doi:10.1016/j.eclinm.2020.100527

[322**]** "FernándezSarmiento J, De Souza D, Jabornisky R, Gonzalez GA, Arias López MDP, Palacio G. Paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMSTS): a narrative review and the viewpoint of the Latin American Society of Pediatric Intensive Care (SLACIP) Sepsis Committee. BMJ Paediatr Open. 2021;5(1):e000894. Published 2021 Feb 4. doi:10.1136/bmjpo2020000894

[323**]** https://en.wikipedia.org/wiki/Multisystem_inflammatory_syndrome_in_children

[324**]** „Multisystem Inflammatory Syndrome in Children (MISC) Interim Guidance" May 14, 2020,

https://services.aap.org/en/pages/2019novelcoronavirusCovid-19infections/clinicalguidance/multisysteminflammatorysyndromeinchildrenmiscinterimguidance/

[325**]** Pisetsky, D.S. Pus: the Rodney Dangerfield of immunology . Arthritis Res Ther 13, 131 (2011). https://doi.org/10.1186/ar3477

[326**]** Peter M. Irving, MRCP, Marion G. Macey, PhD, Urooj Shah, BSc, Lee Webb, MSc, Louise Langmead, MRCP, David S. Rampton, DPhil, Formation of Plateletleukocyte Aggregates in Inflammatory Bowel Disease, Inflammatory Bowel Diseases, Volume 10, Issue 4, 1 July 2004, Pages 361–372, https://doi.org/10.1097/00054725200407000000007

[327**]** Kurose I, Pothoulakis C, LaMont JT, et al. Clostridium difficile toxin Ainduced microvascular dysfunction. Role of histamine. J Clin Invest. 1994;94(5):19191926. doi:10.1172/JCI117542

[328**]** Calderón GM, TorresLópez J, Lin TJ, et al. Effects of toxin A from Clostridium difficile on mast cell activation and survival. Infect Immun. 1998;66(6):27552761. doi:10.1128/IAI.66.6.27552761.1998

[329**]** Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. Thromb Res. 2012;129(3):290295. doi:10.1016/j.thromres.2011.10.013**]**

[330**]** Sattar A, Willman JE, Kolluri R. Possible warfarin resistance due to interaction with ascorbic acid: case report and literature review. Am J Health Syst Pharm. 2013;70(9):782786. doi:10.2146/ajhp110704

[331**]** ChihYuan Ma, GueyYueh Shi, ChungSheng Shi, YuanChung Kao, ShuWha Lin and HuaLin Wu J Monocytic Thrombomodulin Triggers LPS and GramNegative BacteriaInduced Inflammatory Response Immunol 9 May 2012, 1102266; DOI: https://doi.org/10.4049/jimmunol.1102266

[332**]** Wang X, Meng X., Kuhlman J.R., Nelin L.D., Nicol K.K., English B.K.,Y. J. Liu., Knockout of Mkp1 Enhances the Host Inflammatory Responses to GramPositive Bacteria Immunol April 15, 2007, 178 (8) 53125320; DOI: https://doi.org/10.4049/jimmunol.178.8.5312

[333**]** Selye H. A syndrome produced by diverse nocuous agents. 1936;138:32–3. J Neuropsychiatry Clin Neurosci. 1998;10(2):230231. doi:10.1176/jnp.10.2.230a

[334**]** Leki na alergię i astmę ograniczają liczbę zakażeń COVID-19 i łagodzą przebieg choroby. 12 April 2021
https://forsal.pl/lifestyle/zdrowie/artykuly/8138029,alergicylekiwziewnerzadziejzakazajasieCovid-19.html

[335**]** Alergicy mniej podatni na zakażenie COVID-19. „Lżej przechodzą wirusa" 12.04.2021

https://www.tvp.info/53256033/alergicymniejpodatninazakazenieCovid-19

[336**]** Ekspertka: Alergicy zwykle łagodnie przechodzą COVID-19 11 April 2021

https://zdrowie.radiozet.pl/Choroby/Alergie/AlergiaiCOVID-19alergicylagodniejchorujanaCOVID-19

