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Where is our Place in Interspecial Interactions and the Holobiont

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Abstract

Introduction: Throughout our recorded history, humanity has repeatedly encountered pandemics caused by viral and bacterial pathogens with high mortality rates. Is pathogenicity alone the cause of mortality or rather the critical accumulation of processes/interactions in our body lead to the adverse course of diseases? This necessitates the study of interactions between viral and bacterial pathogens and components of the microbiota and the host.

Materials: The concept of the holobiont, in which the host and its taxonomically and ecologically related communities of microorganisms or microbiota are considered as a single whole. Trophic, metabolic and protective functions of the microbiota provides significant benefits to our health.

Every microorganism needs colonization to survive in a given ecosystem. Viral pathogens, facilitating the subsequent colonization of pathogenic bacteria, change the diversity and functions of the human microbiota. Our goal is to study interspecies interactions and clarify when and how we can best intervene. Linking the infectious spectrum, pharmacological and dietary interventions, factors determining susceptibility to infections, vaccinations, platforms for testing potential pathogens and pre- and probiotics can help us better address such challenges.

Conclusion: Knowledge of the interactions between viral and bacterial pathogens and components of the holobiont will help us better understand immune responses and perhaps try to modify them in certain situations. Our place in cross-species interactions is to combine the opportunities that pharmacological, non-pharmacological and dietary interventions provide to modulate immune responses in personalized treatment of patients with infectious diseases and develop more effective measures for control and protection against various pathogens.

Keywords: Holobiont; Pathogens; Probiotics; Prebiotics; Vaccines; Prevention; Interactions

Abbreviations

AIP: Autoinducing Peptide; AMP: Antimicrobial Peptide; AMR: Antimicrobial Resistance; AdV: Adenovirus; CoV: Corona Viruses; DC: Dentritic Cells; DNA: Deoxyribonucleic Acid; DS: Double-Stranded; DSF: Diffusible Signal Factors; GIT: Gastro Intestinal Tract; GTDB: Genome Taxonomy Database; HBV: Hepatitis B Virus; HDV: Hepatitis D Virus; HE: Hemagglutinin Esterase; HMPV: Human Metapneumovirus; HRV: Human Rhinovirus; IAV: Influenza A Virus; IFN: Interferon α/β and γ; IL: Interleukin; iNKT: Invariant Natural Killer T Cells; IPA: Indole-3-Propionic Acid; ISGs: Interferon Stimulated Genes; LAB: Lactic Acid Bacteria; LEV: Live Enterovirus Vaccine; L-SIGN: Lectin Specific Intercellular Adhesion Molecule-3 Capturing Non-Integrin; MC: Mast Cells; MDCK: Madin-Darby Canine Kidney Cells; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; NAAT: Nucleic Acid Amplification Test; OUT: Operational Taxonomic Unit; PCV: Pneumococcal

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Conjugate Vaccine; PIV: Para Influenza Virus; PPSV: Pneumococcal Polysaccharide Vaccine; PspA: Surface Protein Antigen; QS: Quorum Sensing; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species; RSV: Respiratory Syncytial Virus; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; SIDS: Sudden Infant Death Syndrome; SS: Single-Stranded; WGS - Whole Genomic Sequencing

Introduction

Climate and environmental changes have led to increased pressure on the host-pathogen-environment system. In recent decades, we have observed the emergence of diseases caused by highly pathogenic viruses with zoonotic origin that have crossed the interspecies barrier and stabilized in humans. In-depth study of interactions among pathogens, between them and the holobiont, as well as tracking horizontal gene transfer will help us understand the reasons for the different course of the same disease in patients and the possible effects of our interventions. Throughout recorded history, mankind has repeatedly faced pandemics caused by viral pathogens with high mortality rates. For one or another reason, these are RNA viruses [1-7]. Only the second plague pandemic (1346-1350) caused by Yersinia pestis was more deadly, killing 30-50% of the population of Afro-Eurasia [8,9]. Is pathogenicity alone the cause of mortality or rather the critical accumulation of processes/interactions in our body lead to the adverse course of diseases?.

The conducted researches has helped to understand the interactions between the host and its associated microbial communities, as well as their central role in the biology, ecology and evolution of the host. Individual phenotypes should be considered as expressions of the interactions between the host and the associated microbial genomes. The study of symbiosis between species is the basis of the concept of the holobiont. Lynn Margulis formulated it in 1991 and initially it considered a simple biological unit - a host and a single hereditary symbiont. Subsequently, the holobiont was considered as a single entity between the host and its associated taxonomically and ecologically diverse communities of microorganisms or microbiota. Within this unit occur, interactions ranging from synergistic to antagonistic, including mutualism. In 2007, Ilana Zilber-Rosenberg and Eugene Rosenberg introduced the term hologenome, which represents the sum of the host genome and the genomes of its associated microbial communities, or the collective genome of the holobiont. The human genome contains about 20,000 genes, but our hologenome contains>33 million genes [10-17]. Understanding of the causes of rapidly increasing antibiotic resistance has also expanded [18,19]. Our area of interest is the upper and lower respiratory tract, but in light of the holobiont concept, it is not correct to consider the interactions in the different ecological niches of the human body separately.

The human microbiota consists of archaea, viruses, bacteria and fungi. It performs trophic, metabolic and protective functions. The metabolic activity of the intestinal microbiota is expressed in the regulation of positive or negative metabolic homeostasis and the formation of an anaerobic environment that suppresses the virulence of pathogens. Its metabolites are products of the metabolic pathways of tryptophan(Trp), histidine(His) and phenylalanine(Phe). The protective one is expressed in the production of bacteriocins that inhibit the growth or survival of the pathogen, and the trophic one in the mobilization of bacteriophages that attack specific bacterial strains, minimizing their impact on the commensal microbiota. Colonization of the host occurs in waves during ontogenesis and through various mechanisms enters into constant contact with it.

