Науково-практична міжнародна
дистанційна конференція

МІКРОБІОЛОГІЧНІ ТА ІМУНОЛОГІЧНІ ДОСЛІДЖЕННЯ В СУЧАСНІЙ МЕДИЦИНІ

24 березня 2022р,
м. Харків , Україна

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА МІКРОБІОЛОГІЇ, ВІРУСОЛОГІЇ ТА ІМУНОЛОГІЇ

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
DEPARTMENT OF MICROBIOLOGY, VIROLOGY AND IMMUNOLOGY

МІКРОБІОЛОГІЧНІ ТА ІМУНОЛОГІЧНІ ДОСЛІДЖЕННЯ В СУЧАСНІЙ МЕДИЦИНІ
MICROBIOLOGICAL AND IMMUNOLOGICAL RESEARCH IN MODERN MEDICINE

Матеріали
Науково-практичної міжнародної
дистанційної конференції
Materials of the Scientific and Practical International
Distance Conference

ХАРКІВ
KHARKIV
2022

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

КАФЕДРА
МІКРОБІОЛОГІЇ, ВІРУСОЛОГІЇ ТА ІМУНОЛОГІЇ

МІКРОБІОЛОГІЧНІ ТА ІМУНОЛОГІЧНІ ДОСЛІДЖЕННЯ В СУЧАСНІЙ МЕДИЦИНІ

Матеріали
Науково-практичної міжнародної
дистанційної конференції

24 березня 2021 року
Харків

УДК: 579:578:61(06)

Конференція внесена до реєстру з'їздів, конгресів, симпозіумів та науково-практичних конференцій, які проводитимуться у 2022 році, реєстраційне посвідчення УкрІНТЕІ № 893, від 08 листопада 2021 року.

Мікробіологічні та імунологічні дослідження в сучасній медицині: матеріали науково-практичної міжнародної дистанційної конференції (24 березня 2022 р., м. Харків). – Електрон. дані. – Х. : НФаУ, 2022. – 108 с. –Назва з тит. екрана.

Збірка містить матеріали науково-практичної міжнародної дистанційної конференції «Мікробіологічні та імунологічні дослідження в сучасній медицині». Розглянуто актуальні питання фармацевтичної мікробіології, перспективи створення антимікробних препаратів, їх застосування в медичній практиці, вивчення антибіотикорезистентності мікроорганізмів та визначення шляхів її подолання, клінічної патофізіології та епідеміології інфекційних захворювань, клінічної імунології та алергології, досягнень вірусологічних, молекулярно-генетичних досліджень в лабораторній діагностиці, актуальні питання ветеринарної мікробіології, інформаційних технологій і автоматизації наукових досліджень з розробки антимікробних лікарських засобів, маркетингових досліджень сучасного фармацевтичного ринку хіміотерапевтичних препаратів.
Для широкого кола наукових, науково-педагогічних і практичних працівників, що займаються питаннями мікробіології, вірусології, імунології, алергології та фармації в цілому.

Матеріали подаються мовою оригіналу в авторській редакції.
За достовірність матеріалів відповідальність несуть автори.

УДК: 579:578:61(06)

UDC: 579:578:61(06)

The Conference has been included in the list of meetings, congresses, symposia, and scientific-practical conferences to be held in 2022, registration certificate UkrIntel № 893, dated October, 08, 2021.

Microbiological and Immunological Research in Modern Medicine: Materials of Scientific and Practical International Distance Conference (24 March 2021, Kharkov). – Electron. data. – Kharkiv: National University of Pharmacy, 2022. – 108 p.

The collection contains materials of scientific and practical international distant conference "Microbiological and immunological research in modern medicine". Shows the latest issues of pharmaceutical microbiology, prospects of antimicrobial drugs, their use in medical practice, antibiotic resistance of microorganisms and ways to counteract it, clinical pathophysiology and epidemiology of infectious diseases, clinical immunology and allergology, advances in virological, molecular genetic studies in laboratory diagnostics, current issues of veterinary microbiology, information technologies and automation of scientific research into antimicrobial medicines development, marketing research of modern pharmaceutical market of chemotherapeutic preparations.
For a wide range of scientists, educators and practitioners involved in microbiology, virology, immunology, allergology and pharmacy in general.

Materials are submitted in the original author's language.
Authors are responsible for the authenticity of the materials.

UDC: 579:578:61(06)

IMMUNE SYSTEM CELLS IN THE DYNAMICS OF EXPERIENCED OSTEOMIELITIS AND CHANGES IN THE BLOOD LEUKEYTO NUMBER

Ergashev V.A.

Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan

valialimovich777@gmail.com

Experimental study and statistical analysis of the degree of changes in the cells of the central and peripheral organs of the immune system, quantitative and qualitative indicators of changes in blood leukocytes in laboratory animals in the dynamics of acute and chronic osteomyelitis.

Due to the need for immediate treatment with the detection of acute and chronic osteomyelitis, their pathogenetic mechanisms, immuno-microbiological aspects are still unclear, as the impact of treatment on the microorganism, as well as specific and non-specific protective factors of macroorganism. Based on the above findings, chronic experimental osteomyelitis under the influence of pathogenic strains of S. aureus and P. aureginosa was induced in laboratory animals, i.e., white non-mice, with tuberculous bone injuries. In chronic osteomyelitis, the pathological process was observed to be different from the acute one. The fact that leukocytes are one of the drivers of purulent-inflammatory processes and their nature and the severity of the transition, their quantitative changes indicate the intensity and duration of this process in the body. On the 30th day of chronic experimental osteomyelitis in laboratory animals, the leukocyte count increased significantly from an average of 4.5 ± 0.2x109 / l (control group) to 6.9 ± 0.3x109 / l (main group) by 1.55 times (P <0, 05) observed.

A significant increase in the number of leukocytes in the blood in the main group is a sign not only of the development and continuation of a chronic process (chronic experimental osteomyelitis), but also its high level for so long that the immune system is not active enough. A similar trend was observed with changes in the number of leukocytes in the blood was determined. Compared with the previous period of chronic experimental osteomyelitis, it was noted that their number increased even more, and the difference between groups increased even more. This is an indication that the process of purulent inflammation is not only ongoing, but intensifying.

Thus, when chronic experimental osteomyelitis was called, the study of quantitative indicators of immune system cells showed a significant decrease in them in the main group compared to the control group (R <0.05-R <0.001), the intensity of the decrease was different across cells, compared with the previous study period (30 days) was recognized as a relative deepening of the gap. Thus, when chronic experimental osteomyelitis was called, the study of quantitative indicators of immune system cells showed a significant decrease in them in the main group compared to the control group (R <0.05-R <0.001), the intensity of the decrease was different across cells, compared with the previous study period (30 days) was recognized as a relative deepening of the gap. An increase in the difference between the numbers was more pronounced on the stimulation indices.

Also, the tendency to increase the number of leukocytes was synchronized with the quantitative decrease of cells and was inversely proportional to them, i.e., an increase in one indicator was followed by a decrease in other parameters.

On the 30th day of the course of chronic experimental osteomyelitis, specific changes in the quantitative indicators of cells of the immune system were also observed. The amount of antibody-forming cells (ABFC antibodies forming cells) in the main group decreased significantly 1.90 times compared to the control group - 1496 ± 184 cells ($R < 0.001$) 1 million against 2841 ± 174 cells, respectively. There was also a downward trend in the amount of ABFC per cell, but the intensity of the decrease was less than the previous parameter -1.38 times (16 ± cells against 22 ± 2 cells, $R < 0.05$).

In spleen, there was a downward trend in the number of nuclear storage cells (NSCS nuclear storage cells of spleen) as in the previous parameter — 137 ± 6 cells (1.17 times, $R < 0.05$) versus 160 ± 4 cells, respectively. The intensity of the decline in this indicator was also lower than in the ABFC. We explained this condition by the different degrees of impact of chronic osteomyelitis on the cells of the immune system, showing that the cells directly involved in the immune response were more damaged than others. The comparative study of the number of cells of the central organs of the immune system (thymus, bone marrow) and peripheral organs (lymph nodes-peyerov nodes) did not show significant differences, the trend of changes was the same as in the control group. Thymus (18 ± 2 cells vs. 56 ± 4 cells $R > 0.05$), bone marrow (15 ± 1 cells vs. 14 ± 2 cells), a small number of unreliable decrease lymph node cells (24 ± 2 vs. 20 ± 1 cells, $R < 0.05$) was in sync with the decrease. If in acute experimental osteomyelitis the main group showed a tendency to increase the number of cells of these three organs compared to the control group, in chronic experimental osteomyelitis we observed the opposite. In acute osteomyelitis, the level of activity of the immune system is high, which indicates that the pathogens and the inflammatory process they cause are combated, but in the chronic process, the body's reserves of compensatory-adaptive mechanisms are depleted, cells do not proliferate and differentiate. In other words, the deficit in the immune system is deepening. This, in turn, indicates that the immune system has little influence on this pathological process and allows it to persist.

Conclusion: The study of quantitative indicators of immune system cells recognized that their reduction in the main group was significantly lower than in the control group, the intensity of the decrease was different from each other in the cells, the difference was deeper than in the previous study (30 days) showed a decrease in the ability of the system to cope with the process of purulent inflammation, which deepened the deficit.

THE DISTRIBUTION OF *S.* PULLORUM IN DIFFERENT ORGANS OF CHICKEN USING IN SITU HYBRIDIZATION

Liu Zhike, Anatoliy Fotin, Tetiana Fotina
Sumy National Agrarian University, Sumy, Ukraine
624039729@qq.com, fotin53@ukr.net, tif_ua@meta.ua

Salmonella enterica serovar Pullorum (*S.* Pullorum) is a host-restricted serotype of *Salmonella*, which has high morbidity and mortality to poultry. The invasion protein A (*invA*) is critical for *Salmonella* virulence, as a diagnostic marker of *Salmonella*. To analyze the distribution of *S.* Pullorum in different organs, 3-day-old Jinghong laying hens (specific pathogen-free) were immunized with *S.* Pullorum at 1×10^7 CFU in 100 μL of PBS by oral gavage. Control groups received 100 μl of PBS. At 3 days post challenge, the liver, lung, spleen, heart, cecum, and bursa were collected from 10 chickens of each group. The organs of infected chicken were fixed with 4% paraformaldehyde for 48 h, embedded in paraffin and cut into 4 μm sections by paraffin slicer. The *invA* expression in organs was detected by the fluorescence assay in situ hybridization (ISH) with an oligonucleotide probe. According to published conserved nucleotide sequence of *invA* (GenBank : NC003197.1), the probe sequence was 5'-AGGTGGTCTTAAGCGTTG-3' as a capture probe, and FITC was labeled at the 5'end as the diagnostic signal. A large number of positive signals were observed in the area of liver necrosis and hepatic sinuses compared to those of control group. Additionally, there were positive signals between myocardial fibers, and also have more positive signals in the red pulp of spleen. A small number of positive signals were observed in the alveolar wall, cecal submucosa, intestinal villi and cortex of the bursa. In conclusion, *S.* Pullorum can colonize in different organs after infecting chickens, and the positive signals are most widely distributed in the liver tissue, especially in the necrotic area. Taken together, This study provides crucial technical support for the study of distribution of *Salmonella* in vivo. Altogether, our work makes a significant contribution to the literature because the results described herein are relevant in understanding the pathogenicity associated with *invA* in Salmonella Pullorum, which is an important pathogen in poultry.

EPIDEMIOLOGICAL FEATURES OF THE COURSE OF LEPTOSPIROSIS

Mansurova M.H.
Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan
malikamansurova630@gmail.com

Leptospirosis is an acute infectious disease caused by bacteria of the genus *Leptospira*.

The disease is characterized with predominant damage to the kidneys, liver, nervous and vascular systems, often with the development of hemorrhagic syndrome and jaundice.

Leptospira are hydrophiles. Therefore, a favorable environment for them is considered high humidity and heat. Leptospirosis is ubiquitous.

Only in the conditions of Antarctica it is impossible to get sick with an illness. The disease is especially common in tropical countries.

The main sources of this infection for humans are mouse-like rodents (primarily rats), some types of domestic (cattle, pigs, dogs) and wild animals (nutria, foxes).

Sick animals excrete leptospiras into the external environment with urine for a long time. A person with leptospirosis is not a source of infection.

Infection of humans most often occurs through contact of the skin and mucous membranes with water contaminated with animal secretions. Contact with moist soil is important, as well as when slaughtering infected animals, cutting meat, and eating infected products contaminated with secretions of infected rodents.

The disease often has an occupational character. Deratizers, people working in wetlands are more likely to get sick.

Leptospirosis has an acute onset, the patient has a sudden increase in body temperature to 39-40 °C, symptoms of severe intoxication (headaches, nausea, vomiting, dizziness, clinically resembles influenza) are rapidly increasing. Then myalgia occurs (pain in the calf muscles and muscles of the lower back), which may be accompanied by skin hyperesthesia.

The temperature remains at high values for ten days, and already on the third day the first manifestations of the hemorrhagic syndrome are observed (hemorrhages in the subcutaneous fatty tissue, internal bleeding - intestinal, gastric, pulmonary, hemarthrosis, etc.). Pain in the muscles reaches such a level that patients with leptospirosis practically cannot move independently.

DIFFERENTIATION OF BACTERIA OF THE GENUS *PROTEUS* FROM BACTERIA OF THE GENUS *SALMONELLA*

Nazarov J.-S. E.
Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan
sultannazarov050@gmail.com

Bacteria of the genera *Proteus* and *Salmonella* are Gram-negative, facultative anaerobic, non-spore-forming bacteria. Most representatives of these genera have flagella (peritrichous) and, as a rule, do not ferment lactose. However, if bacteria of the genus *Proteus* are opportunistic microorganisms, then *Salmonella* is pathogenic for humans and animals, causing salmonellosis. The main test for differentiating *Proteus* from *Salmonella* is a positive test for urease, as well as seeding on Olkenitsky's medium. Salmonella are lactose-negative gram-negative rods that do not ferment lactose. According to these properties, proteuses are similar to salmonella, which, unlike the former, can break down urea.

Another characteristic property of proteuses is their ability to swarm. Like Proteus, the character of ancient Greek mythology, who had the unique ability to reincarnate (metamorphosis), bacteria of this genus often show pleomorphism on a dense nutrient medium. Bacteria form many daughter colonies, and their population is constantly increasing in the environment. Foods contaminated with *Proteus* are usually discarded, and water containing *Proteus* should not be drunk. The detection of these bacteria in the water of open reservoirs and in the study of therapeutic mud is officially called "Proteus meter". Water Proteus meter is officially recognized in the USA and in some countries of the European Union. In the Russian Federation, Proteus meter is recommended for the study of water in open reservoirs, therapeutic mud. The presence of bacteria of the genus *Proteus* in water and soil may indicate faecal contamination of the environment in which these proteolytic bacteria are considered as allochthonous. Proteuses live in the intestines of humans and many animals, and enter the external environment along with feces. The detection of *Proteus mirabilis* bacteria in water sources is considered as an indicator of faecal contamination, and *Proteus vulgaris* as an indicator of object contamination with organic substances. According to these data, proteuses are classified as sanitary indicative microorganisms.

In July 2021, a water sample was taken from Samanid Lake, located in the western part of the city of Bukhara, to detect salmonella. When sown on Endo's medium, the next day, colorless colonies were found characteristic of lactose-negative bacteria, but growth of colonies was noted in the form of a veil-like plaque, which is inherent in proteuses. For differentiation, suspicious colonies were isolated on Olkenitsky's medium (the triple sugar iron medium with urea). The culture was inoculated by piercing the medium with a microbiological loop in the center of the agar column to the very bottom of the tube.

The samples were placed in a thermostat at 37°C for 24 hours. After that, an assessment was made of the change in the appearance of the environment. Initially, the

medium was pink in color, blackening of the medium upon injection (formation of hydrogen sulfide) was observed in the column, while the sloping part of the nutrient medium was bright crimson. In Olkenitsky's medium, with the growth of a culture that hydrolyzes urea, the medium acquires a diffuse bright red-crimson color. These facts indicated the absence of Salmonella and the presence of *Proteus vulgaris* (formation of indole and H_2S). Fermentation of glucose by Salmonella is manifested by a change in the color of the column of the medium to yellow, while maintaining the pink color of the "tongue" of the medium. The formation of a blackening zone and a change in the color of the medium from pink to raspberry red indicated the absence of *Salmonella spp*. and the presence of *Proteus spp*. Although the presence of *Proteus vulgaris* indicated the contamination of this water body with organic substances, nevertheless, the absence of pathogenic enterobacteria in the Samanid Lake was proved.

PARTICULARITIES OF THE CLINICAL-MICROBIOLOGICAL STATE OF THE ORAL MUCOSAL IN GRAVID FEMALES

Nodar Sulashvili [1]., Kakhaber Robakidze [2]., Magda Davitashvili [3]., Irma Buchukuri [4]., Lela Grigolia [5]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia,
[2]National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;
[3] Iakob Gogebashvili Telavi State University, Telavi, Georgia.
[4] Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;
[5] Caucasus International University; Tbilisi, Georgia
n.sulashvili@ug.edu.ge

Maternal and child health protection is the most important task of medicine, in the solution of which representatives of various health departments are involved, including the dental service. This is due to the fact that pregnancy leads to neurohumoral changes that cause changes in the activity of a number of organs and body systems, including the oral cavity. It is known that pregnant women have a high intensity of dental diseases. At the same time, the pathology of teeth and periodontal disease can create "dental chronic foci", which are detected not only by the return of microbial penetration into the body, but also as a source of long-term pathological reflex irritation in the body, causing complications during pregnancy, childbirth and the postpartum period. Therefore, among the various types of medical care, dental, is mandatory at all stages of maternal and child health. All this testifies to the unreasonableness of a one-time examination and sanitation of the oral cavity of pregnant women. It is necessary to conduct dynamic monitoring of the state of the oral organs of a woman throughout pregnancy in order to identify the initial forms of the disease, monitor the effectiveness of sanitation and prevent the development of complications. Therefore, the prevention of dental diseases in pregnant women at all stages is of great importance. According to leading dentists, pregnancy is a critical period for a woman's dental health. Its consequences are progressive periodontal

diseases, the development of dental caries and inflammatory and destructive lesions of the mucosa. The relationship between oral dysbiosis and disorders of local factors of mucosal protection in the onset and development of dental diseases is obvious.

Pregnancy is one of the most important stages in a woman's life. But pregnancy is stress for the female body, which in its own way and in different ways affects all its systems and organs, including the oral cavity. During this period, the teeth begin to crumble, crumble and fall out, and the gums begin to bleed. Changes in the hormonal background of pregnant women are reflected even in the composition and properties of saliva, which during this period contributes to the development of caries. Gums during pregnancy are supplied with a large amount of blood, which makes them loose and accessible to pathogenic bacteria. The result is inflammation in the mouth. The consequence is gingivitis. Untreated, it develops into periodontitis, the main symptom of which is bleeding. In view of the above, the study of the microflora of the oral cavity in pregnant women was considered relevant.

As it known that pregnancy is constantly affected by hormonal, metabolic and immunological factors, which can affect the oral microbiota, leading to gingivitis during pregnancy. However, it is not yet clear how microbial dysbiosis in the oral cavity modulates oral disease, since the oral microbiome is poorly characterized during pregnancy. In addition, the recent discovery that the placenta microbiome is similar to the oral microbiome reinforces the importance of oral dysbiosis in adverse pregnancy outcomes. Thus, using the rRNA gene sequencing method, we present a snapshot of the changes in the microbial composition of the oral cavity, depending on the progression of pregnancy and the period of birth and its relationship with gingivitis during pregnancy. Despite the stability of oral microbial diversity during pregnancy and postpartum, we observed that the microbiome undergoes pathogenic changes during pregnancy and returns to a healthy microbiome in the postpartum period. The network-based coexistence analysis provided a mechanistic explanation for the pathogenicity of the microbiome during pregnancy and foreseen frequencies in the interaction centers. Individual dachshunds that form organic companies in the main microbiome can modulate the pathogenicity of microbes during pregnancy and reduce the risk of oral disease and adverse pregnancy outcomes. Our study also highlighted the potential for the appearance of new species in subgingival plaques and saliva, which are important contributors to the development of gingivitis during pregnancy. The key species may offer opportunities to develop strategies to modulate the microbiome and improve the health of the host during pregnancy. Infection-related premature births have been cited as the main cause of infant mortality and morbidity. As the literature shows, 40% of premature births are vaginal and associated with intrauterine infections and 50% are associated with intra-amniotic infections. Given this history, it is necessary to understand the origin of the attacking bacteria and the invasive routes of the placenta and amniotic fluid cavity. Literature shows that the most common intra-amniotic bacterial toxins were types associated with the vagina, although other types are often associated with the oral cavity, gastrointestinal tract, and respiratory tract. The authors concluded that the pooled

data indicate a primary role for the ascending route of infection during pregnancy and a possible secondary role for the hematogenous invasion route.

Based on the foregoing, we set the goal of the study - to study the quantitative and qualitative composition of the oral microflora and indicators of local protection factors in pregnant women suffering from periodontitis according to trimesters. According comprehensive study results found 100 pregnant women aged 25-45 years, suffering from periodontitis and being examined at the perinatal center of the National Health Center named after V.I. acad. About Gudushauri Tbilisi. The surveyed women were equally (25 women) divided into 4 groups: the first group consisted of pregnant women with no oral diseases; the second group included pregnant women who had periodontitis in the 1st trimester; the third group consisted of pregnant women suffering from periodontitis from the 2nd trimester and the fourth group consisted of pregnant women suffering from periodontitis from the 3rd trimester of pregnancy.

Microbiological research. Oral fluid was taken from all examined pregnant women by flushing from the mucous membrane. The material obtained by this method was considered as the first dilution; a series of serial dilutions were prepared from this material in the laboratory. Subsequently, a certain volume was poured onto the surface of differential diagnostic media: agar for anaerobes, Endo's medium, milk-salt agar, Sabouraud's medium, freshly cut mesopatamia agar, etc. Inoculations on blood agar, Endo, milk-salt agar, Saburo were cultivated under normal conditions for 18-24 hours at a temperature of 37 ° C, and the cultivation of anaerobes was carried out in an anaerobic container, which was placed in a thermostat for 3-5 days. After the indicated time, the dishes with the inoculations were taken out of the thermostat, the grown colonies were counted, the group and species belonging of the isolated colonies of microbes were determined on the basis of microscopy data of smears stained according to Gram, the nature of growth on selective and differential diagnostic media. When working according to the modified method, the result was taken into account according to the last dilution, in which the growth of bacteria was obtained, the number of microbes was expressed in lq M ± m colony-forming units (KFU)/ml. Microbiological studies to study the quantitative and qualitative indicators of the oral microflora in pregnant women showed that the oral microflora of healthy pregnant women is quite diverse. At the same time, lactobacilli prevail in the anaerobic group of microbes, their number was 4.4 ± 0.18 CFU / ml. In the facultative group of microbes, streptococci and staphylococci are dominant, while among streptococci the most popular are Str. Salvarius. A completely different picture in the microecology of the oral cavity in pregnant women in the first trimester, suffering from periodontitis. In particular, in the examined pregnant women, significant dysbiotic changes are observed, both in the anaerobic and in the facultative group of microbes. So in the anaerobic group there is a significant decrease, while it is especially pronounced in lactobacilli, their number was 2.8 ± 0.4 CFU / ml, which is more than 2 orders of magnitude lower than the norm. However, even more pronounced changes were noted in the optional group. This is how the number of Str. mutans increased significantly and was equal to 5.35 ± 0.15 CFU / ml, but the appearance of

pathogenic staphylococcus strains in this arsenal is especially alarming. Most likely, these strains possessing a wide range of pathogenic enzymes and will determine the monitoring of the oral cavity in these pregnant women. The next group of pregnant women with periodontitis consisted of women in the second trimester of pregnancy. The analysis of the obtained microbiological studies of the oral cavity in this group of women shows that all the existing dysbiotic changes in the first trimester of pregnancy passed into the second, more of this change deepened even more, especially with regard to a decrease in the number of lactobacilli, but against this background, an increase in the number of microbes such as: strains of golden and Staphylococcus epidermidis, Escherichia and fungi of the genus Candida. A rather interesting picture was obtained during microbiological studies of the oral cavity in pregnant women with periodontitis in the third trimester of pregnancy: in this trimester, generally positive changes appeared, which affected both the anaerobic and the optional group. Particularly significant changes affected microbes such as streptococci, the number of strains of which increased in all three colonies. At the same time, it is especially positive that pathogenic strains of staphylococci and fungi of the genus Candida were eliminated from the oral cavity. Thus, summing up the studies carried out, it can be argued with a high degree of reliability that the most pronounced dysbiotic changes in the oral cavity in pregnant women with periodontitis are observed in the second trimester, which must be taken into account by dentists. Based on the conducted microbiological studies in pregnant women with periodontitis, who are in different trimesters, almost the same type of changes was revealed. Although it should be noted that these changes actually have a positive correlation between indices of local defense factors and dysbiotic changes in the oral flora. The conducted studies allow us to draw the following conclusions: In pregnant women suffering from periodontitis in all three trimesters, dysbiotic changes occur, a characteristic feature of which is a decrease in lactobacilli and an increase in the number of staphylococci and fungi of the genus Candida. At the same time, it should be noted that the changes are most pronounced in the second trimester of pregnancy.

The conducted studies allow us to draw the following conclusions: In pregnant women suffering from periodontitis in all three trimesters, dysbiotic changes occur, a characteristic feature of which is a decrease in lactobacilli and an increase in the number of staphylococci and fungi of the genus Candida. At the same time, it should be noted that the changes are most pronounced in the second trimester of pregnancy.

SOME MICROBIOLOGICAL INDICATORS OF THE ORAL CAVITY OF ORTHOPEDIC PATIENTS

Nodar Sulashvili[1], Kakhaber Robakidze[2], Irma Buchukuri [3], Lela Grigolia[4], Magda Davitashvili[5]

[1]Alte University, International School of Medicine, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[3]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;

[4]Caucasus International University; Tbilisi, Georgia;

[5]Iakob Gogebashvili Telavi State University, Telavi, Georgia

n.sulashvili@ug.edu.ge

The microflora of the oral cavity is a set of representatives of various taxonomic groups of microorganisms that inhabit the oral cavity as a kind of ecological niche of the human body, entering into biochemical, immunological and other interactions with the microorganism and with each other. Any imbalance in this set is a harbinger of diseases of the oral mucosa. Orthopedic devices cause regular irritation of the mucous membrane. These irritations reduce the activity of oral natural resistance factors, which, in turn, causes an imbalance in the oral microflora.

The successes achieved to date in the treatment of malocclusion pathology using orthodontic technology can significantly expand the indications for its use. A wealth of clinical experience has been accumulated in achieving functional and aesthetic effects in adult patients, aggravated by chronic inflammatory periodontal diseases, including those accompanied by destructive lesions. Nevertheless, studies by a number of authors indicate an increase in the percentage of complications of orthodontic treatment, the most frequent of which is an exacerbation of chronic inflammatory periodontal diseases. A kind of risk zone for exacerbation of chronic inflammatory periodontal diseases are those parts of the dentition to which force is applied. Orthodontic constructions change the relief of the dentition, significantly increase the potential area of possible adhesion of microorganisms, make it difficult to remove plaque, which prompts the search for informative criteria for monitoring the course of a chronic infectious and inflammatory process in the oral cavity under permanently acting conditions.

It is known that biotopes of the oral cavity are the most contaminated areas of the human body, characterized by qualitative and quantitative diversity. At the same time, pathogenicity is maximally manifested in the presence of dental plaque, a multi-species community of microorganisms located on the surface of the teeth in the form of a biological layer. These Bio-layers have a high level of tolerance to antiseptics and phagocytes. Literary sources indicate that with unsatisfactory oral hygiene in orthodontic patients, the concentration of fungal flora (yeast and fungi of the genus Candida) increases relative to the normal microflora of the oral cavity. Carriage of periodontal pathogenic strains was established by some authors in 70 % of the examined, of which 30 % of those in need of orthodontic treatment are at risk of

developing periodontitis. However, we did not find information on the dynamics of qualitative and quantitative changes in the microbial landscape in the process of orthodontic treatment, which determined the purpose of this study.

The study involved 60 patients (20 men and 40 women) aged 25 to 45 years, undergoing orthodontic treatment using fixed structures. All patients in the study group were diagnosed with the crowded position of the anterior teeth of the upper and lower jaw. The patients of the study group were ranked into three subgroups (based on the burden of inflammatory periodontal diseases): the first subgroup – patients with intact periodontal disease, the second – patients with chronic generalized gingivitis, the third – with chronic generalized mild periodontitis. Patients in all groups were divided equally – 20 persons. The criteria for the inclusion of patients in the study group were: confirmed diagnosis of dentoalveolar anomaly (based on data from clinical, X-ray studies, diagnostic models of the jaws), absence of endocrinological / somatic burden; denial of a history of taking medications, dietary supplements, probiotics, toothpastes containing antibacterial additives; consent to participate in the study. The comparison group consisted of 50 patients, comparable in gender and age composition, burden of orthodontic pathology, chronic inflammatory periodontal diseases, who did not receive orthodontic treatment. All patients in the comparison group were also ranked into 3 subgroups according to the above principle: the first subgroup included 15 patients, the second – 15 patients, and the third – 20 patients. All patients of the study group and the comparison group confirmed their consent to participate in the study. To verify the periodontal diagnosis, a complex of clinical and radiological research methods was used. Assessment of the state of the oral cavity and periodontal tissues was carried out using hygienic (Green – Vermillion) and periodontal (periodontal index (PI) according to Russell, index of bleeding according to Mullemann-Cowell) indices. To determine the degree of microbial contamination, the material was taken on an empty stomach or 3-4 hours after a meal. On the day of taking the material for research, the patient must refrain from brushing his teeth, using drugs and rinsing the mouth with elixirs or rinses containing antiseptic components of plant/chemical origin.

Material for research was obtained from the cervical area of the teeth in the area of the orthodontic construction, the gingival sulcus / periodontal pocket using sterile paper endodontic pins, which were then placed in a test tube with a transport medium. The material was taken three times: at the diagnostic stage, 3-4 weeks, 3 and 6 months after fixation of fixed orthodontic equipment, at the beginning of the retention period. Before fixing the structural elements, all patients with inflammatory periodontal diseases underwent periodontal treatment. The biomaterial was sown on solid and semi-liquid nutrient media for the cultivation of microorganisms under aerobic and anaerobic conditions. Used 5 % blood agar, Sabouraud's medium, streptococcal selective agar, yolk-salt agar, thioglycolic medium, de Man's medium, Rogosa, Sharpe (MRS) agar, Blaurock's medium. The isolated microorganisms were identified by conventional methods, taking into account the morphological, cultural and biochemical properties. To determine the degree of microbial contamination of the studied biotopes with

periodontal pathogenic strains, the PCR method was used. For statistical processing, we used the Statistical Package for Social Science – Statistical Package for Social Sciences. To check the normality of the distributions, the Student's test was used; the differences were considered significant at $p < 0.05$.

Microbiological data obtained in the course of studying the degree of contamination with bacterial and periodontal pathogenic microflora of the gingival sulcus and periodontal pocket, expressed in colony-forming units (CFU) per 1 cm^2, showed that streptococcus salivans and Streptococcus sangius are sown in patients with intact periodontal disease at the diagnostic stage; at the same stage, in patients with chronic generalized gingivitis, along with streptococcus salivans and Streptococcus sangius, Prevotella intermedia are also sown; and at the same stage, in patients with chronic generalized periodontitis, along with the listed microorganisms, other bacteria prevail (Treponema denticola, Porphyromonas gingivalis and Candida albicans). In patients with intact periodontium, after three months, Streptococcus salivans and Streptococcus sangius again prevail in the oral cavity along with lactobacillus spp; in the same patients, Streptococcus salivans disappear from the oral cavity in six months. In patients with chronic generalized gingivitis, after three months, microbial discharge of the oral cavity is enriched with Leptotrichia, and is preserved practically unchanged at the sixth month too. In patients with chronic generalized periodontitis, after three months, the microbial discharge of the oral cavity is very rich and diverse, the following types of microorganisms represent it: streptococcus mutans, Streptococcus sangius, Lactobacillus spp, Prevotella intermedia, Treponeba denticola, Actinobacillus actinomycetem-comirans, Porphyromonas gingivalis, candida albicans, Leptotrichia. In these patients, after six months, the non-qualitative, nonquantitative composition of the microbial life of the oral cavity practically does not change.

