LANG, Miriam, BEREZA, Dawid, KULAK-WAŚNIEWSKA, Maria, MOREAU, Igor, POLAŃSKA, Paulina, SOKOŁOWSKA, Katarzyna and WOCH, Barbara. The influence of the sinonasal microbiome on the development and management of rhinosinusitis. Journal of Education, Health and Sport. 2025;77:56769. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.77.56769
https://apcz.umk.pl/JEHS/article/view/56769

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 08.12.2024. Revised: 02.01.2025. Accepted: 02.01.2025. Published: 03.01.2025.

The influence of the sinonasal microbiome on the development and management of rhinosinusitis.

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Abbreviations used:

EPOS 2020 - European Position Paper on Rhinosinusitis and Nasal Polyps 2020
CRS - chronic rhinosinusitis
ARS - acute rhinosinusitis
TSLP - thymic stromal lymphopoietin
IL-33 - interleukin 33
IL-1 - interleukin 1
mDCs - myeloid dendritic cells
ILC2 - type 2 innate lymphoid cells
IL-5 - interleukin 5
IL-13 - interleukin 13
CRSwNP - CRS with nasal polyps
CRSsNP - CRS without nasal polyps
ESS - endoscopic sinus surgery

ABSTRACT:

Introduction and purpose: Chronic rhinosinusitis (CRS) is a frequently diagnosed condition in patients seeking medical care. It encompasses a range of disorders that can be classified based on underlying causes, clinical symptoms, or inflammatory types. Although the precise cause of CRS remains unclear, the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) has recently offered updated insights, treatment strategies, and recommendations.

State of knowledge: Recent research has increasingly focused on the role of the microbiota in inflammatory diseases. The optimal bacterial environment in the sinonasal mucosa, where inhaled bacteria, viruses, fungal spores, and particles initially interact, is still not fully understood. The dysbiosis theory, which emphasizes the importance of the microbiome and its relationship with the host, is the predominant model explaining CRS pathogenesis. Disruptions in this balance can lead to a variety of clinical manifestations in CRS patients.

Conclusions: Given the impact of CRS treatment on the composition of sinus and nasopharyngeal microbiota, the dysbiosis theory highlights the importance of addressing this aspect in therapeutic strategies. Ongoing research is exploring the potential use of pre- and probiotics as novel treatment options. A more thorough understanding of the microbiological factors involved in CRS is crucial for developing personalized, targeted therapies for affected individuals.

Keywords: microbiome; nasal polyps; rhinosinusitis

1. Introduction and purpose

Chronic rhinosinusitis (CRS) represents one of the most common healthcare problems. The role of the microbiota in the context of inflammatory changes in the sinuses is being underlined in more and more scientific papers. The current state of knowledge on this disease is presented in the recommendations of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020). The studies about sinonasal microenvironment are still in their beginning; many findings have not been replicated due to small study cohorts and variable experimental methods. Because of the rapid evolution of the knowledge in this matter, the purpose of this review is to encourage a thorough discussion on the nasopharyngeal and sinus microbiota regarding pathogenesis, risk factors, current treatments, and future therapeutic directions.

2. Definition and prevalence

Rhinosinusitis is a heterogeneous group of inflammatory diseases of the paranasal sinuses, which is almost always accompanied by the inflammation of the nasal cavities [1]. The estimated one-year prevalence of acute rhinosinusitis (ARS) is 6-15%, while for chronic rhinosinusitis the numbers vary depending on the applied criteria [2]. Although the presence of either symptoms or objective findings alone has yielded CRS prevalence estimates of over 10%, the presence of both - consistent with guideline-based diagnostic criteria - has suggested that the true prevalence of CRS is less than 5% [3]. Therefore, it is one of the most commonly diagnosed medical conditions, leading to significant medical costs, loss of productivity, and a decrease in the quality of life.

3. Diagnosis and symptoms.

The diagnosis of rhinosinusitis in adults is based on the clinical symptoms in addition to objective evidence of inflammation. Required is the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip). Other cardinal symptoms are facial pain or pressure and

reduction or loss of smell. Objective evidence of CRS are nasal polyps, mucopurulent discharge, and oedema or mucosal change and they may be obtained on physical examination (anterior rhinoscopy, endoscopy) or radiography, preferably from sinus computed tomography. They were added as a diagnostic criterion because although the presence of symptoms is sensitive for the diagnosis of CRS, it is not specific [1]. According to the guidelines, the symptoms must be present for at least 12 consecutive weeks to diagnose chronic rhinosinusitis [2].

