

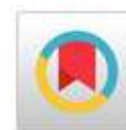


Chronic infection: as an ecological model for emergence of the chronic obstructive pulmonary disease

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Abstract



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Chronic infections; emerging as complications of some primary diseases, can hardly be considered as classical infectious processes. Such infections may be caused by the non-traditional pathogenic bacteria; as in the cases of cystic fibrosis; chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases, etc. Emergence of these complications is caused by several disorders in the ecosystem; constituting the human body and its microbiota. It is reasonable to extrapolate some ecological principles of the bacterial community's assembly in the humans; as there is a wide variety of factors affecting this, which can be considered as ecological ones. The human microbiota is formed during changes of the different bacterial succession types; under the influence of stochastic and deterministic ecological processes, in addition to different types of the selection pressure. During certain diseases, such as COPD, the normal course of the bacterial community's formation is disrupted. It is associated with anatomical and physiological defects, which cause changes in the properties of the ecological niche; occupied by the communities (*i.e.*, airways in the case of COPD). Altered niches can be occupied by the virulent microorganisms, which get resource advantage and form new stable community. The severity of such chronic infections is correlated with biological diversity in the communities, which tends to decrease in the more severe cases and in the exacerbations. The aim of this study was to create an ecological model of the chronic infections; through synthesizing the ecological and medical knowledge. This model, such as the COPD; may establish new approach to the chronic infections etiopathogenesis, which enables to get better understanding of the clinical course in these diseases and to propose more effective therapies in the future.

Keywords: Chronic infections, COPD, Bacterial communities, Bacterial successions, Airway microbiota

1. Introduction

Traditional antibiotic therapy is based on the concept of classical infectious process, which is frequently not efficient in treatment of the chronic infections ([Rybtke et al., 2020](#); [Shi et al., 2022](#)). Infectious complications arising from the cystic fibrosis and chronic obstructive pulmonary disease are usually considered only as typical microbial infections. In a broader sense, these conditions are not limited to the impact of the pathogenic bacteria and their pathogenicity factors on the humans. However, they are a consequence of complex interactions in the "bacteria-host" and "bacteria-bacteria" systems ([Magalhães et al., 2016](#); [Khanolkar et al., 2020](#)). Consequently, in order to get better understanding of their pathogenesis, as well as to get an opportunity to identify the new directions in their therapy in the future; a broader approach to the chronic infections etiology is highly necessitated. This approach must include assessment of the microecological factors influencing the course and outcomes of these bacterial infections.

2. Features of the bacterial communities in nature and the human body

Biological niches in the environment are formed during the ecological successions, which are successive changes of one biological community by the other. Bacterial communities often play a fundamental role even in the complex successions ([Chang and Turner, 2019](#); [Osburn et al., 2023](#)). For the bacterial communities, it is possible to distinguish the specific features of functioning at the ecological level, which are related with high diversity of the physiological properties. This is mainly caused by competition for the nutritive resources. Excess or lack of these resources may lead to a significant variety of the metabolic pathways for the individual nutrient substrates on one hand. On the other hand, it provides resource advantage for the individual groups of microorganisms ([Bauer et al., 2018](#)). In addition to the

classical chemotrophs and heterotrophs, there are species that can switch from one type of metabolism to another, which is associated with a wide representation of the electron donors and acceptors in the metabolic pathways ([Ho et al., 2017](#)). It is also crucial to consider the significant phylogenetic diversity of the microorganisms in the ecological niches ([Kim et al., 2017](#)). The consequence of this phylogenetic diversity is expressed in more complex interactions within the microbiota and in less predictable succession models ([Fierer et al., 2010](#)).

Considering the fact that the human microbiota is formed during several stages, it is reasonable to assume that it may be characterized by successional processes, which makes the data described for the ecological processes more interesting from a clinical point of view.

For microbial communities in the environment; shifts of their species composition strictly obey the laws of succession, in accordance with the definite changes, including the availability of nutritive resources; temperature conditions of the environment, physical and chemical conditions (i.e., pH, chemical composition, oxygen saturation), and several other factors, which affect the processes of emigration and immigration ([Lucas et al., 2020](#); [Da Silva et al., 2021](#)).

