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The role of microbial biofilms in the development of respiratory system complications in patients with COVID-19: A literature review

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Abstract. One of the complications of COVID-19 is the development of acute respiratory failure, which may require artificial ventilation using an endotracheal tube to correct hypoxaemia. However, the establishment of biofilms during intubation of patients can pose a risk of microbial growth that can cause severe complications. Therefore, the research on the microbial composition of biofilms that causes such diseases becomes an urgent issue. The purpose of the research was to analyse and summarise the data from current studies on the role of microbial biofilms and their impact on the development of respiratory system complications in patients with COVID-19. After reviewing the literature, it was determined that *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Candida albicans* accounted for the majority of biofilms isolated from endotracheal tubes in patients with COVID-19. The level of antimicrobial resistance among the isolated strains was almost 70%. The examination of samples from endotracheal tubes identified representatives of the lung microbiome, *Prevotella* spp. and some species of *Streptococcus*, *Veillonella*. However, in the research on the microbial composition of biofilms isolated from endotracheal tubes, pathogenic representatives dominated, such as *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp., *Stenotrophomonas* spp., *Enterobacterales*, *Haemophilus* spp. and *Actinomyces* spp. Changes in the composition of the lung microbiome in patients with COVID-19 can lead to the development of severe complications accompanied by the establishment of biofilms. Microorganisms in biofilms can be a reservoir for secondary pulmonary infections, which affects the duration of mechanical ventilation and the admission of patients with COVID-19 to intensive care units. The development and implementation of effective measures for the prevention and treatment of biofilm-related infections is an important task for modern medical practice

Keywords: microbial biofilms; espiratory failure; pneumonia; secondary infection

INTRODUCTION

Secondary bacterial infections play a crucial role in the morbidity and mortality of patients with COVID-19. One of the complications of coronavirus infection is the development of acute respiratory failure, which requires artificial lung ventilation (ALV) using an endotracheal tube to correct hypoxaemia. Most microorganisms in natural and artificially designed environments exist as structured forms attached to biotic or abiotic surfaces, forming complex microbial communities surrounded by an exopolysaccharide matrix called biofilms [1]. The establishment of biofilms during the intubation of patients poses a risk of the growth of microorganisms that can cause pneumonia and other complications of the respiratory system. Such undesirable consequences can affect the treatment of patients and prolong their hospital stay. Despite ongoing research in this area, the impact of biofilms on the

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mortality rate of patients with coronavirus infection remains unexplored.

Lung damage in COVID-19 and impaired immune response can promote the growth and persistence of microorganisms in hospitalised patients and increase the risk of biofilm development. Studies by F.M. Carvalho *et al* [2] demonstrate that secondary bacterial pneumonia is a potential risk factor for severity and complications in patients with COVID-19. L. Meng *et al.* [3] and F. Zhou *et al.* [4] believe that mechanical ventilation is necessary to treat patients with acute respiratory symptoms and hypoxia, can increase the risk of pneumonia and promote the establishment of biofilms. Changes in oxygen levels, alveolar ventilation, and the density of affected cells affect microbial growth conditions in the lungs.

According to a study by T.M. Rawson *et al.* [5], the overuse of broad-spectrum antibiotics creates an ideal environment for opportunistic bacterial colonisation, secondary bacterial infections and increased levels of multidrug resistance, which leads to microflora disruption, the spread of resistant strains among COVID-19 patients and contributes to the ability of pathogens to form biofilms. Studies demonstrate that bacteria spend most of their life cycle in the biofilm matrix. J. Yan & B.L. Bassler [6] found that the planktonic stage can only be considered as a way of moving a microbial cell from one surface to another, a short-term state in the life of bacteria that are free in the environment. Microorganisms in biofilms increase their resistance to disinfectants, antibacterial drugs, bacteriophages, antibodies and phagocytes by 50-500 times [7, 8].