4. Classification

The further classification of CRS takes into account the presumed aetiology, clinical phenotype, and endotype inflammatory patterns. Since CRS is heterogeneous regarding its pathophysiology, prognosis, severity, and response to treatment, it is essential to precisely assign the disease to the proper category. The authors of EPOS 2020 proposed a classification of CRS into primary and secondary CRS and a division of each into localised and diffuse diseases based on anatomic distribution. In both of these groups, the disease is considered by endotype dominance, either type 2 or non-type 2.

This classification takes into consideration the immunological mechanism of inflammatory reactions and cytokine release, which leads to the inflammation and remodelling of the mucosa [4]. There are three types of immune response:

- type 1 (T1) - a reaction directed against intracellular pathogens (viruses, bacteria, and parasites);
- type 2 (T2) - a reaction directed against extracellular parasites and allergens;
- type 3 (T3) - a reaction directed against extracellular bacteria and fungi.

Type 2 inflammation describes the most common pathogenic mechanism among CRS patients [5]. It can be provoked by multiple factors such as fungi, proteases, bacteria, viruses, and allergens. Activating nasal epithelial cells leads to the production of epithelial-derived cytokines, thymic stromal lymphopoietin (TSLP), IL-33, and IL-1, which activate immune cells. TSLP stimulates myeloid dendritic cells (mDCs) to induce naive $CD4^+$ T-cell differentiation into Th2 cells which then induce adaptive type 2 inflammation. TSLP and IL-33 stimulate type 2 innate lymphoid cells (ILC2s) to induce the production of type 2 cytokines. Mast cells are accumulated in the mucosal and epithelial cells. TSLP, IL-33, and IL-1 stimulate epithelial and mucosal mast cells to produce IL-5 and IL-13 (innate type 2

inflammation). Ag/IgE/IgER complexes on mast cells induce degranulation and thereafter mast cells produce IL-5 and IL-13 (adaptive type 2 inflammation) [6]. The consequences of this activation and migration of the immune cells are significant changes in mucosal physiology and tissue remodelling, such as mucus accumulation, smooth muscle hypercontractility, microbiome dysfunction, and sensory nerve dysfunction [7]. Elevated IgE and eosinophils are also characteristic of type 2 inflammation [8]. The chronic inflammatory process may result in the development of nasal polyps. Neutrophils are present and activated in severe type 2 CRS with nasal polyps (CRSwNP), where they interact with eosinophilic inflammation, causing a mixed inflammation. The presence of this inflammation in CRS is associated with a worse disease outcome, glucocorticosteroid resistance, and recurrence after surgery [9]. The calprotectin concentration in nasal secretion is used as a marker of increased neutrophil presence in CRSwNP [10].

Non-type 2 inflammation presents a mixed type 1 and type 3 inflammation, often associated with significant neutrophil infiltration. The key role plays the interleukins 6 and 8. Pathogen invasion of nasal epithelia leads to the release of IL-6, IL-8, Tumor Necrosis Factor, and various chemokines by nasal epithelia. Interactions of Pathogen Associated Molecule and Toll-like Receptors also result in stimulating the production of these cytokines and recruiting the neutrophils. Neutrophils release a variety of products, including inflammatory cytokines IL-1β, IL-6, and IL-8, and myeloperoxidase (MPO), an enzyme released by neutrophil granulocytes. IFN-γ, secreted by epithelial cells in response to pathogen recognition, directs CD4+ T-cell differentiation toward Th1 maturation, induces apoptosis of nasal epithelial cells, and stimulates neutrophil activity [11]. Th1 cells mediate the type 1 inflammatory response through the production of the characteristic markers: IFN-γ and IL-2. Further interactions cause the secretion of antimicrobial peptides and mucin 1 in an inflammatory environment [12]. In response to different markers, increased mucus production is seen in both types of inflammation. Epithelial cells take a central role in type 3 inflammation, primarily by producing osteopontin. This osteopontin, in turn, activates dendritic cells, leading to the initiation of Th17 differentiation. Clinically, this type of inflammation is associated with purulent nasal discharge [13].