There are several theories describing the types of microbial community's assembly. The most widespread one classifies the successions into primary and secondary ones ([Prach and Walker, 2019](#); [Abed et al., 2019](#)). This classification is based on the prior presence or absence of biological communities. However, in our opinion, the aforementioned processes are described most clearly in the system previously proposed by [Fierer et al., \(2010\)](#).

This classification is based on two main points; mainly the resources for the communities and the degree of microbial influence on the environmental properties

(i.e., spatial characteristics and chemical composition). Depending on this, [Fierer *et al.*, \(2010\)](#) highlighted the autotrophic; endogenous heterotrophic, and exogenous heterotrophic types of succession.

1) Autotrophic type: The communities use light or inorganic substances as resources. Organic carbon is initially absent in the environment composition, but its amount begins to increase over time;

2) Endogenous heterotrophic type: The resource for communities is the organic carbon, whose source is actually the substrate on which the community develops. Qualitative characteristics of the substrate change over time as a result of the bacterial activity. The level of metabolites produced by the community's increases in the environment;

3) Exogenous heterotrophic type: The resource for communities is the organic carbon coming from the outer sources. The community does not make a direct impact on the qualitative characteristics of the substrate. However, an indirect effect is possible due to metabolites produced by the microbial communities ([Fierer *et al.*, 2010](#)).

Availability of the nutritive resources is a specific feature of the environment. It is an internal factor that sets the succession course in a range of large categories of microbial communities. At the same time, there are processes that make an impact on the communities from the outside and define certain patterns in every succession type. Such processes can be divided into stochastic and deterministic.

The stochastic processes are chaotic; as they do not induce selection pressure. As an example, we can consider emigration and immigration of the bacteria and any random changes in the bacterial dispersal as an ecological drift ([Kohl, 2020](#); [Qi *et al.*, 2023](#)). It is assumed that the stochastic processes prevail in the early stages of succession; forming a primary microbial profile with high biological diversity ([Zhou and Ning, 2017](#); [Liebana *et al.*, 2019](#)).

According to [Yuan *et al.*, \(2019\)](#), during the deterministic processes; selection pressure arises under the influence of external factors. Communities that have managed to adapt to the prevailing changes are able to survive. Such processes are specific for the later stages of succession and are usually correlated with the low diversity.

Different environmental parameters can induce selection pressure in a definite direction. Most generally, a selection that occurs during the microbial succession can be classified according to the spatial characteristics of the environment. Depending on this, the microbial communities may be involved in either homogeneous or variable selection ([Dini-Andreote *et al.*, 2015](#); [Brandani *et al.*, 2023](#)).

The homogeneous selection is associated with spatially homogeneous environments; in which the bacteria occupy similar ecological niches and undergo the same selection pressure. However, the variable selection is typical for the spatially heterogeneous environments, where the niches occupied by the microorganisms have higher biological diversity ([Osburn *et al.*, 2021](#); [Peng *et al.*, 2021](#)).

If to draw parallels with the human body, some spatial heterogeneity may be present in this case. The selection pressure can change during the obturation of the respiratory tract, due to mucus hyper-secretion or bronchiectasis formation. This leads to the emergence of different niches within the same environment.

Depending on the succession type during which the bacterial community is assembled, it is possible to predict its changes after exposure to the external factors. Reorganization of the community occurs through adaptive cycles; whereas [Shabarova *et al.*, \(2021\)](#) study has distinguished several recurring phases. According to this study, the phases before the impact of an external factor and before reorganization of the community are similar and are characterized by low diversity and limited resources. However, the phases that occur after exposure to the external factors

are characterized by high diversity and high resources level.

Considering complex morphology of the human body (*i.e.*, spatial heterogeneity) and various changes that occur during certain pathological processes, it is reasonable to assume that certain variability of the successional processes is typical for the human microbiota. If to apply the ecological principles for human microbiota formation in the normal and pathological conditions, we can consider the pathogenesis of chronic infections in a new way. Therefore, there will be an opportunity to consider not only the immunological and etiological components of the pathogenesis, but also the microecological ones.

