Antibiotics and Steroids on Nasal Microbiomein CRS Patients

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Contributor: Antonella Loperfido, Carlo Cavaliere, Elona Begvarfaj, Andrea Ciofalo, Giovanni D'Erme, Marco De Vincentiis, Antonio Greco, Stefano Millarelli, Gianluca Bellocchi, Simonetta Masieri

The nasal microbiome represents the main environmental factor of the inflammatory process in chronic rhinosinusitis (CRS). Antibiotics and steroids constitute the mainstay of CRS therapies.

Keywords: chronic rhinosinusitis ; microbiome ; microbiota ; antibiotic therapy ; steroid therapy

1. Introduction

Chronic rhinosinusitis (CRS) represents a chronic inflammatory disease of the nose and the paranasal sinuses with a high prevalence in the general population (10.9% in Europe) [1]. This condition results in a significant burden on society regarding healthcare costs and lost productivity, and on the individual in terms of reduced quality of life (QoL) [2].

The nasal microbiota represents the major environmental driver of the inflammatory process in CRS, as the dysfunctional interactions that occur between microorganisms and the host immune system is known to trigger mucosal inflammation. In particular, the nasal flora dysbiosis, which means the destruction of the indigenous microbiota, can alter the integrity of the mucosal barrier, leading to the overgrowth of pathogens and inducing greater susceptibility to infections, further contributing to CRS [3][4].

In particular, in many studies on CRS, research has found a decrease in microbiome diversity and richness, as well as evenness. The reported alterations represent typical mucosal features in chronic inflammatory disorders, including CRS [5].

This deterioration may be the result of an increased presence of anaerobic bacteria that grow in biofilms [6]. Interestingly, specific works on this topic showed that in patients with CRS, the overall bacterial load was constant, while the relative richness of specific bacterial species was altered [7].

According to the literature, the microbiome in the nasal cavity of healthy adults is constituted mainly of the Corynebacteriaceae, Staphylococcaceae, and Propionibacteriaceae. However, considerable compositional variability is possible among individuals [5].

Bacterial dysbiosis represents an important biomarker of CRS. Indeed, some authors have highlighted that bacterial organisms are involved in the pathogenesis of CRS, and consequently, an alteration to the normal microbiota community of the nasal and paranasal sinus mucosa is one of the causes of CRS. Changes in the composition of microbiota can be the result of several factors, such as external and environmental triggers, which include seasonal changes, exposure to cigarette smoke, medications taken, smog, and so on; the immune status of the host; age; and intra-microbiota interactions [3][5].

Antibiotics and steroids constitute the mainstay medical treatment of CRS. Antibiotics are often prescribed to these patients to suppress pathogenic bacteria [8]. Nevertheless, it is not clear whether or not long-term antibiotic use has a positive impact on CRS patient outcomes [9]. Indeed, some studies have shown that exposure to antibiotics could be implicated in developing allergic diseases and chronic inflammation of the paranasal sinuses [10][11]. Furthermore, several authors have highlighted how prolonged exposure to antibiotic therapy can lead to an increased risk of cardiovascular events [12][13][14].

2. The Impact of Antibiotics and Steroids on the Nasal Microbiome in

Patients with Chronic Rhinosinusitis:

The human microbiome represents a heterogeneous community of microorganisms that live symbiotic relationships in human microhabitats. This entity is considered integral to maintaining the immune system and health, and due to the specificity of the microbial niche, the microbial composition varies across several anatomical locations, including the airways, gastrointestinal system, and skin [15][16].

Focusing on the airways, it has been demonstrated that the upper airway is continuously subjected to airflow from the external environment, as a healthy adult is able to breathe over 7000 L of air per day. The upper airways therefore provide critical physiological functions, such as humidifying, warming, and filtering inhaled air [17]. Since the nasal cavities communicate with the external environment through the anterior nostrils, they serve as a physical transition, providing an interface between the outside and the lower airways and gastrointestinal tracts [18].

Furthermore, along with the airflow, each individual inhales approximately 10^4–10^6 biological particles per cubic meter of air every day. Moreover, in addition to these bacterial cells, the upper airways are exposed to physical and chemical weathering agents, including oxygen, variable humidity, immunological, or nutritional factors. These factors are very important because they are responsible for the formation of specific microenvironments in the different districts of the upper airway, which include the anterior nostrils, the nose cavities, the sinuses, the nasopharynx, the Eustachian tubes, the middle ear cavities, the oral cavity, the oropharynx, and the larynx [19].

Consequently, all of these different microenvironments that constitute the upper airway host specific microbial communities composed of transient and resident microorganisms in varying proportions [20].

In research, the most frequent sampling sites for analyzing the microbiome of the upper airway are the anterior nostrils, middle meatus, and nasopharynx. The primary function of the nasal mucosa, which is the elimination of inhaled air, may explain the greater diversity of mucosal samples among these districts [21][22].

The surfaces of the nasal vestibule and anterior nostrils are relatively drier than the other districts of the upper airway. These parts are the most exposed to the external environment, and their epithelium includes sebaceous glands and vibrissae. These hairs capture the larger particles (>3 μm) of inhaled air, while smaller particles including microorganisms are trapped in a blanket of mucus covering the nose cavity and then transported by ciliated epithelial cells from the nose into the esophagus according to the process known as mucociliary clearance [23][24].