The foregoing indicates that in patients with intact periodontium, the microbial landscape of the gingival sulcus at the stages of observation changes slightly qualitatively. So, the dominant microbial groups are streptococci and lactobacilli, and the seeding density was the highest after 3-4 weeks and 3 months after fixing the braces. In patients with chronic generalized gingivitis, the coccal flora also appeared to be the dominant flora; however, at the diagnostic stage, prevotella was cultured in 2 patients.3-4 weeks after fixation, the titer of the coccal flora increases, the qualitative (species) composition changes: representatives of the fungal flora appear, and the number of patients in whom prevotella and treponema are detected increases. At the observation period of 3 months, the diversity of the species composition is enhanced by the strains of Sandida albicans and Leptotrichia, the seeding density of other bacteria increases. After 6 months and by the beginning of the retention period, a depletion of the species composition and a decrease in the density of sowing of microflora were stated. The greatest qualitative and quantitative diversity was observed in the microbial landscape of periodontal pockets in patients with chronic generalized periodontitis at the observation stages of 3-4 weeks and 3 months. The dominant microflora at these stages is periodontal pathogenic. Coccal and candidal microflora in this case is accompanying.

It should be noted that when comparing the features of microbial contamination of the cervical region of the teeth, on which the braces are fixed, and periodontal pockets, we identified fundamental differences. Thus, periodontal pathogenic strains were detected only in periodontal pockets, which is due to the conditions of anaerobiosis.

Thus, the information we have obtained dictates the need for a differentiated development of professional hygiene regulations for orthodontic patients, aggravated by inflammatory periodontal diseases.

THE SCIENTIFIC DISCUSSIONS OF FEATURES PHARMACEUTICAL REGULATION EMISSIONS, ELABORATED BY THE PATIENTS IN GEORGIA

Nodar Sulashvili[1], Margarita Beglaryan[2], Ia Egnatievi[3], Magda Davitashvili[4], Kakhaber Robakidze[5], Lela Grigolia[6]

[1]Alte University, International School of Medicine, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Yerevan State Medical University, Pharmaceutical Management, Yerevan, Armenia.

[3]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

[4]Iakob Gogebashvili Telavi State University, Telavi, Georgia.

[5]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[6]Caucasus International University; Tbilisi, Georgia;

n.sulashvili@ug.edu.ge

Aim and objectives was to study features pharmaceutical regulation emissions, elaborated by the patients in Georgia. The study was quantitative investigation by using survey (Questionnaire). Research objectives are materials of sociological research: Surveys was for patients; 1506 patients were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program.

At present in Georgia this regulatory legislative base is not perfect, because the pharmacists' certification, re-certification, accreditation and licensing state programs are not conducted. Today; the pharmacist profession in Georgia is deleted from the health adjustable medical fields. Therefore degree in pharmacy or higher education in this aspect use their professional characters and values, so that profession of pharmacist specialty becamen a position given by the pharmacy owner and does not require qualification awarded from the university. Since the higher pharmaceutical education is not a necessity for pharmacist position in pharmacys in Georgia, very often non-professionals without special medical or pharmaceutical education get the right to work at a pharmacist position according to pharmacy owner's desire, meanwhile the pharmacy profession granting needs 4-5-year study at the medical and other universities. At the same time the problem of Georgian pharmaceutical graduates consists possible lack of jobs for the pharmacethical facilities because of easy access of other subject specialists.

In Georgia a pharmacy pharmacist is interpreted as the only drug-dealer-seller, and basically pharmacists as regulated medical specialists are ignored in Georgian health care system. That is why the higher pharmaceutical education system should be moved to a new model direction, which will be more focused on pharmacotherapy, pharmaceutical care, and clinical pharmacy, becoming the most important issue. Hence, in the state health policy the pharmacist profession's concepts and common principles are to be developed.

Pharmacist are experts in pharmacotherapy, they can provide extra understanding, knowledge, skills, and regards to other public health and health care specialists within a multidisciplinary team atmosphere. Concretely, the pharmacists be able to contribute to health care group by discovering and solving or preventing drug associated issues; they supporting to guarantee the safely and efficiently pharmacotherapy principles; ensuring exhaustive information about the drug to patients and other health care and public health specialists; contributing medication compliance; and strengthening fundamental health promotion and prevention lifestyle modification activities in the society. In opposite, in primary health care, pharmacists generally have more restricted straightforward approach to clinical patient records and another health care specialists, like clinical-based pharmacists are highly accessible to patients. This provides patients with nice and good opportunities to search advices for the control of minor diseases or preventive care medicine, and occasionally more serious circumstances, constantly before searching assistance from the family Doctors. Pharmacist according patients' need transferring patients to the family Doctor, hospital or insurance company. Therefore, pharmacists are in perfect situation and position to ensure a first full point of communication within the health care system, in a triage- pattern role or as a connection between other health care professionals, mainly family doctors and general medical practitioners. Above mentioned aspirations are shown by some pharmacist scientists in western countries, who studied the pharmaceutical care services, where doctors access was limited. The pharmacists distinguish the beneficial assistance and promotion to functioning as a bond between the various sites of health care division, such as distinction care, pharmacotherapy or pharmaceutical care or public safety. The cooperation of pharmacists with various health care providers have as well demonstrated to have an affirmative influence in the judicial framework. Research objectives are materials of sociological research: the study was quantitative investigation by using survey (Questionnaire). Surveys was for patients; 1506 patients were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. Results and discussion: The survey was conducted through the questionnaires.1506 patients were interviewed in Georgia. Questions and answers are given in the tables. On each question are attached diagrams or table. Questionnaire and diagrams are numbered.

On the question mark the most significant factors while choosing a pharmacy (you can indicate no more than 5 answers)? Patients'50.7% answer service culture; Patients'53% answer wide range of products ; Patients'49.3% answer possibility to receive consultation about drugs with a physician/ a pharmacist;

Patients'58.2% answer reasonable prices; Patients'36.3% answer high qualification of personnel, Patients'45.2% answer convenient or comfortable location of the pharmacy; Patients' 31.7% answer absence of queues, Patients' 19.5% answer friendly staff, patients'31.3% answer the existence of high-quality drugs.

For the majority of respondent patients', mostly significant factors, while choosing a pharmacy are: Service culture, wide range of products, reasonable prices. For less than half of respondent patients, mostly significant factors, while choosing a pharmacy are: Possibility to receive consultation about drugs with a physician or a pharmacist, convenient location of the pharmacy, high qualification of pharmacist personnel.

On the question- What are questions mostly you ask to pharmacists? (You can indicate several answers)? Patients'63.1% answer about rule of intake of drugs , patients'41.5% answer about adverse effects of drugs , patients'61.4% answer about prices of drugs, Patients'29.8% answer about help in selection of analogue of drugs (medication), patients'42.5% answer about quality of drugs , patients'26.5% answer about existence of drugs patients' in a pharmacy, Patients'31.3% answer about indication/contraindication of drugs patients',Patients'30.8% answer about terms and conditions of storage (conditions and shelf-life), patients'33.5% answer about drugs patients' dosage , patients'19.4% answer about routes of drug administration , patients'19.2% answer about drug forms , patients'8.6% answer about drug design, patients'19.7% answer about drugs toxic effects(toxicity), patients'3.7% answer about principles of pharmacotherapy, patients'25.6% answer about rules of drug administration, patients'10.4% answer about drugs generic, chemical and brand names, Patients'27.2% answer about selection of (Over-the-counter) OTC drugs, patients'25.2% answer Information about drug, patients'20.7% answer effectiveness of drug, Patients' 18.9% answer about drug(s) action and drug(s) interactions, , Patients' 21.3% answer about drugs safety, Patients'3.4% answer about cost-effectiveness and cost-benefits of drugs.

On the question - Do you think that the government should make the certification of pharmacists? Patients'82.6% answer I agree, patients' 11.6% answer I partly agree, patients' 5.8% answer I do not agree. The vast majority of respondent Patients consider, that the government should make the certification of pharmacists.

Thus**,** the higher pharmaceutical education and the pharmacist specialists' certifications programs are guarantee for higher professionalism of pharmacist specialists and of higher pharmaceutical service provision in pharmacies. Only the pharmacists with higher pharmaceutical education have the right to work at the pharmacist position in the pharmacies.

THE SCIENTIFIC DISCUSSIONS OF THE DETECTION OF COVID-19 DISEASES CAUSED BY SARS-COV-2 AND ITS EFFECTS ON THE ORAL MUCOSA, UROGENITAL SYSTEM AND SKIN

Nodar Sulashvili[1], Kakhaber Robakidze[2], Irma Buchukuri[3], Lela Grigolia[4], Magda Davitashvili[5]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia;
[2]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;
[3]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;
[4]Caucasus International University; Tbilisi, Georgia;
[5]Iakob Gogebashvili Telavi State University, Telavi, Georgia.
n.sulashvili@ug.edu.ge

A Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The review is devoted to the skin manifestations of new coronovirus infection (SARS-CoV-2), information about which is constantly updated. However, this information has not been systematized yet. The purpose of this review is to analyze the dermatological manifestations of a new coronavirus infection. On average, 12.5—20.4% of patients with confirmed COVID-19 have developed skin manifestations. The question of whether the skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at the moment. The possible mechanisms of development of skin lesions and the role of diseases of complement system and blood hypercoagulation in the pathogenesis of the disease are discussed in the article. The review also provides descriptive and clinical examples of skin manifestations in COVID-19. Since COVID-19 tends to be asymptomatic within 14 days, skin manifestations can be an indicator of infection, which leads to the timely diagnosis. In addition, doctors' awareness about skin symptoms associated with COVID-19 infection plays a big role in preventing misdiagnosis of the disease.

Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The first information about the new disease was registered in December 2019 in China. Since January 2020, the disease has spread to other countries of the world. Since February 2020, residents of South Korea, Iran, Italy, Spain and the United States have been infected with covid-19, and later almost the whole world. On March 11, 2020, WHO declared a pandemic caused by COVID-19.

The high level of contagiousness and asymptomatic transmission of the infection led to its rapid spread around the world and a pandemic. SARSCoV-2 is a single-stranded RNA virus and belongs to the coronavirus family. The virus enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor located on the surface cells. The lungs are a major target organ for COVID-19, with patients experiencing symptoms ranging from mild flu-like symptoms to fulminant pneumonia and potentially fatal respiratory distress syndrome. A number of cases have been recorded during the pandemic COVID-19 who reported skin manifestations of the infection**.** The purpose of this article is to systematize the literature on various skin manifestations in COVID-19. According to literary sources, during the pandemic period, a number of cases of COVID-19 with skin manifestations were recorded: Similar information was first reported from Italy - Gianotti described Exanthema, Purple maculopapular vesicular, Papular- erythematous, and Diffuse maculopapular eruption resembling Grover's disease; Recalcati reported an erythematous and vesicular rash, as well as urticaria; Present, Case described a maculopapular pruritic rash resembling Grover's disease, Diffuse maculopapular rash, macular hemorrhagic rash, and Papular-vesicular pruritic rash; Marzano described a papulo-vesicular exanthema similar to the chicken pox rash, and Mazzotta described erythematous rounded lesions; Erythematous rash was described by the French dermatologist Mahé, and disseminated erythematous rash and urticaria were described by Henry; Spanish investigators Estébanez reports erythematous pruritic papules (yellow) and Fernandez reports urticaria; In Thailand, researchers described petechiae, in Iran - an erythematous rash, and in Qatar - cranial ischemic lesions, which are red-violet papules, in Belgium - infiltrated plaques on an erythematous background, in Russia - papulo-necrotic angiitis, hemorrhagic angiitis, acroangiitis (acrodermatitis), papulo-vesicular rashes, disseminated maculopapular rash and purpurous rash (toxidermia), in the homeland of infection in China, acroischemia with digital cyanosis, blistering or dry gangrene, and urticaria, and in the United States, transient non-pruritic unilateral livedo reticularis, unilateral asymptomatic livedo reticularis and diffuse to maculopapular non-pruritic rash similar to dermatological symptoms in measles (Najarian, Hunt [20]). In the course of treatment of a patient with COVID-19, we described several skin symptoms, but only one differed from the literature symptoms: an erosive element against the background of erythema on the genitals in a 64-year-old man, developing associated hyperthermia on the 4th day after diagnosis. The pathological element was eliminated from the skin 8 days after the patient's hospitalization; 14 days passed until the complete regeneration of the skin against the background of local treatment with combined topical preparations.

Among the literary sources, there are only a few reports about the manifestation of COVID-19 on the oral mucosa. On the part of scientists, special attention is paid to the violation of taste in the form of hypogeusia, dysgeusia or ageusia during the disease. Apparently, oral manifestations dominate in the main post- COVID-19 period in the form of hyperemia, dry atrophy, hemorrhage, erosion, ulcers of the mucous membrane,

pseudomembranous-erythematous form of candidiasis, aphthous rash in the oral cavity, dryness and peeling of the upper and lower lips.

As you know, a rash is not uncommon among infectious pathologies, the most common and characteristic symptoms of such viral infections as measles, rubella and Dengue fever are skin rashes (exanthema). With coronavirus infection caused by COVID-19, the formation of exanthema may be associated with an inflammatory response of tissues to the effects of toxins and metabolites of the pathogen during the implementation of the main mechanisms of inflammation; However, while skin manifestations associated with COVID-19 have been increasingly reported recently, the pathological mechanisms of skin lesions in patients with COVID-19 remain poorly understood. Skin manifestations of COVID-19 can be divided into two main groups depending on the pathophysiological mechanism of their development: clinical signs similar to viral exanthems (immune response to viral nucleotides) and skin rashes secondary to systemic consequences caused by COVID-19 (especially vasculitis and thrombotic vasculopathy).

To assess the possible impact of SARS-CoV-2 on human skin, one must take into account the fact that SARS-CoV-2 is a single-stranded RNA virus consisting of 16 non-structural proteins (NSP 1-16) that play a role in the replication of coronoviruses. For example, NSP3 has the ability to block the host's innate immune response and stimulate cytokine expression, NSP5 can inhibit interferon (IFN) signaling, and NSP16 avoids MAD5 (melanoma differentiation-associated gene 5) recognition by suppressing hostile immunity [24]. Some studies have shown a direct effect of viral infection on T cells by detecting SARS-like particles and SARS-CoV-2 RNA in T lymphocytes. It has been shown that in some patients an overactive immune response can cause a "cytokine storm" (an increase in the level of pro-inflammatory cytokines, in particular, IL-6); these cytokines can reach the skin and stimulate dermal dendritic cells, macrophages, mast cells, lymphocytes, neutrophils, and promote rashes such as erythema, urticaria, vesicles, and others. Intervention in the host by SARS-CoV-2 results in infection of functional receptor-target cells expressing type II (ACE2) angiotensin-converting enzyme (ACE), such as type 2 alveolar cells or other unknown target cells. ACE2 is also present in the skin in the basal layer of the epidermis, in the endothelial cells of dermal blood vessels, and in the tissue of the eccrine appendages. Some researchers have suggested a direct pathogenic effect of the virus on the epidermis through ACE2, leading to acantholysis and dyskeratosis. COVID-19-endothelitis through ACE2 may explain the systemic impairment of microcirculatory function in various vascular beds and its clinical consequences in patients with COVID-19. It has been shown, in particular, that virus-induced endothelial damage may be a key mechanism in the pathogenesis of “frostbite” in COVID-19, and possibly also in the development of microangiopathy.

Considering the data of the analyzed literary sources, it can be concluded that in case of COVID-19, lesions of the skin and mucous membranes of the oral cavity can be the first or only signs of the disease. The question of whether skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself

remains open at the moment. The probable mechanisms of development of skin lesions and the role of diseases of the complement system and the state of blood hypercoagulability in the pathogenesis of their development are discussed. In this regard, much remains to be explored, from this point of view, this scientific work can be considered as a step in the process of studying COVID-19 caused by SARS-CoV-2.

THE SCIENTIFIC REVIEW OF THE FEATURES OF REMDESIVIR AND ITS PERSPECTIVES IN THE CONTEXT OF COVID-19 DISEASE THERAPY

Nodar Sulashvili[1], Ia Egnatievi[2], Giorgi Kvlividze[3], Bacho Rajebashvili[4], Nika Beridze[5], Kristina Chitadze[6], Mikheil Injgia [7], Lamanda Rusiashvili[8], Mariam Kacharava[9], Elisabeth Makharadze[10], Rodami Ghorjomeladze[11], Ani Kharazishvili[12]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia;

[2,3,4,5,6,7,8,9,10,11,12]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

n.sulashvili@ug.edu.ge

The aim of the study was to investigate and analyze the properties of remdesivir and its outlook in the treatment of COVID-19 disease. The antiviral remdesivir, a nucleotide analog prodrug, has a broad spectrum of activity against viruses of several families. After showing its strong antiviral activity against coronaviruses in preclinical studies, remdesivir has emerged as a drug candidate for the treatment of 2019's novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome 2 (SARS-CoV-2) coronavirus infection now a worldwide pandemic. . The use of remdesivir to treat COVID-19 began in early 2020 and has shown promising results so far. In 2020, many countries have conditionally approved the use of remdesivir in patients with severe COVID-19. This was followed by a rapid series of conditional approvals across countries / regions. Briefly, remdesivir has been shown to inhibit the coronavirus and improve lung function for prophylactic and therapeutic purposes (early infection) based on in vitro and in vivo data. However, data on COVID-19 patients remained limited.

The global pandemic of the 2019 novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an urgent need for effective antiviral drugs. Remdesivir (formerly GS-5734) is a prodrug of a nucleoside analogue that is currently being investigated in clinical trials for COVID-19. Its unique structural features enable the intracellular delivery of high concentrations of the active triphosphate metabolite and avoid re-inhibiting efficiently viral RNA synthesis. In preclinical models, remdesivir has shown strong antiviral activity against a variety of human and zoonotic β-coronaviruses, including SARS-CoV-2. This article critically evaluates the available data on remdesivir, focusing on microbiology, biochemistry, pharmacology, pharmacokinetics and in vitro anticoronaviral activity, as well as on clinical experience and ongoing advances in COVID-19 clinical trials.

Remdesivir's potential mechanism of action against coronavirus remains unclear. Several reasons have been suggested for interpreting the effects of remdesivir. First, remdesivir can disrupt the function of the nsp12 polymerase even when the corrective activity of the exonuclease is intact. Furthermore, remdesivir can efficiently generate the pharmacologically active nucleoside triphosphate (NTP), which serves as an alternative substrate and terminator of the RNA chain. NTP can then inhibit the coronavirus by incorporating active triphosphates into the viral RNA. Additionally, there is a high genetic barrier to coronavirus resistance to remdesivir, suggesting that remdesivir may maintain the efficacy of coronavirus therapy.

Remdesivir is a phosphoramidized prodrug of the 1'-cyano-substituted nucleoside analog (GS-441524). It inhibits viral replication by competing with endogenous nucleotides for integration into viral RNA replication by RNA-dependent RNA polymerase (RdRp). The non-structural protein RdRp (nsp12) is highly conserved in coronaviruses, making it an attractive target for broad-spectrum antiviral drugs. Upon entering cells, remdesivir is rapidly metabolised by intracellular kinases to nucleoside triphosphate, the active metabolite (GS443902). The rate-limiting step in the activation of nucleoside analogs is usually the formation of nucleoside monophosphate. Phosphoramide nucleosides such as remdesivir (and GS-441524) are monophosphate bioisoters and can therefore bypass this limiting step.6 However, phosphoramide nucleosides must be administered as prodrugs to sequester the charged phosphonate group and allow for faster entry into the cell. In the case of remdesivir, the negative charge is masked by the 2-ethylbutyl and L-alanine groups, which are rapidly removed by the intracellular esterases. Furthermore, the 1'-CN group of remdesivir and its metabolites offers a high selectivity for RdRp with respect to human polymerases.

Remdesivir is a prodrug; Concentrations declined rapidly after intravenous administration (plasma half-life, T ~ 1 hour), followed by the sequential appearance of the alanine intermediate metabolite GS-704277 and the nucleoside monophosphate metabolite GS-441524 (plasma T 5.5 hours). In cells, GS-441524 is rapidly converted to the pharmacologically active triphosphate analog, GS-443902, with prolonged intracellular Tmax (peripheral blood mononuclear cells, T PBMC ~ 40 h). Both remdesivir and GS-441524 show linear pharmacokinetics after single doses of 3 to 225 mg, and no accumulation of remdesivir was observed after once daily dosing for 5 days.

Remdesivir has demonstrated broad spectrum activity in several in vitro systems against a heterogeneous group of zoonotic and clinically significant human coronaviruses including SARS-CoV-1, SARS-CoV-2 and MERS-CoV with micromolar EC50 or IC50 values. For example, in cultures of human respiratory epithelial cells, remdesivir inhibited the replication of SARS-CoV-1 and MERS-CoV. New evidence suggests that remdesivir also shows potent activity against SARS-CoV-2. Remdesivir has been proposed as a promising treatment option for COVID-19 based on laboratory experiments and charity use reports. Its safety and efficacy in humans require high-quality evidence from well-designed and well-designed clinical trials. Launched for more details.

Similar to the inconclusive effect on SARS-CoV and MERS-CoV, the impact of remdesivir on the SARS-CoV-2 outbreak in current clinical practice should not be overestimated. More research is urgently needed to cure COVID-19 and control SARS-CoV-2.

The evolution of coronavirus resistance to remdesivir was assessed using cell culture in MHV with EC50 values comparable to those of SARS-CoV-1, SARS-CoV-2 and MERS-CoV.11. The side effects of remdesivir should be taken into account. Remdesiviro's safety profile information is changing rapidly. Until recently, most clinical experience has been in patients infected with Ebola virus, whose clinical manifestations are very different from those of COVID-19, making it difficult to extrapolate drug safety to populations. During the study, patients treated with remdesivir for an Ebola virus infection experienced serious side effects that the researchers believe could be related to remdesivir. The most serious of these was hypotension after taking the full dose, followed by rapid cardiac arrest and death. Of those who survived Ebola virus infection and were enrolled in the unique phase II PREVAIL IV study, patients required a dose reduction of remdesivir due to increased transaminase activity. Safety data from four phase 1 pharmacokinetic studies in healthy volunteers were also partially presented. In these studies, subjects received single doses of up to 225 mg of remdesivir or multiple doses of 150 mg once daily for 7 or 14 days, or 200 mg once followed by 100 mg daily for a total of 5 or 10 days. The most common side effects were phlebitis, constipation, headache, bruising, nausea, and body aches. Asymptomatic transient increase in the level of alanine aminotransferase (ALT) of 1 or 2 degrees.

Remdesivir has caused drug interactions. At the time of writing, no in vivo interaction studies with remdesivir have been published, but remdesivir's ability to inhibit or induce cytochrome P450 enzymes and transporters (CIP450) has been tested in vitro. However, it is important to note that as a prodrug, remdesivir is rapidly cleared in vivo, limiting the potential for clinically significant drug-drug interactions. Data on the ability of remdesivir metabolites to react with drugs is even less. In in vitro studies, remdesivir was a weak inhibitor of CIP1A2, CIP2C9, CIP2C19 and CIP2D6. The IC50 of remdesivir for CIP3A was 1.6 M, suggesting that short-term inhibition may occur at normal human exposure. Inhibition of remdesivir by the metabolites of the CIP450 enzyme has not been studied.14 Tests on the induction of CIP450 with remdesivir have been conflicting; can induce CIP1A2 and CIP2B6.14. Here, too, the clinical relevance is questionable. GS-441524 and GS-704277 did not demonstrate CIP450 induction in these studies. Remdesivir has been found to be a substrate (OATP1B, P-glycoprotein) or inhibitor (OAT1B1, OAT1B3) of several drug transporters. In current clinical studies with remdesivir there are no exclusion criteria for drug interactions.

There are currently no scientifically proven treatments that reduce mortality from COVID-19. Current treatment focuses heavily on supportive care and prevention of complications. Therefore, effective and safe antiviral drugs are urgently needed to relieve the burden on healthcare systems. As described in this review, remdesivir is a nucleoside analogue prodrug with unique structural features that allow intracellular

delivery of high concentrations of the active metabolite triphosphate. Coronaviruses, including SARS-CoV-2, in both in vitro and animal models. These data, combined with early safety data from clinical experience with Ebola virus infections, provide strong rationale for prioritizing remdesivir testing in COVID-19 clinical trials. However, the unpredictability of the pandemic poses many challenges for researchers attempting to conduct clinical trials. The first randomized controlled trial evaluating remdesivir for COVID-19 was conducted at multiple sites in the epicenter of the first epidemic, but failed to reach the targeted sample size due to slow recruitment after the peak levels subsided, and did not produce conclusive results.

Remdesivir, a nucleotide analog prodrug, is metabolized in host cells to the pharmacologically active nucleoside triphosphate. As an analogue of adenosine triphosphate (ATP), remdesivir triphosphate competes with the natural substrate ATP for integration into new viral RNA filaments using RNA-dependent RNA polymerase. When the triphosphate from the strip is accidentally inserted into the chain and a small number of extra nuclei are added (usually three for corona virus), RNA production stops. Remdesivir has a broad spectrum of antiviral activity against various viruses, including Ebola, Nipah and respiratory virus, as well as endemic and coronary heart disease in animals. In primary cultures of human respiratory epithelial cells, remdesivir inhibited severe acute respiratory distress syndrome (SARS-CoV) and Middle East coronavirus (MERS-CoV) with an inhibitory half microstructure value (IC 50). These results suggest that remdesivir is an antiviral agent with potential activity against novel coronaviruses.

In vitro, remdesivir demonstrated antiviral activity against SARS-CoV-2 in primary cultures of human respiratory epithelium and inhibited highly dose-dependent SARS-CoV-2 replication at a half maximum active concentration (EC50) of 0.01 μM. This antiviral activity appears to be specific to the virus; Remdesivir is non-cytotoxic in this culture system at a dose of ≤ 10 μg. In Vero-E6 cells, EC50 levels of remdesivir and its anti-SARS-CoV-2 metabolite GS-441524 were 1.65 μM and 0.47 μM, respectively, reflecting the reduced capacity of Vero-E6 cells. E6 for remdesivir metabolism. When co-cultured at clinically important concentrations of remdesivir and chloroquine phosphate in respiratory virus-infected HEp-2 cells, chloroquine phosphate inhibited the antiviral activity of remdesivir in a dose-dependent manner. Higher remdesivir EC50 levels and lower remdesivir triphosphate levels in normal human bronchial epithelial cells have been observed with elevated levels of chloroquine phosphate. Therefore, co-administration of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

In mice infected with a chimeric SARS-CoV virus that encodes the SARS-CoV-2 RNA-dependent RNA polymerase, treatment with remdesivir significantly reduced viral load in the lungs and improved it in vehicle-treated subjects. loss of lung function. A similar therapeutic effect was observed in a model of SARS-CoV-2 infection in rhesus monkeys. Although the possibility of QT interval prolongation in humans has not been

fully evaluated, current preclinical and clinical data do not indicate a risk of QT interval prolongation with remdesivir.

Limited data are available to evaluate the side effects of remdesivir. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported relatively rarely during and after administration of remdesivir. A transient increase in aminotransferase activity was observed with the use of remdesivir in phase 1 studies in healthy volunteers. A serious adverse event, fatal hypotension, likely related to the use of remdesivir, was reported in the phase 3 Ebola study.

THE SCIENTIFIC REVIEW OF THE PECULIARITIES OF MOLNUPIRAVIR PHARMACOLOGY IN THE CONTEXT OF PHARMACOTHERAPY AND TREATMENT OF THE COVID-19 INFECTION GLOBALLY

Nodar Sulashvili[1], Ia Egnatievi[2], Nika Bzhinava[3], Soso Bzhalava[4], Zurab Gavasheli[5], Nia Tsaguria[6], Anri Kalandadze[7], Nazi Siradze[8], Nino Tarielashvili[9], Nodar Baliani[10], Megi Samnidze[11], Kabila Khalilova[12]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia;
[2]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.
[3,4,5,6,7,8,9,10,11,12]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.
n.sulashvili@ug.edu.ge

The objective of the study was to review the scientific literature on the pharmacological properties of molnupiravir in the context of pharmacotherapy and treatment of covid-19 infection worldwide. Despite the availability of vaccines, there is still an urgent need for highly potent antiviral drugs against SARS-CoV-2, the cause of COVID-19. Millions of people are immunosuppressed and may not be able to elicit a full protective immune response after vaccination. There is also a growing need for a drug that covers new variants of SARS-CoV-2, against which existing vaccines may be less effective. Here we describe the development of Molnupiravir, a broad-spectrum antiviral agent originally designed to treat alphavirus infections, into a potential medicine for the prevention and treatment of COVID-19. At the start of the pandemic, molnupiravir was in preclinical development for the treatment of seasonal influenza. With the spread of COVID-19, the timeline for the development program has changed significantly and the focus has shifted to treating coronavirus infections. Real-time consultations with regulators helped speed up the program. Molnupiravir is a new oral antiviral drug that was recently tested in COVID-19. Our goal is to conduct a systematic review of the literature to determine the efficacy and safety of molnupiravir in patients with COVID-19. We carried out a systematic search in electronic databases of PubMed, Elsevier and Google Scholar.

Ongoing studies of molnupiravir with COVID-19 have also been reviewed at Trials.Gov and ctri.nic.in/ClinicalTrials. All available granular details were taken from phase 1-3 of Molnupiravir in the COVID-19 study.

Therapeutic strategies to combat COVID-19 also have to do with the drug reuse approach, that is, identifying an effective treatment from the set of existing drugs. Reusing FDA-approved chemical drugs not only reduces the costs associated with drug discovery, but also shortens development time. Several drugs with different mechanisms of action have been clinically studied to develop a possible treatment for COVID-19. Some of the drugs that have been evaluated before use in clinical trials include antimalarial drugs (hydroxychloroquine and chloroquine), antiparasitic drugs (ivermectin), anti-inflammatory corticosteroids (dexamethasone and prednisolone), antibacterial drugs (azithromycin), lopinavir, antivirals, antivirals, etc. It appears that repurposed antiviral drugs that inhibit the enzyme RNA-dependent RNA polymerase (RdRp) are the most effective target and thus a promising target for anti-COVID-19 drugs.

In order to understand the pathogenic mechanisms and therapeutic targets of SARS-CoV-2, we need to consider some aspects such as the replication cycle, structure and genome of the virus. The structure of the positive-stranded RNA-CoV virus consists of an envelope and a nucleocapsid. The SARS-CoV-2 virion has a 29.9 kbp ssRNA+ genome. and diameters from 50 to 200 nm. It is the largest RNA virus, known for its 3' poly-A tail and 5' cap structure, with fourteen open reading frames (ORFs) containing 27 individual proteins code. Virion structural proteins include spike (S), envelope (E), nucleocapsid (N), and membrane (M). Surrounding the RNA genome and N protein are the M, S, and E proteins. The S protein facilitates binding of the virus to the ACE2 receptor and allows the virus to fuse with the host cell membrane. After binding to ACE2, SARS-CoV-2 uses host transmembrane serine protease 2 (TMPRSS2) to modify S protein for entry into target cells. There are two subunits of the SARS-CoV-2 S protein to affect the virion-receptor relationship, resulting in membrane fusion; S1 binding receptor and S2 fusion protein. Cellular proteases cleave the spike protein at the S1-S2 cleavage site, allowing the virus to bind to the receptor and fuse with the cell membrane. Analysis of the SARS-CoV-2 S protein revealed the presence of an insertion in the S1/S2 region that is not found in other SARS-CoV strains. It appears that this specific integration provides variation with function for both easy cellular infection and efficient spread in the human host.

Identification of a broad-spectrum antiviral agent for the treatment of RNA virus infections. The desired product profile will be determined by the pathophysiology of alphavirus encephalitis and the conditions associated with the potential combat or public health use of the antiviral agent. First, the drug candidate had to show high activity in cell culture infection models and animal models of alphavirus disease. It would also be desirable for the drug candidate to be active against at least all three encephalitic alphaviruses.

Molnupiravir (EIDD-2801/MK-4482) is a prodrug of the ribonucleoside analogue β-d-N4-hydroxycytidine (NHC; EIDD-1931) that has been shown to be useful in the treatment of RNA viral infections such as influenza. . and pathogenic coronaviruses and encephalitis alphaviruses (such as Eastern, Western, and Venezuelan equine encephalitis viruses). In plasma, molnupiravir is rapidly cleaved to EIDD-1931 and converted to 5'-triphosphate after distribution to various tissues. EIDD-1931 5'-triphosphate is a substrate for virus-encoded RdRP and causes a catastrophic replication failure upon integration into the nascent RNA chain. When the mutation rate in a virus exceeds an acceptable threshold, the virus dies.