So far, no evidence has been found that archaea can independently cause diseases in humans. The virobiota/virome is a poorly understood component of the microbiota. Its main components are bacteriophages, eukaryotic viruses and human-specific viruses [20,21]. Bacteriophages were discovered and described by Twort in 1915. They are single-stranded(ss) and double-stranded(ds) DNA and RNA, but dsDNA phages are predominant. Benign viral loads have been observed in healthy controls, similar to commensal bacteria. Most enteric viruses(mainly phages) are strictly dependent on their hosts and are difficult to culture [22].

The rapid colonization of the human body begins immediately after birth due to contact with the mother‘s skin, milk and vaginal mucosa. The intestines of infants are free of microorganisms at birth, but within a few hours after birth, rapid colonization begins and becomes the habitat of a growing microbial diversity. During the first 4 days, a poor bacteriome and a rich phageome are observed, while at 2 years of age the bacteriome is rich and diverse and the phageome is poorer [23]. Initially, gut-colonizing phages are induced phages originating from bacteria that are the first colonizers of the infant‘s gut. For example, bifidobacteria transmitted during breastfeeding contain prophages known as bifidophages [24]. Viruses and bacteria colonize the human body synchronously, which is due to their close interactions. The composition of the gut virome is very dynamic. Bacteriophages are an important component of it. Phages target bacterial “prey” by recognizing specific receptors on its membrane and through lysis they can penetrate layer by layer into the bacterial biofilm and destroy it through their depolymerases, exopolymer degrading and endolytic enzymes [25].

Phages are temperate and lytic or non-temperate. The former are predominant and are characterized by a

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lysogenic life cycle as a result of which they integrate into the chromosomes of bacterial hosts as extrachromosomal episomes or prophages. Phage predation and their lysogenic transformation in bacterial cells play a key role in horizontal gene transfer and the regulation of bacterial abundance. Phage insertion can both alter bacterial genes and suppress their functions, as well as encode genes that enhance the ability of host bacteria to expand their ecological niche. The transduction of genes responsible for toxin production (Shiga toxin) and antibiotic resistance by phages has been well studied and is an example of this [26,27]. Genes encoding of prophages can cause lysis of related strains and reduce competition(kill relatives) [28]. Prophages also have the ability to transmit themselves to the host's offspring through vertical transmission. But they are not the only ones capable of doing this. Retroviruses infected our ancestors about 30 million years ago and their viral DNA fragments stabilized in our DNA. They mutated over time and lost their ability to make viruses. Endogenous retroviruses, considered "junk" or DNA with no biological function, have been found to be involved in gene regulation or "viral switches." In addition to positive regulatory processes (immunity, brain and placental development), their DNA sequences have also been associated with regulatory proteins in cancer cellstypes of cancer) [21-29].

Adverse conditions can induce prophages to pass a lytic replication cycle. Lytic phages are parasitic in nature and can perform horizontal gene transfer within the host population. Interactions between phages and bacteria can be divided into negative/predatory association(lytic phages) and positive - inactive/dormant lysogenic phage providing an evolutionary advantage in replication and survival of the host. Predatory association is highly specific, selectively infecting only a specific host while ignoring other bacteria. Phage induction is regulated by a signaling pathway - quorum sensing(QS). Prophage induction can create a huge burden on the bacterial host and the potential to change the composition of the gut microbiota [25]. Another type of association is mutualism - virions carry lysogens(idiots) that have no role in the life cycle of the virus, but provide benefits to the bacterial host. Most intestinal bacteria are known to be colonized by more than one temperate phage. On the one hand, these phages help the bacterial host to adapt by expressing newly acquired phenotypes - resistance to other phage superinfections, resistance to antibiotics, pathogenicity and tolerance to stresses, while on the other hand, lysogenic phages by integrating their genome with that of the bacterial chromosome, avoid recognition and elimination by macrophages [24,30].

Factors responsible for the diversity and composition of the phageome include diet, age, disease, therapies and environment [31,32]. Diet is the most significant differentiating factor for the gut virome. Identical diets in different individuals have the potential to produce microbiota with more similar, but not identical phageome composition [24].

Early in life the abundance of temperate phages is high because there is a shortage of potential bacteriophage hosts. With the growth of the infant along with the expansion of bacterial species in the different niches of the gut, there is increased colonization of virulent phages from the crAss-like and Microviridae families, which stabilize in early childhood. In adults, the virome is abundant, resistant and consists mainly of the aforementioned families. These families are considered specific to human hosts, with only some being shared between individuals. 50% of the phageome is unique to each individual [33]. Phages interact with host cells, inducing inflammatory and antiviral immune responses. This occurs through activation of virus-recognition receptors, secretion of proinflammatory cytokines and activation of adaptive immune responses without the involvement of host bacteria. They also participate in the regulation of anti-inflammatory mechanisms of the immune system on the one hand by eliminating bacterial pathogens and on the other by directly interacting with proinflammatory cytokines and by reducing the overproduction of reactive oxygen species(ROS). Phages can also directly suppress bacterial growth by binding to intestinal mucosal cells [34-38]. Phagospecific secretory IgA is a key regulatory factor limiting phage activity [39]. Immune regulation against viruses is primarily modulated by the intestinal microbiota.