3. Bacterial successions in the respiratory tract

In this section, successional processes in the respiratory system of the healthy humans will be explored. These anatomical structures have been chosen for analysis as they are one of the most microbial-populated environments in the human body. Consequently, extrapolation of the ecological model to airway the microbiota formation will provide clear representation of the microecological impact on the humans' health conditions. In addition, chronic infections of the respiratory system are among the most severe infectious diseases with high mortality rates, so it is crucial to establish new approaches to this problem ([Troeger *et al.*, 2018](#); [Mahowald *et al.*, 2019](#); [Niederman and Torres, 2022](#)).

Pathogenesis of these respiratory diseases can be explored not only from the standpoint of classical infectious theory, but also according to the ecological principles of the microbial successions. Considering the phylogenetic and physiological diversity of the bacteria, it is reasonable to propose that certain communities may become active participants in the pathological processes; as a result of the changes in the metabolic pathways. This, in turn, may be attributed to changes in the environmental conditions.

Assembly of the respiratory microbiota is affected by several processes, which can be classified as

stochastic (associated with microbial dispersal) and deterministic (associated with changes in the physicochemical environmental properties). Such processes create a certain ecological niche for the microbiota in the normal conditions.

Various chronic infections occur in the presence of anatomical and physiological defects; associated with the hereditary or acquired diseases. These defects cause the emergence of new ecological niches, which are associated with atypical patterns of successions in the different chronic infections. Such defects are local, thus the bacterial communities are affected by variable types of selection. To understand the pathogenesis of the chronic infections from an ecological perspective, it is also necessary to realize the formation and functioning of the human respiratory microbiota under the normal conditions.

The human microbiota is a complex biological community that is formed during a multi stage assembly. Microbiota is vital for normal functioning of the human body. It performs an immune-stimulating function; has an anti-inflammatory effect, provides energy nutrition for the human cells, and form colonization resistance ([Ducarmon *et al.*, 2019](#); [Yuksel *et al.*, 2023](#)). Accordingly, the processes that disrupt the normal course of ecological assembly can affect not only the bacterial community, but also the macroorganism as an element of the ecosystem.

The oropharynx is usually considered as a direct source of colonization of the respiratory tract, because extensive salivation creates favorable conditions for migration of the oropharynx microbiota. Compared with the nasopharynx, its secretions have less volume and are more viscous ([Venkataraman *et al.*, 2015](#); [Belachew *et al.*, 2023](#)).

The processes affecting the initial respiratory pathways colonization can be characterized as stochastic ([Yagi *et al.*, 2021](#)). In the course of these processes, dispersal of the microorganisms on the occupied substrates occurs. Colonization of the respiratory tract is complex; as the processes of

immigration and elimination are mutually directed. The mechanisms of immigration are represented by inhalation of the bacteria; microaspiration, and dispersal of bacteria in the mucous membrane. Meanwhile, elimination occurs due to the mucociliary clearance. Stochasticity of the microbial successions is determined by the balance between immigration and elimination.

The deterministic processes include fluctuations in the various physical and chemical characteristics, which create specific ecological niches for certain bacterial species. One of such characteristics is the pH. In this regard, the respiratory tract provides more soft conditions for bacterial community formation; compared with the gastrointestinal tract, which sharply includes the acidic gastric juice and the alkaline intestinal environment. On the other hand, the respiratory system has more complex temperature conditions; as there is a gradient between the body temperature and the atmospheric air temperature ([Wypych *et al.*, 2019](#)).

Oxygen saturation is another significant parameter. The respiratory microbiota is mainly represented by the anaerobic microorganisms; since despite of the high level of oxygen supplied to the respiratory system; however, most of it passes into the bloodstream during gas exchange. Nevertheless, it is important to take into account the communication of the respiratory tract with the atmospheric oxygen; since in spite of the complication arising due to the various respiratory diseases, several chronic infections caused by the aerobic microorganisms may emerge ([Quinn *et al.*, 2018](#)). The factors that induce a significant selection pressure also include the "bacteria-host" relationship; the microbial interactions, and the antibiotic therapy.