The availability of molnupiravir for rapid testing as a potential therapeutic agent for the prevention and treatment of COVID-19 is a direct result of DRIVE/EIDD's long-standing focus on emerging/emerging infectious diseases and public funding programs to identify and develop biosecurity and novel countermeasures. develop. emerging infectious diseases that persist for more than 20 years. Funding can be obtained from several federal agencies in the United States, including DTRA, NIAID, and BARDA, to implement medical countermeasures against Category A, B, and C pathogens through clinical evaluation and FDA approval. Given this level of support, the lack of early attention from government planning teams to developing direct-acting antivirals to contain the COVID-19 pandemic has been apparent.

For example, the target product profile for molnupiravir is ideal for use in long-term care settings where patient age and/or health conditions may not be able to elicit an effective post-immune response to vaccination, and for use in public health settings where vaccination logistics and timing are critical issues. Planners also need to be clear that a significant portion of the world's population is resistant to vaccines and thus constitutes a permanent reservoir of the virus.

Multiple and single doses of molnupiravir were evaluated in a Phase I clinical study in healthy volunteers, which also assessed the effect of food on pharmacokinetics. Following molnupiravir administration, EIDD-1931 was rapidly detected in plasma with a mean peak time between 1.00 and 1.75 hours, hence the geometric t½ was approximately 1 hour, and the elimination phase was significantly delayed after a single or multiple dose increase. The observed mean peak concentration and area under the time-concentration curve increased with dose and no further accumulation was observed after repeated dosing. When taken with food, a decrease in the rate of absorption was observed, but not in the overall effect. Molnupiravir is generally well tolerated. Complications occurred in less than 50% of the participants and the incidence of side effects was even higher in the placebo group. About 93% of the reported side effects were mild.

In plasma, molnupiravir is converted to the active nucleoside analogue (EIDD-1931) by the action of host esterases. EIDD-1931 has been shown to inhibit a number of viruses, including chikungunya virus, Venezuelan equine encephalitis virus, respiratory syncytial virus, norovirus, influenza A and B virus, Ebola virus, and human coronaviruses. EIDD-1931 spreads to multiple tissues and is converted to triphosphate.

RdRp uses NHC triphosphate as substrate instead of cytidine triphosphate and uridine triphosphate, resulting in mutant RNA. Molnupiravir is a more desirable electron donor that changes the conditions for infectivity. EIDD-1931 appears to affect mitochondrial function of the virus, but in vitro studies indicate no significant toxic effects on mitochondrial function. Molnupiravir inhibits the SARS-CoV-2 RdRp enzyme and causes more errors in the replication of the RNA virus. In other words, remdesivir, like molnupiravir, can reduce the pathogenesis and replication of the coronavirus. The results of the docking study showed that the limited space for mutations in the drug's structure can determine the inhibitory effect of molnupiravir on the occurrence of mutations associated with drug resistance. Molnupiravir may thus be effective in the treatment of remdesivir-resistant patients.

Molnupiravir is a promising new oral drug. This oral drug was developed by Drug Innovation Ventures at Emory University and later acquired by Ridgeback Therapy in conjunction with Merck & Co, USA. In general, antivirals tested so far inhibit RNA chain elongation by acting on viral polymerases, but these antivirals have not shown a promising role in treating SARS-CoV-2 infections caused by exonucleolytics. Newly formed RNA nucleotides. Both molnupiravir and remdesivir (GS-5734) target the enzyme RNA-dependent RNA polymerase (RdRp) used by the coronavirus to transcribe and decode the viral RNA genome. Although remdesivir is a nuke, molnupiravir has a unique mechanism of action very similar to favipiravir. Especially at the start of the pandemic, favipiravir was used without much success. Remdesivir has received classification from the US Food and Drug Administration (FDA), but it has not shown the expected efficacy in some studies, so the WHO does not recommend it. Also, it can only be given intravenously in a hospital and there are limitations. Molnupiravir was originally considered a potential treatment for encephalitic alphaviruses such as influenza virus, Venezuelan equine encephalitis virus, and eastern and western equine encephalitis virus due to its strong inhibitory effect on cell cultures. It appears to work primarily through a "catastrophic failure" mechanism, based on the idea that increasing the mutation rate in the viral genome above a biologically acceptable threshold would render the virus lethal and lead to extinction. The broad-spectrum antiviral activity of this drug is explained by a two-step mechanism of mutagenesis.

Molnupiravir is an isopropyl ether prodrug that is cleaved in plasma by host esterases to the active nucleoside analogue b-D-N4-hydroxycytidine (NHC) or EIDD-1931. This active form of the drug is distributed to different tissues and then converted to the corresponding 50-triphosphate (NHC-triphosphate or MTP). It then targets RdRp, which is encoded by the virus, and competitively inhibits cytidine and uridine triphosphates and receives M instead. forming stable complexes and thus avoiding proofreading by mutated RNA synthesis. The formation of MG and MA base pairs in the active site of RdRp, confirmed by structural studies and after interpretation of the cryo-EM density, suggests that in each case the stable tautomer predominates, that is, the bases of the amino tautomer -M with G and the bases of the imino tautomer-M with A and does not alter the development of RdRp.

Thus, two-step mutagenesis can be summarized as follows: In the first step, RdRp synthesizes negative-stranded genomic RNA (-gRNA) using positive-stranded genomic RNA (þgRNA) as a template. Then, in the second step, the þgRNA or subgenomic RNA is synthesized using RNA containing M as a template. RNA containing M in -g-RNA causes a mutation in þg-RNA and then forms subgenomic RNA, leading to lethal viral mutagenesis. Mechanism of action (scheme) of molnupiravir against SARSCoV-2 and comparison with remdesivir and favipiravir. These mutations also occur in the host cell (mammalian DNA), raising concerns about their impact on vaccination and their potential carcinogenic and teratogenic effects, which are theoretically possible with the use of mutagenic drugs. However, this may be less likely due to the intended short-term use of twice daily for 5 days. It is also interesting to note that RNA synthesis in HCV polymerase or respiratory syncytial virus RNA polymerase is not observed with NHC triphosphate.

Based on pharmacokinetic studies, molnupiravir should be administered twice daily to ensure adequate concentrations in respiratory tissues. Based on the results of clinical studies, molnupiravir is well absorbed when taken orally and has linear pharmacokinetics over the dose range of 50 to 1600 mg. Taking molnupiravir with food can significantly reduce the rate of absorption. However, the degree of absorption is the same with and without food. Therefore, taking molnupiravir with food is controversial. Headache, nausea and diarrhea are the most common side effects of molnupiravir. Other side effects include flu-like illness, back pain, runny nose, hot flashes, and limb pain.

THE SCIENTIFIC REVIEW OF THE SPECIAL FEATURES OF COVID-19 VACCINES AND THEIR TOXICITIES PERSPECTIVES IN GENERAL IN THE CONTEXT OF PREVENTION OF COVID-19 INFECTION DISEASE GLOBALLY

Nodar Sulashvili[1], Ia Egnatievi[2], Eliza Danelia[3], Nino Gogaladze[4], Giorgi Machavariani[5], Tamuna Mikeladze[6], Lizi Mosidze[7], Mariam Khachidze[8], Sophiko Javakhidze[9], Lana Melashvili[10], Anzor Zedginidze[11], Zurab Gorgiladze[12]

1 David Aghmashenebeli University of Georgia; Tbilisi State Medical University, Tbilisi, Georgia; Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia;

2 David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

3,4,5,6,7,8,9,10,11,12 International Third Year Medical Students of the School of Medicine and Dentistry at David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

n.sulashvili@ug.edu.ge

Aim of the research was to study and analyze the special features of covid-19 vaccines and their toxicities perspectives in general in the context of prevention of covid-19 infection disease globally.Vaccines are essential public health tools with a favorable safety profile and prophylactic effectiveness that have historically played significant roles in reducing infectious disease burden in populations, when the majority

of individuals are vaccinated. The COVID-19 vaccines are expected to have similar positive impacts on health across the globe. While serious allergic reactions to vaccines are rare, their underlying mechanisms and implications for clinical management should be considered to provide individuals with the safest care possible. There are different types of allergic adverse reactions that can potentially occur after vaccination and individual vaccine components capable of causing the allergic adverse reactions. The present incidence of allergic adverse reactions during clinical studies and through post-authorization and post-marketing surveillance and provide plausible causes of these reactions based on potential allergenic components present in several common vaccines.

There are a number of vaccines currently used with proven safety and efficacy. Vaccines are potentially associated with adverse events. An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Adverse events can present as local or systemic, immediate or non-immediate, and immune or non–immune-mediated reactions. While all allergic reactions are immune-mediated, not all immune-mediated reactions are allergic. Local non-immediate reactions that are not allergenic are common and may include swelling and erythema at the injection site. These reactions can occur hours or days after administration and are not always mediated through the immune system. Systemic non-allergic reactions including mild fever and vasovagal reactions such as hypotension, nausea, and syncope are also relatively common. Neither the local nor the vasovagal reactions pose any serious risk. Although some of these reactions are immune-mediated, they are not allergic reactions. Rather, soreness at the injection site or fatigue are consequences of activation of the innate immune system. Adverse events, including allergic reactions, are graded according to severity as mild, moderate, and for purposes of this review, serious. Typical signs of an allergic reaction include bronchoconstriction, conjunctivitis, rhinorrhea, gastrointestinal symptoms, and/ or characteristic skin lesions such as generalized urticaria and/or angioedema. These can occur in combination or alone, and onset can be immediate, within minutes, or up to several hours postvaccination. Examples of mild allergic reactions are swelling with itching at the injection site, conjunctivitis, or rhinorrhea. Examples of moderate allergic reactions are bronchoconstriction that can be adequately treated with nebulized beta-agonists or generalized urticaria that may be treated with an antihistamine. Serious adverse events are those events that are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, cause a persistent or significant incapacity or substantial disruption in the ability to conduct normal life functions, a congenital anomaly/ birth defect, or death. Two examples of serious adverse events that are allergic reactions are bronchospasm that requires intensive treatment and life-threatening anaphylaxis. Anaphylaxis, an immediate systemic multi-organ reaction, is rare but can be life-threatening. Organs affected include the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. Anaphylaxis can be either immunological, non-immunological, or idiopathic.

Idiopathic anaphylaxis is diagnosed through exclusion of other known causes and may mask a clonal mast cell disorder. Non-immunological anaphylaxis was previously termed anaphylactoid reactions, but the World Allergy Organization suggested replacing anaphylactoid reactions with non-immunological anaphylaxis. The change in terminology is to reinforce the risk and potential fatality of all types of anaphylaxes, regardless of the underlying mechanism. All three mechanisms of anaphylaxis produce the same clinical picture. Distinguishing between systemic vasovagal reactions and anaphylaxis during immunization is critical to ensure that appropriate and immediate treatment can be administered. Vasovagal reactions usually occur immediately or up to 30 minutes of vaccine administration. Similar to anaphylaxis, organs affected include the cutaneous, gastrointestinal, respiratory, neurological, and cardiovascular systems. Anaphylactic reactions are considered adverse events of special interest, that is, adverse events that are of significant medical and scientific concern for which immediate medical action with ongoing monitoring and rapid communication by the investigator or sponsor is required. Adverse events of special interest reporting are a critical aspect of pharmacovigilance for characterization of the safety profile of a drug or vaccine in context of previous reports of the vaccine or of other vaccines with similar manufacturing processes, formulation, immunogenicity, and novelty. Adverse events of special interest alert regulators to potential risks. Particularly in mass vaccination programs where a large number of adverse reactions may be reported, identification and assessment of Adverse events of special interest are a high priority because they highlight potential risks that may alter risk-benefit profile and may require immediate investigation, regulatory action, and prompt communication with the public.

Anaphylaxis to vaccines is rare and occurs primarily among individuals who have histories of allergies to the components of the vaccines. Allergic reactions after vaccination can be due to any of the vaccine components such as antigens, adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, residual antibiotics, cell culture materials, and inactivating ingredients. Lists components that have been implicated in allergenic reactions and related adverse events. Here, we discuss some of the most common allergenic or potentially allergenic components of vaccines. Many vaccines contain small amounts of the egg protein ovalbumin. Influenza, yellow fever, and rabies vaccines tend to have higher concentrations of ovalbumin because they are cultured in embryonated chicken eggs. Vaccines cultured in chicken embryo fibroblasts, such as the MMR vaccine, have lower concentrations of egg protein than those cultured in embryonic eggs. While egg allergy is common in childhood, studies have shown that vaccinating egg-allergic children with MMR and influenza vaccines is well tolerated and risk of an allergic reaction is similar in the general population. Specifically, egg-allergic children, including those who have had anaphylaxis, were successfully vaccinated with yellow fever89 vaccines with no serious adverse events reported. Since severe allergic reactions to egg-based influenza vaccines are rare, the Advisory Committee on Immunization Practices guidelines that individuals with mild egg allergy can receive any licensed and recommended age-appropriate flu vaccine and

no longer need to be observed for 30 minutes after receiving the vaccine. However, in those with severe egg allergy, the vaccines should only be given under the supervision of a health care provider who is capable of recognizing and managing serious allergic conditions.

Professional administering the vaccine must be capable of managing an anaphylactic reaction and should have the necessary medications and tools on hand. There must be a mandatory observation period after vaccine administration of at least 15 minutes for all individuals, to allow for the administration of adrenaline in an adequate dose. Individuals with a suspected allergic reaction to the first dose of the vaccine should be followed up by an allergist so that administration of the second dose can be performed in a specialized setting equipped to treat anaphylaxis. One approach used successfully for many vaccine-allergic individuals, but which has not been evaluated for the COVID-19 vaccines, is to administer the vaccine in incremental doses. Any adverse allergic reactions should be promptly reported including any additional information including individual characteristics.

Safety: The safety profiles of different types of COVID-19 vaccines are quite different. The incidences of local and systemic adverse reactions are relatively higher in mRNA vaccines and adenovirus vaccines (Local: 88.9%-40%, Systemic: 86%-44%). The side-effects were lowest in inactivated vaccines (Local: 23.3%-5%, Systemic: 18%-4%). However, the AR rate of recombinant protein vaccines varies greatly as different adjuvants are used (Local: 91.7%-9%; Systemic: 65.4-8%). Safety and the level of neutralizing antibodies induced are inversely related, and the adverse reactions rate noted in the elderly is lower than that of adults.

Novel adjuvants and delivery materials used in mRNA vaccines and recombinant vaccines seem to increase side effects, especially after the second dose, which needs to be investigated further for improving the vaccine.

Adverse reactions noted for the Moderna and Pfizer-BioNTech mRNA vaccines increased after the second dose. The local and systemic ARs in the median dose groups of Moderna were 88.9%(Local), 79.4%(Systemic); and those for Pfizer vaccines were >79% (Local), and >59%(Systemic). Severe allergic reactions have been reported after the administration of the two vaccines. This raises a safety concern in population and may impact vaccination compliance. Coated liposomes are considered as the main cause of ARs, and how to improve the packaging and delivery system is crucial for enhancing the safety profile of mRNA vaccines. In addition, vaccine design can also affect vaccine safety. Pfizer-BioNTech designed two mRNA vaccines for clinical trials, namely BNT162b2 and BNT162b1. BNT162b1 encodes the trimerized receptor binding domain, while BNT162b2 encodes full length spike, modified by two proline mutations to lock it in the prefusion conformation. Phase 1 clinical data showed that the two vaccines induced similar dose-dependent neutralizing antibody titers, and the titer was equivalent to or higher than that of convalescent serum. However, the incidence and severity of systemic reactions caused by BNT162b2, especially in the elderly, were lower.

Adverse reactions of Novavax and Clover vaccine are significantly increased after the second dose. The adverse reactions rate of Novavax recombinant vaccine with Matrix M adjuvant (69.2% local; 46.1% systemic) was comparable with that of the Clover vaccine with GSK AS03 adjuvant (68.8% local and 56.3% systemic). The ARs of those two vaccines aforementioned are higher than that of Zhifei vaccine adjuvanted with alum (total ARs <48%).

Antibody-dependent enhancement and vaccine-associated disease enhancement are two major public concerns in vaccine safety evaluation. Antibody-dependent enhancement is mainly mediated by antibody Fc receptor-associated internalization of a virus. vaccine-associated disease enhancement is a disease situation associated vaccine, mainly attributed to antibody-dependent and type 2 T helper cell-dependent mechanisms. For safety consideration, a vaccine should be highly effective in triggering high level of neutralizing antibody and Th1 type cellular responses in vivo. Antibody-dependent enhancement and as well vaccine-associated disease enhancement should be monitored in clinical and preclinical studies. Fortunately, there is still no report revealing an ADE phenomenon in the development process of current candidate COVID-19 vaccines. Further studies should be conducted to clarify the potential risk caused by ADE and VADE during COVID-19 vaccines application.

In order to ensure the effectiveness and safety of COVID-19 vaccines, WHO, FDA, EUA, and NMPA have issued guidance for industry at the early stage (56–58, 93), providing key considerations for vaccine development, quality control and clinical evaluation. Guidance points out that to ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%. An inappropriate (relatively lower) criteria set for the first generation of COVID-19 vaccine can further influence the development of next generation vaccines.

The criterion for defining COVID-19 cases and the methods used for diagnosis have a profound impact on the final calculated vaccine efficacy. At present, developers mainly use symptoms, nucleic acid testing, and serological testing for case determination, though there are no universal standards for case collection and inclusion. Under the circumstance that multi-countries and multi-enterprises are involved in COVID-19 vaccine research and development, the establishment of relatively consistent diagnostic and case collection criteria for clinical research can help obtain reliable and comparable efficacy data for vaccines.

Although we comprehensively analyzed multiple platforms of COVID-19 vaccines based on the clinical research data published by various developers, the analyzed results could be unreliable and incomparable because of instances where no standards that could serve as reference points were incorporated in the studies and where different methods were used for estimating immunogenicity. This is a major obstacle in evaluating and prioritizing current COVID-19 vaccine candidates from the available data.

The establishment and incorporation of reference standards for evaluating antibodies and antigens needs to be implemented.

Recently, a variety of molecular and serological assays have been developed for the detection of SARS-CoV-2 infection, the measurement of antibody response to SARS-CoV-2 infection and the tiers of antibodies induced by COVID-19 vaccines. The WHO collaboration center for biological standardization and the National Institute for Biological Standards and Control recently organized and completed the collaborative calibration of mRNA and antibody standards, and endorsed a proposal to develop a standard for SARS-CoV-2 antigens to support the development, assessment and comparability of antigen-based rapid diagnostic tests.

Since there is variation in the protection conferred by various vaccines and the safety profile of vaccines developed for emergency use, alternative strategies to mitigate the shortcomings of the vaccines need to be investigated. Adoption of a sequential immunization strategy may make up for the deficiencies of existing vaccines to a certain extent. More recently, another important issue regarding emergence of mutant strains of SARS-CoV2 that have lowered the efficacy of the vaccines has cropped up. A safer and more effective next-generation COVID-19 vaccine that can effectively respond to virus mutants should be developed to counter the threat posed by viral variants.

THE SCIENTIFIC TALKS OF CHALLENGES OF SPECIFICITIES OF PHARMACIST OCCUPATION AND HIGHER MEDICAL-PHARMACEUTICAL EDUCATIONAL OUTLOOK IN GEORGIA

Nodar Sulashvili[1], Margarita Beglaryan[2], Ia Egnatievi[3], Magda Davitashvili[4]., Kakhaber Robakidze[5], Lela Grigolia[6]

[1]Alte University, International School of Medicine, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Yerevan State Medical University, Department of Pharmaceutical Management, Yerevan, Armenia.

[3]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

[4]Iakob Gogebashvili Telavi State University, Telavi, Georgia.

[5]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[6]The Department of Dentistry at Caucasus International University; Tbilisi, Georgia

n.sulashvili@ug.edu.ge

The main objective of the study was to analyze the challenges of specificities of pharmacist occupation and higher medical-pharmaceutical educational outlook in Georgia. The study was a quantitative investigation and analysis of the challenges of specificities of pharmacist occupation and higher medical-pharmaceutical educational outlook in Georgia, by using questionnaires. Were conducted a survey study. The in-depth interview method of the respondents was used in the study. The 7 types of approved questionnaires were used (Respondents were randomly selected): Questionnaire for chief

pharmacists: 410 chief pharmacists participated in the study. Questionnaire for patients: 1506 patients (customers of drug-stores) participated in the study. Questionnaire for the employed pharmacy faculty-student: 222 employed pharmacy faculty students participated in the study. Questionnaire for health-care specialists: 307 public health specialists participated in the study. Questionnaire for pharmacist specialist, 810 pharmacist specialists participated in the study. Were used methods of systematic, sociological (surveying, questioning), comparative, mathematical-statistical, graphical analysis. The data were processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined $p< 0.05$ as significant for all analyses. According to the study results, the level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, in pharmacotherapy, in toxicology, in pharmaceutical care, in clinical pharmacy, in pharmacokinetics, in pharmacodynamics, in basic of medicine and in other pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education. It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work. Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide.

Mostly essential pharmaceutical activity issues for the respondents' pharmacists' majority were: new drugs, generic drugs, chemical and brand names of them; psychology of communication (relationships) with customers; issues of pharmacotherapy of certain diseases, pharmacology, pharmacodynamics, ppharmacokinetics and pharmaceutical care. It is apparent, that in the higher pharmaceutical education universities programs should be emphasized on the following subjects: pharmacotherapy, pharmacology, pharmaceutical care, clinical pharmacy and drugs toxicity.

The most impacting factors influencing on the young pharmacists' work satisfaction were found and evaluated during the research. These factors included the correspondence of qualification to work, correspondence of the work nature to capabilities of personality, existence of perspective for professional promotion, possibility to qualifications enhancement, existence of high degree of responsibility for the result of work, information about affairs of the company and of the staff activity, working conditions, existence of the labor contract of working regimen and salary, existence of benefits' scheme for employees, support and assistance of the chief, direct relations with manager(s),relations with colleagues, possibility for the career enhancement.

The study of the professional adaptation of pharmacists indicated that inadequate professional knowledge, improper performance of the acquired professional skills were the main reasons for imperfect pharmaceutical care supply. The majority of the pharmaceutical organizations' heads and also the young specialists considered the coexistence of a mentor (experienced professional pharmacist) as the main factor of professional improvement for pharmacists' professional adaptation. The pharmacists' personnel must show stirring involvement in sharing their cognition, understanding, science, skill and contributing partnership and cooperation within the colleagues and other health care professionals in pharmacy direction.

It is quite significant, that pharmaceutical companies regularly perform study of pharmacists' work satisfaction. The pharmaceutical companies should determine combination of factors that effect on the pharmacists' work satisfaction. Pharmaceutical companies should create favorable working conditions for pharmacists to enable the maximal realization of the pharmacists' professional capabilities, skills and habits. A balance between the workload and pharmacists' personal life should be more harmonized, convenient, resourceful and more poised. This will increase the quality of pharmaceutical care in pharmacies.

It should be noted, that pharmacist's satisfaction with income is a very sensitive factor that has a significant impact on the quality of pharmaceutical services performed in pharmacy, so the pharmacists' salary should be revised and increased.

It should be noted that in developed countries and in many developing countries pharmaceutical specialty is regulated profession alike the family medicine. In western countries pharmacist as a family doctor need higher pharmaceutical education, diploma and continuous pharmaceutical education, pharmaceutical license and periodic accreditation. Only pharmacists with higher pharmaceutical education have the right to work as pharmacists' position in the pharmacies. On the pharmacists' certification programs should be only involved pharmacists who have graduated pharmaceutical faculties from state recognized and accredited universities.

The majority of higher pharmaceutical education pharmacists' specialists were female; among them the largest majorities were working on the pharmacist position at pharmacies. The Government and pharmaceutical companies should create promotional conditions for males to make pharmacist profession attractive for men. It is very important for career advancement and satisfaction to provide a balance between the workload and man personal life for the satisfaction by income, for pharmacists' professional satisfaction, for pharmacist job satisfaction, and also for the career promotion perspectives.

The Government should take care of the profession of pharmacist authority. The pharmacist's profession in the health care system should increase the authority and social importance by the state support. Pharmacist's profession should become of more power and authority; a pharmacist should have a much higher status in the healthcare system.

Therefore, the role of a pharmacist is significantly increased in the healthcare system and is directly related to his professional education level. Therefore, pharmacist should have appropriate higher pharmaceutical education. All the mentioned is achieved then, when the pharmacist profession will move into the health-regulated professions list.

The level of basic training of pharmacists should be in compliance with the contemporary requirements. The pharmacist should have deep knowledge in pharmacology, in pharmacotherapy, in toxicology, in pharmaceutical care, in clinical pharmacy, in pharmacokinetics, in pharmacodynamics, in basic of medicine and in other pre-clinical and clinical directions. Such knowledge can be obtained only in the higher pharmaceutical education institutions. Therefore, pharmacist working in pharmacy must have only higher pharmaceutical education.

To increase the pharmacist's professional qualification, professionalism, professional knowledge and competency the higher pharmaceutical education universities programs should more emphasize the mentioned subjects. It is too important, that a pharmacist should realize and understand that qualification upgrading study courses, professional trainings and professional workshops are of great necessity for further professional advancement. Thus, the Government should develop continuous pharmaceutical education programs accessible to all pharmacists. The qualification upgrading study courses, professional education or training courses should be available for all pharmacists. Pharmacist's education process should not be stopped. Developing a continuous pharmaceutical education system will enhance the professionalism of the pharmaceutical personnel. Experiential education should encourage perfection of critical opinion and the problem resolving processes along with the medicine discovery.

Pharmacy faculty students should take part in the patient care practice in hospitals, society proceeding settings and in other practical experiences. Students should have the possibility to apply the clinical and pharmaceutical information taught in classes when studying in medical facilities by working under the supervision of volunteer mentors (the healthcare specialists or professionals). The research activity of the pharmaceutical faculty students in all fields of pharmaceutical practice should be encouraged.

Quality reliance refers to the necessity to improve higher pharmaceutical education to guarantee a useful, sustainable and steady activity and appropriate skills and competencies of the tomorrow's labor resources. The pharmacy degree programs should be proposed at the higher pharmaceutical institution level and entire experimental constituent element in the clinical facilities.

It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work. Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide.

To achieve that it is necessary to raise awareness of specialists on the essence of pharmacists' profession and functions among the medical personnel and general public.

On the basis of the theoretical and logical analysis the structure and composition of the factors have been developed, considering the objective (external), subjective (internal) and universal factors, which influence on the professional formation of the pharmacist. These factors comprised the content of work, position, correspondence of qualification and nature of work to capabilities, aspirations and inclinations of the pharmacist, the existence of perspective for professional promotion. The existence of perspectives for career promotion, the possibility to enhance qualifications, a high degree of responsibility for the work results, regimen, labor salary and the system of benefits scheme for employees, support and assistance of a manager, direct relations with manager and colleagues serve the essential base for the pharmacists' successful work. The unity of criteria for pharmacist professional formation, for the common professional formation (characteristic to all stages) and the specific professional formation (characteristic to the separate stage) had been developed.

Pharmacists also should be responsible for registration of the drugs' side effect, as well as be attentive in case of improperness and professional defects of drugs they provide. To achieve that it is necessary to raise awareness of specialists on the essence of pharmacists' profession and functions among the medical personnel and general public. It is necessary to provide a deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and healthcare to ensure the patients' health state effective improvement, and also to provide the best feedback regulation and revision in the healthcare specialists' team work.

THE SCIENTIFIC TALKS OF EXHAUSTIVE AND INCLUSIVE DEFIANCE OF COVID-19 INFECTION DISEASE AND ITS DRUG THERAPY PERSPECTIVES PROMOTION CONTRARY OF THE COVID-19 EPIDEMIC IN 2020 GLOBALLY

Nodar Sulashvili[1], Magda Davitashvili[2], Ia Egnatievi[3], Margarita Beglaryan[4], KakhaberRobakidze[5], Lela Grigolia[6]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia; Tbilisi State Medical University, Tbilisi, Georgia;
[2]Iakob Gogebashvili Telavi State University, Telavi, Georgia.
[3]David Aghmashenebeli University of Georgia, Tbilisi, Georgia.
[4]Yerevan State Medical University, Department of Pharmaceutical Management, Yerevan, Armenia.
[5]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;
[6]Caucasus International University; Tbilisi, Georgia;
n.sulashvili@ug.edu.ge

Aim of the research was to study exhaustive and inclusive defiance of COVID-19 infection disease and its drug therapy perspectives promotion contrary of the COVID-19 epidemic in 2020 globally. Some antiviral drugs (Rideliver, favipiravir) and antimalarial drugs (chloroquine, hydroxychloroquine) have emerged as potential drugs. Pharmacotherapy evidence of efficacy and continuous research have been developed in the article. In addition, data were obtained regarding the inflammatory pathogenesis of this virus, leading to a cytokine storm in susceptible individuals. Thus, cytokine anti-inflammatory drugs such as Anakinra and Tocilizumab are undergoing numerous trials and some of the results are encouraging. Likewise, the use of anti-inflammatory cytokines such as IL-37 and IL-38 is believed to be beneficial and under investigation. Several clinical trials are currently underway that test the efficacy of single and combination pharmacotherapy using the drugs advertised in this review, and new drugs are being monitored, developed, developed and improved.

Overview of SARS-CoV-2 virology: The pathogen of COVID-19 is the new coronavirus, officially called SARS-SV-2. It was named after SARS-COVID for genomics. Coronaviruses are large-format RNA viruses (+mRNA) with a positive value from the Coronavirus family. The coronary virus can affect a wide range of vertebrates, including bats, birds, psoriasis, snakes, mice and humans. Due to the sequence similarity exists in bats of the transmits of coronary virus, SARS-CoV-2 is currently believed to be of zoonotic origin and has acquired a secondary ability to be transmitted from person to person. In particular, detection of 1 mutations in the binding receptor area, the position of the division of multi-beta receptor at the intersection of sub bands 1 and 2 protein and the O-glycosylation site where the virus can effectively interact with the high convergence (via nail protein) of real cell receptors (angiotensin 2 [ACE-2] to bypass the immune response, perhaps by hiding O-glycylation.

Viral treatments for COVID-19 include: monoclonal antibodies, new drugs, or antiviral drugs in development. To address the epidemic immediately, the only option is to reuse antiviral drugs for reasons of time, after evaluating their safety and effectiveness. Remdesivir was considered the highest priority among therapeutic agents based on a wide range of antiviral drugs. Among the repurposed drugs, the study of the antiretroviral drug (HIV protease inhibitors), lopinavir / ritonavir, alone or in combination with interferon beta, was considered a second option suitable for rapid use in clinical trials. However, immunotherapy such as convalescent serum or other agents is also contemplated as a treatment option. Viral therapy research should include the identification of multiple therapeutic candidates for clinical evaluation, along with the development of in vitro and in vivo studies. To maximize treatment efficacy, combination therapy should be designed for additive or synergistic effects or to reduce the risk of drug resistance. The lack of information on the clinical course, epidemiological and therapeutic studies, as none of them have been developed for COVID-19, is an important milestone. To achieve rapid success in COVID-19 research and development (R&D), it is urgent to identify animal models that can mimic the characteristics of human diseases for in vivo preclinical studies.

Therapies (antiviral drugs) and clinical trials of prophylactic drugs need to be developed to protect populations at risk. Reduce mortality and improve the clinical outcome of the disease; The research agenda should include preventive research, combination therapy, evaluation and safety research of repurposed agents to advance the fight against the COVID-19 epidemic.

Ribavirin-An analog of nucleosides, ribavirin (Virasol), is a broad-spectrum antiviral agent used to treat hepatitis C, respiratory syncytial virus, and some viral hemorrhagic fevers. Several mechanisms by which ribavirin exerts its antiviral effects have been identified, including lethal mutagenesis, chain termination as specific or non-specific, and inhibition of nucleotide biosynthesis for RNA target viruses. The desired specific mechanism of action of ribavirin has not yet been fully clarified. In addition, it is a broad-spectrum drug and cannot specifically fight coronaviruses. The proposed mechanism of action of ribavirin on SARS-CoV2 is the inhibition of viral RNA synthesis and mRNA capping. The antiviral activity of ribavirin against animal CoVs and SARS-CoV1 has been proven, although the effectiveness with interferon against MERS-CoV is controversial. While several studies have shown the effectiveness of ribavirin and interferon alone the combination of these drugs has not shown positive results in critically ill patients with MERS. The effectiveness of ribavirin has been assessed primarily as a combination therapy. Successful responses to ribavirin monotherapy and/or combination therapy have been reported in several case studies. A multi-center, prospective, open-label, randomized phase II study was conducted in COVID-19 patients in Hong Kong. In the control group, patients received lopinavir 400 mg and ritonavir 100 mg every 12 hours for 14 days, and the combination group received lopinavir 400 mg and ritonavir 100 mg every 12 hours, ribavirin 400 mg every 12 hours, and three doses of 8 million. International units of interferon β-1b for 14 days.