The extracellular matrix accounts for 85% of the biofilm mass, consisting of exopolysaccharides, proteins and nucleic acids. It is synthesised by the extracellular components of attached microorganisms and has important functions in the biofilm's life. The extracellular matrix is a powerful biological glue that allows the biofilm to be firmly fixed to any surface [9, 10]. The synthesis of virulence factors and the development of biofilms occurs only when there is a sufficient population density (Quorum sensing (QS)) [11]. QS is implemented by several means of perception and transmission of information: physical contact between cells; generation of physical fields; and synthesis of chemicals diffusing into the environment, which are called autoinducers. The concentration of extracellular autoinducers correlates with the density of cells in the population, and when certain thresholds are reached, autoinducers enter the cell interior or activate receptors on their surface, which leads to changes in the expression of various genes [12, 13]. Thus, bacteria can "sense" the density of the cell population, and this mechanism allows bacteria to function as a multicellular organism. Studies have demonstrated that the establishment of biofilms in coronavirus infection can affect the development of respiratory system complications and determine the severity and outcome of the disease.

The purpose of the research was to explore the microbial composition of biofilms and their role in the development of respiratory system complications in patients with COVID-19. The research reviewed modern works of scientists from different countries, including scientific researches, clinical data, using Internet resources, publications of professional journals, and the Medscape/PubMed medical database. A comparative analysis was conducted between the composition of the lung microbiome and isolates isolated from endotracheal tubes. The main complications of the respiratory system in patients with COVID-19 and their connection with the development of biofilms were explored. The issues of treatment and prevention of complications in patients with COVID-19 associated with the development of biofilms are considered.

FEATURES OF THE MICROBIAL COMPOSITION OF BIOFILMS ISOLATED FROM PATIENTS WITH COVID-19

The composition of the lung microbiome can vary significantly depending on the influence of many factors. Among the representatives of normal biocinosis are microorganisms of the genus *Prevotella*, *Streptococcus*, and *Veillonella*. In addition, pathogenic representatives, such as *Haemophilus* spp., *Neisseria* spp. and *Pseudomonas* spp. can be isolated from the respiratory tract, but they account for a smaller proportion of the microbiome [14, 15].

S. Alhumaid *et al.* [16] found that against the background of COVID-19, the lung microbiome is usually disturbed and is characterised by an increase in commensals such as *Prevotella* spp. Thus, when examining samples from endotracheal tubes, representatives of the lung microbiome, *Prevotella* spp. and some species of *Streptococcus*, *Veillonella* were identified. However, in the examination of the microbial composition of biofilms isolated from endotracheal tubes, pathogenic representatives, such as *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp., *Stenotrophomonas* spp., *Enterobacterales*, *Haemophilus* spp. and *Actinomyces* spp. dominated [17, 18].

Notably, out-of-hospital bacterial infections associated with COVID-19 are quite rare, while hospital-acquired infections are more common and account for about 47% of cases [19]. Research conducted by G. Giacomo *et al*. [20] demonstrated that the percentage of clinically significant bacterial infections in hospitalised patients ranged from 4 to 14%, with these diseases often being recorded in patients in intensive care units. In COVID-19 infection, hospital-acquired pathogens such as *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae* are spreading. In addition, other pathogens have been identified, including *Enterobacter cloacae*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* [21].

The literature review identified that isolated microorganisms from biofilms established on endotracheal tubes included both commensal and pathogenic agents. *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Candida albicans* accounted for the majority of biofilms. Pathogens such as *Paracoccus yeei* were unusual, but they were detected in several patients. In addition, the isolated strains were tested for antibiotic susceptibility using the disc diffusion method. Thus, the level of antimicrobial resistance among the isolated strains was almost 70%. Among the tested strains were isolates with resistance to meropenem and gentamicin. In addition, differences in antibiotic susceptibility between various isolates of the same species isolated from the same endotracheal biofilm have been reported [22].

Studies have demonstrated a significant role of *Acinetobacter baumannii* in the development of ventilator-associated pneumonia in patients with COVID-19 undergoing

mechanical ventilation. The pathogen is characterised by a significant level of resistance to many clinically relevant antibiotics, including meropenem, imipenem, gentamicin, tobramycin and levofloxacin. Antibiotic resistance has increased through using empirical broad-spectrum antibiotic therapy to treat COVID-19 bacterial superinfections. In addition, these pathogens have been identified as having a high ability to form biofilms [23].

