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Pathogenic Modification of Coinfections During Covid-19

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Abstract: This article discusses the main pathogenetic mechanisms for the development of bacterial co-infection in acute respiratory infections and in coronavirus infection, in particular. Separate mechanisms were analyzed in detail, including impaired mucociliary clearance, decreased activity of local protective factors of the respiratory mucosa, and impaired antibody production. The mechanisms of dysfunction of cytokines, as well as dysfunction of receptors, are also described. Modern data on the effect of coronavirus infection on the immune system and interferon production systems are presented, which contributes to the layering of a bacterial infection.

Keywords: coronavirus infection; viral-bacterial co-infections; pathogenic mechanisms.

It is now known that viral infections can weaken the host's immunity, opening the way for the development of viral-bacterial coinfections. The novel coronavirus infection, COVID-19, is another example of such an infection, as most hospitalized patients with COVID-19 developed a secondary bacterial infection. In some severe forms of COVID-19, patients have had elevated levels of bacterial infection-associated biomarkers and inflammatory cytokines, suggesting potential bacterial co-infection as a result of immune system dysregulation. In addition, the development of resistance could become an additional burden for the healthcare system as a whole, since co-infection with coronavirus pneumonia burdens medical institutions beyond their capabilities and resources.

Predisposition to bacterial co-infection in viral respiratory infections. As a rule, a viral infection causes structural and functional damage to the respiratory tract during infection and the development of the pathological process. Depending on the type of virus, the histopathology of the lesions can vary relatively from mild to more severe. These pathological changes include changes in mucus secretion, cell death, cell hyperplasia, decreased mucociliary clearance of mucous membranes, reduced oxygen metabolism, impaired surfactant secretion, etc. Each of these processes is due to different molecular mechanisms, depending on the type of virus, as well as the degree of immune response. the body's response to an infectious agent. It has been noted that viral infections contribute to bacterial contamination of the respiratory tract through various mechanisms.

In particular, it has been proven that influenza viruses can increase the contamination of the nasopharyngeal mucosa with the bacterium S. pneumoniae. However, then it was found that only certain subtypes mediate the development of bacterial otitis media and sinusitis. This data may explain why bacterial infection rates are high during flu seasons. Influenza virus neuraminidase enzyme receptors have been found to be present on human cells and are used for bacterial adhesion as they have a sialidase ability that promotes alteration of carbohydrate moieties on epithelial cells. This

enzyme is also able to increase the likelihood of bacteria attaching to cells by stimulating transforming growth factor-beta (TGF-β), which is responsible for the regulation of integrins and fibronectin. Integrins and fibronectin act as receptors for bacteria. In addition, interferons (IFN), which are induced by the influenza virus, can cause a decrease in the concentration of chemokine C-C and the expression of ligand-2 (CCL2), which leads to an inability to recruit macrophages necessary for the clearance of pneumococci, thereby enhancing the colonization of S. pneumoniae in vivo.

Influenza virus has also been found to predispose the host to the development of S. aureus pneumonia, where viral and bacterial loads increase during coinfection. It has been suggested that viral load increases after bacterial co-infection due to an increased rate of virus shedding from infected cells. Also, the bacterial load can be increased as a result of dysfunction of the alveolar process of macrophages.

In addition, other viruses that infect the upper respiratory tract increase the ability of bacteria to attach to primary and immortalized epithelial cells to varying degrees. Such differences are determined by the types of epithelial cells and their response to the parainfluenza-3 virus, respiratory syncytial virus and/or influenza virus. Novotny et al. showed that adenovirus and respiratory syncytial virus stimulate the expression of intercellular adhesion molecule 1 (ICAM-1) in airway epithelial cells. ICAM1 acts as a receptor for type 4 villus (T4P) of non-typeable H. influenzae (NTHI), thereby facilitating the binding of this pathogen to cells expressing these molecules. In addition, respiratory syncytial virus increases the binding capacity of P. aeruginosa to normal epithelial cells as well as cells affected by cystic fibrosis. Similar mechanisms are often used by bacteria to increase their virulence towards cells. Studies have shown that after infection with respiratory syncytial virus, the binding rate of epithelial cells of S. pneumoniae serotypes increases by 2–10 times. Similarly, antibody titers against S. pneumoniae are elevated in the nasopharyngeal mucosa affected by respiratory syncytial virus infection, rhinovirus, and community-acquired pneumonia. The degree of colonization of the nasopharynx by S. pneumoniae is also higher with concomitant viral infection of the upper respiratory tract or with human immunodeficiency virus.