The middle meatus represents an area of great interest for research on the nasal microbiome, as the drainage of secretions from the anterior ethmoid, maxillary sinus, and frontal sinus converge in this anatomical district [25].

The nasopharyngeal mucosa is constituted by several crypts and folds, and its surface is characterized by pseudostratified ciliated epithelium and keratinized and nonkeratinized stratified squamous epithelia [26].

In addition, the nasopharyngeal cavity is the site of nasopharynx-associated lymphoid tissue (NALT), which consists of adenoids, the paired palatine tonsils, the paired tubal tonsils, and the lingual tonsil. These are composed of a wide variety of elements of the immune system, including macrophages, lymphocytes, and dendritic cells, and represent important sites for both detection and defense against microbes [27].

The paranasal sinuses play an important role in humidifying and warming the inhaled air. They are lined with ciliated columnar epithelium that creates mucus that drains into the nose cavities. These drainages generate local microniches characterized by specific microbial populations within the nasal fossa [28].

Interest in the olfactory microbiome is also growing [29]. In fact, recent research has shown a potential correlation between olfactory dysfunction and dysbiosis of the nasal microbiome of the olfactory area, specifically located on the roof of the nasal cavity at the lamina cribrosa [30].

If the human microbial community is imbalanced, beneficial and commensal bacteria that act against the excessive growth of pathogenic bacteria are typically lost [31].

The microbiota is influenced by several conditions, which include external and environmental factors, the host's age and immune status, and intra-microbiota interactions. Among environmental factors, exposure to cigarette smoke, both active and passive, affects the nasal microbiome. In fact, cigarette smoke has immediate contact with the nasal mucosa resulting in direct impact on nasal flora through some mechanisms such as oxygen deprivation and antimicrobial activity.

Furthermore, the toxic substances typically associated with cigarette smoke can break effective mucociliary clearance in the airways, impairing the immune responses against pathogens [3].

Compositional or functional alterations to the microbiome can occur in different anatomical districts. This dysbiosis has been linked to several chronic inflammatory disorders, such as inflammatory bowel diseases including ulcerative colitis and Crohn's disease, and skin disorders such as atopic dermatitis, psoriasis, acne, and urticaria [32].

In addition, gut dysbiosis is known to be related to increased susceptibility to respiratory diseases and disorders of immunologic response and lung homeostasis. This pathophysiological mechanism is known in the literature as the gut–lung axis [33].

Changes in the microbiome are also highlighted in CRS, where the phenomenon explicitly affects the upper respiratory tract [34].

Bacterial dysbiosis associated with CRS is typically characterized by decreased diversity, elevated overall bacterial load, fragmentation between networks, loss of critical species, and colonization by pathobionts, such as *Staphylococcus aureus* [35][36].

It was once believed that nasal cavities were sterile in healthy people, with CRS emerging as a consequence of bacterial infection [37]. However, it is now widely known that several microbial communities colonize the healthy nasal region and act symbiotically there [38].

Specifically, the microbiome of a healthy nasal region is constituted mainly of Bacteroidetes, Firmicutes, phyla Actinobacteria and Proteobacteria with representatives of genera *Corynebacterium*, *Bifidobacterium*, *Dolosigranulum*, *Streptococcus*, *Staphylococcus*, and predominant *Moraxella* [39]. However, the majority of studies on this topic focus on the nasal bacterial component, with the possibility that other components of the nasal cavities' microbiome, such as fungi, archaea, and viruses, are undertreated and therefore likely neglected [40].

The nasal cavities, especially the most anterior portion, are directly exposed to thousands of liters of inhaled air each day [41]. So, together with the gastrointestinal system, the nasal cavities are described as the main gateway for pollutants, inhaled pathogens, allergens, and pollen. This can cause possible imbalances in the community composition of the nasal microbial flora [42].

Research on the microbial community residing in the paranasal sinuses is increasingly growing. The capabilities of traditional culture methods have been surpassed, and thanks to advances in molecular technology, it is possible to distinguish numerous microbial species occupying host niches [43].

A work concerning the microbiome of the paranasal sinuses reported that most sinuses of patients with CRS are colonized by the bacterial families of *Pseudomonadaceae*, *Corynebacteriaceae*, *Streptococcaceae*, or *Stafilococcaceae* [44]. Further research revealed a *Corynebacterium tuberculostearicum* overgrowth and an enrichment in *Staphylococcus* in the paranasal sinuses [45]. Other authors have also isolated *Corynebacterium*, *Staphylococcus*, *Pseudomonas*, *Curtobacteria*, and *Haemophilus influenzae* as dominant bacterial species, specifically in the middle meatus of patients suffering from CRS [46][47].

CRS represents a chronic inflammatory disease of the nasal and paranasal sinuses. It affects up to 16% of the population and, although it is assumed to be an inflammatory disorder rather than an infectious one, it is important to consider bacterial contributions to the initiation and progression of inflammation [1].