The development of tracheobronchitis in patients with COVID-19 on mechanical ventilation is not uncommon, with an incidence of almost 15%. Microbiological studies have demonstrated that potentially resistant gram-negative bacteria such as *P. aeruginosa* and carbapenem-resistant strains of *Klebsiella pneumoniae* are isolated from the pathological material of such patients [24]. Other enterobacteria are isolated: *Alcaligenes xylosoxidans*, *Acinetobacter* spp. and *Stenotrophomonas*. Depending on the type and virulence of the bacteria and their interaction with the immune system, colonisation and biofilm development subsequently occur.

Thus, normal biocinosis of the respiratory system plays an important role in maintaining homeostasis. Changes in the microbiome and the development of biofilms during using endotracheal tubes during coronavirus infection can affect the course of the disease and lead to the development of severe complications.

MAIN COMPLICATIONS OF THE RESPIRATORY SYSTEM IN PATIENTS WITH COVID-19

Both innate and acquired immunity are involved in the response to the infectious process. The development of complications in coronavirus infection is associated with significant dysfunction of the immune system. I. Sulaiman *et al*. [25] established that patients with COVID-19 had a decrease in the number of CD4+ and CD8+ T lymphocytes, an increase in neutrophils, and a decrease in the concentration of gamma interferon in the serum. Further studies confirmed these findings and identified the presence of such processes as a cytokine storm, characterised by an excess of proinflammatory molecules, inhibition of natural killer cells and cytotoxic lymphocytes, and morphological and phenotypic changes in monocytes [26]. Such immune response disorders can contribute to increased adhesion, growth, and spread of bacteria that can form biofilms. In addition, bacterial infection leads to an increased probability of virus survival and replication, and tissue damage promotes the further spread of pathogens, which increases the risk of bloodstream infections. Thus, the presence of secondary infection in COVID-19 leads to further complications, including the development of septic shock.

Acute respiratory distress syndrome (ARDS), which often develops in patients with COVID-19, is a life-threatening form of respiratory failure. According to statistics, ARDS develops in about 1/3 (33%) of hospitalised patients and almost 3/4 (75%) of patients in intensive care units [27]. The known mechanisms of ARDS are associated with the development of severe pulmonary infiltration, oedema and inflammation, which leads to a violation of alveolar homeostasis, changes in lung physiology, pulmonary fibrosis, endothelial inflammation and thrombosis. ARDS can occur both as a result of direct exposure to the virus and due to the action of substances synthesised by host cells. Activated cells of the immune system secrete specific enzymes and pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), which leads to the induction of a cytokine storm. Patients with ARDS require ALV and have a high mortality rate due to shock, septicaemia and multiple organ dysfunction syndrome. Invasive ventilation in patients with ARDS can directly lead to lung damage, and prolonged use of mechanical ventilation causes the development of biofilms by microorganisms, which significantly worsens the prognosis for recovery [27].

The most common bacterial complication of COVID-19 is ventilator-associated lower respiratory tract infection, which includes ventilator-associated pneumonia and ventilator-associated tracheobronchitis. The mechanism underlying bacterial secondary infection in viral pneumonia is damage to ciliated cells, which leads to impaired mucociliary clearance and increased bacterial adhesion and colonisation of the airways [28].

During complications of coronavirus infection, mechanical ventilation using an endotracheal tube can support pulmonary gas exchange disorders in critically ill patients. The development of biofilms inside the endotracheal tube and their subsequent movement to the distal airways during mechanical ventilation cycles is considered a possible pathogenic pathway for the development of ventilator-associated pneumonia. Previous studies have demonstrated that biofilm formation on endotracheal tubes affects the incidence of bacterial infections in intubated patients and is a factor in the development of ventilator-associated pneumonia, which occurs in 20-40% of cases [29]. T. Sakano *et al*. [30] established that a biofilm can be established on the surface of the tube within 24 hours after intubation and can be a reservoir for microorganisms that subsequently cause infection in the lungs. In addition, biofilm cells are inherently more resistant to antibiotics for a variety of reasons, including the lower metabolic rate of bacteria in the biofilm and poor penetration of antimicrobial drugs. The hypothesis that biofilms on endotracheal tubes play a role in the development of ventilator-associated pneumonia is supported by the fact that in many cases the same bacteria are identified in tube biofilms and other airway specimens [31]. Such pathogenetic features can complicate the treatment of biofilm-related infections.