The bacterial component of the human microbiota also evolves in parallel with its human host. Its composition and abundance can be regulated by phages. The upper respiratory tract microbiota of healthy individuals contains several genera. During the first year of life, the genera Staphylococcus, Streptococcus, Corynebacterium, Moraxella, Haemophilus and Alloicoccus/Dolosigranulum predominate. After the third Staphylococcus, Streptococcus, Corynebacterium, Prevotella, Veillonella, Propionibacterium and Fusobacterium are most commonly found. Corynebacterium, Dolosigranulum, Streptococcus epidermidis, and Staphylococcus lugdunensis are primarily responsible for reducing the incidence of disease caused by S. pneumoniae, H. influenzae, S. aureus and M. catharralis. The gut microbiota is predominantly anaerobic and includes the species Bacteroides and Ruminococcus [40-46]. The bacterial component consists of transient and permanent members. The transient are the opportunistic pathogens responsible for infectious diseases and most of the commercially available probiotics. The permanent members are most of the non-pathogenic bacteria - colonizers or commensals, living in symbiosis with the macroorganism. They colonize the host in waves during ontogenesis and through various adaptation mechanisms

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enter into a permanent relationship with it. While the primary colonization can last for months, subsequent waves are shortened and in adults can reach 2-4 weeks. Commensal microorganisms protect themselves from innate immunity by localizing in the superficial layer of the mucus of the mucosa, while the acquired immunity kills pathogens that have invaded the deep layer through lysis [25]. Pneumococcus, although considered the main cause of pneumonia, is a member of the healthy nasopharynx in eubiosis, as Staphylococcus aureus and other microorganisms. Microbes constantly move along the commensal-pathogen continuum. From the permanent members, those bacteria that have an immunomodulatory effect are called autobionts and those that can cause diseases are called pathobionts. They are also permanent members, but in limited populations. In eubiosis, autobionts and pathobionts are in perfect balance with the host. Autobionts are an evolutionarily developed part, actively participating in the immune regulation of the host [47]. Their regulation of the host immune responses is achieved through their influence on the maturation and functioning of different types of immune cells – IgA secreting plasmatic cells, Th17, Treg lymphocytes, invariant natural killer T cells(iNKT), NK cells, macrophages, dendritic cells(DC) and etc [48]. The immune effects controlled by the microbiota also play an autoregulatory role on the microbiota itself. IgA secreting plasmatic cells induced by commensal bacteria participate in the control of their number and composition, a mechanism also observed in limiting the activity of phages [49,50]. The microbiota controls the immune status in an effector or regulatory direction [51]. Its barrier function in the nose and nasopharynx is expressed in the competition between commensal and potentially pathogenic bacterial species through direct competition and indirect immune modulation. When pathogens attempt to colonize mucosal surfaces, they elicit a strong immune response aimed at clearing them. In eubiosis, commensals suppress pathogen colonization. The used mechanisms are:

- induction of IFN-λ secretion from the nasal mucosa.
- secretion of antimicrobial peptides, bacteriocins and proinflammatory cytokines.
- influence on the adaptive immune response and generation of immune memory. Streptococcus mitis has been found to induce cross-reactive immunity(antibodies and IL-17) against S. pneumoniae in mice. The same has been observed with Neisseria lactamica and N. meningitidis.
- production of antibiotics. Staphylococcus lugdunensis produces lugdunin, an antibiotic with bactericidal activity against S. aureus and S. pneumoniae. Lactobacillus reuteri produces reuterin, inhibiting the growth and development of number of bacteria and fungi. Streptococcus salivarius produces salivaricin A and B.
- inhibition of binding to mucous membranes. Streptococcus salivarius limits the binding of S. pneumoniae. The genus Corynebacterium competes directly with pathogens of the GIT.
- ability of commensals of the genus Streptococcus to destroy the formed biofilms(only hypothesis) [52-62].

The intestine autobionts in healthy individuals produce indole-3-propionic acid(IPA), which is responsible for the regulation of positive and negative metabolic homeostasis. IPA is a tryptophan product produced mainly by Clostridium sporogenes. It is associated with the maturation of lung cells and the prevention of allergic airway inflammation, and the development of asthma. Also, patients with low levels of IPA in the blood have insulin resistance, obesity, a tendency to low-grade inflammation and symptoms of metabolic syndrome, in contrast to those with high IPA. It has been found to be negatively associated with polymorbidity. Patients carrying operational taxonomic units(OTUs) including Ruminococcus, Alistipes, Blautia, Butyrivibrio and Akkermansia are in the high IPA group, while in the low IPA group we observe an abundance of Escherichia-Shigella, Megasphera and the genus Desulfovibrio [63].

The use of the probiotic Clostridium butyricum CBM588 to model the immune homeostasis of the intestinal tract, improve epithelial barrier function and influence inflammation is promising. We need to study better the interactions between intestinal commensals responsible for IPA production, the factors activating or repressing the genes for its production, and the possibility of transduction of genes similar to those responsible for toxin production or antibiotic resistance by phages. The use of antibiotics in the first year of life may have the unintended effect of reducing the beneficial bacteria of the gut microbiota and trigger a cascade of potentially harmful effects. It is associated with a high risk of developing various health problems, including those mentioned above. Changes in taxonomic composition have been directly linked to various inflammatory diseases such as inflammatory bowel disease(IBD) and asthma. Increased numbers of histamine-secreting bacteria have also been observed in the gut of patients with asthma [64-66]. In addition to antibiotics and diuretics, opiates, beta blockers, and other medications can provoke histamine release in one way or another.

The induction of the SOS response or DNA repair system is associated with the regulatory response of bacterial cells against the loss of phage diversity, pathogenic bacteria in the gut, the intestinal microbiota and the induction of prophages [67-69]. Lactobacillus reuteri is thought to induce the SOS response through the activation of specific metabolic pathways used in the GIT [30]. Thus, by using it during the first 3 years of life, we will be able to reduce the potential

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risk of developing the above-mentioned health problems in at least some of our patients after antibiotic therapy by restoring the genus specificity of the microbiota.