Specifically, the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020), provides a clinical definition of CRS in adults as a condition of inflammation of the sinuses typified by the presence for at least twelve weeks of two or more of the following symptoms: nasal discharge (anterior and/or posterior nasal drip), nasal congestion, decreased sense of smell, and facial pressure. In particular, one of the symptoms reported by the patient should be nasal congestion or nasal discharge. In addition to these symptoms, endoscopic signs of nasal polyps and/or mucus discharge and/or mucosal edema/obstruction of the middle meatus and CT scan abnormalities, such as mucosal changes within the ostiomeatal complex and/or sinuses, support this diagnosis.

With these guidelines, clinicians and researchers are experiencing a new era in the approach to this disease since, according to EPOS 2020, the classification of CRS has changed significantly. There has been a shift from a traditional phenotype classification of the disease, established by the presence (CRSwNP) or absence (CRSsNP) of nasal polyps, to an endotype classification, based on molecular biomarkers and specific pathophysiological mechanisms. Based on the

underlying immunological pathophysiology, two dominant endotypes are distinguished: the type 2, related mostly to the Th2 immune response, and non-type 2 [9].

The type 2 immune pathway is defined by an overproduction of cytokines interleukin (IL)-13, IL-4, and IL-5; increased IgE; and eosinophils. Clinically, type 2 endotype is the most common in CRSwNP and is typically related to comorbid asthma, loss of smell, and reduced response to standard treatments, with a higher risk of recurrence compared to non-type 2 endotypes [48].

The non-type 2 immune pathway includes a combination of type 1 and type 3 immune reactions. In these pathways, the epithelial reaction to environmental triggers induces stimulation of dendritic cells and then differentiation of Th1 and Th17 cells, resulting in non-eosinophilic inflammation [49].

Recent studies have shown that *Staphylococcus aureus* is mainly associated with CRS and drives type 2 inflammatory responses through enterotoxin secretion or by binding to Toll-like receptor 2 (TLR2) [50][51]. Consequently, patients with CRSwNP, particularly those with comorbid asthma, are characterized by an increased relative abundance of *Staphylococcus aureus* [52]. Furthermore, *Streptococcus* and *Hemophilus* may be involved in neutrophil recruitment and IL-8 release in non-type 2 CRS [53][54].

Besides the nasal sinus microbiome disruption, there are many theories reported in the literature underlying the pathogenesis of CRS, including proinflammatory biofilms, underlying immune responses to airborne fungi, Staphylococcal enterotoxins, and host barrier disfunctions with inadequate immune responses. In particular, the final hypothesis on host barrier discontinuity is interesting because it includes all the components of all these hypotheses. Indeed, this hypothesis implies the loss of the barrier function, the colonization by bacteria and fungi, the impairment of host defense with increased local autoimmune response, and increased local innate and adaptive immune response. According to the most recent literature, treatment of CRS does not consider the underlying pathophysiology of the disease, but rather targets the downstream inflammatory response [55].

Regarding the role of topical steroids, while Liu et al. found no significant changes in the nasal microbiome when treating patients with topical budesonide, Latek et al. demonstrated that treatment with topical mometasone had a significant effect on improving sinonasal biodiversity and improving the QoL of young patients [56][57].

Even regarding the therapeutic role of antibiotics in CRS, the conclusions of the collected papers differ. Chen et al., detecting a decrease in *Streptococcus pneumoniae*, stated that long-term oral administration at low doses of clarithromycin may have a regulatory effect on the nasal microbiota, allowing for mucosal epithelialization and improvement in clinical symptoms in patients with RCRS [58]. In contrast, Siu et al. found no significant changes in community or bacterial load, thus highlighting the poor sinonasal penetration of the drug as well as the unproven efficacy and possible impact of dysbiosis in sinuses and off-target sites. Hauser et al. also noted no significant changes, emphasizing the high degree of resilience of the microbiome. In addition, Lux et al. concluded that the unpreventable antibiotic impact on the sinus microbiota does not justify antibiotic therapy in the preoperative setting for patients with CRS [59][60][61].

Concerning the use of both antibiotics and steroids, Alammar et al. supported the avoidance of systemic antibiotics in CRS unless there is evidence of active infection, while Renteria et al. found a decrease in *Staphylococcus aureus* in the nasal microbiome in patients treated with antibiotics and concluded that azithromycin may constitute a valid therapeutic option for disease control [62][63].

Concerning studies on mixed medical treatments that include antibiotics or steroids, the authors could not ascertain whether the changes in the microbiome associated with the various treatments have clinical significance and, according to these papers, the use of systemic therapy in patients with CRS should be rationalized to minimize bacterial dysbiosis and the risk of resistance associated with antibiotics [64][65][66].

Some of the studies assessed the effects of antibiotics on the microbiome of patients affected by RCRS. RCRS is a subtype of CRS with unclear pathophysiology characterized by increased recurrence rates after sinus surgery, greater severity of symptoms, and associated comorbidities. As well as the impact of steroids and antibiotics, the improvement in ciliary function and the mechanical effect of saline irrigations on the stagnant secretions may account for the changes in the nasal microbiome.

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