Ventilator-associated tracheobronchitis is a frequent and clinically significant infectious complication in patients on mechanical ventilation for more than 48 hours, with a frequency similar to ventilator-associated pneumonia. Studies conducted by D. Koulenti *et al*. [32] demonstrated that tracheobronchitis can be considered as an intermediate process leading to ventilator-associated pneumonia. In addition, ventilator-associated tracheobronchitis has a limited impact on overall mortality but demonstrates a significant association with increased patient costs, length of hospital stay, antibiotic use, and duration of mechanical ventilation.

Thus, patients affected by the coronavirus can develop various complications, the most common of which are pneumonia and ARDS. One of the important factors leading to such complications is using endotracheal tubes and the development of biofilms, which worsen the patient's

condition and increase mortality. The impact on microbial biofilms and the treatment of associated infections is a complex and unresolved problem.

STRATEGIES FOR THE TREATMENT AND PREVENTION OF MICROBIAL BIOFILM FORMATION IN PATIENTS WITH COVID-19

Since antibiotic therapy is ineffective in the treatment of biofilm infections, maximum efforts should be devoted to preventing the formation of biofilms. The main measures are designed to prevent the adhesion of microorganisms when using endotracheal tubes in patients with severe coronavirus infection. For this purpose, modified endotracheal tubes coated with antimicrobial compounds can be used, which has a high clinical effect. Using antimicrobial-coated endotracheal intubation tubes for prolonged mechanical ventilation allows delaying contamination of the respiratory tract tissues with microflora and reduces the microbial load on the lung parenchyma. Animal studies have demonstrated that endotracheal tubes coated with silver ions lead to reduced adhesion of *P. aeruginosa* and a lower prevalence of ventilator-associated pneumonia compared to uncoated tubes [33]. Other modifications are used, including silicone or noble metal coating. Such modified endotracheal tubes can be used in combination with devices for drainage of bronchial secretions, which prevents the development of respiratory system complications.

In addition, it is necessary to constantly monitor endotracheal aspirate in patients with COVID-19 on mechanical ventilation. Such monitoring allows identifying pathogens that colonise the lower respiratory tract and determining their quantitative content. M.L. Blasco *et al.* [34] note that timely detection of pathogens will allow for early targeted antibiotic therapy and prevent the development of ventilator-associated pneumonia.

Prevention of biofilm development in patients with COVID-19 on mechanical ventilation consists of measures designed to reduce mucus viscosity and activate its evacuation. Mucus viscosity can be reduced with mucolytic agents. Special attention should be devoted to using N-acetylcysteine, which can prevent the establishment and destruction of bacterial biofilms, which is becoming especially important in the era of antibiotic resistance. There is a growing body of evidence confirming the antimicrobial and antibiofilm activity of N-acetylcysteine against many respiratory pathogens, including pathogens of the following genera and species: *Escherichia*, *Pseudomonas*, *Staphylococcus*, *Acinetobacter*, *Haemophilus influenze*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Klebsiella*. F.L. Poe & J. Corn [35] proved that this mucolytic inhibits the establishment of biofilms by bacteria and fungi, and destroys mature biofilms. The destruction of the biofilm matrix facilitates the penetration of antibacterial drugs into the deeper layers of biofilms and significantly increases the effectiveness of treatment of bacterial infections.

Clear criteria for prescribing antimicrobial therapy should be followed to prevent the development of antibiotic resistance. Antibiotic therapy in patients with a diagnosed coronavirus infection is justified if there are convincing signs of bacterial infection. These signs include: a change from a dry cough to a productive cough (especially with purulent sputum) in a patient with confirmed SARS-CoV-2 infection, a significant increase in blood procalcitonin levels, an increase in white blood cell count > 10-12-109/L and/or a stain shift > 10%, signs of consolidation (alveolar infiltration) of the lung parenchyma according to computed tomography [36].

In addition, inappropriate treatment with broad-spectrum antibiotics may increase the level of mycobacterial resistance and mortality of patients with COVID-19. C. Rhee *et al.* [37] believe that early antibiotic treatment should be avoided in more than 75% of cases if the aetiology of superinfection is not proven using standard microbiological diagnostic methods.