5. Nasal polyps.

Chronic rhinosinusitis may be also phenotypically differentiated based on the presence of nasal polyps; CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [14]. Other phenotypes of CRS are fungal rhinosinusitis (including invasive and noninvasive subtypes), infectious rhinosinusitis, aspirin-exacerbated respiratory disease, cystic fibrosis, paediatric CRS, and CRS associated with systemic diseases [15]. The clinical presentation of chronic rhinosinusitis is closely related to the inflammatory endotypes. Some patients may present a single endotype with one predominant immunology pattern, while another may have a mixed endotype, which can involve all three types of inflammatory reactions. Stevens et al. described that patients with the T2 endotype are significantly more likely to have nasal polyps, asthma, smell loss, and allergic mucin and less likely to report rhinorrhea, cough, and pus. In addition, the presence of pus was significantly more common in T1 and T3 endotypes [5]. Tomassen et al. tried to identify the endotypes of patients suffering from CRS using immune markers and then matched the clusters with the phenotypes to find the correlation [16]. In this multicenter case-control study patients with CRS and control subjects underwent surgery, and tissue was analysed for inIL-5, IFN-g, IL-17A, TNF-a, IL-22, IL-1b, IL-6, IL-8, eosinophilic cationic protein, myeloperoxidase, TGF-b1, IgE, Staphylococcus aureus enterotoxin–specific IgE, and albumin. In the analysis of 173 cases, 10 clusters were identified, of which 4 clusters with low or undetectable IL-5, eosinophilic cationic protein, IgE, and albumin concentrations, and 6 clusters with high concentrations of those markers. In the group of IL-5–negative clusters, 3 clusters clinically presented a predominant CRSsNP phenotype without increased asthma prevalence, and 1 cluster had a TH 17 profile and had mixed CRSsNP/CRSwNP. Among the IL–5–positive clusters two groups were distinguished: a group with moderate IL-5 concentrations, a mixed CRSsNP/CRSwNP and increased asthma phenotype, and a group with high IL-5 levels - an almost exclusive nasal polyp phenotype with strongly increased asthma prevalence. In the latter group, 2 clusters demonstrated the highest concentrations of IgE and asthma prevalence, with all samples expressing Staphylococcus aureus enterotoxin–specific IgE. Eosinophilia is also a characteristic of CRSwNP in comparison to CRSsNP or control sinus mucosa. As mentioned in multiple scientific papers, CRSwNP is associated with increased *S. aureus* presence, in comparison to CRSsNP, presumably because of the multiple niches created by the presence of nasal polyps [14]. *S aureus* can form biofilms, the microenvironment, where the microorganisms are more likely to survive antibiotic treatment, or it might penetrate the mucosa and reside inside the cells or the mucosa and form enterotoxins with superantigenic activity [17].

6. Healthy microbiota

The perception of diseases, especially inflammatory ones, has been changing a lot in the last few years. The role of the microbiota, defined as the combined genetic material of the microorganisms in a particular environment, seems to be essential for the human body to maintain its functions at a proper level. It generally serves a mutualistic purpose; organisms gain a nourishing milieu while the human host receives benefits such as improved immunologic development and metabolism. The host-microbial interactions are involved in the stimulation of the innate immune system, preparing it for exposure to external pathogens [18]. The nasal mucosa is the place of the first contact with inhaled bacteria, viruses, fungal spores, and many other particles. The healthy microbiologic environment is largely composed of bacteria, especially strains of *Staphylococcus aureus*, *Streptococcus epidermidis,* and *Corynebacterium* genera, which are known to produce substances that interfere with the function of the mucociliary system of the epithelium and influence the junction between the cells [14,19]. A loss or reduction in the richness of these commensal species may result in a decrease in epithelial integrity in patients with chronic sinusitis. The type of bacteria varies not only between individuals but also between anatomical spaces in the sinuses and the nasopharyngeal cavity, making it hard to determine the most representative sampling site while doing the research [20]. The middle meatus is often used as this site for the deeper sinuses, because of its high agreement in culture comparison studies with the maxillary sinus, its location as a common drainage pathway of the three major (maxillary, anterior ethmoid, and frontal) sinuses, and its accessibility for sampling [21]. Another important factor influencing the local microenvironment of the sinuses and nasopharyngeal space are viruses and fungi - yet not been researched enough to be able to determine their exact role and the hypothesised interactions with bacteria [22]. Multiple studies have demonstrated its presence in CRS [22–25]. Virus replication can cause epithelial damage and increase bacterial mucosal adhesion, whereas fungi may act synergistically with pathogenic bacteria to play a role in the pathogenesis of CRS [25,26].