[337**]** Zolnowska B., „Allergic alveolitis" Borgis Postępy Nauk Medycznych 1/2001, s. 1316

http://www.czytelniamedyczna.pl/2860,alergicznezapaleniepcherzyklwpucnych.html

[338**]** LiebermanCribbin W, Rapp J, Alpert N, Tuminello S, Taioli E. The Impact of Asthma on Mortality in Patients With COVID-19. Chest. 2020;158(6):22902291. doi:10.1016/j.chest.2020.05.575

[339**]** Morán Blanco JI, Alvarenga Bonilla JA, Homma S, Suzuki K, FremontSmith P, Villar Gómez de Las Heras K. Antihistamines and azithromycin as a treatment for COVID-19 on primary health care A retrospective observational study in elderly patients. Pulm Pharmacol Ther. 2021;67:101989. doi:10.1016/j.pupt.2021.101989

[340**]** Dutta, Sanchari Sinha. (2021, June 08). Antihistamines might be effective in longCOVID. NewsMedical. Retrieved on July 18, 2021 from https://www.newsmedical.net/news/20210608/AntihistaminesmightbeeffectiveinlongCOVID.aspx.

[341**]** Reznikov L.R., Norris M.H., Vashisht R., Bluhm A.P., Li D., et at. „Identification of antiviral antihistamines for COVID-19 repurposing" 29 January 2021 Biochemincal and Biophysical Research Communications.

[342**]** Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V.V.; Guo, J.Z.; Swaney, D.L.;et al. „A SARSCoV2 protein interaction map reveals targets for drug repurposing".Nature 2020,583, 459–468

[343**]** Jutel, M.; Watanabe, T.; Klunker, S.; Akdis, M.; Thomet, O.A.R.; Malolepszy, J.; ZakNejmark, T.; Koga, R.; Kobayashi, T.; Blaser, K.; et al. Histamine regulates Tcell and antibody responses by differential expression of H1 and H2 receptors. Nat. Cell Biol. 2001,413, 420–425

[344**]** Dutta, Sanchari Sinha. "Antihistamines might be effective in longCOVID". NewsMedical. 16 July 2021.
https://www.newsmedical.net/news/20210608/AntihistaminesmightbeeffectiveinlongCOVID.aspx

[345**]** Ge S., Wang X., Hou Y., Lu Y., Wang C., He H., Repositioning of histamine H1 receptor antagonist: Doxepin inhibits viropexis of SARSCoV2 Spike pseudovirus by blocking ACE2 https://www.sciencedirect.com/science/article/pii/S0014299921000509)???

[346**]** Geurdes H. „Histamine Antagonists to Temper the Cytokine Overproduction inGastrointestinal Cells Infected by SARSCoV2" Virology & Mycology Virol Mycol Open Access, Vol.9 Iss.2 No:189

[347**]** Lui, C.T. Prescription practice of antihistamines for acute upper respiratory tract infections in pediatric patients in a localemergency department in Hong Kong. World J. Emerg. Med. 2017, 8,47–54.

[348**]** He, S.; Lin, B.; Chu, V.; Hu, Z.; Hu, X.; Xiao, J.; Wang, A.Q.; Schweitzer, C.J.; Li, Q.; Imamura, M.; et al. Repurposing of theantihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. Sci. Transl. Med. 2015, 7, 282ra49.

[349**]** Theoharides, T.C. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. BioFactors 2020, 46, 306–308.

[350**]** Qu C, Fuhler GM, Pan Y. Could Histamine H1 Receptor Antagonists Be Used for Treating COVID-19?. Int J Mol Sci. 2021;22(11):5672. Published 2021 May 26. doi:10.3390/ijms22115672

[351**]** Tachoua W.; Kabrine M.; Mushtaq M.; UlHaq Z. „An insilico evaluation of COVID-19 main protease with clinically approved drugs" J. Mol. Graph. Model. 2020

[352**]** Cirino G, Cicala C, Bucci MR, Sorrentino L, Maraganore JM, Stone SR. Thrombin functions as an inflammatory mediator through activation of its receptor. J Exp Med 1996;183:8217