This combination therapy was well tolerated and shortened the time to a negative nasopharyngeal swab and hospital stay in patients with mild to moderate COVID-19. In addition, an open, prospective, randomized and controlled clinical trial is being conducted at a single center to assess the efficacy and safety of various antiviral therapies (ribavirin + interferon α-1b, lopinavir/ritonavir + IFN α-1b and ribavirin + lopinavir/ritonavir + IFN α-1b) in 108 COVID-19 patients. The results of this study may be useful to provide clear evidence for the use of these therapies in the treatment of patients with mild to moderate COVID-19.

It is also worth noting that ribavirin had several known side effects such as hemolytic anemia, hypocalcemia, and hypomagnesemia. It is also contraindicated in autoimmune hepatitis, hemoglobin disorders, kidney failure, pregnant women or men with pregnant partners, and people who are hypersensitive to it. Due to the inconsistent benefits of ribavirin for COVID-19 and its serious safety concerns, as well as the very poor quality of the evidence, current evidence does not warrant its use to treat COVID-19. Combination therapy appears to offer the best chance of clinical effectiveness.

Therefore, extensive randomized controlled clinical trials are needed to confirm its effectiveness in terms of mortality, virological and clinical outcomes of COVID-19. The effects of ribavirin in combination with other therapies are being investigated in clinical studies.

Bevacizumab-is a recombinant humanized monoclonal antibody against VEGF, was first approved by USFDA on 26th February 2004 for the first-line treatment for metastatic colorectal cancer. Subsequently, the FDA approved this product along with chemotherapy to treat many cancers like lung cancer, renal cancer, cervical cancer, ovarian cancer, etc. In addition, recent studies suggest that higher levels of blood VEGF in COVID-19 patients compared with normal and also pulmonary edema, dyspnea, acute respiratory distress and acute lung injury are the most detrimental symptoms of COVID-19. Numerous studies reported that VEGF was a critical factor in pulmonary edema, acute respiratory distress and acute lung injury.

Siltuximab (CNTO 328) is a monoclonal antibody conjugate of interleukin-6 (IL-6) and therefore neutralizes IL-6 bioactivity. It also promotes tumor cell death and is approved for the treatment of certain viral diseases such as HIV, human herpesvirus-8 (HHV-8), multicentric Castleman's disease (CDM), multiple myeloma (MM), myelodysplastic syndrome (MDS), prostate cancer, ovarian cancer, lung cancer and reduced anorexia and cancer-associated cachexia.

IL-6 pathway inhibitors – Tocilizumab is an interleukin (IL)-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome. Elevated IL-6 levels have been described in patients with severe COVID-19, and case reports have described good outcomes with tocilizumab, but systematic evaluation of the clinical impact of tocilizumab on COVID-19 has not yet been published. Treatment guidelines from China's National Health Commission include the IL-6 inhibitor tocilizumab for patients with severe COVID-19 and elevated IL-6 levels. Tocilizumab, as well as sarilumab and siltuximab, which also target the IL-6 pathway, are being evaluated in clinical trials.

About other indicated agents against COVID -19: **Atazanavir** (ATV) with a protease inhibition mechanism is approved for the treatment of HIV or AIDS. As mentioned in previous sections, the pathogenicity of CoV requires non-structural proteins such as protease, an enzyme that is critical for the conversion of polyproteins to CoV. Hence, atazanavir prevents the formation of a mature viral particle and suppresses SARS-CoV2 infection. In a study based on molecular docking analysis of SARS-CoV2 helicase inhibitors, Borgio and colleagues showed that atazanavir can interfere with SARS-CoV-2 helicase activity [105]. A recent study by Beck and his colleagues based on the target transformer molecule interaction (MT-DTI) also showed that atazanavir was the best compound tested to inhibit SARS-CoV2-like proteinase activity. Order atazanavir> remdesivir> efavirus> ritonavir> dolutegravir.

Baricitinib is an anti-inflammatory drug used to treat refractory rheumatoid arthritis. The most important anti-inflammatory mechanism of baricitinib in rheumatoid arthritis is the inhibition of Janus kinase (JAK) enzymes. With SARS-CoV2, however, baricitinib prevents the virus from entering cells through various mechanisms. It inhibits AP2-associated protein kinase 1 (AAK1): an enzyme that promotes viral endocytosis. Baricitinib also inhibits viral endocytosis by interacting with cyclin-associated kinase G (GAK). It is also suggested that baricitinib reduces inflammation by inhibiting JAK1 / 2 enzymes [15-16]. Consequently, baricitinib may have beneficial clinical effects in COVID-19 patients and be an alternative treatment option for COVID-19, especially in patients with coexisting rheumatoid arthritis. However, inhibition of JAK-STAT kinase by baricitinib disrupts the antiviral activity of congenital interferons [17-18]. Also, baricitinib may cause some symptoms of upper respiratory tract infections, nausea and thrombosis in rheumatoid arthritis patients receiving this medicine. Therefore, the efficacy and safety of baricitinib in COVID-19 infected patients are still unclear. At the time of writing, several clinical and observational studies have been recorded on the efficacy and safety of baricitinib for the treatment of COVID-19. One of these has been completed and the main outcome of this pilot study was the safety assessment of baricitinib. It did not increase the risk of infections, cardiovascular and hematological side effects after 2 weeks of treatment.

Levamisole, levisomer and tetramisole, belong to the class of medical membranes and are the first representative of a new class of drugs that increase cell resistance, a synthetic compound with low molecular weight. The immunosuppressive and immunostimulatory effects of levamisole have been demonstrated on the basis of dosage and timing of clinical use. According to previous studies, the in vitro combination of levamisole and ascorbic acid can reverse the proliferation of depressed accessory / stimulating ganglion cells. Levamisol lymphocyte spread often occurs when standard lymphocytes are treated with measles virus in vitro. Therefore, levamisole may also be considered for the treatment of COVID-19.

Darunavir: As an HIV protease inhibitor, darunavir (DRV) can prevent the formation of mature infectious virus particles by selectively inhibiting the cleavage of the Gag-Pol polyprotein in cells infected with the virus. In February 2020, Chinese

researchers announced the suppressive effects of DRV on SARS-CoV-2 infection. Cell experiments have shown that virus replication is significantly inhibited by DRV at a concentration of 300 μM. Darunavir in combination with cobicistat (DRV / c) has been shown to significantly inhibit SARS-CoV2 replication. This combination therapy has been approved by the US Food and Drug Administration (FDA) for the treatment of AIDS patients. To improve the pharmacokinetics and pharmacodynamics of darunavir, cobicistat, like ritonavir, may act as an LPV / r booster and inhibit cytochrome P450 (CYP3A). In addition to in-vitro and clinical studies, several in-silico studies have also confirmed the effectiveness of the antiviral activity of DRV against SARS-CoV2. DRV's potential therapeutic effect against SARS-CoV2 may be primarily due to its inhibitory effects on papain-like viral protease (PLVP) and basic protease. Darunavir has been shown to have high ligand affinity and is a potential candidate that may interfere with communication between the SARS-CoV2 receptor binding domain and ACE2. Therefore, it is currently proposed that DRVs be reassigned for the treatment of SARS-CoV2 infection due to their potential impairment in cell recognition, attachment, and invasion.

Oseltamivir (Tamiflu) is an antiviral neuraminidase inhibitor used to treat and prevent influenza A and B. Oseltamivir exhibits its antiviral activity by inhibiting viral neuraminidase activity and viral replication. Oseltamivir suppressed viral replication at least in some cases. Coronaviruses do not use neuraminidase to replicate viruses; Therefore, oseltamivir is unlikely to have therapeutic value. It was removed from the SARS-CoV2 treatment protocol. The only study that looked at the effects of oseltamivir on coronaviruses found that even at high concentrations of the drug, it was ineffective in preventing SARS-CoV1.

Chloroquine and hydroxychloroquine have received a lot of attention due to their inhibition of enzymes or viral processes, particularly in Iran, the United Kingdom, and France. However, the FDA has withdrawn the emergency use permit due to serious side effects and other potential side effects. The potential benefits of chloroquine and hydroxychloroquine no longer outweigh the potential risks with permitted use. hydroxychloroquine is better than chloroquine and has reported positive results in some pre-clinical in vitro data and protocols. Both antimalarial drugs can do more harm than good due to the many side effects and should not be prescribed for more than 7 days. In rare cases, cardiac arrest, retinal damage, and eye toxicity are major concerns, especially since people with heart disease are at higher risk for difficulties.

Thus, various studies are currently underway to evaluate vaccines against SARS-CoV2. However, due to genetic changes in viral nucleic acid in different hosts, these specific vaccines may not have a clear preventive effect., treatment approaches that are currently being studied include antiviral and anti-inflammatory cytokines, anti-infective and life-sustaining therapy, monoclonal antibodies, and passive immunotherapy, especially in patients with severe illness. However, while a therapeutic strategy against the disease is important, the most important way to prevent the spread of the virus is to develop a widely available effective and safe medicines and vaccines.

PARTICULARITIES OF THE CLINICAL-MICROBIOLOGICAL STATE OF THE ORAL MUCOSAL IN GRAVID FEMALES

Nodar Sulashvili[1], Kakhaber Robakidze[2], Magda Davitashvili[3], Irma Buchukuri[4], Lela Grigolia[5]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[3]Iakob Gogebashvili Telavi State University, Telavi, Georgia.

[4]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;

[5]Caucasus International University; Tbilisi, Georgia;

n.sulashvili@ug.edu.ge

Maternal and child health protection is the most important task of medicine, in the solution of which representatives of various health departments are involved, including the dental service. This is due to the fact that pregnancy leads to neurohumoral changes that cause changes in the activity of a number of organs and body systems, including the oral cavity. It is known that pregnant women have a high intensity of dental diseases. At the same time, the pathology of teeth and periodontal disease can create "dental chronic foci", which are detected not only by the return of microbial penetration into the body, but also as a source of long-term pathological reflex irritation in the body, causing complications during pregnancy, childbirth and the postpartum period. Therefore, among the various types of medical care, dental, is mandatory at all stages of maternal and child health. All this testifies to the unreasonableness of a one-time examination and sanitation of the oral cavity of pregnant women. It is necessary to conduct dynamic monitoring of the state of the oral organs of a woman throughout pregnancy in order to identify the initial forms of the disease, monitor the effectiveness of sanitation and prevent the development of complications. Therefore, the prevention of dental diseases in pregnant women at all stages is of great importance. According to leading dentists, pregnancy is a critical period for a woman's dental health. Its consequences are progressive periodontal diseases, the development of dental caries and inflammatory and destructive lesions of the mucosa. The relationship between oral dysbiosis and disorders of local factors of mucosal protection in the onset and development of dental diseases is obvious.

Pregnancy is one of the most important stages in a woman's life. But pregnancy is stress for the female body, which in its own way and in different ways affects all its systems and organs, including the oral cavity. During this period, the teeth begin to crumble, crumble and fall out, and the gums begin to bleed. Changes in the hormonal background of pregnant women are reflected even in the composition and properties of saliva, which during this period contributes to the development of caries. Gums during pregnancy are supplied with a large amount of blood, which makes them loose and accessible to pathogenic bacteria. The result is inflammation in the mouth. The consequence is gingivitis. Untreated, it develops into periodontitis, the main symptom of which is bleeding. In view of the above, the study of the microflora of the oral cavity in

pregnant women was considered relevant.

As it known that pregnancy is constantly affected by hormonal, metabolic and immunological factors, which can affect the oral microbiota, leading to gingivitis during pregnancy. However, it is not yet clear how microbial dysbiosis in the oral cavity modulates oral disease, since the oral microbiome is poorly characterized during pregnancy. In addition, the recent discovery that the placenta microbiome is similar to the oral microbiome reinforces the importance of oral dysbiosis in adverse pregnancy outcomes. Thus, using the rRNA gene sequencing method, we present a snapshot of the changes in the microbial composition of the oral cavity, depending on the progression of pregnancy and the period of birth and its relationship with gingivitis during pregnancy. Despite the stability of oral microbial diversity during pregnancy and postpartum, we observed that the microbiome undergoes pathogenic changes during pregnancy and returns to a healthy microbiome in the postpartum period. The network-based coexistence analysis provided a mechanistic explanation for the pathogenicity of the microbiome during pregnancy and foreseen frequencies in the interaction centers. Individual dachshunds that form organic companies in the main microbiome can modulate the pathogenicity of microbes during pregnancy and reduce the risk of oral disease and adverse pregnancy outcomes. Our study also highlighted the potential for the appearance of new species in subgingival plaques and saliva, which are important contributors to the development of gingivitis during pregnancy. The key species may offer opportunities to develop strategies to modulate the microbiome and improve the health of the host during pregnancy. Infection-related premature births have been cited as the main cause of infant mortality and morbidity. As the literature shows, 40% of premature births are vaginal and associated with intrauterine infections and 50% are associated with intra-amniotic infections. Given this history, it is necessary to understand the origin of the attacking bacteria and the invasive routes of the placenta and amniotic fluid cavity. Literature shows that the most common intra-amniotic bacterial toxins were types associated with the vagina, although other types are often associated with the oral cavity, gastrointestinal tract, and respiratory tract. The authors concluded that the pooled data indicate a primary role for the ascending route of infection during pregnancy and a possible secondary role for the hematogenous invasion route.

Based on the foregoing, we set the goal of the study - to study the quantitative and qualitative composition of the oral microflora and indicators of local protection factors in pregnant women suffering from periodontitis according to trimesters. According comprehensive study results found 100 pregnant women aged 25-45 years, suffering from periodontitis and being examined at the perinatal center of the National Health Center named after V.I. acad. About Gudushauri Tbilisi. The surveyed women were equally (25 women) divided into 4 groups: the first group consisted of pregnant women with no oral diseases; the second group included pregnant women who had periodontitis in the 1st trimester; the third group consisted of pregnant women suffering from periodontitis from the 2nd trimester and the fourth group consisted of pregnant women suffering from periodontitis from the 3rd trimester of pregnancy.

Microbiological research. Oral fluid was taken from all examined pregnant women by flushing from the mucous membrane. The material obtained by this method was considered as the first dilution; a series of serial dilutions were prepared from this material in the laboratory. Subsequently, a certain volume was poured onto the surface of differential diagnostic media: agar for anaerobes, Endo's medium, milk-salt agar, Sabouraud's medium, freshly cut mesopatamia agar, etc. Inoculations on blood agar, Endo, milk-salt agar, Saburo were cultivated under normal conditions for 18-24 hours at a temperature of 37 ° C, and the cultivation of anaerobes was carried out in an anaerobic container, which was placed in a thermostat for 3-5 days. After the indicated time, the dishes with the inoculations were taken out of the thermostat, the grown colonies were counted, the group and species belonging of the isolated colonies of microbes were determined on the basis of microscopy data of smears stained according to Gram, the nature of growth on selective and differential diagnostic media. When working according to the modified method, the result was taken into account according to the last dilution, in which the growth of bacteria was obtained, the number of microbes was expressed in lq M ± m colony-forming units (KFU)/ml. Microbiological studies to study the quantitative and qualitative indicators of the oral microflora in pregnant women showed that the oral microflora of healthy pregnant women is quite diverse. At the same time, lactobacilli prevail in the anaerobic group of microbes, their number was 4.4 ± 0.18 CFU / ml. In the facultative group of microbes, streptococci and staphylococci are dominant, while among streptococci the most popular are Str. Salvarius. A completely different picture in the microecology of the oral cavity in pregnant women in the first trimester, suffering from periodontitis. In particular, in the examined pregnant women, significant dysbiotic changes are observed, both in the anaerobic and in the facultative group of microbes. So in the anaerobic group there is a significant decrease, while it is especially pronounced in lactobacilli, their number was 2.8 ± 0.4 CFU / ml, which is more than 2 orders of magnitude lower than the norm. However, even more pronounced changes were noted in the optional group. This is how the number of Str. mutans increased significantly and was equal to 5.35 ± 0.15 CFU / ml, but the appearance of pathogenic staphylococcus strains in this arsenal is especially alarming. Most likely, these strains possessing a wide range of pathogenic enzymes and will determine the monitoring of the oral cavity in these pregnant women. The next group of pregnant women with periodontitis consisted of women in the second trimester of pregnancy. The analysis of the obtained microbiological studies of the oral cavity in this group of women shows that all the existing dysbiotic changes in the first trimester of pregnancy passed into the second, more of this change deepened even more, especially with regard to a decrease in the number of lactobacilli, but against this background, an increase in the number of microbes such as: strains of golden and Staphylococcus epidermidis, Escherichia and fungi of the genus Candida. A rather interesting picture was obtained during microbiological studies of the oral cavity in pregnant women with periodontitis in the third trimester of pregnancy: in this trimester, generally positive changes appeared, which affected both the anaerobic and the optional group. Particularly significant

changes affected microbes such as streptococci, the number of strains of which increased in all three colonies. At the same time, it is especially positive that pathogenic strains of staphylococci and fungi of the genus Candida were eliminated from the oral cavity. Thus, summing up the studies carried out, it can be argued with a high degree of reliability that the most pronounced dysbiotic changes in the oral cavity in pregnant women with periodontitis are observed in the second trimester, which must be taken into account by dentists. Based on the conducted microbiological studies in pregnant women with periodontitis, who are in different trimesters, almost the same type of changes was revealed. Although it should be noted that these changes actually have a positive correlation between indices of local defense factors and dysbiotic changes in the oral flora. The conducted studies allow us to draw the following conclusions: In pregnant women suffering from periodontitis in all three trimesters, dysbiotic changes occur, a characteristic feature of which is a decrease in lactobacilli and an increase in the number of staphylococci and fungi of the genus Candida. At the same time, it should be noted that the changes are most pronounced in the second trimester of pregnancy.

The conducted studies allow us to draw the following conclusions: In pregnant women suffering from periodontitis in all three trimesters, dysbiotic changes occur, a characteristic feature of which is a decrease in lactobacilli and an increase in the number of staphylococci and fungi of the genus Candida. At the same time, it should be noted that the changes are most pronounced in the second trimester of pregnancy.

SOME MICROBIOLOGICAL INDICATORS OF THE ORAL CAVITY OF ORTHOPEDIC PATIENTS

NodarSulashvili[1], Kakhaber Robakidze[2], Irma Buchukuri[3], Lela Grigolia[4], Magda Davitashvili[5]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi State Medical University, Tbilisi, Georgia;
[2]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;
[3]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;
[4]Caucasus International University; Tbilisi, Georgia;
[5]Iakob Gogebashvili Telavi State University, Telavi, Georgia.
n.sulashvili@ug.edu.ge

The microflora of the oral cavity is a set of representatives of various taxonomic groups of microorganisms that inhabit the oral cavity as a kind of ecological niche of the human body, entering into biochemical, immunological and other interactions with the microorganism and with each other. Any imbalance in this set is a harbinger of diseases of the oral mucosa. Orthopedic devices cause regular irritation of the mucous membrane. These irritations reduce the activity of oral natural resistance factors, which, in turn, causes an imbalance in the oral microflora.

The successes achieved to date in the treatment of malocclusion pathology using orthodontic technology can significantly expand the indications for its use. A wealth of clinical experience has been accumulated in achieving functional and aesthetic effects in adult patients, aggravated by chronic inflammatory periodontal diseases, including those accompanied by destructive lesions. Nevertheless, studies by a number of authors indicate an increase in the percentage of complications of orthodontic treatment, the most frequent of which is an exacerbation of chronic inflammatory periodontal diseases. A kind of risk zone for exacerbation of chronic inflammatory periodontal diseases are those parts of the dentition to which force is applied. Orthodontic constructions change the relief of the dentition, significantly increase the potential area of possible adhesion of microorganisms, make it difficult to remove plaque, which prompts the search for informative criteria for monitoring the course of a chronic infectious and inflammatory process in the oral cavity under permanently acting conditions.

It is known that biotopes of the oral cavity are the most contaminated areas of the human body, characterized by qualitative and quantitative diversity. At the same time, pathogenicity is maximally manifested in the presence of dental plaque, a multi-species community of microorganisms located on the surface of the teeth in the form of a biological layer. These Bio-layers have a high level of tolerance to antiseptics and phagocytes. Literary sources indicate that with unsatisfactory oral hygiene in orthodontic patients, the concentration of fungal flora (yeast and fungi of the genus Candida) increases relative to the normal microflora of the oral cavity. Carriage of periodontal pathogenic strains was established by some authors in 70 % of the examined, of which 30 % of those in need of orthodontic treatment are at risk of developing periodontitis. However, we did not find information on the dynamics of qualitative and quantitative changes in the microbial landscape in the process of orthodontic treatment, which determined the purpose of this study.

The study involved 60 patients (20 men and 40 women) aged 25 to 45 years, undergoing orthodontic treatment using fixed structures. All patients in the study group were diagnosed with the crowded position of the anterior teeth of the upper and lower jaw. The patients of the study group were ranked into three subgroups (based on the burden of inflammatory periodontal diseases): the first subgroup – patients with intact periodontal disease, the second – patients with chronic generalized gingivitis, the third – with chronic generalized mild periodontitis. Patients in all groups were divided equally – 20 persons. The criteria for the inclusion of patients in the study group were: confirmed diagnosis of dentoalveolar anomaly (based on data from clinical, X-ray studies, diagnostic models of the jaws), absence of endocrinological / somatic burden; denial of a history of taking medications, dietary supplements, probiotics, toothpastes containing antibacterial additives; consent to participate in the study. The comparison group consisted of 50 patients, comparable in gender and age composition, burden of orthodontic pathology, chronic inflammatory periodontal diseases, who did not receive orthodontic treatment. All patients in the comparison group were also ranked into 3 subgroups according to the above principle: the first subgroup included 15 patients, the

second – 15 patients, and the third – 20 patients. All patients of the study group and the comparison group confirmed their consent to participate in the study. To verify the periodontal diagnosis, a complex of clinical and radiological research methods was used. Assessment of the state of the oral cavity and periodontal tissues was carried out using hygienic (Green – Vermillion) and periodontal (periodontal index (PI) according to Russell, index of bleeding according to Mullemann-Cowell) indices. To determine the degree of microbial contamination, the material was taken on an empty stomach or 3-4 hours after a meal. On the day of taking the material for research, the patient must refrain from brushing his teeth, using drugs and rinsing the mouth with elixirs or rinses containing antiseptic components of plant/chemical origin.

Material for research was obtained from the cervical area of the teeth in the area of the orthodontic construction, the gingival sulcus / periodontal pocket using sterile paper endodontic pins, which were then placed in a test tube with a transport medium. The material was taken three times: at the diagnostic stage, 3-4 weeks, 3 and 6 months after fixation of fixed orthodontic equipment, at the beginning of the retention period. Before fixing the structural elements, all patients with inflammatory periodontal diseases underwent periodontal treatment. The biomaterial was sown on solid and semi-liquid nutrient media for the cultivation of microorganisms under aerobic and anaerobic conditions. Used 5 % blood agar, Sabouraud's medium, streptococcal selective agar, yolk-salt agar, thioglycolic medium, de Man's medium, Rogosa, Sharpe (MRS) agar, Blaurock's medium. The isolated microorganisms were identified by conventional methods, taking into account the morphological, cultural and biochemical properties. To determine the degree of microbial contamination of the studied biotopes with periodontal pathogenic strains, the PCR method was used. For statistical processing, we used the Statistical Package for Social Science – Statistical Package for Social Sciences. To check the normality of the distributions, the Student's test was used; the differences were considered significant at $p < 0.05$.

Microbiological data obtained in the course of studying the degree of contamination with bacterial and periodontal pathogenic microflora of the gingival sulcus and periodontal pocket, expressed in colony-forming units (CFU) per 1 cm^2, showed that streptococcus salivans and Streptococcus sangius are sown in patients with intact periodontal disease at the diagnostic stage; at the same stage, in patients with chronic generalized gingivitis, along with streptococcus salivans and Streptococcus sangius, Prevotella intermedia are also sown; and at the same stage, in patients with chronic generalized periodontitis, along with the listed microorganisms, other bacteria prevail (Treponema denticola, Porphyromonas gingivalis and Candida albicans). In patients with intact periodontium, after three months, Streptococcus salivans and Streptococcus sangius again prevail in the oral cavity along with lactobacillus spp; in the same patients, Streptococcus salivans disappear from the oral cavity in six months. In patients with chronic generalized gingivitis, after three months, microbial discharge of the oral cavity is enriched with Leptotrichia, and is preserved practically unchanged at the sixth month too. In patients with chronic generalized periodontitis, after three

months, the microbial discharge of the oral cavity is very rich and diverse, the following types of microorganisms represent it: streptococcus mutans, Streptococcus sangius, Lactobacillus spp, Prevotella intermedia, Treponeba denticola, Actinobacillus actinomycetem-comirans, Porphyromonas gingivalis, candida albicans, Leptotrichia. In these patients, after six months, the non-qualitative, nonquantitative composition of the microbial life of the oral cavity practically does not change.

The foregoing indicates that in patients with intact periodontium, the microbial landscape of the gingival sulcus at the stages of observation changes slightly qualitatively. So, the dominant microbial groups are streptococci and lactobacilli, and the seeding density was the highest after 3-4 weeks and 3 months after fixing the braces. In patients with chronic generalized gingivitis, the coccal flora also appeared to be the dominant flora; however, at the diagnostic stage, prevotella was cultured in 2 patients.3-4 weeks after fixation, the titer of the coccal flora increases, the qualitative (species) composition changes: representatives of the fungal flora appear, and the number of patients in whom prevotella and treponema are detected increases. At the observation period of 3 months, the diversity of the species composition is enhanced by the strains of Sandida albicans and Leptotrichia, the seeding density of other bacteria increases. After 6 months and by the beginning of the retention period, a depletion of the species composition and a decrease in the density of sowing of microflora were stated. The greatest qualitative and quantitative diversity was observed in the microbial landscape of periodontal pockets in patients with chronic generalized periodontitis at the observation stages of 3-4 weeks and 3 months. The dominant microflora at these stages is periodontal pathogenic. Coccal and candidal microflora in this case is accompanying. It should be noted that when comparing the features of microbial contamination of the cervical region of the teeth, on which the braces are fixed, and periodontal pockets, we identified fundamental differences. Thus, periodontal pathogenic strains were detected only in periodontal pockets, which is due to the conditions of anaerobiosis.

Thus, the information we have obtained dictates the need for a differentiated development of professional hygiene regulations for orthodontic patients, aggravated by inflammatory periodontal diseases.

THE SCIENTIFIC DISCUSSIONS OF FEATURES PHARMACEUTICAL REGULATION EMISSIONS, ELABORATED BY THE PATIENTS IN GEORGIA

Nodar Sulashvili[1], Margarita Beglaryan[2], Ia Egnatievi[3], Magda Davitashvili[4], Kakhaber Robakidze[5], Lela Grigolia[6]

[1]Alte University, International School of Medicine, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Yerevan State Medical University, Head of the Department of Pharmaceutical Management, Yerevan, Armenia.

[3]David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

[4]Iakob Gogebashvili Telavi State University, Telavi, Georgia.

[5]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[6]Caucasus International University; Tbilisi, Georgia;

n.sulashvili@ug.edu.ge

Aim and objectives was to study features pharmaceutical regulation emissions, elaborated by the patients in Georgia. The study was quantitative investigation by using survey (Questionnaire). Research objectives are materials of sociological research: Surveys was for patients; 1506 patients were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program.

At present in Georgia this regulatory legislative base is not perfect, because the pharmacists' certification, re-certification, accreditation and licensing state programs are not conducted. Today; the pharmacist profession in Georgia is deleted from the health adjustable medical fields. Therefore degree in pharmacy or higher education in this aspect use their professional characters and values, so that profession of pharmacist specialty becamen a position given by the pharmacy owner and does not require qualification awarded from the university. Since the higher pharmaceutical education is not a necessity for pharmacist position in pharmacys in Georgia, very often non-professionals without special medical or pharmaceutical education get the right to work at a pharmacist position according to pharmacy owner's desire, meanwhile the pharmacy profession granting needs 4-5-year study at the medical and other universities. At the same time the problem of Georgian pharmaceutical graduates consists possible lack of jobs for the pharmacethical facilities because of easy access of other subject specialists. In Georgia a pharmacy pharmacist is interpreted as the only drug-dealer-seller, and basically pharmacists as regulated medical specialists are ignored in Georgian health care system. That is why the higher pharmaceutical education system should be moved to a new model direction, which will be more focused on pharmacotherapy, pharmaceutical care, and clinical pharmacy, becoming the most important issue. Hence, in the state health policy the pharmacist profession's concepts and common principles are to be developed.

Pharmacist are experts in pharmacotherapy, they can provide extra understanding, knowledge, skills, and regards to other public health and health care specialists within a

multidisciplinary team atmosphere. Concretely, the pharmacists be able to contribute to health care group by discovering and solving or preventing drug associated issues; they supporting to guarantee the safely and efficiently pharmacotherapy principles; ensuring exhaustive information about the drug to patients and other health care and public health specialists; contributing medication compliance; and strengthening fundamental health promotion and prevention lifestyle modification activities in the society. In opposite, in primary health care, pharmacists generally have more restricted straightforward approach to clinical patient records and another health care specialists, like clinical-based pharmacists are highly accessible to patients. This provides patients with nice and good opportunities to search advices for the control of minor diseases or preventive care medicine, and occasionally more serious circumstances, constantly before searching assistance from the family Doctors. Pharmacist according patients' need transferring patients to the family Doctor, hospital or insurance company. Therefore, pharmacists are in perfect situation and position to ensure a first full point of communication within the health care system, in a triage- pattern role or as a connection between other health care professionals, mainly family doctors and general medical practitioners. Above mentioned aspirations are shown by some pharmacist scientists in western countries, who studied the pharmaceutical care services, where doctors access was limited. The pharmacists distinguish the beneficial assistance and promotion to functioning as a bond between the various sites of health care division, such as distinction care, pharmacotherapy or pharmaceutical care or public safety. The cooperation of pharmacists with various health care providers have as well demonstrated to have an affirmative influence in the judicial framework. Research objectives are materials of sociological research: the study was quantitative investigation by using survey (Questionnaire). Surveys was for patients; 1506 patients were interviewed in Georgia. We used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. Results and discussion: The survey was conducted through the questionnaires.1506 patients were interviewed in Georgia. Questions and answers are given in the tables. On each question are attached diagrams or table. Questionnaire and diagrams are numbered.

On the question mark the most significant factors while choosing a pharmacy (you can indicate no more than 5 answers)? Patients'50.7% answer service culture; Patients'53% answer wide range of products ; Patients'49.3% answer possibility to receive consultation about drugs with a physician/ a pharmacist; Patients'58.2% answer reasonable prices; Patients'36.3% answer high qualification of personnel, Patients'45.2% answer convenient or comfortable location of the pharmacy; Patients' 31.7% answer absence of queues, Patients' 19.5% answer friendly staff, patients'31.3% answer the existence of high-quality drugs.

For the majority of respondent patients', mostly significant factors, while choosing a pharmacy are: Service culture, wide range of products, reasonable prices. For less than half of respondent patients, mostly significant factors, while choosing a pharmacy are:

Possibility to receive consultation about drugs with a physician or a pharmacist, convenient location of the pharmacy, high qualification of pharmacist personnel.

On the question- What are questions mostly you ask to pharmacists? (You can indicate several answers)? Patients'63.1% answer about rule of intake of drugs , patients'41.5% answer about adverse effects of drugs , patients'61.4% answer about prices of drugs, Patients'29.8% answer about help in selection of analogue of drugs (medication), patients'42.5% answer about quality of drugs , patients'26.5% answer about existence of drugs patients' in a pharmacy, Patients'31.3% answer about indication/contraindication of drugs patients',Patients'30.8% answer about terms and conditions of storage (conditions and shelf-life), patients'33.5% answer about drugs patients' dosage , patients'19.4% answer about routes of drug administration , patients'19.2% answer about drug forms , patients'8.6% answer about drug design, patients'19.7% answer about drugs toxic effects(toxicity), patients'3.7% answer about principles of pharmacotherapy, patients'25.6% answer about rules of drug administration, patients'10.4% answer about drugs generic, chemical and brand names, Patients'27.2% answer about selection of (Over-the-counter) OTC drugs, patients'25.2% answer Information about drug, patients'20.7% answer effectiveness of drug, Patients' 18.9% answer about drug(s) action and drug(s) interactions, , Patients' 21.3% answer about drugs safety, Patients'3.4% answer about cost-effectiveness and cost-benefits of drugs. On the question - Do you think that the government should make the certification of pharmacists? Patients'82.6% answer I agree, patients' 11.6% answer I partly agree, patients' 5.8% answer I do not agree.

The vast majority of respondent Patients consider, that the government should make the certification of pharmacists.

Thus**,** the higher pharmaceutical education and the pharmacist specialists' certifications programs are guarantee for higher professionalism of pharmacist specialists and of higher pharmaceutical service provision in pharmacies. Only the pharmacists with higher pharmaceutical education have the right to work at the pharmacist position in the pharmacies.