Antoni van Leeuwenhoek(1632-1723) was the first to investigate the possibility of bacterial coexistence and developed the concept of microorganisms associating with surfaces in the form of dental plaque. Bacteria exist in the human body as individual planktonic forms and in organized ecosystems (biofilms). Up to 99% of bacteria in the human body exist in the form of biofilms. The latter form a complex system after individual planktonic forms merge and attach to different surfaces through glycoconjugated bonds and form an exopolysaccharide matrix. After maturation, the biofilm releases cells that are directed to colonize another surface [70]. It usually contains several strains of bacteria. The oxygen tension gradient determines the increased metabolic activity at the surface of the matrix and the reduced/ quiescentce in the deeper layers. The spatial arrangement of the different strains in the biofilm determines the positive and negative(competition) interactions. Its cells are in constant contact with each other by means of chemical signaling quorum sensing(QS), similar to the regulation of the rate of phage induction. The molecules involved in QS can modulate the spatiality between the interacting microorganisms. Two types of signaling molecules determine the expression of specific genes responsible for the synthesis of biofilm components as well as bacteriocins, spousal transfer of plasmids and the stress response. These molecules or autoinducers have a function similar to signaling hormones and when accumulated, trigger a cascade of events when a threshold concentration or quorum is reached. Communication between bacterial cells involves the production of self-secreted extracellular signaling molecules that accumulate in the local environment and correlate with cell density. They are: acyl homoserine lactones(AHLs), autoinducer-2, oligopeptides, diffusible signaling factors(DSFs) and autoinducing peptides(AIPs). After reaching a threshold concentration, the molecules signal back to the cell, coordinating the expression of virulence factors, sporulation and biofilm formation. In gram-positive(+) bacteria, an autoinducing peptide(AIP) or peptide pheromone has been found that provides a species-specific communication signal [71-73]. Biofilms are characterized by their high degree of resistance to antibiotics and host immune mechanisms - low susceptibility to opsonization and phagocytosis [74].

The upper and lower respiratory tracts possess distinct ecological niches that are a combination of taxonomically rich, such as the nose, nasopharynx, and oropharynx, and taxonomically poor, such as the sinuses and lower respiratory tract, as well as the middle ear. The microbiota is composed of diverse species of aerobic and anaerobic microorganisms, with the latter being predominant. When the microbial community is imbalanced, pathogens spread from the nose and nasopharynx to the more microbially poor niches and cause disease. Loss of oral-nasopharyngeal distinction typically precedes respiratory tract infections [75-79].

The viral load in healthy controls suggests a benign carriage, similar to commensal bacteria [80]. Both in nature and in real life, the attacker always has the initiative and advantage. Metagenomic analysis, in contrast to PCR-based analysis, showed the presence of many more viral sequences in children with unexplained fever. This is due to the fact that the virome is a common cause of upper respiratory tract diseases. Respiratory viruses that most often attack the human respiratory tract are: ssRNA - influenza virus, parainfluenza virus(PIV), RSV, measles virus, rhinovirus(HRV), coronavirus(CoV) and dsDNA - adenovirus(AdV) [81].

Determining the causes and mechanisms leading to the replacement of a "healthy carrier" by viral pathogens can help us understand the interactions between the virobiota and viral pathogens, the establishment of individual infectious risk and the dynamics of the course of the disease. Viral interactions or interferences depend on:

- the ability of the interfering virus to induce a rapid IFN response expressed in the expression of IFN-stimulating genes(ISGs) type I(IFN-α/β) and type III(IFN-λ) and providing temporary non-specific immunity to the host. The release of effectors that directly inhibit viral replication - chemokines and cytokines, triggering viral defense [82,83].
- the degree of sensitivity of the second virus to immune mediators.
- the extent to which different viruses counteract the induction and antiviral effects of IFN and
- the pattern of virus-induced innate immune responses in the respiratory tract [84].

Depending on whether infection of the first virus enhances or attenuates infection and replication of the second virus, we observe a positive(synergistic) or negative(antagonistic) interaction. The viruses can infect the respiratory tract simultaneously or sequentially.

Positive interactions between viruses allow a reduction in metabolic burden by creating a division of labor. Positive interactions have been observed with:

a. SARS-CoV-2, RSV and pandemic influenza A(pH1N1) [85]
b. PIV1 and PIV2
c. RSV and HMPV.

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In HBV and HDV, the surface antigen of the former serves as a receptor for the second (HbSg of HBV for HDV). These are not respiratory viruses, but they clearly illustrate how our defenses can be circumvented. Coinfection increases the severity of the disease by excessive production of IFN and proinflammatory cytokines or by reduced secretion of non-inflammatory mediators such as IL10 [86].

In negative interviral interactions, we observe blocking and/or reduction of cell surface receptors and competition for cellular resources. They are homologous and heterologous depending on whether the viruses belong to the same or different families.

In homologous interaction, cross-reactive immunity against the first virus prevents infection by the second virus. A hierarchical pattern has been observed for IAVs(pH1N1, H1N1 and H3N2) and time pattern for RSV, HMPV and PIV. These are an expression of their taxonomic affiliation to the same family.

In heterologous interaction the provoking of a non-specific immune response by the first virus reduces or prevents infection and replication of the second virus:

- coinfection with IAVs(H1N1 or H3N2) in MDCK cells inhibits RSV replication by removing sialic acid from the cell surface and competing for viral protein synthesis [87-89].
- oral administration of live enterovirus vaccines(LEV) in children reduces the detection of some unrelated respiratory viruses - influenza, PIV, RSV, HRV and AdV [90,91].
- previous infection with IAVs(H1N1 or H3N2) prevents subsequent infection with retroviruses.
- IBV prevents subsequent infection with RSV [92].
- IBV reduces the rate of AdV infection [93].
- RSV reduces the rate of HRV infection.
- RSV reduces the probability of detection of HMPV.
- HRV limits the replication of SARS-CoV-2.
- HRV reduces the likelihood of IAV detection.
- Influenza and SARS-CoV-2 viruses employ a broader range of mechanisms to evade IFN induction and signaling compared to RSV, HMPV and HRV.