The use of antibiotics in the classical acute infections is based on the exclusion of such links with the infectious process, such as the pathogen and its pathogenicity factors. In the chronic infections, the altered microecological conditions that arise during the main diseases may affect the pharmacological

properties; specifically for each drug and each disease. For example, in the case of cystic fibrosis; the hypoalbuminemia and dysfunction of the renal tubules increase the antibiotics clearance ([Thompson *et al.*, 2016](#)).

Also, the infectious diseases may become less susceptible to the effects of antibiotic therapy over time ([Clark *et al.*, 2018](#)), due to vital activity of the bacteria. As an example, in the chronic soft tissue infections; certain chemical gradients are formed in the infected area, including a decrease in the level of oxygen and glucose and an increase of the bacterial metabolic products. These gradients may lead to a decrease in the bacterial metabolic activity, and consequently to lower susceptibility to the antibiotics ([Bjarnsholt *et al.*, 2022](#)).

A previous study reported by [Caverly *et al.*, \(2019\)](#) that the antibiotics can also be considered as an ecological factor, as they are able to influence the structure of the bacterial communities; reduce their diversity, and trigger the adaptive cycles during which the communities become reorganized. According to [Clark *et al.*, \(2018\)](#), it is evident that the bacterial communities may receive resistance to the repetitive exposure to the antibiotic therapy.

The relationships between the individual microorganisms make a significant contribution to the ecological successions. The primary and intermediate microbial species prepare the foundation for the establishment of a climax community; typical for a particular main disease, in which an infectious process subsequently emerges. This can occur by morphological transformation of the environment (*i.e.*, direct destruction of the tissue and stimulation of the inflammatory processes) and by changing the physicochemical properties of the environment ([Khanolkar *et al.*, 2020](#)). The metabolites of the individual microorganisms can stimulate or inhibit the activity of the other community members ([Hotterbeekx *et al.*, 2017](#)).

In several studies that consider infections from an ecological perspective, there is often not enough attention paid to the relationship between a macroorganism and microbial community at the molecular level. Many researchers have underestimated the influence of microecology on normal functioning of the macroorganism. Certain defects can create an environment that is favorable for the microbial communities, which can thus cause chronic infections. For example, the cystic fibrosis pathogens, such as *Burkholderia cenocepacia*, are able to synthesize the siderophores; special molecules for receiving iron from the human cells, thus contributing to disorders to the human health ([Kozlov, 2019](#)).

In order to extrapolate an ecological model on the human microbiota formation, it is reasonable to say that the bacterial community initially goes through the stage of endogenous heterotrophic succession; during which there is a direct interaction with the substrate, *i.e.* with the macroorganism. The microbiota interact with the human body mainly *via* stimulation of its immune system development and *via* influencing the general development during ontogenesis (*i.e.*, by metabolizing certain nutrients and making them more accessible for human), as reported by [Gensollen *et al.*, \(2016\)](#); [Yu *et al.*, \(2016\)](#); [Colella *et al.*, \(2023\)](#).

Existence of the microbial community begins to be supported mainly by the external trophic resources, since at this moment the microbes interact with the substrate more indirectly; mostly by producing definite metabolites. Therefore, the prevailing type of succession for a healthy human body is the exogenous heterotrophic type.

4. Mechanisms of chronic infections emergence from an ecological perspective

Emergence of the chronic infections can be considered as a transition from an exogenous heterotrophic type of succession into an endogenous heterotrophic type. In other words, the microbiota begins to affect the substrate in a more pronounced way during adaptation to the altered environmental

conditions. The congenital or acquired defects of the substrate begin to be aggravated by the activity of the microbiota. The bacterial communities undergo structural and functional changes, due to the influence of certain ecological factors of the altered environment. As a result, the bacteria, which are traditional for a particular infectious disease; begin to dominate in the ecological niche. Over the time, the bacteria acquire resistance to several factors that cause fluctuations in the microbiota; forming a new stable community and thereby causing the chronic infectious diseases. These changes in microecology during the chronic infection can be demonstrated in more details using the chronic obstructive pulmonary disease (COPD) as an example.