THE SCIENTIFIC DISCUSSIONS OF THE DETECTION OF COVID-19 DISEASES CAUSED BY SARS-COV-2 AND ITS EFFECTS ON THE ORAL MUCOSA, UROGENITAL SYSTEM AND SKIN

Nodar Sulashvili[1], Kakhaber Robakidze[2], Irma Buchukuri[3], Lela Grigolia[4], Magda Davitashvili[5]

[1]Alte University, International School of Medicine, Tbilisi State Medical University, Tbilisi, Georgia;

[2]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;

[3]Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia;

[4]Caucasus International University; Tbilisi, Georgia;

[5]Iakob Gogebashvili Telavi State University, Telavi, Georgia.

n.sulashvili@ug.edu.ge

A Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The review is devoted to the skin manifestations of new coronovirus infection (SARS-CoV-2), information about which is constantly updated. However, this information has not been systematized yet. The purpose of this review is to analyze the dermatological manifestations of a new coronavirus infection. On average, 12.5-20.4% of patients with confirmed COVID-19 have developed skin manifestations. The question of whether the skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at the moment. The possible mechanisms of development of skin lesions and the role of diseases of complement system and blood hypercoagulation in the pathogenesis of the disease are discussed in the article. The review also provides descriptive and clinical examples of skin manifestations in COVID-19. Since COVID-19 tends to be asymptomatic within 14 days, skin manifestations can be an indicator of infection, which leads to the timely diagnosis. In addition, doctors' awareness about skin symptoms associated with COVID-19 infection plays a big role in preventing misdiagnosis of the disease.

Over the past centuries, it is difficult to find diseases similar in resonance to the corona-virus infection COVID-19 caused by SARS-CoV-2. From the day of manifestation of the infection, it has become the dominant nosology, and its etiological agent has dramatically changed, in its favor, the species spectrum of anthropogenic pathological microorganisms. The first information about the new disease was registered in December 2019 in China. Since January 2020, the disease has spread to other countries of the world. Since February 2020, residents of South Korea, Iran, Italy, Spain and the United States have been infected with covid-19, and later almost the whole world. On March 11, 2020, WHO declared a pandemic caused by COVID-19. The high level of contagiousness and asymptomatic transmission of the infection led to its rapid

spread around the world and a pandemic. SARSCoV-2 is a single-stranded RNA virus and belongs to the coronavirus family. The virus enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor located on the surface cells. The lungs are a major target organ for COVID-19, with patients experiencing symptoms ranging from mild flu-like symptoms to fulminant pneumonia and potentially fatal respiratory distress syndrome. A number of cases have been recorded during the pandemic COVID-19 who reported skin manifestations of the infection**.** The purpose of this article is to systematize the literature on various skin manifestations in COVID-19. According to literary sources, during the pandemic period, a number of cases of COVID-19 with skin manifestations were recorded: Similar information was first reported from Italy - Gianotti described Exanthema, Purple maculopapular vesicular, Papular- erythematous, and Diffuse maculopapular eruption resembling Grover's disease; Recalcati reported an erythematous and vesicular rash, as well as urticaria; Present, Case described a maculopapular pruritic rash resembling Grover's disease, Diffuse maculopapular rash, macular hemorrhagic rash, and Papular-vesicular pruritic rash; Marzano described a papulo-vesicular exanthema similar to the chicken pox rash, and Mazzotta described erythematous rounded lesions; Erythematous rash was described by the French dermatologist Mahé, and disseminated erythematous rash and urticaria were described by Henry; Spanish investigators Estébanez reports erythematous pruritic papules (yellow) and Fernandez reports urticaria; In Thailand, researchers described petechiae, in Iran - an erythematous rash, and in Qatar - cranial ischemic lesions, which are red-violet papules, in Belgium - infiltrated plaques on an erythematous background, in Russia - papulo-necrotic angiitis, hemorrhagic angiitis, acroangiitis (acrodermatitis), papulo-vesicular rashes, disseminated maculopapular rash and purpurous rash (toxidermia), in the homeland of infection in China, acroischemia with digital cyanosis, blistering or dry gangrene, and urticaria, and in the United States, transient non-pruritic unilateral livedo reticularis, unilateral asymptomatic livedo reticularis and diffuse to maculopapular non-pruritic rash similar to dermatological symptoms in measles (Najarian, Hunt [20]). In the course of treatment of a patient with COVID-19, we described several skin symptoms, but only one differed from the literature symptoms: an erosive element against the background of erythema on the genitals in a 64-year-old man, developing associated hyperthermia on the 4th day after diagnosis. The pathological element was eliminated from the skin 8 days after the patient's hospitalization; 14 days passed until the complete regeneration of the skin against the background of local treatment with combined topical preparations.

Among the literary sources, there are only a few reports about the manifestation of COVID-19 on the oral mucosa. On the part of scientists, special attention is paid to the violation of taste in the form of hypogeusia, dysgeusia or ageusia during the disease. Apparently, oral manifestations dominate in the main post- COVID-19 period in the form of hyperemia, dry atrophy, hemorrhage, erosion, ulcers of the mucous membrane, pseudomembranous-erythematous form of candidiasis, aphthous rash in the oral cavity, dryness and peeling of the upper and lower lips.

As you know, a rash is not uncommon among infectious pathologies, the most common and characteristic symptoms of such viral infections as measles, rubella and Dengue fever are skin rashes (exanthema). With coronavirus infection caused by COVID-19, the formation of exanthema may be associated with an inflammatory response of tissues to the effects of toxins and metabolites of the pathogen during the implementation of the main mechanisms of inflammation; However, while skin manifestations associated with COVID-19 have been increasingly reported recently, the pathological mechanisms of skin lesions in patients with COVID-19 remain poorly understood. Skin manifestations of COVID-19 can be divided into two main groups depending on the pathophysiological mechanism of their development: clinical signs similar to viral exanthems (immune response to viral nucleotides) and skin rashes secondary to systemic consequences caused by COVID-19 (especially vasculitis and thrombotic vasculopathy).

To assess the possible impact of SARS-CoV-2 on human skin, one must take into account the fact that SARS-CoV-2 is a single-stranded RNA virus consisting of 16 non-structural proteins (NSP 1-16) that play a role in the replication of coronoviruses. For example, NSP3 has the ability to block the host's innate immune response and stimulate cytokine expression, NSP5 can inhibit interferon (IFN) signaling, and NSP16 avoids MAD5 (melanoma differentiation-associated gene 5) recognition by suppressing hostile immunity [24]. Some studies have shown a direct effect of viral infection on T cells by detecting SARS-like particles and SARS-CoV-2 RNA in T lymphocytes. It has been shown that in some patients an overactive immune response can cause a "cytokine storm" (an increase in the level of pro-inflammatory cytokines, in particular, IL-6); these cytokines can reach the skin and stimulate dermal dendritic cells, macrophages, mast cells, lymphocytes, neutrophils, and promote rashes such as erythema, urticaria, vesicles, and others. Intervention in the host by SARS-CoV-2 results in infection of functional receptor-target cells expressing type II (ACE2) angiotensin-converting enzyme (ACE), such as type 2 alveolar cells or other unknown target cells. ACE2 is also present in the skin in the basal layer of the epidermis, in the endothelial cells of dermal blood vessels, and in the tissue of the eccrine appendages. Some researchers have suggested a direct pathogenic effect of the virus on the epidermis through ACE2, leading to acantholysis and dyskeratosis. COVID-19-endothelitis through ACE2 may explain the systemic impairment of microcirculatory function in various vascular beds and its clinical consequences in patients with COVID-19. It has been shown, in particular, that virus-induced endothelial damage may be a key mechanism in the pathogenesis of “frostbite” in COVID-19, and possibly also in the development of microangiopathy.

Considering the data of the analyzed literary sources, it can be concluded that in case of COVID-19, lesions of the skin and mucous membranes of the oral cavity can be the first or only signs of the disease. The question of whether skin symptoms are a secondary consequence of a respiratory infection or a primary infection of the skin itself remains open at the moment. The probable mechanisms of development of skin lesions and the role of diseases of the complement system and the state of blood

hypercoagulability in the pathogenesis of their development are discussed. In this regard, much remains to be explored, from this point of view, this scientific work can be considered as a step in the process of studying COVID-19 caused by SARS-CoV-2.

THE SCIENTIFIC REVIEW OF THE FEATURES OF REMDESIVIR AND ITS PERSPECTIVES IN THE CONTEXT OF COVID-19 DISEASE THERAPY

Nodar Sulashvili[1], Ia Egnatievi[2], Giorgi Kvlividze[3], Bacho Rajebashvili[4], Nika Beridze[5], Kristina Chitadze [6]., Mikheil Injgia [7] ., Lamanda Rusiashvili[8], Mariam Kacharava[9], Elisabeth Makharadze [10]., Rodami Ghorjomeladze[11], Ani Kharazishvili[12]

[1] Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia;

[2] David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

[3,4,5,6,7,8,9,10,11,12] International Third Year Medical Students of the School of Medicine and Dentistry at David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

n.sulashvili@ug.edu.ge

The aim of the study was to investigate and analyze the properties of remdesivir and its outlook in the treatment of COVID-19 disease. The antiviral remdesivir, a nucleotide analog prodrug, has a broad spectrum of activity against viruses of several families. After showing its strong antiviral activity against coronaviruses in preclinical studies, remdesivir has emerged as a drug candidate for the treatment of 2019's novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome 2 (SARS-CoV-2) coronavirus infection now a worldwide pandemic. . The use of remdesivir to treat COVID-19 began in early 2020 and has shown promising results so far. In 2020, many countries have conditionally approved the use of remdesivir in patients with severe COVID-19. This was followed by a rapid series of conditional approvals across countries / regions. Briefly, remdesivir has been shown to inhibit the coronavirus and improve lung function for prophylactic and therapeutic purposes (early infection) based on in vitro and in vivo data. However, data on COVID-19 patients remained limited.

The global pandemic of the 2019 novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an urgent need for effective antiviral drugs. Remdesivir (formerly GS-5734) is a prodrug of a nucleoside analogue that is currently being investigated in clinical trials for COVID-19. Its unique structural features enable the intracellular delivery of high concentrations of the active triphosphate metabolite and avoid re-inhibiting efficiently viral RNA synthesis. In preclinical models, remdesivir has shown strong antiviral activity against a variety of human and zoonotic β-coronaviruses, including SARS-CoV-2. This article critically evaluates the available data on remdesivir, focusing on microbiology, biochemistry, pharmacology, pharmacokinetics and in vitro anticoronaviral activity, as well as on clinical experience and ongoing advances in COVID-19 clinical trials.

Remdesivir's potential mechanism of action against coronavirus remains unclear. Several reasons have been suggested for interpreting the effects of remdesivir. First, remdesivir can disrupt the function of the nsp12 polymerase even when the corrective activity of the exonuclease is intact. Furthermore, remdesivir can efficiently generate the pharmacologically active nucleoside triphosphate (NTP), which serves as an alternative substrate and terminator of the RNA chain. NTP can then inhibit the coronavirus by incorporating active triphosphates into the viral RNA. Additionally, there is a high genetic barrier to coronavirus resistance to remdesivir, suggesting that remdesivir may maintain the efficacy of coronavirus therapy.

Remdesivir is a phosphoramidized prodrug of the 1'-cyano-substituted nucleoside analog (GS-441524). It inhibits viral replication by competing with endogenous nucleotides for integration into viral RNA replication by RNA-dependent RNA polymerase (RdRp). The non-structural protein RdRp (nsp12) is highly conserved in coronaviruses, making it an attractive target for broad-spectrum antiviral drugs. Upon entering cells, remdesivir is rapidly metabolised by intracellular kinases to nucleoside triphosphate, the active metabolite (GS443902). The rate-limiting step in the activation of nucleoside analogs is usually the formation of nucleoside monophosphate. Phosphoramide nucleosides such as remdesivir (and GS-441524) are monophosphate bioisoters and can therefore bypass this limiting step.6 However, phosphoramide nucleosides must be administered as prodrugs to sequester the charged phosphonate group and allow for faster entry into the cell. In the case of remdesivir, the negative charge is masked by the 2-ethylbutyl and L-alanine groups, which are rapidly removed by the intracellular esterases. Furthermore, the 1'-CN group of remdesivir and its metabolites offers a high selectivity for RdRp with respect to human polymerases.

Remdesivir is a prodrug; Concentrations declined rapidly after intravenous administration (plasma half-life, T ~ 1 hour), followed by the sequential appearance of the alanine intermediate metabolite GS-704277 and the nucleoside monophosphate metabolite GS-441524 (plasma T 5.5 hours). In cells, GS-441524 is rapidly converted to the pharmacologically active triphosphate analog, GS-443902, with prolonged intracellular Tmax (peripheral blood mononuclear cells, T PBMC ~ 40 h). Both remdesivir and GS-441524 show linear pharmacokinetics after single doses of 3 to 225 mg, and no accumulation of remdesivir was observed after once daily dosing for 5 days.

Remdesivir has demonstrated broad spectrum activity in several in vitro systems against a heterogeneous group of zoonotic and clinically significant human coronaviruses including SARS-CoV-1, SARS-CoV-2 and MERS-CoV with micromolar EC50 or IC50 values. For example, in cultures of human respiratory epithelial cells, remdesivir inhibited the replication of SARS-CoV-1 and MERS-CoV. New evidence suggests that remdesivir also shows potent activity against SARS-CoV-2. Remdesivir has been proposed as a promising treatment option for COVID-19 based on laboratory experiments and charity use reports. Its safety and efficacy in humans require high-quality evidence from well-designed and well-designed clinical trials. Launched for more details. Similar to the inconclusive effect on SARS-CoV and MERS-CoV, the impact of remdesivir on the

SARS-CoV-2 outbreak in current clinical practice should not be overestimated. More research is urgently needed to cure COVID-19 and control SARS-CoV-2.

The evolution of coronavirus resistance to remdesivir was assessed using cell culture in MHV with EC50 values comparable to those of SARS-CoV-1, SARS-CoV-2 and MERS-CoV.11. The side effects of remdesivir should be taken into account. Remdesiviro's safety profile information is changing rapidly. Until recently, most clinical experience has been in patients infected with Ebola virus, whose clinical manifestations are very different from those of COVID-19, making it difficult to extrapolate drug safety to populations. During the study, patients treated with remdesivir for an Ebola virus infection experienced serious side effects that the researchers believe could be related to remdesivir. The most serious of these was hypotension after taking the full dose, followed by rapid cardiac arrest and death. Of those who survived Ebola virus infection and were enrolled in the unique phase II PREVAIL IV study, patients required a dose reduction of remdesivir due to increased transaminase activity. Safety data from four phase 1 pharmacokinetic studies in healthy volunteers were also partially presented. In these studies, subjects received single doses of up to 225 mg of remdesivir or multiple doses of 150 mg once daily for 7 or 14 days, or 200 mg once followed by 100 mg daily for a total of 5 or 10 days. The most common side effects were phlebitis, constipation, headache, bruising, nausea, and body aches. Asymptomatic transient increase in the level of alanine aminotransferase (ALT) of 1 or 2 degrees.

Remdesivir has caused drug interactions. At the time of writing, no in vivo interaction studies with remdesivir have been published, but remdesivir's ability to inhibit or induce cytochrome P450 enzymes and transporters (CIP450) has been tested in vitro. However, it is important to note that as a prodrug, remdesivir is rapidly cleared in vivo, limiting the potential for clinically significant drug-drug interactions. Data on the ability of remdesivir metabolites to react with drugs is even less. In in vitro studies, remdesivir was a weak inhibitor of CIP1A2, CIP2C9, CIP2C19 and CIP2D6. The IC50 of remdesivir for CIP3A was 1.6 M, suggesting that short-term inhibition may occur at normal human exposure.

Inhibition of remdesivir by the metabolites of the CIP450 enzyme has not been studied.14 Tests on the induction of CIP450 with remdesivir have been conflicting; can induce CIP1A2 and CIP2B6.14. Here, too, the clinical relevance is questionable. GS-441524 and GS-704277 did not demonstrate CIP450 induction in these studies. Remdesivir has been found to be a substrate (OATP1B, P-glycoprotein) or inhibitor (OAT1B1, OAT1B3) of several drug transporters. In current clinical studies with remdesivir there are no exclusion criteria for drug interactions.

There are currently no scientifically proven treatments that reduce mortality from COVID-19. Current treatment focuses heavily on supportive care and prevention of complications. Therefore, effective and safe antiviral drugs are urgently needed to relieve the burden on healthcare systems. As described in this review, remdesivir is a nucleoside analogue prodrug with unique structural features that allow intracellular delivery of high concentrations of the active metabolite triphosphate. Coronaviruses, including SARS-

CoV-2, in both in vitro and animal models. These data, combined with early safety data from clinical experience with Ebola virus infections, provide strong rationale for prioritizing remdesivir testing in COVID-19 clinical trials. However, the unpredictability of the pandemic poses many challenges for researchers attempting to conduct clinical trials. The first randomized controlled trial evaluating remdesivir for COVID-19 was conducted at multiple sites in the epicenter of the first epidemic, but failed to reach the targeted sample size due to slow recruitment after the peak levels subsided, and did not produce conclusive results.

Remdesivir, a nucleotide analog prodrug, is metabolized in host cells to the pharmacologically active nucleoside triphosphate. As an analogue of adenosine triphosphate (ATP), remdesivir triphosphate competes with the natural substrate ATP for integration into new viral RNA filaments using RNA-dependent RNA polymerase. When the triphosphate from the strip is accidentally inserted into the chain and a small number of extra nuclei are added (usually three for corona virus), RNA production stops. Remdesivir has a broad spectrum of antiviral activity against various viruses, including Ebola, Nipah and respiratory virus, as well as endemic and coronary heart disease in animals. In primary cultures of human respiratory epithelial cells, remdesivir inhibited severe acute respiratory distress syndrome (SARS-CoV) and Middle East coronavirus (MERS-CoV) with an inhibitory half microstructure value (IC 50). These results suggest that remdesivir is an antiviral agent with potential activity against novel coronaviruses.

In vitro, remdesivir demonstrated antiviral activity against SARS-CoV-2 in primary cultures of human respiratory epithelium and inhibited highly dose-dependent SARS-CoV-2 replication at a half maximum active concentration (EC50) of 0.01 μM. This antiviral activity appears to be specific to the virus; Remdesivir is non-cytotoxic in this culture system at a dose of ≤ 10 μg. In Vero-E6 cells, EC50 levels of remdesivir and its anti-SARS-CoV-2 metabolite GS-441524 were 1.65 μM and 0.47 μM, respectively, reflecting the reduced capacity of Vero-E6 cells. E6 for remdesivir metabolism.

When co-cultured at clinically important concentrations of remdesivir and chloroquine phosphate in respiratory virus-infected HEp-2 cells, chloroquine phosphate inhibited the antiviral activity of remdesivir in a dose-dependent manner. Higher remdesivir EC50 levels and lower remdesivir triphosphate levels in normal human bronchial epithelial cells have been observed with elevated levels of chloroquine phosphate. Therefore, co-administration of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

In mice infected with a chimeric SARS-CoV virus that encodes the SARS-CoV-2 RNA-dependent RNA polymerase, treatment with remdesivir significantly reduced viral load in the lungs and improved it in vehicle-treated subjects. loss of lung function. A similar therapeutic effect was observed in a model of SARS-CoV-2 infection in rhesus monkeys. Although the possibility of QT interval prolongation in humans has not been fully evaluated, current preclinical and clinical data do not indicate a risk of QT interval prolongation with remdesivir.

Limited data are available to evaluate the side effects of remdesivir. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported relatively rarely during and after administration of remdesivir. A transient increase in aminotransferase activity was observed with the use of remdesivir in phase 1 studies in healthy volunteers. A serious adverse event, fatal hypotension, likely related to the use of remdesivir, was reported in the phase 3 Ebola study.

THE SCIENTIFIC REVIEW OF THE FEATURES OF REMDESIVIR AND ITS PERSPECTIVES IN THE CONTEXT OF COVID-19 DISEASE THERAPY

Nodar Sulashvili[1], Ia Egnatievi[2], Giorgi Kvlividze[3], Bacho Rajebashvili[4], Nika Beridze[5], Kristina Chitadze[6], Mikheil Injgia[7], Lamanda Rusiashvili[8], Mariam Kacharava[9], Elisabeth Makharadze[10], Rodami Ghorjomeladze[11], Ani Kharazishvili[12]

[1] David Aghmashenebeli University of Georgia; Alte University, International School of Medicine, Tbilisi, Georgia;

[2] David Aghmashenebeli University of Georgia , Tbilisi, Georgia.

[3,4,5,6,7,8,9,10,11,12] International Third Year Medical Students of the School of Medicine and Dentistry at David Aghmashenebeli University of Georgia, Tbilisi, Georgia.

n.sulashvili@ug.edu.ge

The aim of the study was to investigate and analyze the properties of remdesivir and its outlook in the treatment of COVID-19 disease. The antiviral remdesivir, a nucleotide analog prodrug, has a broad spectrum of activity against viruses of several families. After showing its strong antiviral activity against coronaviruses in preclinical studies, remdesivir has emerged as a drug candidate for the treatment of 2019's novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome 2 (SARS-CoV-2) coronavirus infection now a worldwide pandemic.

The use of remdesivir to treat COVID-19 began in early 2020 and has shown promising results so far. In 2020, many countries have conditionally approved the use of remdesivir in patients with severe COVID-19. This was followed by a rapid series of conditional approvals across countries / regions. Briefly, remdesivir has been shown to inhibit the coronavirus and improve lung function for prophylactic and therapeutic purposes (early infection) based on in vitro and in vivo data. However, data on COVID-19 patients remained limited.

The global pandemic of the 2019 novel coronavirus disease (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an urgent need for effective antiviral drugs. Remdesivir (formerly GS-5734) is a prodrug of a nucleoside analogue that is currently being investigated in clinical trials for COVID-19. Its unique structural features enable the intracellular delivery of high concentrations of the active triphosphate metabolite and avoid re-inhibiting efficiently viral RNA synthesis. In preclinical models, remdesivir has shown strong antiviral activity against a

variety of human and zoonotic β-coronaviruses, including SARS-CoV-2. This article critically evaluates the available data on remdesivir, focusing on microbiology, biochemistry, pharmacology, pharmacokinetics and in vitro anticoronaviral activity, as well as on clinical experience and ongoing advances in COVID-19 clinical trials.

Remdesivir's potential mechanism of action against coronavirus remains unclear. Several reasons have been suggested for interpreting the effects of remdesivir. First, remdesivir can disrupt the function of the nsp12 polymerase even when the corrective activity of the exonuclease is intact. Furthermore, remdesivir can efficiently generate the pharmacologically active nucleoside triphosphate (NTP), which serves as an alternative substrate and terminator of the RNA chain. NTP can then inhibit the coronavirus by incorporating active triphosphates into the viral RNA. Additionally, there is a high genetic barrier to coronavirus resistance to remdesivir, suggesting that remdesivir may maintain the efficacy of coronavirus therapy.

Remdesivir is a phosphoramidized prodrug of the 1'-cyano-substituted nucleoside analog (GS-441524). It inhibits viral replication by competing with endogenous nucleotides for integration into viral RNA replication by RNA-dependent RNA polymerase (RdRp). The non-structural protein RdRp (nsp12) is highly conserved in coronaviruses, making it an attractive target for broad-spectrum antiviral drugs. Upon entering cells, remdesivir is rapidly metabolised by intracellular kinases to nucleoside triphosphate, the active metabolite (GS443902). The rate-limiting step in the activation of nucleoside analogs is usually the formation of nucleoside monophosphate. Phosphoramide nucleosides such as remdesivir (and GS-441524) are monophosphate bioisoters and can therefore bypass this limiting step.6 However, phosphoramide nucleosides must be administered as prodrugs to sequester the charged phosphonate group and allow for faster entry into the cell. In the case of remdesivir, the negative charge is masked by the 2-ethylbutyl and L-alanine groups, which are rapidly removed by the intracellular esterases. Furthermore, the 1'-CN group of remdesivir and its metabolites offers a high selectivity for RdRp with respect to human polymerases. Remdesivir is a prodrug; Concentrations declined rapidly after intravenous administration (plasma half-life, T ~ 1 hour), followed by the sequential appearance of the alanine intermediate metabolite GS-704277 and the nucleoside monophosphate metabolite GS-441524 (plasma T 5.5 hours). In cells, GS-441524 is rapidly converted to the pharmacologically active triphosphate analog, GS-443902, with prolonged intracellular Tmax (peripheral blood mononuclear cells, T PBMC ~ 40 h). Both remdesivir and GS-441524 show linear pharmacokinetics after single doses of 3 to 225 mg, and no accumulation of remdesivir was observed after once daily dosing for 5 days.

Remdesivir has demonstrated broad spectrum activity in several in vitro systems against a heterogeneous group of zoonotic and clinically significant human coronaviruses including SARS-CoV-1, SARS-CoV-2 and MERS-CoV with micromolar EC50 or IC50 values. For example, in cultures of human respiratory epithelial cells, remdesivir inhibited the replication of SARS-CoV-1 and MERS-CoV. New evidence suggests that remdesivir also shows potent activity against SARS-CoV-2. Remdesivir

has been proposed as a promising treatment option for COVID-19 based on laboratory experiments and charity use reports. Its safety and efficacy in humans require high-quality evidence from well-designed and well-designed clinical trials. Launched for more details. Similar to the inconclusive effect on SARS-CoV and MERS-CoV, the impact of remdesivir on the SARS-CoV-2 outbreak in current clinical practice should not be overestimated. More research is urgently needed to cure COVID-19 and control SARS-CoV-2.

The evolution of coronavirus resistance to remdesivir was assessed using cell culture in MHV with EC50 values comparable to those of SARS-CoV-1, SARS-CoV-2 and MERS-CoV.11. The side effects of remdesivir should be taken into account. Remdesiviro's safety profile information is changing rapidly. Until recently, most clinical experience has been in patients infected with Ebola virus, whose clinical manifestations are very different from those of COVID-19, making it difficult to extrapolate drug safety to populations. During the study, patients treated with remdesivir for an Ebola virus infection experienced serious side effects that the researchers believe could be related to remdesivir. The most serious of these was hypotension after taking the full dose, followed by rapid cardiac arrest and death. Of those who survived Ebola virus infection and were enrolled in the unique phase II PREVAIL IV study, patients required a dose reduction of remdesivir due to increased transaminase activity. Safety data from four phase 1 pharmacokinetic studies in healthy volunteers were also partially presented. In these studies, subjects received single doses of up to 225 mg of remdesivir or multiple doses of 150 mg once daily for 7 or 14 days, or 200 mg once followed by 100 mg daily for a total of 5 or 10 days. The most common side effects were phlebitis, constipation, headache, bruising, nausea, and body aches. Asymptomatic transient increase in the level of alanine aminotransferase (ALT) of 1 or 2 degrees.

Remdesivir has caused drug interactions. At the time of writing, no in vivo interaction studies with remdesivir have been published, but remdesivir's ability to inhibit or induce cytochrome P450 enzymes and transporters (CIP450) has been tested in vitro. However, it is important to note that as a prodrug, remdesivir is rapidly cleared in vivo, limiting the potential for clinically significant drug-drug interactions. Data on the ability of remdesivir metabolites to react with drugs is even less. In in vitro studies, remdesivir was a weak inhibitor of CIP1A2, CIP2C9, CIP2C19 and CIP2D6. The IC50 of remdesivir for CIP3A was 1.6 M, suggesting that short-term inhibition may occur at normal human exposure. Inhibition of remdesivir by the metabolites of the CIP450 enzyme has not been studied.14 Tests on the induction of CIP450 with remdesivir have been conflicting; can induce CIP1A2 and CIP2B6.14. Here, too, the clinical relevance is questionable. GS-441524 and GS-704277 did not demonstrate CIP450 induction in these studies. Remdesivir has been found to be a substrate (OATP1B, P-glycoprotein) or inhibitor (OAT1B1, OAT1B3) of several drug transporters. In current clinical studies with remdesivir there are no exclusion criteria for drug interactions.

There are currently no scientifically proven treatments that reduce mortality from COVID-19. Current treatment focuses heavily on supportive care and prevention of

complications. Therefore, effective and safe antiviral drugs are urgently needed to relieve the burden on healthcare systems. As described in this review, remdesivir is a nucleoside analogue prodrug with unique structural features that allow intracellular delivery of high concentrations of the active metabolite triphosphate. Coronaviruses, including SARS-CoV-2, in both in vitro and animal models. These data, combined with early safety data from clinical experience with Ebola virus infections, provide strong rationale for prioritizing remdesivir testing in COVID-19 clinical trials. However, the unpredictability of the pandemic poses many challenges for researchers attempting to conduct clinical trials. The first randomized controlled trial evaluating remdesivir for COVID-19 was conducted at multiple sites in the epicenter of the first epidemic, but failed to reach the targeted sample size due to slow recruitment after the peak levels subsided, and did not produce conclusive results.

Remdesivir, a nucleotide analog prodrug, is metabolized in host cells to the pharmacologically active nucleoside triphosphate. As an analogue of adenosine triphosphate (ATP), remdesivir triphosphate competes with the natural substrate ATP for integration into new viral RNA filaments using RNA-dependent RNA polymerase. When the triphosphate from the strip is accidentally inserted into the chain and a small number of extra nuclei are added (usually three for corona virus), RNA production stops. Remdesivir has a broad spectrum of antiviral activity against various viruses, including Ebola, Nipah and respiratory virus, as well as endemic and coronary heart disease in animals. In primary cultures of human respiratory epithelial cells, remdesivir inhibited severe acute respiratory distress syndrome (SARS-CoV) and Middle East coronavirus (MERS-CoV) with an inhibitory half microstructure value (IC 50). These results suggest that remdesivir is an antiviral agent with potential activity against novel coronaviruses.

In vitro, remdesivir demonstrated antiviral activity against SARS-CoV-2 in primary cultures of human respiratory epithelium and inhibited highly dose-dependent SARS-CoV-2 replication at a half maximum active concentration (EC50) of 0.01 μM. This antiviral activity appears to be specific to the virus; Remdesivir is non-cytotoxic in this culture system at a dose of ≤ 10 μg. In Vero-E6 cells, EC50 levels of remdesivir and its anti-SARS-CoV-2 metabolite GS-441524 were 1.65 μM and 0.47 μM, respectively, reflecting the reduced capacity of Vero-E6 cells. E6 for remdesivir metabolism. When co-cultured at clinically important concentrations of remdesivir and chloroquine phosphate in respiratory virus-infected HEp-2 cells, chloroquine phosphate inhibited the antiviral activity of remdesivir in a dose-dependent manner. Higher remdesivir EC50 levels and lower remdesivir triphosphate levels in normal human bronchial epithelial cells have been observed with elevated levels of chloroquine phosphate. Therefore, co-administration of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

In mice infected with a chimeric SARS-CoV virus that encodes the SARS-CoV-2 RNA-dependent RNA polymerase, treatment with remdesivir significantly reduced viral load in the lungs and improved it in vehicle-treated subjects. loss of lung function. A

similar therapeutic effect was observed in a model of SARS-CoV-2 infection in rhesus monkeys. Although the possibility of QT interval prolongation in humans has not been fully evaluated, current preclinical and clinical data do not indicate a risk of QT interval prolongation with remdesivir.

Limited data are available to evaluate the side effects of remdesivir. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported relatively rarely during and after administration of remdesivir. A transient increase in aminotransferase activity was observed with the use of remdesivir in phase 1 studies in healthy volunteers. A serious adverse event, fatal hypotension, likely related to the use of remdesivir, was reported in the phase 3 Ebola study.