The bacterial pathogens that most commonly attack the human respiratory tract are: Gram(+) - Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes and Mycobacterium tuberculosis, Gram(-) - Haemophilus influenzae, Neisseria meningitidis, Bordetella pertussis and in immunocompromised patients Pseudomonas aeruginosa [94].

Viral-bacterial interactions play a critical role in the pathogenesis of bacterial infections. Knowledge of the interactions between viral pathogens with pathobionts and exogenous pathogens will allow us to predict the severity of respiratory diseases. We observe three types of interactions:

- The virus potentiates bacterial colonization,
- Proteases of respiratory tract bacteria cause structural changes leading to increased pathogenicity and tissue tropism of the virus, and
- Bacteria enhance viral infection by activating host proteases [95-99].

Together, viruses and bacteria cause diseases that are more severe than that caused by either pathogen alone. This is why the majority of deaths during influenza epidemics are the result of secondary bacterial infections [100-104]. These positive interactions are extremely important because:

a. facilitation of bacterial colonization of the airway surface by damage of the mucociliary system from a previous viral attack. In RSV infection, we observe loss of cilia in human bronchial cells in vitro and influenza virus damage to the ciliated epithelium and bronchial epithelial lining [105-107].

b. Virus-induced alteration of host cell membrane potential leads to increased bacterial adhesion. Viral glycoproteins expressed on host cell membranes serve as bacterial receptors.

- changes in the glycoconjugate structure of murine nasopharyngeal mucosa caused by influenza infection are associated with changes in lectin binding patterns [108-109]. Hemagglutinin esterase(HE) of influenza virus on infected MDCK cells serves as a receptor for group B streptococci. As a possible mechanism for staphylococci to adhere to virus-infected cells in vivo, it has been suggested that they may be coated by a viral antibody that serves as a receptor for staphylococcal protein A. Staphylococci attack only those parts that are damaged by the virus.

- in turn, immunoglobulin superantigens such as protein A of *S. aureus* can bind to immunoglobulins secreted by mast cells(MCs). Activation by this mechanism leads to degranulation and release of histamine and leukotrienes. Examples of activation of MS by bacterial superantigens include enterotoxins A and B and superantigen-like proteins (exotoxins) from *S. Aureus* [110-113]. Damage to the respiratory epithelium by other viruses is likely to follow a similar pattern [114,115].

- the glycoproteins F and G of RSV promote increased attachment of Neisseria meningitidis to infected cells [116].

c. viral infection suppresses host defense mechanisms against bacterial attack - nonspecific humoral factors, nonspecific phagocytosis by neutrophils and macrophages early in the infection and later specific antibody-mediated immune responses. Influenza virus-induced polymorphonuclear dysfunction is a major cause of

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secondary pneumococcal disease. Its action on human neutrophils in vitro causes reduced chemotaxis, phagocytic activity and reduced bactericidal potency of neutrophils and macrophages against staphylococci [117], and a reduction in their bactericidal potency due to impaired lysozyme production by both types of phagocytes [118-120]. Influenza virus is the most studied example of positive cooperation between a virus and bacteria. It primarily causes upper respiratory tract infections, but when the lungs are involved it can be fatal due to pulmonary edema and hemorrhage. RSV suppresses TNFα production and bactericid activity against H. influenzae and S. Pneumoniae [121].

When viral infections cause a weakening or damage to the immune system, almost any infection can become opportunistic. Depending on the causative agent, they can be: viral, bacterial, fungal or parasitic.

Viral opportunistic infections include: a. Cytomegalovirus(CMV) from the respiratory virus family, b. Human polyomavirus or John Cunningham virus causing multifocal leukoencephalopathy and Human herpesvirus 8 or Kaposi sarcoma.

Opportunistic bacterial infections include: a. *Clostridium difficile* causing gastrointestinal infection, *Legionella pneumophila* - respiratory, *Mycobacterium avium* complex - a typical coinfection caused by two bacteria-*Mycobacterium avium* and M. *intracellulare*-respiratory, *Mycobacterium tuberculosis* - respiratory, *Pseudomonas aeruginosa* - respiratory, Salmonella - gastrointestinal, *Staphylococcus aureus* including methicillin-resistant strains, *Streptococcus pneumoniae* and *Streptococcus pyogenes* - respiratory.

Fungal infections include: Aspergillus - respiratory, *Candida albicans* - most often oral and gastrointestinal, *Coccidioides immitis* - coccidioidomycosis or Valley fever, *Cryptococcosis neoformans* - cryptococcosis causing both respiratory and nervous system infections including meningitis, Histoplasma capsulatum-histoplasmosis - respiratory, Microsporidia - microsporidiosis mainly in immunocompromised patients, *Pneumocystis jirovecii* or *Pneumocystis carinii* - causes pneumocystis pneumonia.

Opportunistic parasitic infections include: *Cryptosporidium toxoplasma gondii*.

d. Mast cell activation. Mast cells(MC) are responsible for the secretion up to 200 different mediators and the protection of the host from pathogens. They are found in "control" zones interacting with the environment such as the skin, mucous membranes, lungs and intestines. They are components of innate immunity. Located mainly in the subepithelial layer adjacent to blood vessels, they are also in contact with other control cells - dendritic cells. The connection between MC and blood vessels help to quickly attract effector cells from outside the bloodstream. This facilitates the production of cytokines – TNF and IL-1β, activating the endothelium and lipid mediators facilitating vasodilation and the production of chemokines. MC are a major local source of IFN types I and III. Their interactions with viruses and their products are complex and can lead to both harmful and positive effects. MS in infection can stimulate effective immunity in some cases and at the same time have the potential to cause tissue damage and endothelial barrier dysfunction in secondary infection when their numbers are increased. Their activation causes symptoms in the cardiovascular, digestive, nervous, respiratory systems, skin and mucous membranes as well as hormonal imbalance.