[353**]** Huilan Z., Bihua L., Runxiang L., Jiayan L., Luyang L., Zhenjie L., „Features of antihistamineresistant chronic urticaria and chronic urticaria during exacerbation" Department of Dermatology, Guangzhou Institute of Dermatology, Guangzhou, Guangdong, China, Year 2015, Volume 60, Issue 3, Page 32

[354**]** Conti P, Caraffa A, Tetè G, et al. Mast cells activated by SARSCoV2 release histamine which increases IL1 levels causing cytokine storm and inflammatory reaction in COVID-19. J Biol Regul Homeost Agents. 2020;34(5):16291632. doi:10.23812/202EDIT

[355**]** Smolinska S, Jutel M, Crameri R, O'Mahony L. Histamine and gut mucosal immune regulation. Allergy. 2014;69(3):273281. doi:10.1111/all.12330

[356**]** Flippo TS, Holder WD. Neurologic Degeneration Associated With Nitrous Oxide Anesthesia in Patients With Vitamin B12 Deficiency. Arch Surg. 1993;128(12):1391–1395. doi:10.1001/archsurg.1993.01420240099018

[357**]** Wicinski M., Marciniak A. „Skrypt do ćwiczeń z farmakologii" Warszawa 2015 https://wsiiz.pl/dokumenty/wydawnictwo/publikacje/skrypt_do_cwiczen_z_farmakologii.pdf

[358**]** TarchalskaKrynska B. "H1, antihistamines used in treatment of allergic diseases" z Katedry i Zakładu Farmakologii Doświadczalnej i Klinicznej Akademii Medycznej w Warszawie, Borgis Nowa Medycyna 1/1999, s. 1418

[359**]** Takehara M, Seike S, Sonobe Y, et al. Clostridium perfringens αtoxin impairs granulocyte colonystimulating factor receptormediated granulocyte production while triggering septic shock. Commun Biol. 2019;2:45. Published 2019 Jan 31. doi:10.1038/s4200301902802

[360**]** Strandberg K., Mollby R., Wadstrom.T., „Histamine release from mast cells by highly purified phospholipase C (alphatoxin) and thetatoxin from Clostridium perfringens" Toxicon, Volume 12, Issue 2 March 1974, Pages 199208

[361**]** „Katzung B.G., Masters S.B., Trevor A.J., Farmakologia ogolna i kliniczna" 2012

[362**]** Wadelek J., „Pulmonary atelectasis in anaesthetic practice Part II. Prevention and treatment”

https://www.akademiamedycyny.pl/wpcontent/uploads/2018/01/74.pdf

[363**]** Poopalalingam R, Goh MH, Chan YW. The effect of heat and moisture exchanger and gas flow on humidity and temperature in a circle anaesthetic system. Singapore Med J. 2002;43(11):563565

[364**]** Matjaz Preseren Scientific Affairs & Education Manager IPD, ‚Prezentacja na temat: "Normotermia okołooperacyjna wytyczne i rekomendacje"— Zapis prezentacji” CEE Region Lodz, May 19, 2015 https://slideplayer.pl/slide/4867409/

[365**]** Young VL, Watson ME. Prevention of perioperative hypothermia in plastic surgery. Aesthet Surg J. 2006;26(5):551571. doi:10.1016/j.asj.2006.08.009

[366**]** Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020;16(8):413414. doi:10.1038/s4158402004487

[367**]** Akca U.K., Kesici S., et al. Kawasaki like disease in children with Covid-19. 16 Sep 2020 PMC7492688

[368**]** Liu ZQ, Li XX, Qiu SQ, et al. Vitamin D contributes to mast cell stabilization. Allergy. 2017;72(8):11841192. doi:10.1111/all.13110

[369**]** Yoshikawa T, Nakamura T, Yanai K. Histamine NMethyltransferase in the Brain. Int J Mol Sci. 2019;20(3):737. Published 2019 Feb 10. doi:10.3390/ijms20030737

[370**]** Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol. 2011;4:10. Published 2011 Mar 22.

[371**]** Showing metabocard for Amantadine (HMDB0015051) https://hmdb.ca/metabolites/HMDB0015051