THE SCIENTIFIC TALKS OF THE CHARACTERISTICS AND OUTLOOK OF COVID-19 VACCINES FOR PROPHYLAXIS OF THE COVID-19 INFECTION WORLDWIDE

Nodar Sulashvili[1], Magda Davitashvili[2], Margarita Beglaryan[3], Ia Egnatievi[4], Kakhaber Robakidze[5], Lela Grigolia[6]

[1]Alte University, International School of Medicine, Division of Pharmacology, Tbilisi, Georgia;
[2]Iakob Gogebashvili Telavi State University, Telavi, Georgia.
[3]Yerevan State Medical University, Department of Pharmaceutical Management, Yerevan, Armenia.
[4]David Aghmashenebeli University of Georgia, Tbilisi, Georgia.
[5]Caucasus International University; National Health Center named after Academician O. Gudushauri; Tbilisi, Georgia;
[6]Caucasus International University; Tbilisi, Georgia
n.sulashvili@ug.edu.ge

Aims of the study was to analyzed and determine literature review for the characteristics and perspectives of covid-19 vaccines for prophylaxis of the covid-19 infection worldwide. The development of SARS-CoV subunit vaccines was initially associated with full-length protein vaccines and later focused on RBD-S protein vaccines. None of the SARS-CoV subunit protein vaccines have been clinically tested but have elicited strong antibody responses and protective effects in preclinical models. Studies have shown that full-length S protein, protein S extracellular domain and trimeric S-proteins (triSpike) are immunogenic and may provide protection against SARS-CoV infection. The TriSpike vaccine can also induce Fcγ-II receptor mediated SARS-CoV (FcγRII) infection in human B cells in vitro. On the other hand, RBD-S protein vaccines can induce high titer neutralizing antibodies without causing obvious pathogenic effects. This is likely because RBD vaccines do not contain more non-neutralizing epitopes than full-length protein S vaccines. One study found that RBD vaccines not only protect most SARS-CoV-infected mice without detectable viral RNA in their lungs, but can also induce long-acting S-specific antibodies that can persist for 12 months. In addition, RBD-based SARS-CoV vaccines have been shown to induce

RBD-specific IFN-γ and elicit a cellular immune response in mice. As a result, SARS-CoV RBD has become a major target for SARS vaccines. Finally, SARS-CoV subunit vaccines based on the S2 subunit, structural proteins N and M have been tested. However, there is no evidence that they can induce neutralizing or protective antibodies against viral infections.

Based on previous experience with SARS-CoV, most of the MERS-CoV protein subunits are vaccines targeting RBD-based vaccines. RBD-based MERS-CoV vaccines are generally highly immunogenic and elicit strong neutralizing antibodies, cellular immunity, and protective effects against MERS-CoV infections. A study by Tai et al. found that vaccines containing trimeric RBD proteins can induce long-acting neutralizing antibodies for 6 months. Recombinant RBD proteins from different strains of MERS-CoV can induce antibodies that cross-neutralize with different strains of human and camel MERS-CoV. These results indicate that MERS-CoV RBD serves as a promising vaccine target with the ability to induce long-term, broad-spectrum neutralizing antibodies against infections. In addition to RBD vaccines, S1 subunit vaccines containing RBD have been shown to induce neutralizing antibodies and protection against MERS-CoV. In particular, the N-terminal domain (DTN) binds to protein S sialic acid and is important for MERS-CoV infection in some cell types. Jiaming et al. showed that immunization with NTD vaccine also confers protection against MERS-CoV and induces strong humoral and cellular immunity. However, since NTD SARS-CoV-2 does not have the same sialic acid binding function as MERS-CoV, the NTD-based strategy cannot be extended to develop a vaccine against SARS-CoV-2.

DNA vaccines contain genes encoding viral antigenic components that are expressed by plasmid vectors and delivered to cells by electroporation. Compared to other vaccine technologies, DNA vaccines offer a fast and flexible platform for vaccine development and production, making them an attractive technology for dealing with emerging epidemics such as SARS-CoV-2. In addition, antigen production in DNA vaccines in target cells helps restore the native conformation and post-translational modification of viral antigens. However, the main disadvantage of DNA vaccines is their limited immunogenicity due to their inability to multiply and amplify in vivo. Therefore, it is important to consider strategies that can improve the effectiveness of DNA vaccines, for example: B. adding an adjuvant or using a basic booster therapy. Moreover, genomic integration of DNA vaccines into the host chromosome is another biosafety problem that can lead to mutagenesis and oncogenesis. Although previous studies have shown that the risk of injecting a vaccine plasmid into the host chromosome is quite low, the FDA and WHO still recommend that integration testing be included in the DNA vaccine safety program.

Several potential SARS-CoV DNA vaccines have been reported, including vaccines based on the S, M and N proteins. While all can elicit specific levels of cellular and antibody responses, only one DNA vaccine has been shown to elicit protective the effect of protein S against SARS-CoV infection is likely due to the irreplaceable role of protein S in receptor binding. Yang et al. Showed that immunization with DNA encoding full-length protein S, protein S lacking a portion of the cytoplasmic domain,

protein S lacking cytoplasmic and transmembrane domains, can induce neutralizing antibodies and T-cell immune responses and has a protective effect in mice. This promising result led to the next phase of Phase I clinical trials, based on the entire SARS-CoV protein S-DNA vaccine, which demonstrated that the vaccine is well tolerated by patients and can induce neutralizing antibodies. and T cell response in healthy adults. In addition, two studies used a basic booster strategy to improve the efficacy of the SARS-CoV-DNA-S protein vaccine. reported that a combination of DNA and completely inactivated SARS-CoV vaccines can increase antibody response and induce a more desirable Th1 immune response. Woo et al. showed that the use of a DNA-based vaccine in combination with an E. coli-expressed recombinant protein S enhancer can also induce higher neutralization titers than a DNA or protein subunit vaccine.

As with SARS-CoV, several studies of MERS-CoV DNA vaccines have shown optimistic results. Muthumaniet al. reports that a complete MERS-CoV protein S DNA vaccine can induce strong cellular immunity and antigen-specific neutralizing antibodies in mice, monkeys and camels, as well as monkeys vaccinated with this vaccine. DNA was protected from MERS-CoV without clinical or radiographic evidence of pneumonia. Based on these encouraging data, Phase I clinical trials of this MERS-CoV DNA vaccine (GLS-5300 or INO-4700) have been completed. The results showed that GLS-5300 was well tolerated without serious vaccine-related side effects, and immunization with GLS-5300 elicited a strong immune response in 85% of participants after two vaccinations. These data support the development of the GLS-5300 vaccine. Notably, the SARS-CoV-2 INO-4800 DNA candidate is based on the same construct as GLS-5300 and is currently in phase I/II clinical trials (NCT04447781 and NCT04336410). In addition, another study of the MERS-CoV total S-DNA vaccine plus the S1 booster showed a potent serum neutralizing effect against various strains of MERS-CoV in mice and rhesus monkeys [48]. Immunizing rhesus monkeys with this DNA / protein-based booster vaccine provides protection against MERS-CoV radiological pneumonia and confirms this strategy as a promising approach to developing a MERS-CoV vaccine. In addition to the full S, the S1 subunit is also a good target for the MERS-CoV DNA vaccine. A study by Al-Amri et al. compared the immunogenicity of the complete MERS-CoV vaccine based on S (pS) and S1 (pS1) using the same expression vector. They found that pS1 immunization elicited a balanced Th1 / Th2 response and generally higher levels of all IgG isotypes than pS vaccination, which can be explained by the fact that the S1 subunit is more effective without the transmembrane domain. it is secreted into the extracellular space and thus leads to increased uptake by antigen-presenting cells. This study demonstrated that S1 may be a better target than full-length S for the MERS-CoV DNA vaccine.

Several adenoviral vaccines against MERS-CoV have been developed. Human adenoviruses type 5 (Ad5) and type 41 (Ad41), which express the MERS-CoV protein S or S1, have been shown to induce neutralizing antibodies in mice. However, the protective effect of MERS vaccines based on Ad5 and Ad41 has not been evaluated. It should be noted that the Ad5-MERS-S vaccine was used in combination with Protein-S

nanoparticles. Heterologous immunization by vaccination and enhancement of Ad5 / MERS with advanced protein nanoparticles has shown not only a protective effect in hDPP4-transduced mice against MERS-CoV infection, but also more balanced Th1 / Th2 responses than the main homologous boosters with Ad5 or only with nanoparticles. Vaccine. The Ad5 vector has already been used in the development of a vaccine against SARS-CoV-2, and promising results have been obtained in phase I and II clinical trials.

Several other vaccine platforms have been used to develop a vaccine against MERS-CoV. MERS-CoV protein vaccines based on measles and rabies virus have been shown to induce neutralizing antibodies and provide protective effects against MERS-CoV in hDDP4-transduced mice. Newcastle disease virus and vesicular stomatitis virus have also been used as vaccines expressing the MERS S protein. However, for these two vaccines, only in vitro neutralization data have been found, and no in vivo protection data have been found.

The SARS-CoV and MERS-CoV vaccines, based on many viral vectors, including adenovirus, modified Ankara vaccine virus, venezuelan equine encephalitis virus, parainfluenza virus, vesicular stomatitis virus, measles virus and rabies virus, have proven effective. The virus has shown protective properties. Wire. Resistant to viral problems. Some of these viral vectors have already become promising candidates for the development of a vaccine against SARS-CoV-2.

Completely inactivated vaccines consist of chemically or radiation inactivated virions. They contain the entire repertoire of the immunogenic components of the parent virus and, compared to attenuated viruses, do not carry the risk of virus reactivation if properly inactivated. Although immunogenic epitopes of inactivated viruses are safer than live attenuated vaccines, they can be structurally distorted during inactivation, which can adversely affect the protection they provide. In addition, completely inactivated vaccines against SARS-CoV and MERS-CoV have been reported to cause eosinophil-associated lung disease.

These disadvantages make inactivated whole vaccines a less attractive strategy for the development of a coronavirus vaccine.

Live attenuated vaccines are live viruses attenuated by a deletion or mutation in a pathogenic component of the viral genome. Because inactivated whole vaccines contain almost all of the immunogenic components of the original virus. In addition, they maintain the natural conformation of viral antigens and present antigens to the immune system, as in the case of natural infections. Thus, live attenuated vaccines are the most immunogenic vaccines and have a long history of fighting various infectious diseases. However, live attenuated vaccines also pose a greater risk than other vaccine types, including the potential for virulence to return and the risk of persistent infection in immunocompromised patients. Therefore, the biological safety of live attenuated vaccines must be carefully studied before clinical use.

Compared to SARS and MERS, which usually disappeared spontaneously after an outbreak in the region, the magnitude of the worldwide COVID-19 pandemic has made vaccine development an unprecedented emergency. This pressing need has led to many

different approaches to vaccine development. First, unconventional vaccine platforms such as nucleic acid vaccines and viral vector vaccines are becoming major players in the development of a COVID-19 vaccine as they can only be developed using sequence information. Thus, these new platforms can be easily adapted to new pathogens and their safety profiles have been well studied during the recent outbreaks of influenza, Ebola and Zika. Second, the COVID-19 vaccine clinical development process has been accelerated through parallel research, rather than a linear sequence of steps. For example, several COVID-19 vaccine candidates were directly involved in clinical trials before preclinical data were available in animal models, and many vaccine studies have used an integrated phase I / II or phase II / III approach to buy time. To meet the huge global demand for COVID-19 vaccines, vaccine manufacturers, especially large companies, are increasing their production capacity to about 1 billion doses per year. The governments of the United States and many other countries also play an important role in financing the development of the production of potentially effective vaccines.

Currently, 4 DNA vaccines against SARS-CoV-2 are undergoing clinical trials. Among these developers, Inovio is the leading publisher of DNA vaccine results against MERS-CoV and SARS-CoV-2. Inovio DNA vaccine against SARS-CoV-2 INO-4800 encodes total protein S and is administered intradermally using the CELLECTRA portable skin cell electroporation device. Based on experience from Phase I / IIa studies, their MERS vaccines (INO-4700) use the same platform as the INO-4800 SARS-CoV-2 vaccine. They showed that the vaccine induces neutralizing antibodies and Th1 immune responses in animal models, including mice, guinea pigs and rhesus monkeys. The vaccine is currently undergoing two Phase I / II trials. An interim analysis of two phase I studies showed that it elicited a humoral and T-cell immune response in 94% of participants after two doses, while it caused only grade 1 or less side effects.

In addition to these traditional platforms, researchers have also developed vaccines against COVID-19 using unconventional approaches. Aivita Biomedical, Inc. developed AV-COVID-19, an autologous dendritic cell vaccine containing SARS-CoV-2 antigens. AV-COVID-19 is collected from the patient's peripheral blood monocytes, then differentiates into dendritic cells in vitro and incubated with SARS-CoV-2 antigens before re-injection into the patient's blood. The company has now begun phase I / II clinical trials to assess the safety and efficacy profile in adults. In addition, Symvivo Corporation has developed bacTRL-Spike, a live Bifidobacterium vaccine designed to deliver synthetic plasmid DNA encoding the SARS-CoV-2 spike protein. They also recorded Phase I clinical trials to test the safety of this vaccine. In addition, a team from Nanjing University discovered that microRNA MIR2911 from plants can target SARS-CoV-2, binding to its mRNA and blocking protein translation. Their data showed that MIR2911 suppresses SARS-CoV-2 replication and accelerates negative conversion in infected patients.

Given the rapid transmission and asymptomatic spread of COVID-19, it is clear that an effective global vaccine is needed to get people back to normal. However, although an effective SARS-CoV-2 vaccine is available, the duration of the vaccine-

induced immunity is still largely unknown. Previous SARS studies have shown that neutralizing antibodies specific to IgG and SARS only worked for about 2 years in patients who recovered from SARS-CoV infection. Consequently, long-term immunity to COVID-19 vaccines is unlikely and regular vaccination recommendations may be required in the future. In addition, it is not yet clear what the minimum titer of neutralizing antibodies may have a protective effect against SARS-CoV-2 infection. It is believed that the more neutralizing antibodies a vaccine produces, the better the protective effect will be. This is consistent with the observation that in most cases of COVID-19 reinfection during initial infection, there will be few or no symptoms, which may not be enough to induce strong neutralizing antibodies. Therefore, it is important that more research characterizes the relationship between neutralizing antibodies and protective effects to guide the development of the COVID-19 vaccine. Finally, several mutations have been found in the SARS-CoV-2 genome, the most common of which is the D614G mutation. D614G is a missense point mutation in protein S that increases the infectivity of SARS-CoV-2 by decreasing S1 secretion and increasing the incorporation of protein S into the virion. Fortunately, the D614G mutation does not interfere with the binding of neutralizing antibodies to SARS-CoV-2 and therefore does not confer resistance to the vaccine. However, it is possible that in the future mutations will appear that suppress immunity and impede the development of a vaccine against COVID-19.

ESSENTIAL OILS IN COMBINATION AND THEIR ANTIMICROBIAL PROPERTIES

Seniuk I.V., Benzid Yassine, El-Assri Abdeladim
National University of Pharmacy, Kharkiv, Ukraine
citochrom@gmail.com

Essential oils, also known as volatile oils, are complex mixtures of volatile constituents biosynthesized by plants, which mainly include two biosynthetically related groups. These main groups include terpenes and terpenoids and aromatic and aliphatic constituents, all characterized by low molecular weight.

Most of the antimicrobial activity in EOs is found in the oxygenated terpenoids, while some hydrocarbons also exhibit antimicrobial effects. Interactions between these components may lead to antagonistic, additive or synergistic effects. Some studies have demonstrated that whole EOs usually have higher antibacterial activity than the mixtures of their major components, suggesting that the minor components are critical to the synergistic activity, though antagonistic and additive effects have also been observed.

Usually combinations, either single EOs or artificial mixtures of purified main components, affect multiple biochemical processes in the bacteria, producing a plethora of interactive antibacterial effects. In recent years, there has been an increased interest in the use of natural antimicrobial agents thus the use of these combinations are strategies to control food-borne bacteria and other pathogenic microorganisms. In view of these

findings, the aim of this contribution is to review and highlight the antimicrobial efficacy of these combinations, and to provide the methods to determine the type of interactions and the mechanisms involved in the antimicrobial activities of these combinations.

The combination of pair of components showing synergistic effects will then reduce the concentration needed to yield the same microbial effect when compared with the sum of the purified components. Thus, the synergistic effects of cinnamaldehyde and thymol against *E. coli* had an effective reduction of concentration of 25%, similar reduction at the same ratio was observed for *T. typhinurium*. The combination of cinnamaldehyde and reduced levels of eugenol generated a 50% reduction of the concentration. In the case of cinnamaldehyde and thymol the working ratio was of 1:1, while in the case of cinnamaldehyde and eugenol, lower levels of eugenol (1:4–1:8) were needed to reduce the concentration. Thymol and carvacrol at ratio of 1 to 1 also showed similar results (reduction of 25%), the use of thymol and eugenol at 1 to 4 further reduced the concentration to 50%. In the pair carvacrol/eugenol, the same ratios of 1 to 4 showed a reduction of 25%.

Zhou et al. proposed two hypotheses to explain synergistic effects of cinnamaldehyde/thymol or cinnamaldehyde/carvacrol against *S. typhimurium*: thymol or carvacrol could increase the permeability of the cytoplasmic membrane, and probably enable cinnamaldehyde to be more easily transported into the cell; thymol or carvacrol could increase the number, size or duration of existence of the pores created by the binding of cinnamaldehyde to proteins in the cell membrane, so that a synergistic effect is achieved when these two components are used in combination.

These authors proposed three hypothesis that could explain the synergistic effect between thymol/carvacrol against *S. typhimurium*: the antibacterial mechanism of thymol and carvacrol might be different; they act on the different targets of *S. typhimurium*; the synergistic effect could be due to the similarity of their mechanism; and the synergistic effect occurs only when they inhibit together *S. typhimurium*. More recently, Fei et al. showed that the synergistic combinations of EOs of oregano/basil against *E. coli*, basil/bergamot against *S. aureus*, oregano/bergamot against *B. subtilis* and oregano/perilla against *S. cerevisiae* significantly disrupted the integrity of cell membranes when compared with control untreated membranes.

The practical implications of these observations are important at the time of using EOs components in food systems since the use of the lower concentration needed to yield a similar antibacterial activity will mean reduced flavour notes in foods products. For certain foods, some EO components in high concentrations can impart undesirable notes to foods (e.g., eugenol).

Mechanisms of interaction that produced antagonistic effects were less studied. Some of the studies included combinations of bactericidal and bacteriostatic agents, use of compounds that act on the same target of the microorganism and chemical (direct or indirect) interactions among compounds such as the reduction of the active aqueous terpene solubility by non-aqueous monoterpene hydrocarbons

There are limited number of studies on the effects of the test medium physical and chemical parameters on the interaction between essential oil components and their

antimicrobial activities. Physical (temperature) and chemical (sodium chloride) parameters were also found to modulate the antimicrobial responses of the mixtures. Sodium chloride was found to have antagonistic effects when combined with carvacrol and *p*-cymene against *B. cereus*. It was also observed that carvacrol and p-cymene worked synergistically, but this effect was reduced when sodium chloride was added (1.25 g/l). It has been reported that the combination of cinnamon and clove EOs showed better antimicrobial activity in vapor phase than in liquid phase. In the study of the combined effects of thymol, carvacrol and temperature on the quality of non conventional poultry patties by using a simplex centroid mixture design, the best effects were obtained when the patties were mixed with both compounds and stored at low temperature 0 to 3°C.

Due to the limited number of studies and in order to optimize the synergy potential of mixtures, research should focus on: the effects of intrinsic and extrinsic parameters of test medium (pH, fat, protein, water content, incubation time/temperature, packaging procedure, and physical structure) on the combinations of essential oils or their components and their antimicrobial properties; the mechanism of action of the synergisms, additions or antagonisms to optimize the activity in food preservation, medicine and cosmetic; possible toxicity of combined essential oils or components; development of standardized methods for the evaluation of the interaction between essential oils or their components.

Essential oils are natural plant products containing complex mixture of components and thus having multiple antimicrobial properties. Most of the antimicrobial activity in EOs appears to derive from oxygenated terpenoids, particularly phenolic terpenes, phenylpropanoids and alcohols. Other constituents (e.g., hydrocarbons) that typically showed low activities can be used in combinations to increase their bioactivities. Interactions between these components may lead to antagonistic, additive or synergistic effects. Checkerboard, graphical and Time-kill methods are the most widely used procedures to assess of the interaction of essential oil components. Investigations should be carried out on their mode of action and their probable toxicological effects in order to optimize their use.

TWO-WAY COMMUNICATION: COVID-19 CAN LEAD TO DIABETES

Seniuk I.V., El Mehdi Tolbi
National University of Pharmacy, Kharkiv, Ukraine
citochrom@gmail.com

Doctors have warned that coronavirus can cause diabetes. A coronavirus can cause diabetes - this has been found out by scientists in the international CoviDiab Registry study. Doctors suspect it could be a completely new, previously unexplored type of this disease. They also warned that COVID-19 has the potential to cause serious complications to newly-onset diabetes.

A coronavirus can lead to the development of diabetes mellitus, experts from an international team of scientists from the UK, Australia, France and several other countries have announced in the CoviDiab Registry research project. The study was published in the New England Journal of Medi. It has previously been reported that the coronavirus may be more dangerous for people with diabetes - the WHO has said that diabetics are at risk of a severe course of coronavirus infection. Between 20% and 30% of patients who died from COVID-19 had this pathology. However, they have now found that the link between the diseases is "two-way". The findings on the relationship between diabetes and coronavirus do not yet allow us to give a complete answer about the effect of this infection on carbohydrate metabolism. The mechanisms of diabetes in humans infected with the new coronavirus are not yet known, nor is it completely clear what happens to the endocrine system after infection with COVID-19. The main cause of diabetes in coronavirus infection may be that COVID-19 is a systemic disease. Coronavirus does not run like a normal flu virus, it acts on many organs at once. It has been compared to systemic vasculitis (inflammation of the vascular wall, causing damage to other organs and tissues as well, which contributes to the disruption of carbohydrate metabolism, which in turn causes diabetes. According to CoviDiab Registry researchers, this is because SARS-CoV-2 in the body acts on angiotensin-converting enzyme 2, a receptor found in major metabolic organs and tissues including pancreatic cells, fatty tissue, small intestine and kidneys.

Scientists speculate that, once infiltrated, the coronavirus triggers multiple dysfunctions in the carbohydrate metabolism machinery.

However, any bacterial or viral infection can be a trigger for type 1 diabetes. It is an autoimmune disease, and this kind of pathology is usually triggered by external factors. It may be due to illness or severe stress. COVID-19 therapy can also lead to the development of diabetes. For example, in the treatment of coronavirus pneumonia, glucocorticoids may be used in therapy, which can themselves cause a disruption of carbohydrate metabolism. These include diabetic ketoacidosis and hyperosmolarity, an extreme metabolic disorder that requires extremely high doses of insulin. Such effects are possible because of the reduction in blood glucose that occurs during the illness. Any viral or bacterial infection, exacerbation of chronic diseases, as well as trauma and even surgery worsen glycaemic values in diabetics, which in turn can cause diabetes to decompensate - it will no longer respond to treatment, and this often leads to complications.

If you are infected with COVID-19, you can protect yourself from developing diabetes by checking your blood glucose regularly. To prevent diabetes, it is important to follow a diet that limits carbohydrates.

PREPARATION OF POLYACRYLONITRILE-BASED FIBRES WITH CHELATED AG IONS FOR ANTIBACTERIAL APPLICATIONS

Seniuk I.V., Filimonova N.I.
National University of Pharmacy, Kharkiv, Ukraine
citochrom@gmail.com

In our daily lives, we are inevitably exposed to harmful microbes that can grow and propagate rapidly under suitable environmental conditions; these pathogens can even transmit diseases through interpersonal contact and endanger our health. Textile fibres are excellent habitats for these microorganisms and can propel the spread of disease because of their hollow structures. Endowing fibres with antimicrobial abilities can not only kill bacteria but also protect the textile against the degradation caused by moulds. There are many ways to impart antibacterial properties to fibres; among which, chemical modification has become the main focus in chemical and biomedical research. Due to the strong binding between antibacterial agents and fibres, the as-prepared antibacterial fibres maintain superb and long-lasting antibacterial effects. Various antibacterial components are used for preparing antibacterial materials, such as quaternary ammonium groups, quaternary phosphonium groups, silver nanoparticles, silver ions, extracts from Chloranthus henryi and capsaicin. Further, silver is the oldest antibacterial agent known to humans, having been used for more than two thousand years. To date, silver has been used in various forms such as silver ions, silver nanoparticles and silver complexes, or implemented in composite materials. Moreover, it has been employed in many applications, including dental and medical implants, the healing of burn wounds, cosmetics, food packaging, water and air purification, and domestic appliances. The widespread use of silver is attributable to its broad spectrum of antibacterial activity, and more importantly, its low toxicity towards mammalian cells. In addition, silver has the advantages of thermal stability, low volatility, and biocompatibility, among others. Furthermore, unlike antibiotics, silver does not incur obvious bacterial resistance and has good antimicrobial activities against common drug-resistant bacteria and fungi. Currently, there is an urgent need to develop a novel antibacterial material with excellent activity that is powerful enough to outpace bacterial evolution.

In this study, the antibacterial activities of the different fibres were tested by the improved shake flask method. PANF and SH-PANF demonstrate no antibacterial performance against the tested pathogens, as set by the National Standard of China (GB/T 20944.3-2008), which states that fibres have antimicrobial activity when the antimicrobial ratio is greater than or equal to 70% against *E. coli* and *S. aureus* and greater than or equal

to 60% against *C. albicans*. Hence, we focused only on Ag-SH-PANF, and we compared its antibacterial activities for different Ag contents and exposure times. For *E. coli*, none of the Ag-SH-PANF samples showed antibacterial activity after 30 min contact. Within 1 h, only Ag-SH-PANF 10 (containing 17.46% Ag) proved effective, with an antibacterial ratio of 85.99%. Upon extending the contact time to 2 h, neither Ag-SH-PANF 1 (containing 2.40% Ag) nor Ag-SH-PANF 2 (4.68% Ag) showed any bactericidal properties, but the antibacterial ratios of the Ag-SH-PANF 3–10 fibres were above 93.69%. Ag-SH-PANF 2 achieved optimal antibacterial activity only after 4 h, when its antibacterial ratio reached 85.78%. Ag-SH-PANF 1 proved effective only after 8 h, with a corresponding antibacterial ratio of 97.23%. When the contact time with *E. coli* was extended to 24 h, all fibres showed excellent antibacterial activities and antibacterial ratios up to 99.9%. The trends in antibacterial activity against S. *aureus* and *C. albicans* followed that against *E. coli.* With a short duration (30 min), none of the fibres showed activity. Within 1 h, the antibacterial ratios of Ag-SH-PANF 10 against *S. aureus* and *C. albicans* were 89.39% and 80.54%, respectively. Ag-SH-PANF 1 and 2 were not effective against these two pathogens after 2 h, whereas Ag-SH-PANF 3 (8.60% Ag) was inactive against *C. albicans* (fungi are usually more resistant than bacteria). In addition, after 2 h, Ag-SH-PANF 4 (10.93% Ag) produced an antibacterial ratio of only 66.76% against *C. albicans*. After 4 h, Ag-SH-PANF 2 was active towards *S. aureus* but inactive towards *C. albicans*; however, Ag-SH-PANF 1 was not active against either of these two pathogens. Eventually, after 6 h, all the fibres showed antibacterial activities against *S. aureus* and *C. albicans*; the longer the time, the higher the antibacterial activity. In summary, the antibacterial activities of these fibres were directly proportional to their silver contents and the exposure time to the pathogens. For comparison, the antibacterial properties of $AgNO_3$ were also investigated. Further, the used silver mass of $AgNO_3$ was the same as the content of silver in 0.1 g Ag-SH-PANF 10. The results indicated that $AgNO_3$ also did not exhibit antibacterial performance against the tested pathogens after 30 min, but its antibacterial ratios were much higher than Ag-SH-PANF 10. Within 1 h, the antibacterial ratios of $AgNO_3$ against *E. coli, S. aureus* and *C. albicans* were 85.65%, 91.18% and 83.58%, respectively, and the difference between Ag-SH-PANF 10 and $AgNO_3$ almost disappeared. After 2 h, the antibacterial ratio of $AgNO_3$ reached up to 100% against all the tested pathogens. Therefore, the antibacterial trends of Ag-SH-PANF were consistent with $AgNO_3$. Moreover, the antibacterial activities of the fibres were the same as $AgNO_3$ against the tested pathogens and followed the order: *S. aureus* > *E. coli* > *C. albicans.*

In this study, we successfully prepared a series of new antibacterial fibres, Ag-SH-PANF, with different Ag contents by a grafting and chelation sequence. The presence of Ag ions on the surface of Ag-SH-PANF was confirmed by XPS and FT-IR spectroscopy, which showed that chelation takes place between Ag ions and amino, sulfhydryl and disulphide groups. Moreover, XRD analysis confirmed that no silver crystals were produced on Ag-SH-PANF. Antibacterial testing showed that Ag-SH-PANF are excellent antibacterial agents against *S. aureus*, but less effective against *E. coli*, which is ascribed to structural differences between the two bacteria. Furthermore,

we observed that the antibacterial activity of the fibres increased with the contact time between bacteria and fibres, as well as with the initial Ag content of the fibres. In addition, the results of washing durability experiments indicated the good washing durability of Ag-SH-PANF, whose antibacterial efficiency against *E. coli* remained above 98% after washing the fibres 100 times, even though the Ag content of the fibre was only 2.40%. Finally, silver release experiments elucidated the antibacterial mechanism of Ag-SH-PANF was the same as silver ions, in which silver ions are the main antibacterial factors, acting as catalysts and therefore are not consumed in the antibacterial process. Nonetheless, a relatively high concentration of silver ions can accelerate bacterial cell death within a certain concentration range.

ANTIMICROBIAL ACTIVITIES OF SILVER NANOPARTICLES OF EXTRA VIRGIN OLIVE OIL AND SUNFLOWER OIL AGAINST HUMAN PATHOGENIC MICROBES

Seniuk I.V., Tkachenko O.V., Anas Ladid
National University of Pharmacy, Kharkiv, Ukraine
citochrom@gmail.com

Recently, both gold and silver nanoparticles have generated particular interest as a developmental research tool covering many subjects of sciences. In general, silver nanoparticles (AgNPs), have a number of significant applications in many exclusive areas. It is commonly used as an antifungal and antibacterial agents due to its have good optical characteristics ideal for biochemical imaging and sensing. The presently work investigate the synthesis of silver nanoparticles from extra virgin olive oil (*O. europaea*) and sunflower oil (*H. annuus*) and ascertain their comparative characterization. The crude oil of extra virgin olive oil (*O. europaea*) and sunflower oil (*H. annuus*) and their synthesized nanoparticles were examined against human pathogenic microbes *Viz, Proteus mirabilis, Shigella flexneri, Pseudomonas aeruginosa, Candida albicans, Micrococcus luteus, Staphylococcus aureus and Klebsiella pneumoniae.*

Crude oil of extra virgin olive (EVOO), synthesized nanoparticle of extra virgin olive oil (EVOO-NPs), crude sunflower oil (SFO) and synthesized nanoparticle of sunflower oil (SFO-NPs) were tested for their antimicrobial activity by a test of well diffusion against human pathogenic microbes. Every strain was uniformly swabbed onto the individual plates using sterile cotton swab and in each plate wells of 6 mm size were made on Muller – Hinton agar plates using gel puncture. Using micropipette, 100ul from each sample either from crude oil or nanoparticles solution were poured into 3 wells on each plate. Dimethyl sulphide (DMS) 10% was applied as a negative control and 30 mcg Cefoxitin as a positive control. All plates were incubated at 35°C for 48 h, then resulted inhibition zones were observed and measured in millimetres.

Antimicrobial inhibition activities of extra virgin olive oil (EVOO), extra virgin olive oil nanoparticles (EVOONPs), sunflower oil (SFO) and sunflower oil nanoparticles

(SFO-NPs) against pathogenic microbes. It was found that crude oil of extra virgin olive oil, sunflower oil and their synthesized nanoparticles exhibited antimicrobial activities with various potency against all tested microbes. For all antimicrobial inhibition activities, it was evident that the synthesized nanoparticle showed a potent activity against all tested micro-organisms than the crude oil itself recording increments by (81.14% to 174.65%) than (EVOO) and by (111.65% to 192.31%) than (SFO). In addition, each of (EVOO-NPs) and (EVOO) had a potent antimicrobial activities than (SFO-NPs) and (SFO) by (6.87% to 27.69%) and by (2.63% to 10.75%) respectively. The negative control did not show any antimicrobial activities, while the positive control showed halo indicative zone in the range between (21.93±0.26 mm to 36.83±2.08 mm). However, both NPs from natural oils either from (EVOO) or (SFO) showed more potent activities than Cefoxitin by (5.89% to 38.35%) and by (3.18% to 33.68%) respectively. EVOONPs showed the maximum antibacterial activities against *K. pneumoniae* with inhibition killing activities of (39.00±3.51 mm) followed by *P. aeruginosa* with inhibition zone of (30.90±2.15 mm). S. *aureus, M. luteus, C. albican, S. flexneri* and *P. mirabilis* affected by the EVOO (NPs) in the range between (26.90±3.50 mm to 29.63±2.15 mm). The antimicrobial trends obtained from (SFO-NPs) had the maximum activities against *K. pneumoniae* with inhibition zone of (38.90±2.51 mm) followed by *P. aeruginosa, S. aureus, M. luteus, C. albican* and *P. mirabilis* having inhibition zone between (28.69±2.99 mm to 26.10±2.50 mm). *S. flexneri* had the lowest susceptibility from SFO (NPs) having inhibition zone of (26.10±2.50 mm).