Bacterial co-infection may alter some of the immune properties of the mucosa, leading to its ineffectiveness in controlling bacterial replication in that area. Some key points related to the effect of viral infection on phagocytic activity are discussed below. The reduction in the number of alveolar macrophages by the influenza virus facilitates bacterial coinfection. Tracing of dye-labeled alveolar macrophages showed that 90% of resident alveolar macrophages were lost in the first weeks after influenza infection, while 95% of the original bacteria were removed within 3 hours by alveolar macrophages in non-influenza infected organisms. It has also been suggested that the activity of phagocytes, along with cell proliferation, can be influenced by a viral infection. The influenza virus causes a pronounced decrease in the levels of cytokines and chemokines, which leads to a decrease in the recruitment rate and stimulation of neutrophils. It can also suppress phagocytic bacterial clearance mediated by nicotinamide adenine dinucleotide phosphate (NADPH), thereby increasing susceptibility to secondary bacterial infections.

As mentioned earlier, dysregulation of pro-inflammatory cytokines caused by viral infection plays a significant role in cell susceptibility to secondary bacterial infection. Type 1 IFN is now known to have antiviral and immunostimulatory effects and can have negative effects on human cells when expressed inappropriately and excessively. Interferons have been reported to play a fundamental role

in the production of anti-inflammatory cytokines such as IL-10 and IL-6, as well as the inhibition of pro-inflammatory cytokines that link innate immunity to adaptive immune responses, such as IL-17 and IL-23. They also reduce the activity of macrophages, dendritic cells, natural killer cells, along with the number of CD4- and CD8-positive T cells, which leads to impaired bacterial eradication.

Impact of coronavirus infection on the immune system. Under the action of SARS-CoV-2 on the human body, a two-stage immune reaction develops in a non-severe variant of the disease, the essence of which is to destroy the virus and prevent the progression of the disease into a severe form. In this regard, the tactics of treating such forms of the disease is to enhance the immune response through the use of antisera and pegylated IFNα, which is of decisive importance in this variant of the course of the infection. In order to provide a protective immune response at an early stage, it is necessary that the body be in good general condition and have a favorable genetic background, which will make it possible to provide an acceptable antiviral response. It is well known that genetic differences can cause specific changes in the immune system in response to various microbial pathogens. The course of the pandemic allowed a rather deep study of the course of the process of elimination of the virus and inflammatory reactions that develop during infection with SARS-CoV-2.

In particular, scientists drew attention to the fact that SARS-CoV-2 has developed a special "escape" mechanism to avoid the action of IFN in infected cells of the body. In addition, it has become clear that much of the inflammatory response in COVID-19 is regulated by inflammatory cytokines. and chemokines such as IL-6, interferon-γ-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1). It also became known that the penetration of inflammatory cells such as macrophages into infected host tissues and suppression of the synthesis of type I antiviral interferons is one of the pronounced protective properties of the SARS-CoV-2 virus, as well as other coronaviruses. It has been proven that there is a violation of the formation of type I interferon in cells infected with SARS-CoV-2, but at the same time, the action of interferon is able to suppress the growth of SARS-CoV-2. This proves that these viruses have developed specific mechanisms to overcome the action of IFN in infected cells. Type I interferons are rare in SARS patients, and SARS-CoV-2 is sensitive to pegylated IFN-α, as shown in in vivo mouse models. Studies have also shown that the suppression of type I interferon synthesis in an organism infected with SARS-CoV-2 is mediated by the inactivation of the IRF-3 protein (interferon regulatory factor 3), a transcription factor that controls the production of interferon.

In addition, other SARS-CoV accessory proteins act as potent interferon antagonists through various mechanisms. For example, N proteins inhibit interferon expression, while open reading frame 3b and 6 proteins inhibit interferon signaling and expression. In addition, open reading frame proteins can stop the translocation of signal transducer and transcription activator 1 (STAT1). The open reading frame 3b protein is a shuttle protein that prevents stimulation of type I interferon, which is triggered by retinoic acid inducible gene 1 (RIG-I) and mitochondrial antiviral signaling protein (MAVS). The SARS-CoV complex, called papain-like protease, is able to inhibit the phosphorylation and nuclear translocation of IRF-3, which leads to impaired type I interferon activation. In addition, infected SARS-CoV cells can stimulate the expression of protein kinase R (PKR) and PKR-like kinases of the endoplasmic reticulum (PERK).

Understanding the mechanisms underlying the synergy between COVID-19 and bacterial infection paves the way for the development of new methods to reduce mortality in patients with

COVID-19 and bacterial coinfection. In the current situation, a proper systematic analysis of patients with COVID-19 complicated by bacterial co-infection should be implemented in order to determine the necessary groups of antibiotics to improve patient survival and limit the spread of drug-resistant bacteria.

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