When MC are infected with PIV, histamine and leukotrienes are released [122]. In rat models, there is evidence of a higher number of activated MC in the airways, Th2 dominance and more severe airway inflammation [123,124].

In bovine models, RSV infection-associated degranulation of MC in vivo has been demonstrated. It is their activation with subsequent degranulation and release of lipid mediator that is the cause of bronchospasm in infants with RSV infection. Depending on the presence or absence of virus-specific IgE, MC activation causes complement activation or not with degranulation and release of lipid factor or limited degranulation and generation of leukotrienes respectively. RSV demonstrates limited transcription in human MC. Upon contact, the latter induce significant production of chemokines and type I IFN [125-127].

In human MC lines, there is limited evidence for productive replication of IAV and production of cytokines, chemokines and type I IFN [128].

HRV infection is the best-studied infection associated with asthma exacerbations. MC lines release mediators, generate leukotrienes, and induce IFN. In asthmatics, insufficient production of IFNβ is observed. HRV provokes apoptosis of human MC lines.

In HRV infection, MCs themselves are productively infected but retain their ability to activate host defenses. In contrast to influenza and RSV, MCs are resistant to productive infection but trigger a protective response that includes the production of cytokines, chemokines and the recruitment of antiviral effector cells. Human MCs produce significant amounts of type I IFN, contributing to a local antiviral response and increased resistance to infection. However, in cases of severe infection and increased MC numbers, these immune responses can lead to potentially damaging inflammation [129-131].

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e. Seasonal association of viral and bacterial infections - influenza, pneumococcal infection and meningococcal disease during the winter months [132-134]. Similar interactions with S. pneumoniae have been found for RSV and PIV [135,136]. There is no evidence of a seasonal association with bacteria for the seasonal coronaviruses(HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) [137].

e. Proteases of respiratory tract bacteria can induce cleavage of influenza virus HA and increase the pathogenicity of the virus in vivo. This was first established for the protease of S. aureus and then for those of Streptomyces griseus and Aerococcus viridans. Cleavage of HA from S. aureus and A. viridans increases in vitro virus replication and pathogenicity in mice [108,109,138-141].

Some of the more well-known positive virus-bacterial interactions should be mentioned. These are:

- Adenovirus and *Moraxella catharralis*
- Adenovirus and *Bordetella pertussis*
- Measles virus and *Streptococcus pneumoniae*
- RSV and *Haemophilus influenzae*
- RSV and *Streptococcus pneumoniae*
- RSV and *Bordetella pertussis*
- RSV and Staphylococcus aureus
- PIV and *Streptococcus pneumoniae*
- Rhinovirus A and *Streptococcus pneumoniae*
- Rhinovirus A and Haemophilus spp
- Rhinovirus C and *Streptococcus pneumoniae*
- Rhinovirus C and *Moraxella catharralis*
- Influenza A virus and *Streptococcus pneumoniae*
- Influenza A virus and *Staphylococcus aureus*
- Influenza A virus and *Neisseria meningitidis*
- Influenza A virus and *Haemophilus influenzae* [136,142-146].

In children, cooperation between RSV and bacteria may occur more frequently than between influenza virus and bacteria.

Other positive virus-bacterial interactions observed are:

- Sendai virus enhanced respiratory infections with *Mycoplasma pulmonis* [147]
- Reovirus – Staphylococcal infections [148]
- CMV – *P. aeruginosa* infections[149]

Several respiratory viruses are thought to be associated with sudden infant death syndrome(SIDS). These include RSV, influenza virus, PIV, adenovirus and HRV. Changes in the bacterial population of the nasopharynx, particularly increases of Staphylococcus aureus and Enterobacteriaceae, have also been associated with SIDS [150,151].

Bacterial pathogens also compete with each other for space and energy resources, and so information about their interactions is extremely useful to us. Our enemies' competitors sometimes become our allies. Intraspecies competition occurs when two different groups of S. aureus are coinfected. The first group of *S. aureus*, through QS inhibition, suppresses the other group by secreting auto-induced peptides (AIPs). Nasopharyngeal colonization with S. pneumoniae protects us from S. aureus and reduced S. pneumoniae microbial counts after pharmacological intervention lead to increased S. aureus. Reduced S. pneumoniae colonization also leads to increased *H. influenzae, S. aureus*, *N. meningitidis* and *M. Catarrhalis* [152-155]. Therefore, we need to carefully consider our antibiotic interventions. Another interesting phenomenon is that pneumococcal vaccines (PCV-10/13/21 and PPSV-23) due to limited coverage cause replacement of vaccine serotypes of *S. pneumoniae* with non-vaccine ones in the nose and nasopharynx and increased carriage of non-typable Haemophilus influenzae. Although they reduce disease caused by vaccine serotypes, overall colonization rates have not changed. Here we can benefit from probiotics. The surface protein antigen(PspA) of *Lactobacillus casei* induces antibodies against *S. pneumoniae*. *Streptococcus mitis* influences the adaptive immune response and the generation of immune memory, inducing cross-reactive immunity(antibodies and IL-17) to S. pneumoniae in mice.