5. Application of an ecological model to COPD

The chronic obstructive pulmonary disease (COPD) is a disorder characterized by the incomplete reversible restriction of airflow, which is associated with an abnormal inflammatory reaction of the lungs to form harmful particles or gasses ([Christenson *et al.*, 2022](#); [Kaur *et al.*, 2022](#)).

Among the etiological aspects of this disease, it is possible to outline the hereditary factors and definite the external influences, including smoking; previous respiratory infections, atmospheric air pollution, and inhalation of harmful gasses ([Hattab *et al.*, 2016](#); [Martinez, 2016](#)). As noted above, under the normal conditions, the oropharynx microbiota contributes mainly to the formation of the lower respiratory tract microbiota. Microorganisms from the oropharynx migrate to the lower respiratory tract through micro-aspiration, and then dispersal in the ecological niche is modulated by the elimination processes (*i.e.*, mucociliary clearance) ([Budden *et al.*, 2019](#)).

In COPD, changes in the respiratory microbiota begin with disturbances in the stochastic processes that determine the initial course of succession. Patients with COPD have impaired functioning of the mucociliary clearance, due to hyper-secretion of mucus during the inflammation. This fact provides

more favorable conditions for adhesion of the microorganisms to the respiratory epithelium ([Martinez-Garcia and Miravittles, 2022](#)). It is also more likely that air flow restriction and subsequent hyperventilation play a role in the stochastic microbial distribution, since air flow is the main factor in dispersal ([O'Donnell, 2006](#)). Thus, the balance between immigration and elimination in the formation of respiratory microbiota is disrupted. Closed selective niches may emerge, which can be occupied by the microorganisms with pathogenic potential.

[Tanno *et al.*, \(2020\)](#) reported that after primary changes in the microbiota structure, deterministic processes begin to affect the succession; causing the emergence of specific niches for the typical COPD microbiota. It is reasonable to consider a disorder in the immune system as an example of such process. In COPD, the overall level of immune protection of the respiratory tract worsens, and the phagocytic activity and secretory IgA volume decrease.

Changes in the oxygen saturation may have some influence on the course of microbial succession. During the increased mucus secretion; obturation of the individual airways may occur, thus there can be local decrease of the air flow. Oxygen does not transfer in the bloodstream and oxygen saturation gradients emerge. Therefore, the aerobic bacteria begin to dominate in the upper layers of mucus. On the other hand, in the lower layers having reduced access to oxygen, the proportion of anaerobic microorganisms increases. Normally, the anaerobic microbes prevail in the structure of the respiratory microbiota ([Quinn *et al.*, 2018](#)).

It is also important to consider the changes in chemical composition of the environment, where hyper-secretion of the mucus content of mucins increases. In the study conducted by [Singanayagam *et al.*, \(2022\)](#), the production of certain mucins has been associated with a decrease in the pulmonary function, which may be attributed to the correlation of the mucin level with the increased neutrophilic elastase production. In addition; with the increased content of

mucins, the probability of emergence of secondary bacterial infections increases. Destruction of the antimicrobial peptides resulting from the increased production of elastase can be considered as one of the underlying mechanisms ([Mallia *et al.*, 2012](#)). This may also be attributed to the fact that mucins can act as trophic resources for certain bacterial species ([Siegel *et al.*, 2014](#)). So microorganisms which are normally atypical for this environment may get resource advantage.

Along with the inflammatory reactions in COPD; destruction and subsequent incomplete restoration of the lung tissue occurs ([Giangreco *et al.*, 2009](#)). Additionally, COPD has a high risk of bronchiectasis emergence ([Martinez-Garcia *et al.*, 2021](#)). All these contribute to spatial changes in the environment, which gets a more complex spatial structure. Development of the bacterial community is directed to the variable selection type, which results in the formation of niches that are favorable for the typical COPD microbiota.

Normally, the microbiota of the lower respiratory tract is dominated by several oropharyngeal bacteria; mainly *Veillonella* spp. and *Prevotella* spp. ([Bassis *et al.*, 2015](#)). As a result of all the above mentioned factors, a typical COPD microbiota is formed instead.