Scanning electron microscopy (SEM) analysis is performed for studying the surface morphology and shapes of silver nanoparticles. It is observed that the silver nanoparticles are more or less semi clearly cubic in shape for EVOO (NPs) and in agglomeration shape than SFO (NPs). This indicates the formation of Ag NPs by EVOO (NPs) differs from SFO (NPs) which supported by the intensity in XRD pattern and the area under peak in surface plasmon resonance region. The average particle size was 42.3 nm and 46.8 nm for EVOO (NPs) and SFO (NPs), respectively.

The detailed study on silver nanomaterial biosynthesis by Extra Virgin Olive oil (EVOO) and Sunflower Oil (SFO) were reported in this research. The aqueous silver ions were reduced to silver nanoparticles when added to Extra Virgin Olive oil (EVOO) and Sunflower Oil (SFO). It was observed that the colour of the solution turned from yellowish to brown and then to dark brown after 1 minute for Extra Virgin Olive oil (EVOO) and the time increased little to be brown then to dark brown for Sunflower Oil (SFO) which indicated the formation of silver nanoparticles. The formation and stability of the reduced silver nanoparticles for Extra Virgin Olive oil (EVOO) and Sunflower Oil (SFO) in the colloidal solution was monitored by UV-vis spectrophotometer analysis. The UV-vis spectra showed maximum absorbance at 418 nm for Extra Virgin Olive oil NPs whereas for Sunflower Oil NPs were noticed at 434 nm corresponding to the surface plasmon resonance of silver nanoparticles.

Recent studies had reported that light conditions, genotypes, and fertilization levels significantly affect chemicals in plants. In addition various oils under the same

conditions showed various SPR peak and shapes of the particles as in Sacha inch (*Plukenetia volubilis L*.) oil that revealed two main SPR peaks (at 380 and 480 nm) often observed for cubical/square shape AgNPs. However, coconut oil revealed single SPR peak at 410 nm and spherical shape using TEM images.

The results showed that silver nanoparticle gained from (EVOO) and Sunflower Oil (SFO) had more inhibitory efficacy than crude oils *against P. mirabilis, S. flexneri, P. aeruginosa, C. albicans, M. luteus, S. aureus* and *K. pneumoniae* with various diameter of inhibition zone. This is probably due that synthesized nanoparticles had the ability to damage the cell wall or/and damage the DNA chemical structure by interacting with phosphorus and sulfuric residues leading microbial cell death. Differences in the nature of the size particles between the Extra Virgin Olive oil (EVOO) and the Sunflower Oil (SFO) may be lead to the differences between their antimicrobial activities in agreement with previous research. It was found that the factor affecting bactericidal properties of silver nanoparticles is their shape, size, surface area, whereas the small size of silver nanoparticles has high surface reactivity. In addition, reported that the bactericidal abilities of silver nanoparticles are correlated with the electrostatic reaction between the negative charge of the bacterial cell wall and the positive charge of metal ions. In future it is worth to do more details study about Extra Virgin Olive oil (EVOO) to characterize and identify specific chemical and generate NPs against specific human pathogenic microbes.

USE OF IMMUNOCORRECTION AND ANTI-HELICOBATER THERAPY IN PATIENTS WITH DUODENAL ULCER

Suleymanov S.F., Suleymanov F.S.

Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan

ss-1961@mail.ru

Introduction. It is known that the etiology and pathogenesis of duodenal ulcer (DU) is closely related to Helicobacter pylori (HP) infection. At the same time, the researchers revealed damage to the mucous membrane of the duodenum and its colonization with cytotoxic strains of HP. With a sharp decrease in the immunoreactivity of DU patients, the manifestation of the cytotoxic properties of HP occurs, i.e. HP infection is involved in immune processes in patients with the above pathology.

The purpose of the study: to study the immune system (SI) in patients with chronic DU (CUD) and the effects of immunostimulating therapy (IST) and anti-Helicobacter therapy (AHT).

Materials and methods. SI indicators were studied in 52 patients with a diagnosis of CUD aged 33 to 54 years. 34 patients were male (65.4%), 18 (34.6%) were female. The duration of peptic ulcer was 5.6 ± 2.7 years. The average size was 1.4 ± 0.5 cm. Patients, depending on the treatment performed, were randomized into 2 representative groups. There were 28 patients in the 1st group and they received AHT from omeprazole (40 mg/day), de-nol (480 mg/day), tinidazole (1500 mg/day) for tech. 12–14 days; The 2nd group (24 patients) received a therapy regimen similar to the 1st group, but it also included the immunodrug Thymoptinum (Uzbekistan) (1 ml of 0.01% solution subcutaneously every other day; for a course of 10-12 infusions) as an additional means of treatment and immunocorrection.

When determining the main parameters of the cellular component of SI, monoclonal antibodies to the surface cluster of CD receptors (Sorbent-Servis LLC, Russia) were used: T-lymphocytes with the CD3 phenotype; T-helpers with the CD4 phenotype; T-suppressors with the CD8 marker; B-lymphocytes with the marker CD19, also the immunoregulation index (IRI) is the ratio of CD4/CD8. The levels of serum immunoglobulins (SeIg) - Ig - classes A, M and G were assessed by the method of double radial immunodiffusion according to Mancini (1968). Immune parameters were determined before and after 1 month of treatment. The control group for comparison of immunological parameters consisted of 27 healthy individuals (21-52 years old).

Results. The conducted studies indicated that the exacerbation of CUD led to immunosuppression of the total pool of CD3-lymphocytes up to 38.6 ± 1.8% at a rate of 52.4 ± 1.9%. We demonstrated lower values of T-cells with the CD3 phenotype in the 1st group, in contrast to the 2nd group of patients. In two representative groups, disturbances in the functioning of T-lymphocyte subpopulations were observed in the form of imbalance and inversion of IRI. At the same time, a decrease in the level of T-helpers with the CD4 phenotype and an increase in the number of Ts(CD8) was noted;

also verified a statistically significant decrease in IIR to 1.3 ($p<0.01$) due to a decrease in the relative proportion of Th(CD4). With regard to the production of B(CD19)-lymphocytes, one can also state their noticeable decrease to 12.3 ± 1.5% (the norm is 14.8 ± 1.1%), which, of course, indicates a noticeable decrease in most cellular parameters of immunoreactivity in patients with CUD. In the acute phase of CUD in patients of two groups, a decrease in two parameters of humoral immunity, namely IgA and IgM, was noted. At the same time, there was a tendency to increase the production of antibodies of class G - IgG - 15.27 ± 1.6 g/l at different levels of significance - $p<0.01$ in the 1st; $p<0.001$ in the 2nd group, which directly indicates a disorder of the immune system in the humoral link of immunity. We found that healing and / or scarring of the ulcer in a short time with successful AHT and effective HP eradication was achieved in the 2nd group, where the eradication efficiency (EE) was 76% in 16.7 ± 0.9 days, and in the 1st EE group was low - 58% and it was achieved in 27.3 ± 1.8 days. At the same time, we note a decrease in the number of lymphocytes in the same group 1, where the level of T-lymphocytes with the CD3 marker was reduced to 41.5 ± 1.6%, helper fraction T (CD4) ($p<0.01$) was also reduced against the background of high values of suppressor cells - Ts(CD8). A decrease in IRI to 1.5 at a rate of 2.1 indicates an imbalance in the CD4/CD8 ratio in patients with ineffective eradication. In patients of the 2nd group who took IST, a significant increase in the total pool of lymphocytes T (CD3) was observed: up to 64.3 ± 2.4%, B (CD19) up to 18.5 ± 1.7% with a parallel increase in Th(CD4) and IRI up to 2.4 (norm 2.1), which was, of course, higher than similar values in the 1st group with a high level of significance ($p<0.001$). It is likely that the marked positive shift in the functioning of the T-cell component of immunity (increased levels of CD3, CD4 and a decrease in the proportion of CD8. Moreover, in this group, there was an increase in B-lymphocytes (CD19) and IgA levels to 2.8 ± 0.64 g/l compared with pre-treatment data of 2.2 ± 0.29 g/l ($p<0.001$).

Conclusions:

1. CUD in the stage of relapse is characterized by a significant depression of the majority of SeIg with high HP infection of the duodenal mucosa.

2. Criteria for ineffective or ineffective eradication are depressive processes in the immune system of patients with CUD.

3. Conversely, the remission of patients with CUD of the 2nd group was accompanied by a significant increase in cellular humoral immunity, which, apparently, contributed to the improvement of their treatment results.

USE OF THYIMOPTINUM IN PATIENTS CHRONIC PANCREATITIS

Suleymanov S.F., Suleymanov F.S.
Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan
ss-1961@mail.ru

Introduction. Chronic pancreatitis (CP) is one of the most complex diseases of the digestive system, which is explained by the variety of etiological factors, the complexity of pathogenesis, the difficulties of diagnosis and the lack of effectiveness of treatment.

At present, the role of inflammatory mediators in damage to the pancreas is being widely studied, the role of immune and cytokine status disorders in diseases of internal organs has been highlighted.

The aim of the work is to study the parameters of the immune system and conduct immunocorrective treatment with thymoptin in patients with chronic pancreatitis.

Material and methods. 36 patients (33-65 years old) diagnosed with CP were examined. The patients were treated in the Therapy Department of the Bukhara Regional Multidisciplinary Medical Center. The control group of donors consisted of 32 practically healthy individuals (25–55 years old).

The concentration of serum immunoglobulins (SI) of classes A, M and G was determined by radial immunodiffusion according to G. Mancini. The parameters of cellular immunity (T-lymphocytes and its subpopulations, B-lymphocytes) were identified using monoclonal antibodies (OOO Sorbent-Service, Russia). Quantitative assessment of the levels of TNFα, IL-6, IL-4 in blood serum was carried out using the ProCon reagent kit (LLC "Protein contour", St. Petersburg) by enzyme-linked immunosorbent assay. Immunocorrective therapy was carried out in 15 patients. Thymoptinum (Uzbekistan) 0.8–1.0 mg per course of treatment (dose 100 μg/day for 8–10 days) was used as an immunopreparation. Immunity parameters were studied twice: before and after 1 month. after treatment.

Results. In patients with chronic pancreatitis, immunodeficiency was determined on the part of the T-cell component of the immune response: 0.7-fold suppression of the total pool of lymphocytes - T(CD3) - 35.3 ± 2.6% compared with the control group of healthy individuals - 52.4 ± 1.8% ($p<0.001$); 0.8-fold decrease in T(CD3)-cells ($p<0.05$) in their absolute terms. We also revealed the suppression of subpopulations of T-lymphocytes with a helper-suppressor function - Th(CD4) - 29.5 ± 1.1% ($p<0.001$) and 341.8 ± 32.1 cells/1 μl of blood ($p<0.001$) (in the control 36.5 ± 0.7% and 616.4 ± 44.3 cells/1 μl of blood, respectively), the content of Ts(CD8) - 13.8 ± 1.4% ($p<0.05$) and 127 .3 ± 9.8 cells/1 μl of blood ($p<0.01$). On the part of the B(CD19)-cell link, on the contrary, there was a tendency to increase as a relative parameter - 20.6 ± 2.3% ($p<0.05$), which was 1.4 times higher than the indicated values of the control group, so and absolute - 1.7-fold increase - 385.8 ± 33.4 cells / 1 μl of blood (in control - 230.1 ± 26.7 cells / 1 μl of blood).

Significant activation of the B-cell component of the immune system against the background of T-cell immunosuppression in CP was reflected in the SI spectrum. For example, an increase in IgA synthesis up to 3.97 ± 0.41 g/l ($p<0.05$) can be distinguished. A significantly high content of IgG was demonstrated up to 22.42 ± 0.75 g/l ($p<0.001$) (in the control 15.9 ± 0.94 g/l). The IgM concentration was within the normal range of 1.7 ± 0.2 g/l ($p>0.05$). Under the influence of conservative treatment, there was no recovery of T(CD3) cells and its subpopulation profile. At the same time, a trend was revealed in the reduction of SI of two classes - IgA and IgG.

An analysis of the spectrum of cytokines showed that in patients with CP during the exacerbation, the values of pro-inflammatory cytokines significantly increased: TNFα up to 202.6 ± 22.3 pg/ml (normal - 24.5 ± 5.1 pg/ml; $p<0.001$), and IL-6 was increased 6 times (317.4 ± 53.5 pg/ml and 47.8 ± 11.2 pg/ml, respectively, at $p<0.001$. The level of anti-inflammatory cytokine IL-4 y increased 4.3 times compared with the norm, which was statistically confirmed (157.5 ± 36.7 pg/ml and 32.6 ± 14.3 pg/ml, respectively; $p<0.001$).

To eliminate the identified disorder, we used Thymoptinum, which was used in combination with traditional therapy (antienzymatic agents, antispasmodics, antibacterial drugs, etc.). Immunocorrective therapy led to an increase in both relative - 54.7 ± 3.2%, and absolute values of T(CD3) -lymphocytes - 992.3 ± 64.8 cells / 1 μl. In parallel, an increase and stabilization of Th(CD4) and Ts(CD8) was observed. The immunoregulatory index was 2.2. The IgA concentration decreased moderately during treatment. In CP patients, we noted an increase in the production of IgM to 2.23 ± 0.2 g/l and IgG to 23.7 ± 1.62 g/l 1 month after treatment, however, it should be noted that during the period of remission, the level of IgG was high, which was probably due to the severity, duration and chronicity of the pathological process, as well as a decrease in reparative processes in the pancreas.

During traditional treatment in patients with CP, there was a moderate decrease in the levels of TNFα, IL-6 ($p>0.05$; compared with the data before treatment) and a slight increase in IL-4 to 172.3 ± 41.1 pg/ml.

Under the influence of immunocorrective therapy carried out against the background of traditional treatment, patients with CP showed a marked decrease in pro-inflammatory cytokines: TNFα to 118.4 ± 29.1 pg/ml, IL-6 to 133.6 ± 51.8 pg/ml. In addition, a decrease in the production of the anti-inflammatory cytokine IL-4 by 95.2 ± 27.4 pg/ml was observed.

Conclusions: in patients with CP, significant changes in the functioning of most parameters of the immune system were observed.

In patients with CP, there was a trend towards an increase in the levels of pro- and anti-inflammatory cytokines, which to a certain extent characterizes the pathological process occurring in the pancreas.

The combination of traditional treatment and Thymoptinum was effective in patients with CP, as it contributed to the restoration and stabilization of most parameters of the immune system.

ПАТОГЕННІ ВЛАСТИВОСТІ *M. BOVIS*, ВИДІЛЕНИХ ВІД ОНДАТР ЯК ПРИРОДНОГО РЕЗЕРВУАРА ЗБУДНИКА МІКОБАКТЕРІАЛЬНОЇ ІНФЕКЦІЇ

Бусол В.О[1]. Мазур В.М.[2] Шевчук В.М.[2]

[1]Національний науковий центр «Інститут експериментальної і клінічної ветеринарної медицини», м. Харків, Україна

[2]Національний університет біоресурсів та природокористування України м. Київ, Україна

[1] larbuko@gmail.com [2] vmmazyr@gmail/com [2] vishev08@ukr.net

Аналіз даних фахової літератури свідчить, що туберкульоз людей і великої рогатої худоби є одним з найбільш поширеніших захворювань у світі. Серед об'єктивних чинників, які обумовили такий стан, є те, що до цього часу вчені концентрували увагу переважно на вивченні етіології та епізоотологічних особливостях хвороби переважно в стадах сільськогосподарських тварин і птиці. Такий методичний підхід залишав поза увагою екологічні особливості циркуляції збудника, його генотипову і фенотипову мінливість.

Метою наших досліджень, результати яких представлено у цих тезах, було вивчення особливостей взаємовідносин макроорганізму сприйнятливих тварин до збудника туберкульозу та патогенних мікобактерій, виділених від ондатр. Для її досягнення проведено відповідні епізоотологічні, екологічні та експериментальні дослідження мікобактерій, виділених із організму ондатр, виловлених у невеликих водоймах довготривало неблагополучного господарства щодо туберкульозу ВРХ (дослід, n=5,) та вільного від інфекції (контроль, n=6). У двох з п'яти ондатр дослідної групи було виявлено збільшення селезінки та печінки у 1,3–1,5 разу порівняно з контролем. Після посіву гомогенатів органів ондатр на щільне яєчне середовище отримано культуру мікобактерій (ізолят "Ондатра"). За результатами культуральних, морфологічних та молекулярно-генетичних досліджень вони були віднесені до виду патогенів *M. bovis.*

У досліді з вивчення патогенності мікобактерій, виділених з організму ондатр після трьохразового пасажування через організм мурчаків, доведено, що у всіх мурчаків дослідної групи (n=5), заражених культурою мікобактерій, спостерігали утворення виразок на 20–28 добу, загибель тварин – на 50-125 добу. Патологоанатомічні зміни, характерні для туберкульозу проявились у всіх тварин, а у трьох було виявлено патологічні зміни, не описані у фаховій літературі: на 62-91 добу ураження шкіри ділянок шиї, спини, живота і менш інтенсивні в інших ділянках тіла. Загальний стан таких тварини динамічно погіршувався. На розтині виявлено туберкули, збільшення пахових лімфатичних вузлів у 1,5 разу і ознаки катаральної пневмонії.

У курей клінічні ознаки туберкульозу на 8–10 добу виявили погіршення апетиту та блідість гребенів та борідок, відмову від корму.

На 21–22 добу біопроби дослідна птиця загинула. За патолого-анатомічного розтину в печінці та селезінці дослідних курей виявлено яскраво виражені зміни, характерні для туберкульозу.

З найвищою динамічністю розвиток інфекційного процесу проходив у кролів. Так, уже на сьому добу, після зараження суспензією культури мікобактерій ізоляту "Ондатра", тварини відмовилися від корму і виглядали пригніченими, шерсть втратила блиск. На 9–10 добу після зараження всі тварини загинули. Патологоанатомічним розтином у кожної тварини встановлено збільшення селезінки в 4–5 разів порівняно з органом тварин контрольної групи, спостерігалась зміна кольору печінки до глинистого.

У мазках з легень і печінки, які були відібрані від тварин і курей дослідних груп та пофарбовано за методом Ціля-Нільсена виявлено короткі та довгі (1–4 мкм) мікобактерії, розташовані як вільно, так і в середині макрофагів.

Отримані нами дані дозволяють обґрунтовано стверджувати, що виділений від ондатр ізолят відноситься до підвиду виду M. bovis з підвищеною патогенністю, оскільки при зараженні кролів та курей мікобактерями бичачого виду прояв туберкульозного процесу не є характерним. Це дає підставу передбачити здатність мікобактерій ізоляту «Ондатра» викликати туберкульозний процес у великої рогатої худоби та людей.

Отримані нами дані з вивчення особливостей виникнення та функціонування епізоотичного процесу туберкульозу у водному середовищі свідчать, що ондатра є сприйнятливою ланкою та джерелом збудника, а також формує епізоотичний ланцюг чинників спричинення епізоотичного ланцюга зі зворотнім зв'язком: ондатра (сприйнятливий організм *M. bovis* та джерело збудника) ↔ збудник туберкульозу → тварини, сприйнятливі до патогена, які переходять у ранг ланки епізоотичного ланцюга ↔ джерело збудника інфекції. На цьому епізоотичному етапі започатковується розвиток стабільного епізоотичного процесу з прямим і зворотним розвитком від ондатри як джерела збудника інфекції до ондатри як сприйнятливої тварин до *M. bovis*. Концептуально можна допустити симбіотичне підвищення патогенності збудника туберкульозу цього виду після пасажування через організм ондатри у водному середовищі, що може стати підґрунтям для подальших досліджень.

Вищенаведене є підставою для конкретизації сутності епізоотичного процесу, в основу якої ставляться відношення в системі паразит – господар та необхідності екологічного підходу до вивчення епізоотичного та інфекційного процесів в залежності від змін в екології та біосфері.

ОСВІТНІ КОМПОНЕНТИ ХІМІЧНОГО НАПРЯМКУ ЯК ПЕРЕДУМОВА ФОРМУВАННЯ ФАХОВИХ КОМПЕТЕНЦІЙ ФАРМАЦЕВТА

Калитовська М.Б., Жукровська М.О.
Львівська медична академія імені Андрея Крупинського, м. Львів, Україна
kalytovska.myroslava@gmail.com

Появі будь-якого лікарського засобу на фармацевтичному ринку передує низка доклінічних та клінічних випробувань безпечності застосування даного препарату в лікувальній практиці. Сам процес синтезу діючої речовини, перевірки його безпечності та ефективності вимагає участі в даному процесі кваліфікованих фахівців. Підготовку таких кадрів проводять вищі навчальні медичні заклади України.

Передумовою формування фахових компетенцій майбутнього фармацевта є освоєння загальноосвітніх компонентів хімічного напрямку. Базові поняття розуміння основних хімічних процесів та взаємодії речовин фармацевти освоюють на початкових курсах навчання при вивченні загальної та неорганічної хімії, фізичної та колоїдної хімії. Це становить основу для подальшого вивчення технології ліків, яке не можливе без розуміння теорії та практики приготування розчинів, суспензій, твердих і рідких форм лікарських засобів в апечних умовах чи на виробництві.

Вивчення аналітичної хімії є ключовим для встановлення якості та безпечності лікарського засобу в фармацевтичному аналізі. Державна фармакопея України базується на якісному і кількісному аналітичному аналізі лікарської рослинної сировини, готових препаратів на основі природніх речовин та синтетичного походження. Реалізація лікарського засобу на фармацептичному ринку не можлива без проведення цілої низки хімічних досліджень.

Вивчення загальноосвітніх компонентів хімічного напрямку формує в фармацевтів здатність проводити дослідження у практичній професійній діяльності на відповідному рівні, здійснювати пошук, обробку та аналіз інформації з різних джерел, приймати обгрунтовані рішення, здатність до міжособистісної взаємодії та командної роботи. Відповідний рівень знань дозволяє забезпечити раціональне використання лікарських засобів.

ВПЛИВ ТЮТЮНОВОГО ДИМУ НА МІКРОБІОМ РОТОВОЇ ПОРОЖНИНИ ЩУРІВ

Попова Т.М.

Харківський національний медичний університет, м. Харків, Україна

popovatatyanamikh@gmail.com

Вступ. Вживання тютюнових виробів є фактором ризику різноманітних захворювань порожнини рота. На сьогоднішній день залишається актуальним питання впливу тютюнового диму на склад мікробної спільноти ротової порожнини.

Метою даного дослідження була оцінка мікрофлори щурів, які зазнали тривалого впливу диму тютюнових сигарет.

Матеріали та методи. Для дослідження було відібрано п’ятнадцять самців і п’ятнадцять самок щурів лінії WAG у віці 10 тижнів. Усіх щурів випадковим чином розподілили на дві групи. П'ять самців і п'ять самок щурів 1 групи були інтактними тваринами. Протягом 90 діб десять самців і десять самок щурів групи 2 піддавалися дії диму тютюнових сигарет. У експерименті використовували сигарети з фільтром «Liggett & Meyers», Blue Label (Philip Morris International, США), які мають вміст 0,5 мг нікотину та та 6,0 мг смол на сигарету. Щури 2 групи піддавали впливу сигаретного диму за допомогою камери Боярчука протягом двадцяти хвилин на день протягом п'яти днів на тиждень. Щури 1-ї групи піддавали впливу свіжого повітря протягом двадцяти хвилин. Для мікробіологічних досліджень застосовували культуральні методи. Кількість колоній мікроорганізмів реєстрували як колонієутворюючу одиницю на мл (КУО/мл). Під час статистичного аналізу використали програмне забезпечення STATISTICA 7.0. Дані були представлені у вигляді середніх значень і чисел стандартного відхилення (m±SD) КУО/мл. Результати вважали статистично значущими при $p<0.05$.

Результати. Під час експерименту мікробіота ротової порожнини 1 групи була значною мірою представлена грампозитивними аеробними бактеріями (Bacillus spp., Staphylococcus spp., Streptococcus spp., Enterococcus spp., Corynebacterium spp.), тоді як грамнегативні бактерії, починаючи з 60 доби, були домінантними представниками мікрофлори групи 2. Аналіз мікробіологічного складу 2 групи в залежності від тривалості куріння показав статистично значуще збільшення кількості умовно-патогенних представників. На рівні роду в групі 2 переважали Enterobacter spp.. Escherichia spp., Klebsiella spp., Moraxella spp., Candida spp.. Важливо, що значний відсоток (80,0%) щурів у групі 2 на 90-й день експерименту мав високий рівень умовно-патогенних членів, включаючи Moraxella catarrhalis 4.68±0.87 log cfu/cm^2, Candida albicans 3.62±0.05 log cfu/cm^2, Klebsiella pneumoniae 3.23±0.46 log cfu/cm^2 та Escherichia coli 3.65±0.08 log cfu/cm^2, що статистично значуще відрізнялося від групи 1, де Moraxella catarrhalis, Candida

albicans та Klebsiella pneumoniae були відсутні, а Escherichia coli 2.31±0.39 log cfu/cm^2 (Kruskal-Wallis test: H=93.23, p =0.0000).

Висновки. Тривалий вплив тютюнового диму призвів до стійкої колонізаціїї умовно-патогенними мікроорганізмами, такими як Klebsiella pneumoniae, Moraxella catarrhalis, Candida albicans та Escherichia coli.

АНТАГОНІСТИЧНА АКТИВНІСТЬ *LACTOBACILLUS DELBRUECKII SUBSP. BULGARICUS* LB 86 ТА ЇХ ЛИЗАТІВ

Потьомкіна В.О.[1],Орябінська Л.Б.[1], Лазаренко Л.М.[2]

[1]Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського»

[2] Інститут мікробіології та вірусології ім. Д.К. Заболотного НАН України

lbletkin@gmail.com

В останні роки підвищився інтерес до лізатів пробіотичних бактерій, які на сьогодні використовуються у складі ветеринарних лікувальних препаратів, входять до складу косметичної продукції, є інгредієнтами засобів гігієни тощо. Як відомо, однією з властивостей пробіотичних культур є їх виражений антагонізм щодо патогенних та умовно-патогенних бактерій. Тому пробіотики вважаються терапевтичною альтернативою антибіотикам, оскільки здатні модулювати мікробіом кишківнику без прояву побічних ефектів. Здатність пробіотиків пригнічувати розвиток мікроорганізмів обумовлена синтезом ними антимікробних речовин – антибіотиків, літичних ферментів, органічних кислот, спиртів, перекісних сполук, коліцинів тощо. Однак, про антагоністичну активність лізатів пробіотиків є недостатньо відомостей.

У зв'язку з цим, проведено порівняльну оцінку антагоністичної активності *Lactobacillus delbrueckii subsp. bulgaricus* LB 86 та їх лізатів, отриманих методом ферментативної дезінтеграції літичним комплексом цитал-Рк.

Антагоністичну активність лактобактерій оцінювали класичним методом відстроченого антагонізму. Антимікробну активність лізату визначали *in vivo* на моделі інтактних мишей лінії BALB/c. Всі отримані цифрові дані були оброблені шляхом дисперсійного аналізу. Відмінності між групами вважали статистично значущими при p < 0, 05.

Проведені дослідження дозволили встановити, що жива культура *L. delbrueckii subsp. bulgaricus* LB 86 проявляла високу антагоністичну активність щодо $Г^+$ та $Г^-$ мікроорганізмів, взятих в експеримент, у тому числі і таких збудників токсикоінтоксикацій як *Staph. aureus, E. coli, Bac. cereus.* Зони затримки зростання для цих культур варіювали на рівні 30-46 мм. Щодо близьких за родом лактобактерій культура *L. delbrueckii subsp. bulgaricus* LB 86 проявляла вибіркову дію: від нейтральності до часткового пригнічення їх росту або до взаємного придушення одне одного.

Разом з тим, дослідження антагоністичної активності лізатів показало, що вони протягом всього періоду спостереження (18 днів) не впливали на спектр та кількісний вміст кишкової мікрофлори експериментальних тварин. Кількість аеробних, факультативно анаеробних або аеротолерантних бактерій, таких як - стрептококи, стафілококи, коліморфні бактерії, молочнокислі бактерії (лактобактерії та біфідобактерії), а також мікроскопічні гриби підтримувалися на рівні контрольних показників. Таким чином, лизат *Lactobacillus delbrueckii subsp. bulgaricus* LB 86, на відміну від нативних клітин, не виявляє антагоністичну активність та не бере участь у модуляції кишкової мікробіоти.

МІКРОБІОЛОГІЧНЕ ОБГРУНТУВАННЯ СУМІСНОГО ЗАСТОСУВАННЯ ПРЕПАРАТІВ ПРИРОДНОГО ПОХОДЖЕННЯ З ІНШИМИ ГРУПАМИ ХІМІОТЕРАПЕВТИЧНИХ ПРЕПАРАТІВ ДЛЯ ЛІКУВАННЯ ІНФЕКЦІЙ СЕЧОСТАТЕВИХ ШЛЯХІВ

Сілаєва Л.Ф., Шакун О.А.

Національний фармацевтичний університет, м. Харків, Україна

sylaeva.ludmila @gmail.com

Введення. Інфекції сечовивідних шляхів є найчисельнішою групою, посідаючи друге місце серед інфекційних захворювань людини загалом. В останні роки змінюється спектр антимікробної чутливості збудників інфекцій із втратою чутливості до багатьох антибіотиків та антисептиків. Застосування антимікробних композицій, що містять препарати з різним механізмом дії, є пріоритетним напрямком пошуку нових шляхів різнопланового впливу на мікробні клітини з метою попередження формування резистентності.

Мета. Метою наших досліджень було порівняльне вивчення антимікробної активності в умовах in vitro активності 4-х експериментальних зразків: 2-х сечогінних і 2- х протизапальних зборів з настойкою і без настойки прополісу і препаратів рослинного походження - Нокамен і Канефрон з визначення впливу препарату Нокамен на рівень антимікробної активності препаратів Бі-сепТ, Фуразолідон, Ципрофлоксацин і Левофлоксацин.

Матеріали і методи. Антимікробну активність препаратів вивчали в умовах in vitro загально прийнятим в мікробіологічній практиці методом дифузії в агар у модифікації колодязів. В якості тест-мікроорганізмів використовували еталонні штами із американської типової колекції культур: S. aureus ATCC 25923, E. coli ATCC 25922, P. aeruginosa ATCC 27853, B. subtilis ATCC 6633, C. albicans ATCC 885-653 та клінічні штами, виділені із сечі хворих на гломерулонефрит - Kl. pneumoniae кл.С10 і E.coli кл. D 11.

Результати та їх обговорення. В умовах експерименту in vitro встановлено, що введення до складу експериментальних зразків протизапальних і

сечогінних зборів настойки прополісу сприяє підвищенню їх антимікробної активності відносно мікроорганізмів, що є етіологічними факторами в розвитку інфекцій сечастатевих шляхів. Результати мікробіологічних досліджень показали, що препарат Нокамен, у порівнянні з препаратами Канефрон і Уролесан в умовах in vitro проявив більш високий рівень антимікробної акивності. Виявлено синергідний антимікробний ефект препарату Нокамен з препаратом Ципрофлоксацин і практично відсутність ефекту при комбінованому застосуванні препарату Нокамен з препаратами Бі-сепТ, Левофлоксацин, Фуразолідон.

Висновки. Показана перспективність подальшого вивчення можливості сумісного використання препаратів природного походження з іншими групами хіміотерапевтичних препаратів для лікування інфекцій сечостатевих шляхів

МЕХАНІЗМИ СТІЙКОСТІ БІОПЛІВОК ДО АНТИБАКТЕРІАЛЬНИХ ЗАСОБІВ І ПЕРСПЕКТИВИ СТВОРЕННЯ АНТИКВОРУМНИХ ПРЕПАРАТІВ

Сілаєва Л.Ф., Гейдеріх О.Г.

Національний фармацевтичний університет. м. Харків, Україна

sylaeva.ludmila @gmail.com

Вступ. Поширення стійкості збудників інфекційних захворювань до антимікробних засобів та відсутність нових препаратів з антимікробною дією визначають загальнодержавне значення цієї проблеми, що потребує вжиття невідкладних заходів боротьби. Однією з причин стійкості мікроорганізмів не тільки до протимікробних препаратів, але й до факторів довкілля є формування біоплівок. Вони призводять до затяжного перебігу інфекційних захворювань, перешкоджають нормальній імунній відповіді організму-хазяїна, неефективності антибактеріальної терапії. Біоплівки можуть формуватися не тільки в макроорганізмі, але й формуються на катетерах (серцевих, внутрішньовенних, сечовивідних), штучних клапанах серця (будучи основною причиною інфекційних ендокардитів), штучних суглобах, контактних лінзах та ін. В умовах біоплівки темпи еволюції мікроорганізмів є більш швидкими порівняно з альтернативною (планктонною) формою існування.