Recently, using monoclonal antibodies that can affect the proteins of the SARS-CoV-2 spike-like envelope proteins has become widely used to prevent and treat complications in patients with COVID-19. Their mechanism of action is to block the attachment of the virus to the cell membrane, which prevents SARS-CoV-2 from entering human cells, neutralises the virus's effect and helps prevent the development of the disease, reducing the nature and duration of its clinical manifestations. M.P. O'Brien *et al.* [38] found that using a combination of drugs containing monoclonal antibodies in outpatients with coronavirus reduces the incidence of hospitalisation or death by 70% due to a rapid reduction in viral load. Such measures to prevent complications can help reduce the frequency of ventilator use and reduce the risk of biofilm development.

An important task of modern medicine is to develop new approaches to the identification and research of biofilms, including the immune response to these infections, changing the tactics of antibiotics, and searching for and introducing new antimicrobial agents. Scientists from different countries are researching the design of preventive measures and treatment of infections associated with the development of biofilms, but no general recommendations have been established, which requires further research on this issue.

CONCLUSIONS

The literature review demonstrated that patients with COVID-19 may develop severe respiratory complications associated with the development of biofilms. The composition of biofilms is diverse and contains many microorganisms that are clinically important and highly resistant to antibiotics. Among the microorganisms that are part of biofilms, the most common are representatives of the genera *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp., *Stenotrophomonas* spp., *Enterobacterales*, *Haemophilus* spp. and *Actinomyces* spp. These pathogens can cause severe complications associated with the development of ventilator-associated pneumonia, ventilator-associated tracheobronchitis, ARDS and septic shock. The main measures for the treatment and prevention of complications associated with biofilm formation in patients with COVID-19 should include the prevention of microbial adhesion and the principles of rational antibiotic therapy.

The correlation between the microbial composition of biofilms isolated from patients with respiratory system complications and clinical outcomes remains unexplored. However, microorganisms in biofilms can probably be a reservoir for secondary pulmonary infections. These processes can affect the duration of mechanical ventilation

and the admission of patients with COVID-19 to intensive care units. The prospect of this research is to establish the impact of the microbial composition of biofilms on the development of complications, which will reduce the number of bed days spent in hospital and the cost of treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Роль мікробних біоплівок при розвитоку ускладнень дихальної системи у пацієнтів З COVID-19: огляд літератури

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Анотація. Одним із ускладнень COVID-19 є розвиток гострої дихальної недостатності, що може потребувати штучної вентиляції легень із використанням ендотрахіальної трубки для корекції стану гіпоксемії. Однак утворення біоплівок в процесі інтубації хворих може стати ризиком розмноження мікроорганізмів, здатних викликати важкі ускладнення. Тому, актуальним питанням стає дослідження мікробного складу біоплівок, який викликає такі захворювання. Мета дослідження полягала в аналізі та узагальненні даних сучасних досліджень, які стосуються вивчення ролі мікробних біоплівок та їх впливу на розвиток ускладнень дихальної системи у пацієнтів з COVID-19. Після проведеного аналізу літератури встановлено, що в структурі біоплівок, виділених з ендотрахеальних трубок у пацієнтів із COVID-19 більшу частку складали *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* і *Candida albicans*. При цьому рівень резистентності до антимікробних препаратів серед виділених штамів складав майже 70 %. При дослідженні зразків з ендотрахеальних трубок були виявлені представники мікробіому легень, *Prevotella* spp., деякі види *Streptococcus*, *Veillonella*. Однак при дослідженні мікробного складу біоплівок, виділених з ендотрахеальних трубок, домінували саме патогенні представники, такі як, *Pseudomonas* spp., *Staphylococcus* spp., *Streptococcus* spp., *Stenotrophomonas* spp., *Enterobacterales*, *Haemophilus* spp. та *Actinomyces* spp. Зміни складу мікробіому легень у хворих з COVID-19 можуть призводити до розвитку важких ускладнень, які супроводжуються утворенням біоплівок. Мікроорганізми у біоплівках можуть бути резервуаром для вторинних легеневих інфекцій, що впливає на тривалість використання штучної вентиляції легень та прибування пацієнтів з COVID-19 у відділеннях інтенсивної терапії. Розробка та впровадження ефективних заходів для профілактики та лікування інфекцій, пов'язаних з утворенням біоплівок є важливим завданням для сучасної медичної практики

Ключові слова: мікробні біоплівки; дихальна недостатність; пневмонія; вторинна інфекція