In COPD, the microbiota is characterized by an increase in the number of Proteobacteria; in particular the *Haemophilus* spp., in addition to other species, including *Moraxella catarrhalis*; *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. The increased bacterial load caused by these pathogens and the reduced biological diversity correlates with the decrease in the degree of air flow, and subsequently with the severity of the disease ([Garcia-Nuñez *et al.*, 2014](#); [Sivakumaran *et al.*, 2023](#)). At the same time, the proportion of Bacteroidetes and Firmicutes in the structure of the microbial community decreases; especially the proportion of *Prevotella* spp. and *Veillonella* spp. ([Miravittles and Anzueto, 2017](#)). In addition, [Su *et al.*, \(2022\)](#) reported the correlation between the number of *Veillonella* spp. and the more

favorable functional indicators, such as the forced expiratory volume in 1 second (*i.e.*, FEV1). This fact can be considered as another sign of the microecological misbalance that causes infection emergence.

It is worth mentioning that the microbiota changes during exacerbations of COPD. Exacerbations are actually periodic complications in the symptomatic picture, which are expressed in the form of increased cough; shortness of breath, and excretion of purulent sputum ([Viniol and Vogelmeier, 2018](#)). It has been reported that during exacerbations, the proportion of Proteobacteria (*i.e.*, *Stenotrophomonas* spp. and *Haemophilus* spp.) and Actinobacteria (*i.e.*, *Corynebacterium* spp. and *Rothia* spp.) increases in the structure of the airway bacterial community ([Oladunjoye et al., 2020](#)). Meanwhile, a noticeable decrease in the numbers has been observed for *Prevotella* spp. and *Porphyromonas* spp. ([Guo et al., 2021](#)). The microbiota in exacerbations differs not only phylogenetically, but also functionally. The microorganisms may receive modified metabolic properties, *i.e.*, the synthesis of ATP-binding cassette (ABC) transporters increases. The presence of these molecules is associated with the antibiotic resistance ([Depluvere et al., 2016](#)).

The most significant decrease in the biological diversity is observed during exacerbations. The diversity can increase in reverse; when the exacerbations are relieved ([Wang et al., 2016](#)). These patterns are sufficiently correlated with the main purpose of this study, to extrapolate an ecological model in the clinical microbiology; since high diversity is one of the main detected conditions for the ecosystem stability ([Dovciak and Halpern, 2010](#)). Probably, COPD pathogens have limited nutritive resources, which may decrease with time. However, exacerbations can serve as external factors that provide disturbance in the bacterial community. During inflammation and airway tissue destruction, the pathogens receive new amounts of resources, and after such disturbance they may begin to prevail in the community structure again.

Conclusion

Emergence of an infectious process in COPD is considered as a consequence of changes in the successional course. Along with certain disorders in functioning of the lung tissue; several processes may cause modification of the microbiota. The respiratory microbiota in COPD is constantly changing, which indicates that previous communities and ongoing ecological processes are preparing the foundation for establishment of subsequent climax communities. If COPD manifestations are considered as factors that violate normal conditions of the environment; then the adaptive cycles can be extrapolated to the emergence of chronic infections. This is attributed to the fact that during exacerbations, cyclical changes in the bacterial community and the diversity level occur. The described ecological model may be applied to the other chronic infections, which emerge as complications of certain primary diseases. For example, the cystic fibrosis infections are connected with the production of viscous secretions in the respiratory tract. In the inflammatory bowel diseases, destruction of the intestinal epithelial layer occurs, which forces the microbiota to change its ecological niche. Therefore, there must be a theoretical foundation of this method, in addition to researches on the pre-mentioned diseases with respect to their ecological aspects; so as to create new methods for the possible influence on the course and outcomes of the chronic infections.

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Conflict of interest

The authors declare that they do not have conflict of interests.

Ethical approval

Non-applicable.

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Authors' Contributions

Conceptualization, D.V. and A.V.; Data curation, D.V. and K.A.; Investigation, D.V., A.V. and K.A.; Supervision, A.V.; Validation, D.V., A.V. and K.A.; Roles/Writing - original draft, D.V. and K.A.; Writing - review & editing, D.V., A.V. and K.A.

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