Мета дослідження. Аналіз нових даних та узагальнення результатів сучасних вітчизняних та зарубіжних наукових досліджень щодо структури біоплівки, механізмів її стійкості до антимікробних засобів, перспектив створення антикворумних засобів.

Матеріали і методи. У ході досліджень застосовувались методи сучасного інформаційного пошуку, бібліографічний, аналітичний, порівняльний та узагальнюючий аналіз.

Результати та їх обговорення. Як свідчать дані наукових досліджень в теперішній час проблему стійкості до антимікробних засобів слід розглядати не

тільки з точки зору клітинного або популяційного рівнів, але й перш за все молекулярного. Як відомо, існує генотипова стійкість (вроджена та набута), та фенотипова - біоплівки та персистори як метаболічно неактивні учасники мікробної популяції. Однією з причин стійкісті мікроорганізмів до проти-мікробних препаратів є формування саме бактеріальної біоплівки. За допомогою конфокальної та електронної мікроскопії встановлено, що біоплівки мають складну тривимірну структурну організацію. Після незворотної адгезії популяція бактерій починає інтенсивно ділитись з утворенням багатоклітинних шарів і активно синтезувати компоненти екзополімерного матриксу, що є одним із ключових моментів утворення біоплівок. Клітини у слизовому матриксі розміщуються не хаотично, а впорядковано, відповідно до певних структурних принципів. Матрикс розділений каналами, наповненими водними розчинами. Через ці канали транспортуються поживні речовини і проходить кисень від зовнішніх до внутрішніх шарів біоплівки, а також виводяться метаболіти. Стійкість біоплівки до антибактеріальних засобів забезпечується наступними механізмами: затримка проникнення антимікробного агента через тривимірну матрицю біоплівки через дуже повільну дифузію та труднощі досягнення ефективної концентрації; зміни швидкості росту та низький метаболізм мікроорганізмів у біоплівці; зміни у фізіологічних реакціях мікроорганізмів під час росту біоплівки зі зміненою експресією генів стійкості. Процес формування біоплівки регулюється складними механізмами міжклітинної комунікації - Quorum sensing (QS). Будь-яка система QS містить: сигнальную молекулу (автоіндуктор – AI), який легко дифундує через клітинну мембрану, рецепторний регуляторний білок, з яким зв’язується AI, фактор транскрипції, фермент, що каталізує синтез нових молекул індуктора. Іноді рецептор і фактор транскрипції уявляють собою один і той же білок. В теперішній час ідентифіковано понад 50 молекул міжбактеріальної комунікації: аутоіндуктори-1 (1 autoinducer - AI-1), також відомі як N-ацилгомосеринові лактони (AHL), характерні для грамнегативних бактерій; аутоіндуктор-2 (AI-2) у грампозитивних бактерій; молекули фурану - як у грамнегативних, так і грампозитивних бактерій (фуранозілборат); хінолоновий сигнал бактерій Pseudomonas (PQS), олігопептиди (пептиди, що складаються з 5-10 амінокислотних залишків; циклічний тіолактон), відомі як аутоіндуктори - пептиди (AIP); коротколанцюгові ненасичені жирні кислоти з цис-конфігурацією та інші.

В теперішній час в усьому світі йде пошук альтернативних антибіотикам підходів до терапії захворювань, викликаних плівкоутворюючими збудниками. Однією з таких альтернатив є створення антикворумних препаратів з урахуванням наступних можливих механізмів їх дії. Знаючи шлях біосинтезу індуктора, визначають аналоги попередників, які порушуватимуть роботу ферментів-синтаз, внаслідок чого клітина перестає виробляти сигнальні молекули. За допомогою хімічних агентів можно значно зіпсувати якість міжклітинного зв'язку. Перспективним інструментом можуть бути ферменти, що розкладають сигнальні

молекули. Зокрема, AHL можуть розкладатися лактоназами, ацилазами та оксидоредуктазами. Можливим механізмом може бути пригнічення рецепції сигналів за рахунок конкурентного зв'язування зі специфічним сайтом рецептора. У випадку AHL часом достатньо змінити (бажано в більшу сторону) довжину ацильного хвоста сигнальної молекули. Хвіст можна зробити не тільки довшим, але й жорсткішим, збагативши його ненасиченими зв'язками. Серед інгібіторів QS особливий інтерес представляють інгібітори тваринного походження - моноклональні антитіла, отримані із застосуванням гаптенів та напівантигенів, здатних викликати синтез антитіл тільки у зв'язці з іншими молекулами, що містять лактамне кільце. Було показано, що імунізація мишей, заражених синьогнійною паличкою, бичачим сироватковим альбуміном, пов'язаним із сигнальною молекулою (3-оксододеканоілгомосерінлактоном), призводить до істотного збільшення їх виживання. Гіпотетично можливим є створення так званої «антикворумної вакцини», що зможе попереджати зараження організму плівкоутворюючими мікроорганізмами, або у разі потрапляння в організм запобігати збільшенню їх кількості. Критеріями застосовування антикворумніих препаратів для лікування інфекційних захворювань є: відсутність токсичної дії на еукаріотичні клітини, стабільність та специфічність дії саме проти систем QS, відсутність впливу на основні метаболічні процеси в клітині. Скринінгові дослідження стратегій, що нейтралізують плівкоутворення показали перспективність комбінації етіотропного антибактеріального препарату з іншими (антибіотики з групи макролідів, фторхінолони, амфотерицин та ін), комбінацій антимікробних препаратів та нестероїдних протизапальних препаратів, застосування неспецифічних антибактеріальних препаратів для боротьби з поширенням біоплівкоутворювальних штамів. Було доведено антикворумну активність у цілої низки рослинних екстрактів, у тому числі цитрусових, чорниць, журавлини, ванілі, а також деяких лікарських рослин, таких як розмарин та куркума. Цілком можливо, що буде створено такі антикворумні препарати, які зможуть замінити сучасні антибіотики й стати новим поколінням ліків майбутнього.

Висновки. Оскільки QS системи беруть участь у формуванні біоплівок і контролі вірулентності бактерій, інгібітори QS мають фармацевтичне значення, на їх основі розробляються лікарські засоби, спрямовані проти плівкоутворюючих мікробів. На даний час лише мала частина подібних препаратів пройшла клінічні випробування, ефективність більшості з них підтверджена поки що тільки в системах in vitro. За оптимістичними прогнозами, масштабне застосування інгібіторів QS – це питання двох найближчих десятиліть.

СУЧАСНІ ЛАБОРАТОРІНІ МЕТОДИ СПЕЦИФІЧНОЇ ДІАГНОСТИКИ ТУБЕРКУЛЬОЗУ

Шаповалова О.В.

Національний фармацевтичний університет, м. Харків, Україна

shapolga2002@gmail.com

Хоча в останні роки статистична звітність інформує, що захворюваність на туберкульоз в Україні йде на спад, згідно з доповідями фтизіатрів це є результатом суттєвого зниження кількості проведених діагностичних процедур. Зрозуміло, що така ситуація пов'язана з тим, що більша частина ресурсів виділялася на боротьбу з пандемією COVID-19. Однак туберкульоз, як одна з основних причин смертності в світі, потребує пильної уваги фахівців з різних спеціальностей, в тому числі з лабораторної діагностики, оскільки в деяких випадках симптоми обох захворювань подібні. Не зважаючи на те, що з дати відкриття збудника туберкульозу Р. Кохом минуло 140 років, багато питань стосовно специфічної лабораторної діагностики захворювання потребують постійного удосконалення.

Золотим стандартом діагностики залишаються культуральні дослідження, які дозволяють отримати ізолят збудника, провести його ідентифікацію та визначити чутливість до протитуберкульозних препаратів. Сучасною альтернативою цього довготривалого й високо коштовного методу слугують методики, які базуються на молекулярно-генетичних підходах з визначення генетичних маркерів-послідовностей ДНК або РНК, що кодують видоспецифічні ознаки мікобактерій та їх стійкість до лікарських препаратів. Суттєвою перевагою таких досліджень є можливість працювати як з чистою культурою бактерій, так і безпосередньо з біоматеріалом, розрізняти близькоспоріднені види та підвиди мікроорганізмів, а також швидко ідентифікувати навіть такі, що трудно культивуються. До молекулярних маркерів належать певні послідовності нуклеотидів, що повторюються, сайти розпізнавання ендонуклеазами рестрикції, мобільні генетичні елементи, точкові мутації в окремих конститутивних генах, генах вірулентності та некодуючих послідовностях, поліморфні послідовності різної довжини й делеції в ДНК бактеріальних хромосом або плазмід. Прикладом сучасних методів експрес аналізу є технологія картриджів Xpert MTB/XDR (Cepheid, США), що базується на автоматизованій напівгніздовій Real Time-ПЛР для виявлення мікобактерій комплексу M. tuberculosis з множинною лікарською стійкістю. Застосування цих тестів з 2021 р. стало доступним в Україні, що має позитивно вплинути на своєчасне виявлення хворих на туберкульоз та призначення оптимального лікування.

Серед лабораторних методів діагностики туберкульозу, як альтернатива шкірному тесту Манту, широкого застосування у США та більшості країн західної Європи знайшов тест IGRA (Interferon Gamma Release Assay, QIAGEN, США) з виявлення γ-інтерферону в плазмі/сироватці крові методом ІФА. Тестом на гамма-інтерферон другого покоління є квантифероновий тест QFT, який призначений для виявлення латентної форми захворювання та дозволяє визначати рівень цитокіну у

цільній крові після стимулювання комплексом антигенів, що містяться у PPD-туберкуліні *M. tuberculosis*. Починаючи з 2005 р. був рекомендований тест третього покоління QuantiFERON-TB Gold (QFT-G), в якому застосовуються синтетичні аналоги двох специфічних антигенів збудника ESAT-6 та CFP-10. У 2007 році в США почали застосовувати модифікований тест QuantiFERON-TB Gold In-tube, що додатково містить третій специфічний антиген TB 7.7. Цьому тесту натепер надають перевагу при обстеженні вакцинованих осіб. Квантиферонові тести відрізняються від інших діагностичних методів високою чутливістю та специфічністю. На відміну від широко поширеного шкірного тесту, їх перевагою є 95%чутливість (70% реакції Манту), незалежність результату від впливу імунної відповіді на вакцину BCG, 98% специфічність (59% реакції Манту у вакцинованих осіб), отримання результату під час першого візиту пацієнта, висока ефективність при виявленні латентних форм туберкульозу.

В Україні натепер впровадженим є один з найсучасніших засобів для in vitro виявлення інфекції *M. tuberculosis* та захворювання на туберкульоз - непрямий квантифероновий тест QuantiFERON-TB Gold Plus (QFT-Plus), рекомендований для застосування в комплексі діагностичних досліджень разом з іншими медичними процедурами, в тому числі шкірною туберкуліновою пробою. Матеріалом для досліджень в цьому тесті є цільна венозна кров, яка відбирається у кількості 4-5 мл. Методика QFT-Plus базується на відомій технології IGRA, але містить специфічні антигени, що стимулюють інтерферонпродукуючу активність як CD8+, так і CD4+ клітин. Суть тесту полягає у виявленні та кількісному вимірюванні рівня γ-інтерферону, який виробляється Т-лімфоцитами при додаванні крові в пробірку, яка містить суміш пептидів, аналогічних двом специфічним антигенам збудника туберкульозу. Через 16-24 годин інкубації плазма крові видаляється, в ній методом ІФА визначається результат (МО/мл). Контролем слугують окремі проби крові, не стимульовані специфічними антигенами, а також стимульовані неспецифічним мітогеном.

Ефективні технології, покладені в основу квантиферонового тесту, дозволяють лікарю дати всебічну кількісну оцінку клітинно-опосередкованої імунної відповіді пацієнтів, в тому числі тих, хто належить до груп ризику розвитку інфекції, медичних працівників та імунокомпрометованих осіб. Його застосовують як додатковий при наявності рентгенологічних та клінічних ознак активного туберкульозу, а також в якості підтверджуючого тесту після проведення проби Манту у дорослих та дітей старше 5 років. В той же час остаточний діагноз на туберкульоз потребує врахування анамнестичних, клінічних, інших лабораторних та інструментальних даних.

Таким чином, сучасний арсенал лабораторних методів діагностики туберкульозу в Україні та в світі містить високочутливі та специфічні прямі та непрямі методи діагностики. Нова стратегія боротьби з туберкульозом в умовах пандемії COVID-19 передбачає проведення одночасного тестування на обидві інфекції.

ЗАЛЕЖНІСТЬ РІВНЯ ВПЛИВУ ХІМІЧНИХ КОМПОНЕНТІВ ЛІКУВАЛЬНОЇ ЖУЙКИ НА БІОПЛІВКОУТВОРЕННЯ

Філімонова Н.І., Тіщенко І.Ю., Гейдеріх О.Г., Кошова О.Ю.
Національний фармацевтичний університет
microbiology@nuph.edu.ua

Проблема виникнення та розповсюдження інфекційної патології на даний час щільно пов'язана з притаманними мікроорганізмам патогенними властивостями, в т.ч. адгезія та біоплівкоутворення. Згідно з даними наукової літератури відомо, що здатність мікроорганізмів до утворення біоплівок властива більш ніж 90% вивчених видів бактерій, а формування останніх виявлено майже у 80% випадках хронічних захворювань мікробної етіології. Значущу роль біоплівкоутворення пов'язують, перш за все, з підвищеною стійкістю бактерій до агресивних факторів навколишнього середовища, таких як: антибіотики, дезінфектанти і пестициди, фагоцитоз. В умовах біоплівок утворюються унікальні умови з точки зору взаємодії між мікроорганізмами: близький контакт дозволяє різко посилити обмін генетичною інформацією, відповідно, утворення резистентних штамів мікроорганізмів відбувається набагато швидше, ніж у мікроорганізмів, що знаходяться в формі планктону. Враховуючи, що людина перебуває у постійному контакті з мікроорганізмами, стає зрозумілим важливість вирішення питань розвитку та поширення інфекційних захворювань, у т.ч. інфекцій ротової порожнини. На сьогодення одним з актуальних напрямків скринінгових досліджень є пошук нових ефективних засобів для лікування інфекційної патології ротової порожнини.

Метою роботи стало визначення впливу новостворених лікувальних засобів на здатність мікроорганізмів ротової порожнини до біоплівкоутворення.

Матеріали та методи. В якості мікробіологічної моделі були використані штами наступних мікроорганізмів: *S. mutans, S. aureus, S. epidermitidis, Lactobacillus plantaris, C. albicans.* При проведенні експериментальних досліджень керувалися загальноприйнятими методичними рекомендаціями з мікробіологічних досліджень.

Результати та їх обговорення. На початку проведення експерименту було доведена схильність до біоплівкоутворення всіх застосованих тест-культур.

Дослідження впливу на біоплівкоутворення експериментального тест-зразка було проведено в 2 етапи: на першому етапі визначали вплив як окремих складових компонентів тест-зразка жувальної гумки так й їхнього сумісного застосування на процес біоплівкоутворення; на наступному етапі досліджень вивчали здатність компонентів, що входять до складу тест-зразка, руйнувати біоплівки мікроорганізмів.

В ході досліджень було встановлено, що процес біоплівкоутворення має пряму кореляційну залежність від хімічних складових тест-зразка.

Так, встановлено, що під дією аскорбінової кислоти (С), лізоциму (Л) та комплексу аскорбінової кислоти та лізоциму (С+Л) реєструється пригнічення біоплівкоутворення мікроорганізмів. Крім того, стосовно визначення здатності складових компонентів руйнувати біоплівки, доведено, що відносно добових біоплівок *L. plantaris* найбільш виражену здатність до руйнування виявила аскорбінова кислота, яка перевищувала контрольні результати у 8,25 рази. Стосовно добових біоплівок інших мікроорганізмів встановлено, що досліджувані речовини, як самостійно, так й у поєднанні, не виявляють статистично достовірної різниці, у порівнянні з контролем.

Висновки. Встановлено, що процес біоплівкоутворення представників бактерій (*L. plantaris, S. mutans, S.aureus, S.epidermitidis*) та грибів роду *Candida* пригнічується в результаті впливу лізоциму та аскорбінової кислоти як самостійних речовин, так й у поєднанні. Однак, доведено, що зазначені компоненти не виявили достовірної здатності до руйнування добових біоплівок мікроорганізмів.

Таким чином, на підставі проведеного дослідження можна запропонувати застосування аскорбінової кислоти та лізоциму у складі лікувальної жувальної гумки з метою попередження локалізованих гнійно-запальних процесів ротової порожнини.

ИСПОЛЬЗОВАНИЕ ЭЛЕКТРОННЫХ ОБРАЗОВАТЕЛЬНЫХ РЕСУРСОВ ПРИ ПРЕПОДАВАНИИ МИКРОБИОЛОГИИ, ВИРУСОЛОГИИ И ИММУНОЛОГИИ

Чемезов С.А.,[1,2] Литусов Н.В.,[2] Самадов Б.Ш.[1]

Бухарский медицинский институт, Бухара, Узбекистан[1], Уральский государственный медицинский университет, Екатеринбург, Россия[2]

diverdoc78@gmail.com; litusov@yandex.ru; baxodir_samadov@mail.ru,

Современные методики преподавания микробиологии предусматривают использование студентами и преподавателями медицинских университетов электронных ресурсов при подготовке к занятиям, что требует владения информационными технологиями. При разработке электронных учебных пособий программное обеспечение ряда ресурсов дает возможность создания мультимедийных продуктов, с аудио-и видеофрагментами и цветной графикой. Возможность просмотра учебного контента по микробиологии с цветными изображениями важно для качественного обучения, получения нужных компетенций, так как культуральная диагностика и микроскопия нативных образцов предусматривает именно наличие/отсутствие цветовых реакция например окраска по Граму, Циль-Нильсену. В Уральском государственном медицинском университете (УГМУ) есть удачный опыт разработки электронных образовательных ресурсов (ЭОР) с помощью программного обеспечения (ПО)

сайта дистанционного обучения (ДО) http://do.teleclinica.ru. Сотрудником кафедры микробиологии, вирусологии и иммунологии УГМУ профессором Литусовым Н.В. был создано 49 ЭОР (Бруцеллез, История микробиологии, Средства специфической профилактики бактериальных и вирусных инфекций, Сыпной тиф, Туляремия, Чума и т.д.). ПО сайта ДО имело ряд удобных для автора-разработчика опций, недоступных в ПО многих электронных библиотек, платформах ДО, например автору доступен помимо типовой загрузки файлов в формате PDF ввод текста через буфер из файлов, созданных в редакторе word, и доступен режим прямого редактирования текстовых материалов прямо на сайте, в режиме online. Данная возможность существенно облегчает коррекцию текста, оперативное обновление материалов автором, значительно ускоряет создание ЭОР. ПО сайта ДО позволяло создавать рубрикатор древовидного типа, с любым количеством вложений в папку главы/темы и возможностью перехода студентами в нужную главу через левое меню, без поиска нужной информации расположенной по типу «киноленты». На сайте ДО была предусмотрена выгрузка ЭОР на внешний носитель в формате chm, с возможностью работы ofline с сохранением основного функционала, вплоть до работы тестов разного типа в обучающем и экзаменационном режиме, что позволяло студентам не только изучать нужный раздел микробиологии, но и осуществлять самоконтроль знаний. ЭОР, размещенные на портале ДО УГМУ были доступны студентам всех 6 факультетов после авторизации. Защита интеллектуальной собственности на ЭОР помимо ранжированного доступа, авторизации студентов по логину и паролю осуществлялась в виде регистрации в Объединенном фонде электронных ресурсов «Наука и образование» (ОФЭРНИО). Автором электронных пособий получены регистрационные удостоверения от ОФЭРНИО на все свои разработки, защищающие авторские права на ЭОР аналогично патентованию и данные удостоверения учитываются Всероссийской аттестационной комиссией (ВАК) в качестве публикации при защите диссертации.

Очередным этапом использования 13 ЭОР (Столбняк, Чума и т.д.) в процессе преподавания микробиологии, вирусологии стала организация сетевого доступа к ним для студентов из российских вузов партнеров, в том числе было подписано соглашение с Красноярским медицинским университетом им. В.Ф. Войно-Ясенецкого о совместном использовании электронных ресурсов на сайте ДО, что реализовывалось на протяжении 6 лет (2011-2016). На следующем этапе развития использования ЭОР в медицинских вузах стало международное сотрудничество, в частности организация доступа на сайт ДО УГМУ студентов Бухарского медицинского института им. Абу Али ибн Сино Республики Узбекистан. Хорошим подспорьем при самостоятельной работе студентов могут стать онлайн курсы с видео-лекциями, в качестве прообраза можно привести курс «История и технология выживания» разработанных в НИУ Томский государственный университет и размещенном на образовательной платформе «Лекториум», в котором

рассматриваются исторические аспекты и последствия для человечества эпидемий ряда особо опасных инфекций: чума, холера, оспа, лепра.

Выводы. Владение информационными технологиями позволяет преподавателям создавать ЭОР по микробиологии, вирусологии, иммунологии с размещением на сайте ДО вуза, в ЭБС, на внешних носителях, платформах электронного обучения.

Для быстрого создания мультимедийных ЭОР требуется качественное программное обеспечение и помощь преподавателю в разработке сотрудников отдела ДО, специалистов по компьютерной графике, web-дизайну. Наличие ЭОР по микробиологии с размещением на сайте ДО позволяет осуществлять вузам межуниверситетское сотрудничество, которое может быть и межгосударственным. При международном сотрудничестве, совместном использовании ЭОР по микробиологии важен не только дизайн ЭОР, но и наличие версии на английском языке, или на официальном государственном языке страны, где находится вуз-партнер.

РОЛЬ ІНФЕКЦІЙНОГО ФАКТОРУ У РОЗВИТКУ РЕВМАТОЇДНОГО АРТРИТУ

Чікіткіна В. В., Кононенко Н. М.

Національний фармацевтичний університет, м. Харків, Україна

valentina.chikitkina@gmail.com

Ревматоїдний артрит (РА) - системне запальне автоімунне захворювання, яке виникає в результаті аномальної імунної відповіді та характеризується хронічним ерозивним поліартритом. Розповсюдженість РА у всьому світі коливається від 0,5 до 1%, захворювання призводить до зниження якості життя, ранньої інвалідизації, підвищеної смертності. Дотепер етіологія РА повністю невідома, проте вважається, що важливу роль у схильності організму до РА відіграють складні взаємодії між сприятливим генетичним фоном та широким спектром факторів навколишнього середовища (наприклад, тютюновий дим, вплив пилу), серед яких безперечними лідерами є бактерії та віруси. Відомо, що хворі на РА мають вищу сприйнятливість до бактеріальних та вірусних інфекцій та дисбаланс імунної системи, ніж популяція у цілому, у пацієнтів виявляють вроджену нездатність контролювати запальні реакції.

На цей час існує значний перелік мікроорганізмів, які можуть провокувати РА, хоча достовірний зв'язок між конкретним інфекційним агентом та захворюванням не встановлений. Різними авторами в суглобах і сироватці хворих на РА виявлялися декілька мікроорганізмів або їх компонентів, таких як хламідія, мікоплазма, гелікобактер, *золотистий стафілокок, піогенний стрептококк,*

*кишк*ова та гемофільна паличка, мікобактерії туберкульозу, герпесвіруси, вірус імунодефіциту людини, вірус Епштейна-Барр, гриби та інш.

Проте, досі не доведена наявність певного спектру патогенних мікроорганізмів, які ініціюють РА, оскільки він може бути полімікробним або містити кумулятивний ефект декількох бактеріальних/вірусних факторів. Деякі автори вважають, що патогенна дія інфекційного фактора може реалізуватися лише за певних сприятливих умов, наприклад, при поєднанні з психологічним стресом та/або хронічною мікротравмою тканин суглобів. Клінічні прояви, викликані інфекційними збудниками можуть варіювати у процесі розвитку РА: на стадії маніфестації захворювання багато пацієнтів мають виражений певний інфекційний синдром, який зменшується з тривалістю захворювання, в той час як на пізніх стадіях існує ризик розвитку інфекційних ускладнень внаслідок терапії протиревматичними препаратами.

Також у виникненні захворювання можуть відігравати роль генетичні відмінності та особливості імунної системи. Досі вчені не дійшли спільного висновку щодо первинності двох аспектів у розвитку РА: 1) часті та тривалі інфекції порушують толерантність організму до власних антигенів та викликають набутий імунодефіцит; 2) вроджений дефіцит толерантності та контролю запалення, який може мати місце навіть за звичайної частоти та тривалості інфекційних захворювань.

За умови первинності інфекційного фактору патологічні автоімунні реакції можуть запускатися шляхом молекулярної мімікрії, поширення епітопів, активації поліклональних лімфоцитів та вірусної персистенції. Молекулярна мімікрія виникає, коли чужорідні антигени мають достатню структурну схожість із власними антигенами (тобто подібні епітопи). Внаслідок цього імунна відповідь на патогенні мікроорганізми може призвести до перехресної реактивності з власними антигенами, продукції перехресно-реактивних антитіл, які можуть викликати пошкодження тканин господаря. За наявності несприятливих умов імунна відповідь господаря на патогени, а також пряма атака патогену на господаря може призвести до пошкодження власної тканини та вивільнення аутоантигена, внаслідок чого розвивається автоспецифічна імунна відповідь. Так, дослідження Bo M. та співавт. (2018) показали, що молекулярна мімікрія між вірусом Епштейна-Барр, мікобактеріями туберкульозу та пептидами господаря діє як патогенний механізм РА.

Крім того, бактеріальні інфекції можуть призводити до проліферації та диференціювання В- та Т-лімфоцитів без їх антигенної специфічності, що призводить до прямих запальних реакцій проти господаря, викликаючи активацію поліклональних лімфоцитів. Також мікробна інфекція може запускати запальні шляхи, активуючи реактивні клітини лімфоцитів, що призводить до аутоімунних реакцій, які називаються активацією свідка.

На користь переважання вродженого механізму запуску РА свідчить асоціація з генами HLA-DR і варіантами генів, як не відносяться до HLA.

Також підтвердженням є асоціювання з РА алелей DRB1∗01 та ∗04 (загальні епітопи), які при експресії ефективно зв'язують цитрулініновані пептиди і представляють їх рецепторам Т-клітин, що є оптимальним для розвитку імунної відповіді проти цитрулінованих пептидів та для активації продукції прозапальних Th1-цитокінів. У роботі M. I. Arleevskaya (2016), показано, що HLA-DRB1*04 пов'язаний з низькою частотою Т-лімфоцитів, які мають вирішальне значення в контролі інфекції вірус Епштейна-Барр, тоді як навпаки, HLA-DRB1* 07, алель, пов'язаний з низьким ризиком розвитку РА, асоціюється з найвищими частотами Т-лімфоцитів периферичної крові.

Адекватна противірусна відповідь багато в чому залежить від активації сигнального шляху NF-κB, який вважається прототипом прозапального сигнального шляху, що контролює як патогенез РА, так і вірусну інфекцію, завдяки експресії прозапальних генів хемокінів, цитокінів, рецепторів, регуляторів апоптозу, внутрішньоклітинних сигнальних молекул і факторів транскрипції. Стимуляція сигнального шляху NF-κB та інгібування пов'язаного з TNF апоптозу (ослабленого при РА навіть без цієї додаткової дії) потенціюють розвиток РА. Такий шлях може посилюватися у разі цитомегаловірусної інфекції та вірусу Епштейна-Барр, оскільки вірусам потрібні живі, функціональні та активовані «лімфоцити», чого можна досягти, контролюючи один і той же сигнальний шлях NF-κB і, у свою чергу, блокуючи TNF-споріднений апоптоз.

Таким чином, на цей час доведено зв'язок між впливом патогенних мікроорганізмів та розвитком РА, що дозволяє розробляти ефективні терапевтичні стратегії ранньої терапії захворювання.

ВПЛИВ ЙОДОФОРМУ НА АДГЕЗИВНІ ВЛАСТИВОСТІ *KOCURIA SPP.*

Чумак Ю.В., Лобань Г.А., Ананьєва М.М., Фаустова М.О.
Полтавський державний медичний університет, м. Полтава, Україна
67parallel@ukr.net

Актуальність. Альвеоліт щелеп, або так звана суха лунка представляє собою найбільш поширене інфекційно-запальне ускладнення після операції видалення зуба під час амбулаторного прийому. Однією з головних причин виникнення інфекційно-запального постекстракційного ускладнення є мікроорганізми.

Бактерії мають фактори патогенності, які допомагають взаємодіяти з клітинами-мішенями організму людини під час патологічного процесу. До таких факторів можна віднести адгезивність мікроорганізмів, яка забезпечує прикріплення та колонізацію бактеріального агента, чим може спричинити розвиток інфекційного процесу. Здатність до адгезії характеризує вірулентність мікроорганізму за наявністю адгезинів, які представлені поверхневими білками, капсульними полісахаридами, тейхоєвими кислотами та іншими.

Мікроорганізми які відносяться до роду *Kocuria spp.* входять до складу мікрофлори порожнини рота. Згідно літературних джерел даний мікроорганізм також був ідентифікований від хворих на менінгіт та ендокардит. Науковці пов'язують участь *Kocuria spp.* в патологічних процесах з високою адгезивною властивістю бактерій даного роду.

Відомо, що антисептичні препарати мають здатність знижувати адгезивні властивості бактерій. Тому залишається актуальним пошук антисептиків, застосування яких допоможе вирішити проблему з лікуванням та профілактикою інфекційно-запальних постекстракційних ускладнень.

Мета. Вивчення дії йодоформу на адгезивні властивості клінічних ізолятів *Kocuria kristinae і Kocuria rosea* виділених з порожнини рота хворих на інфекційно-запальні постекстракційні ускладнення.

Матеріали і методи. Дослідили клінічні ізоляти *Kocuria kristinae і Kocuria rosea,* які були виділені від хворих, що проходили лікування інфекційно-запального постекстракційного ускладнення у лікувально - хірургічному відділенні комунальної установи «Полтавський обласний центр стоматології – стоматологічна клінічна поліклініка». Ідентифікацію виділених культур проводили за допомогою автоматичного бактеріологічного аналізатора Vitec – 2 compact bioMarieux (Франція).

В досліджуванні використовували антисептик Йодоформ (дрібнокристалічний порошок виробництва ПП«Латус» м.Харків). В якості носія йодоформу застосовували 5% йодоформний бинт, приготований самостійно.

Адгезивні властивості клінічних ізолятів під дією йодоформу, визначали за методикою В.І. Бриліса з використанням еритроцитів людини групи крові 1(О) Rh+. Адгезивні властивості досліджуваних ізолятів оцінювали за індексом адгезивності мікроорганізмів (ІАМ), що враховує наступні критерії: при ІАМ ≤ 1.75 - мікроорганізми не проявляють адгезивність, при ІАМ 1,75-2,49 – мікроорганізми відносяться до низькоадгезивних, при ІАМ 2,50-4,0 – мікроорганізми є середньоадгезивними, при ІАМ > 4,0 – мікроорганізми проявляють високі адгезивні властивості.

Результати і висновки. Досліджувані клінічні ізоляти *Kocuria spp* мали високу адгезивну властивість, про що свідчив ІАМ > 4,0. Після дії йодоформу адгезивність ізолятів *Kocuria kristinae і Kocuria rosea* залишалась високою, на що вказував ІАМ > 4,0. Дія антисептика не спричинила гальмування здатності до адгезії, якими володіють досліджувані клінічні ізоляти *Kocuria kristinae і Kocuria rosea.* Наше дослідження показує, що традиційний метод лікування та профілактики інфекційно-запальних постекстракційних ускладнень з використанням тампонади лунки зуба з антисептиком йодоформом, не впливає на фактори вірулентності клінічних ізолятів роду *Kocuria spp.* Враховуючи вищезазначене, актуальним залишається питання, щодо пошуку нових методів лікування та профілактики інфекційно-запальних постекстракційних ускладнень з використанням інших антисептиків, які дадуть можливість знизити вірулентність етіологічних мікробних чинників інфекційно-запального процесу порожнини рота.

ЗМІСТ CONTENT

Наукове видання

МІКРОБІОЛОГІЧНІ ТА ІМУНОЛОГІЧНІ ДОСЛІДЖЕННЯ В СУЧАСНІЙ МЕДИЦИНІ

Матеріали
Науково-практичної міжнародної
дистанційної конференції

26 березня 2021 року
м. Харків

Національний фармацевтичний університет вул. Пушкінська, 53, м. Харків, 61002 Свідоцтво суб'єкта видавничої справи серії ДК № 3420 від 11.03.2009