The imbalance of the microbiota following acute respiratory infections and antibiotic treatment allows pathogens to spread to neighboring poorer ecological niches and cause disease. Cocolonization and polymicrobial interactions between pneumococci and other respiratory colonizers, non-typeable *H. influenzae*, and *M. catarrhalis* lead to an increased risk of acute otitis media [156-160]. The antibiotic treatment, especially in the first year of life, may have the unintended effect of reducing the beneficial bacteria of the gut microbiota and trigger a cascade of potentially harmful effects. It is associated with a high risk of developing various health problems. Viral infections, by suppressing host defense mechanisms, help to replace the normal microbiota. The disturbed balance between auto-, pathobionts, and exogenous pathogens facilitates both colonization by histamine-secreting bacteria and the replacement of strains with histamine-secreting ones in five of the major genera of the human gut microbiota, which can aggravate the course of the disease. Histamine is a biogenic amine that plays a role in vascular permeability, mucus secretion, and neurotransmitter release. It is endogenous and exogenous. It is produced by decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase. Two families of histidine decarboxylases have been identified: pyridoxal-5-phosphate(PLP)-dependent histidine decarboxylases and pyruvoyl-dependent histidine decarboxylases [161,162]. Decarboxylation occurs in the bacterial cytoplasm, and the histidine/histamine antiporter transports histidine into the cell and then removes histamine from the cell. Histamine-secreting bacteria, by generating histamine and other amines, maintain a neutral cytoplasmic pH, which allows them to

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survive in acidic conditions, but also cause symptoms in the cardiovascular, digestive, nervous and respiratory systems, skin and mucous membranes, as well as hormonal imbalance. They are part of the transient and permanent members of the human microbiota. We are interested in exogenous histamine, which has been studied mainly in food poisoning. Food with high concentrations of histamine causes neurological, gastrointestinal and respiratory disorders [163-172]. The discovery of histamine-secreting bacterial transient members - Morganella morganii(Proteus morganii) gram(-) bacterium, Hafnia alvei-gram(-) bacterium - commensal and probiotic strain causing diseases in immunocompromised patients, gram(+) representatives of the genus Clostridium, representatives of the genus Yersiniaceae mainly *Yersinia enterocolitica* - gram(-) bacterium and *Pseudomonas aeruginosa*-gram(-) bacterium in immunocompromised patients is important for us. Antibiotics affect microbial diversity and this is particularly pronounced in anaerobic bacterial species of the gut microbiota. Bacteria important for our health that are damaged by their use include: Clostridia, Bacteroides, Lactobacilli and Bifidobacteria [173]. Increased presence of the genus Proteobacteria, species of which contain PLP-dependent histidine decarboxylase, is considered an indicator of intestinal dysbiosis and a cause of inflammatory diseases [174]. In the Genome Taxonomic Database (GTDB), five genera commonly found in the human gut microbiota have putative histamine-secreting bacteria: Bacteroides, Clostridium, Bifidobacterium, Fusobacterium, and Lactobacillus [22,175,176].

The genomic potential for histamine secretion has been found to be strain-specific within each family. *Streptococcus thermophilus, Staphylococcus warneri, Lactobacillus parabuchneri*, and *Lactobacillus reuteri* have been studied as strain-specific for histamine production [177-180]. This is due to horizontal gene transfer from mobile gene elements such as prophages. In turn, temperate phages help the bacterial host to adapt better due to the expression of newly acquired phenotypes [181-183]. In the above-mentioned five genera, antibiotic therapy is the reason for replacing their composition with histamine-secreting strains [184-187].The presence of histamine-secreting bacteria from the families Enterobacteriaceae and Lactobacillaceae in the small intestine can lead to serious immunological consequences for the organism [188-192].

Strains of histamine-secreting probiotic bacterial transient members Clostridium, Bifidobacterium, and Lactobacillus should also be considered as they may aggravate the course of the disease.

The following factors determine our susceptibility to infection - age, gender, health status, diet, exposure to pathogens, co-infection, immune status and the genome of individuals, but also have the ability to change the abundance and species diversity of the microbiota.

Properly selected and administered antibiotic therapy is an important component of our pharmacological interventions. But it must be based on research that shows that our intervention will bring benefits to the patient, not on assumptions about possible ones. The observed global increase in antibiotic use between 2000 and 2015 is 65%. Sequencing patients early in the illness will help us identify elevated viral loads. Rapid tests help isolate viral agents as the infections they cause are usually difficult to distinguish based on clinical manifestations alone. A respiratory PCR panel is particularly useful. Demonstration of bacterial carriage using laboratory platforms using whole genome sequencing(WGS) is much more sensitive in detecting pathogens after antimicrobial treatment and fluorescence in situ hybridization(FISH) is more sensitive in detecting bacterial pathogens in biofilms [193-196].

Why should antibiotic therapy be well-tailored? Because it is the other most common cause of dysbiosis. Broad-spectrum antibiotics do not distinguish between commensal and pathogenic bacteria and can lead to a 30% reduction in the microbiota and disruption of bacterial and phage communities. Their use has a long-term effect, especially on the intestinal microbiota, and especially in the first years of our life is associated with a high risk of developing health disorders. Separately, pathogens that fill the gap, through the toxins released, provide themselves with an additional advantage necessary for their survival [173,197].

In recent decades, we have been faced with an increasing rate of antimicrobial resistance(AMR), which represents a critical threat to public health. In plasmid-mediated resistance mechanisms, genes can be shared between different microorganisms and spread [198]. The extent of damage to any microbial population depends on the type of antibiotic. It is assumed that antibiotics induce the expression of genes responsible for the induction and transcription of lytic genes in prophages, thereby causing lysis of infected bacterial cells. Quinolones are considered the main inducers of prophages that cause ds DNA break. In the induction of prophages by fluoroquinolones as well as by mitomycin C, the bacterial protein RecA serves as a sensor for the response [199-201]. When the diversity of the healthy phageome is altered, this provokes the excitation of the DNA repair system, regulated by the repressor LexA and the inducer RecA or SOS response. It is a response to the loss of phage diversity, pathogenic bacteria in the gut and the induction of prophages [68]. Antibiotic treatment reduces the amount of commensal bacteria. When bacteria are eliminated, the gap can be filled by other pathogens that cause similar or more severe disease. Replacement with such strains may further worsen the clinical picture of patients.