7. Dysbiosis theory

Many opportunistic pathogens are found at low abundance in healthy sinuses and, therefore, have the potential to cause disease after an acute alteration in the stable microbial community. Changes in the composition of the microenvironment may result in exacerbation of the chronic inflammatory disease and can provoke existing microbial communities to become pro-inflammatory, invasive, or to allow the overgrowth of pathogens [21].

In CRS, as in many chronic inflammatory diseases, a significant dysbiosis is observed between the commensal population and pathogenic bacteria, which leads to changes in sinonasal mucosa. However, not only the microbiome in the mouth-nasal cavity seems to play a role in the pathogenesis of sinusitis - multiple scientific researchers emphasise the correlation between the intestinal microenvironment and the functioning of the respiratory tract [27]. Definitive treatment and understanding of CRS remain unclear, but recent scientific advances in microbiological characterization have accentuated both the protective and pathogenetic roles of the sinonasal microbiota. For example, Copeland et al. identified the genus *Corynebacterium* as an important composition of the sinonasal microbiota that was significantly increased in healthy sinuses compared to the CRS sinuses, supporting a possible probiotic nature of some species within the genus [28]. Other observations in previous studies have also shown a higher abundance of the genus *Corynebacterium* in controls compared to CRS. For instance, Cleland et al. discovered that *C. confusum* was correlated to healthy individuals [29]. Not all members of the genus may show the same relation, as *C. accolens* and *C. tuberculostearicum* are more abundant in CRS sinuses [30,31].

The experiment with *C. tuberculostearicum* followed by Abreu et al. demonstrated goblet cell hyperplasia and mucin hyper-secretion, two important histologic hallmarks of CRS [31]. However, only 7 samples from CRS patients have been analysed, and another study subsequently reported opposing findings that CRS patients with enriched *C. tuberculostearicum* colonisation at the time of endoscopic sinus surgery showed improved surgical outcomes [32]. Aurora et al. found that nasal lavage samples of microbiota collected from CRS patients stimulated the induction of proinflammatory cytokines such as IL-5 in peripheral leukocytes isolated from healthy controls [30]. The collected data indicates that chronic rhinosinusitis involves an altered microenvironment that interacts with an aberrant immune response. Which of these two factors is causative remains unclear.

Because of the different pathogenesis, it was hypothesised that the microenvironment in CRSwNP and CRSsNP patients would also vary. However, Wei et al. compared the bacterial composition of the middle meatus in CRSwNP patients, CRSsNP patients, and

patients without a diagnosis of CRS, and the results were other than expected [33]. In this culture-dependent investigation, the most commonly isolated strains from 136 cases of CRSwNP were *Corynebacterium* (19.9%), *S. epidermidis* (19.1%), *Streptococcus* (14.7%), and *S. aureus* (11.0%); the most prominently isolated strains in the 66 CRSsNP cases were *Corynebacterium* (21.2%), *S. epidermidis* (21.2%), *S. aureus* (13.6%), and *Streptococcus* (7.6%). These four bacteria composed the majority of isolated strains in the 17 control cases, and when compared across the three study cohorts, there was no statistically significant difference in abundance. The only important difference was presented by the strain *Citrobacter*, with a 5.9% isolation rate found in CRSwNP and no isolated strains found in the CRSsNP and control groups. The results obtained by this research have been confirmed in other studies, leading to the conclusion that the existence of nasal polyps has presumably no association with the sinonasal microbiota [34]. However, the stratification of the study groups enabled the identification of an association between the type of bacteria and allergic asthma, along with the eosinophil percentage in the peripheral blood. This correlation has been observed in other research studies as well [33].