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Diet has a significant impact on the microbial composition of the microbiota. Long-term dietary patterns are among the factors determining the enterotype of the gut microbiota [202]. The Bacteroides enterotype is associated with reduced microbial activity and genetic diversity, insulin resistance and risk of obesity and nonalcoholic steatosis, and the Prevotella enterotype with a diet dominated by plant carbohydrates [203]. Changes that occur due to the type of diet play a role in the health-disease balance. The microbiota of infants is much richer even than that of children fed with formula milk supplemented with Dolosigranulum and Corynebacterium. The genus Lactobacillus is widely used in the food industry. It has probiotic characteristics, belongs to LAB and was described by Döderlein(1892). It is a common inhabitant of the gastrointestinal tract of humans and animals [204]. It protective function due to their surface protein layer is expressed in an antimicrobial inhibitory effect for competition for binding sites on the surface of the epithelial cells and in antagonism to entry and replication for viruses, but not for attachment . The genus contains hydrogen peroxide producing (HP+) and hydrogen peroxide non-producing (HP-) strains. Depending on the moment balance, hydrogen peroxide producing (HP+) lactobacilli act in a protective, indifferent or abdicating state(patients with infection). The ability of Lactobacilli to attach to epithelial surfaces is extremely important for maintaining constant colonization in the intestine and other tissues of mammals. A diet rich in dairy products is associated with a richer and more diverse microbiota. A study has shown that the nasal microbiota of dairy farmers is more complex and protects them from infection by competing with *S. aureus* colonization [205]. Qiu, et al. (2021) reported that dietary supplementation with Bacillus subtilis significantly increased the number of Lactobacillus and Bifidobacterium in the ileum and cecum, and decreased coliforms and Clostridium perfringens in the cecum.

But the diet in infectious diseases can have an unintended effect and complicate the course of the disease. Therefore, it is important to limit the use of histamine-rich foods during the disease such as nuts, tomato paste, mature cheese, cocoa, chocolate, sauerkraut, smoked fish, salami, ham, dried fruits, some fruits and vegetables, yeast and others that can increase neurological, gastrointestinal and respiratory complaints. This is due to the fact that almost all organs and systems have four types of histamine receptors - H1, H2, H3 and H4. Two enzymes are responsible for the breakdown of histamine. DAO(diamine oxidase), which is produced by the intestinal mucosa and breaks down extracellular/ free histamine. With reduced secretion or an insufficient amount in the intestine, the latter accumulates in the blood. HNMT (histamine N-methyltransferase) is the other and is responsible for the breakdown of intracellular histamine in the bronchial mucosa, CNS, kidneys, and liver.

Fuller (1992) defines probiotics as living organisms contained in food, which when ingested can change the intestinal microbiota and stimulate the immune system. Taken in sufficient quantities, they have a certain benefit for human and animal health. In poultry farming, they have already proven themselves as an alternative to antibiotics [206]. Their important properties are: acid resistance, specificity, lack of side effects, reduction of microbial numbers of pathogens and viability during storage. The use of probiotics, local vaccines and dietary components for artificial colonization can help us to compensate in part for the impaired functions of the microbiota. By using transient strains to compete for adhesion sites and nutrients with those with pathogenic potential(pathobionts and exogenous pathogens) we will be able to prevent the invasion and overgrowth of the latter [207]. In order to use them, we must know them to achieve maximum effect. It has been shown that some LAB strains cannot produce RNA and DNA precursors or are auxotrophic for nucleosides and nucleic acids [84]. Other LAB strains do not grow or grow poorly in media poor in vitamins(mainly from the B group - pantothenate, pyridoxine, riboflavin, niacin and biotin), peptides and amino acids(mainly leucine, isoleucine, valine, methionine and glutamate). L. lactis is auxotrophic for 14 of the 20 amino acids, while L. plantarum and L. mesenteroides require 3 to 11 amino acids. Some LAB strains have adapted and hydrolyze proteins in the environment by means of cell wall proteinases [208,209].

Conclusion

Every microorganism needs colonization to survive in a given ecosystem. Species survival comes first. There are no only “good” or only “bad” microorganisms. They constantly move along the commensal-pathogen continuum depending on the conditions and co-infections. S. sanguis is the first colonizer and commensal in the oral cavity, a vaccine and probiotic strain, but in some patients it can cause severe endocarditis and even death. Conversely, Pneumococcus, although considered the main cause of pneumonia, is a member of the healthy nasopharynx in eubiosis, as are Staphylococcus aureus and other microorganisms. Knowledge of the interactions between viral and bacterial pathogens and components of the human holobiont will help us better understand the mechanisms of immune responses and perhaps further try to modify them in certain situations. Individual phenotypes should be considered as an expression of interactions between the host and the associated microbial genomes, and our primary task is to preserve them. Sinus infections were thought to be due to the correspondence between pathogens of the nasopharynx and the osteomeatal complex. However, gene sequencing of the microbiota of patients after FESS revealed a microbiome similar to that of the anterior nose. It remained similar to that

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of the nasopharynx for about 6 weeks after surgery and then returned to its original state. This restoration of permanent relationships is an expression of the genus specificity of the microbiota or „memory". There are reports that the intake of prebiotics supports the growth and restoration of the microbiota after antibiotic therapy. The formation of the phenotype during the first three years of our life, especially during the first, is in initial stage because the colonization of the host has not been completed and permanent relationships in the holobiont have not been established. During this period, our interventions must be extremely balanced, as in attempting to restore equilibrium we may push the formation of the phenotype in one direction or another, the consequences of which are currently unpredictable.

Our place is to find the right timing, type and volume of pharmacological, non-pharmacological and dietary interventions in the personalized treatment of patients with infectious diseases. About 50% of the phageome and bacteriome are unique to each of us and our task is how to maximally preserve them or at least restore them more quickly. Our goal is to minimally alter the phenotypes that are an expression of the symbiosis between the host and associated microbial genomes in eubiosis and to prevent the emergence of newly acquired phenotypes. Only then will the development of effective measures for protection against pathogens and modulation of immune responses be successful. Perhaps then we can become a "senior partner" in the holobiont.

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