8. Treatment

The research on dysbiosis in the context of the treatment of CRS is highly challenging since the medical therapies used to cure the disease often affect the sinonasal microbiome. Treatment of CRS is directed at enhancing mucociliary clearance, reducing local infection and inflammation, and removing obstructive defects using medications or surgical procedures. Current first-line treatments for both CRS phenotypes are nasal saline irrigations and intranasal corticosteroid sprays. According to the EPOS 2020 Guidelines antibiotic therapy should be introduced only in the severe form of CRS, with high fever, severe pain, and significantly elevated inflammatory parameters. In case of a failure of medical management, functional endoscopic sinus surgery is performed to help restore sinus ventilation. There is a small number of scientific papers raising the subject of CRS treatment and its influence on microbiota, however, existing ones suggest a correlation between antibiotic therapy and a decrease in microbiota diversity and evenness [35]. Macrolides and doxycycline have been recommended for the treatment of CRS because of their antibacterial and anti-inflammatory properties [36]. The use of antibiotic treatment eliminates pathogens but also has a wide range of unintended side effects and when applied unnecessarily, can lead to the increase of

bacterial resistance. For instance, intranasal mupirocin in CRS patients and mupirocin irrigation during endoscopic sinus surgery were efficient in short-term *S. aureus* decolonization. However, a four-week course of mupirocin washes to eliminate antibiotic-resistant *S aureus* resulted in a high rate of microbiological failure (73.7%) and the selection of non-*S. aureus* pathogens [37]. In one study it was suggested that the T3 endotype in CRS is most strongly linked to bacterial infection, and thus the T3 patients may be the most responsive to the treatment with antibiotics [5].

There is no evidence that nasal saline irrigation, with or without added budesonide, results in a significant alteration in the proportional abundance of commensal bacteria or biofilm-forming pathogens in CRSwNP patients [38]. However, corticosteroids have strong anti-inflammatory properties and suppress T2 inflammation greater than T1 and T3, which explains their better efficacy in CRSwNP than CRSsNP [39,40].

The impact of surgery on the sinonasal microbiome has been poorly investigated. There is a suggestion that the diversity of the bacterial species declines after endoscopic sinus surgery (ESS) [29]. The combination of antibiotics and anti-inflammatory therapy significantly decreased the biodiversity of the microbiota in post-operative maxillary sinuses in one study [35]. On the other hand, some studies prove the increased bacterial richness after ESS, especially the *Staphylococcus spp*. but at the same time underline the unpredictable changes in the microbiological composition after surgical treatment [41].

Oral probiotics were also considered as a method of improvement of the immune system and enrichment of the nasal microbiota. The use of oral *Enterococcus faecalis* showed benefit in treating CRS and recurrent acute rhinosinusitis in two studies [42,43]. The relation between gut and sinus microbiota has been investigated, as the role of protective bacteria in the intestines is well-known. Alteration of the composition of gut microbiota, especially deficiencies of protective and immunostimulant species might play a significant role in healing and regeneration as well as complications after surgical procedures and recurrences of sinusitis [44]. CRS is related to lowered numbers of Bifidobacterium, *Akkermansia muciniphila*, and *Faecalibacterum prauznitz*. Patients with comorbidities also had lowered numbers of Lactobacillus. Deficiencies of the mentioned species and genera might lead to overgrowth of some potential pathogens, for example, *Candida albicans*, *Clostridium difficile*, and Proteus spp. Systemically, ingestion of probiotics enhances the production of γ-interferon, and interleukin-2 lymphocyte responses and shifts the balance of Th cells toward an increased

Th1:Th2 ratio, which may preferentially augment T-regulatory reactions resulting in counterbalancing the excess Th2 activity characteristic for CRSwNP [45].

9. Discussion.

A further microbiologic understanding of CRS can lead to more focused treatment and more detailed conclusions from scientific research. Taking into consideration the pathogenesis of CRS and the constantly actualized knowledge about the human microenvironment, it is essential to determine the healthy microbiome patterns and their alterations in response to various factors. The role of bacterial supplementation and modulation of the microbiota through pre- or probiotics should be further investigated to find the most precise and individual therapy for patients suffering from CRS.

Author contributions

Conceptualization, DB and KS; methodology, ML and BW; software, not applicable; check, KS, PP, DB and BW; formal analysis, PP, MK, IM and KS; investigation, MK and PP; resources, not applicable; data curation, IM, PP, ML, BW; writing - rough preparation, DB; writing - review and editing, DB, BW, MK and ML; visualization, DB, IM, KS; supervision, DB; project administration, KS; receiving funding, not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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