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Katarzyna Molińska[1], Paweł Majak[2]

Dysbiosis and allergy as a background of chronic rhinosinusitis in preschool children

Dysbioza i alergia jako tło przewlekłego zapalenia błony śluzowej nosa i zatok przynosowych u dzieci w wieku przedszkolnym

[1] Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Łódź, Poland
[2] Department of Paediatric Pulmonology, Medical University of Lodz, Łódź, Poland
Correspondence: Katarzyna Molińska, Department of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Kopcińskiego 22, 90-153 Łódź, Poland, e-mail: katarzynamolinska3@gmail.com

ORCID iDs
1. Katarzyna Molińska https://orcid.org/0000-0001-6177-5246
2. Paweł Majak https://orcid.org/0000-0002-2532-9983

Abstract

Allergic diseases and chronic inflammatory diseases of the respiratory system, such as asthma or chronic rhinosinusitis, continue to pose a real challenge to modern medicine. The causes of the growing problem generated by these diseases is thought to be in the interaction of genes and the environment. In the light of current knowledge, it seems that the environmentally dependent interaction between the airway microbiota ecosystem and the epithelium is able to shape the functions of the local immune system, producing a number of molecular and clinical consequences. In this paper, an attempt was made to describe the role of microbiota composition disorders (dysbiosis) of the upper respiratory tract and allergies in the development of chronic rhinosinusitis in children. The research results obtained in a Polish cohort of young children diagnosed with chronic rhinosinusitis with or without concomitant asthma are summarised. Some of the children presented with features of secondary dysbiosis, which was associated with sensitisation to house dust mite allergens. It was noted that frequent courses of antibiotic therapy correlated with microbiota dysfunction, reducing biodiversity. It was also observed that patients suffering from asthma had specific dysbiosis in the upper respiratory tract. It is characterised by an altered proportion between the main types of bacteria and is expressed by a reduced *Patescibacteria/Actinobacteria* ratio, constituting an independent factor of asthma in the study group, similar to atopy and reduced perception of the sweet taste. An attempt was also made to identify possible therapeutic and prophylactic interventions to treat and prevent dysbiosis in children suffering from chronic rhinosinusitis.

Keywords: children, dysbiosis, house dust mite allergy, chronic rhinosinusitis, allergen immunotherapy

Streszczenie

Choroby alergiczne oraz przewlekłe zapalne choroby układu oddechowego, takie jak astma czy przewlekłe zapalenie błony śluzowej nosa i zatok przynosowych, pozostają wciąż istotnym wyzwaniem dla współczesnej medycyny. Przyczyn narastających problemów związanych z tymi chorobami upatruje się we wzajemnym wpływie genów i środowiska. W świetle aktualnej wiedzy wydaje się, że środowiskowo zależna interakcja między ekosystemem mikrobioty dróg oddechowych a nabłonkiem jest w stanie kształtować funkcje lokalnego układu immunologicznego z wieloma konsekwencjami molekularnymi i klinicznymi. W prezentowanej pracy dokonano próby opisu roli zaburzeń składu mikrobioty (dysbiozy) górnych dróg oddechowych i alergii w rozwoju przewlekłego zapalenia błony śluzowej nosa i zatok przynosowych u dzieci. W opracowaniu zawarto zestawienie wyników badań uzyskanych w polskiej kohorcie dzieci w wieku przedszkolnym i wczesnoszkolnym, u których stwierdzono przewlekłe zapalenie błony śluzowej nosa i zatok przynosowych ze współistniejącą astmą lub bez niej. Część dzieci reprezentowała cechy dysbiozy wtórnej, która była powiązana z uczuleniem na alergeny roztoczy kurzu domowego. Zauważono, że częste kursy antybiotykoterapii korelowały z dysfunkcją mikrobioty, powodując redukcję bioróżnorodności. Zaobserwowano też, że u osób chorujących na astmę oskrzelową w górnych drogach oddechowych występuje specyficzna dysbioza, która cechuje się zmienionymi proporcjami głównych typów bakterii i jest wyrażona obniżonym stosunkiem *Patescibacteria/Actinobacteria*, stanowiąc niezależny czynnik astmy w badanej grupie, podobnie jak atopia oraz zmniejszona percepcja słodkiego smaku. W pracy podjęto również próbę określenia możliwych do zastosowania interwencji terapeutycznych i profilaktycznych w celu leczenia dysbiozy i jej zapobiegania u dzieci z przewlekłym zapaleniem błony śluzowej nosa i zatok przynosowych.

Słowa kluczowe: dzieci, dysbioza, alergia na roztocza kurzu domowego, przewlekłe zapalenie błony śluzowej nosa i zatok, immunoterapia alergenowa

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INTRODUCTION

Allergic diseases and chronic inflammatory diseases of the respiratory tract are a growing clinical problem in every age group. IgE-mediated allergies remain part of type 2 inflammation, which underlies atopic diseases such as asthma, atopic dermatitis (AD), and allergic rhinitis. In view of the heterogeneity of these diseases, non-allergic mechanisms often coexist alongside allergic pathways. Current hypotheses suggest that defects in the epithelial/epidermal barrier and local disturbances in the composition of the microbiota may be responsible for non-allergic causes of diseases such as asthma, AD or chronic rhinosinusitis (CRS). The human body is inhabited by millions of different microorganisms, which together form the microbiota. Microbes are found almost everywhere in the human body, playing a fundamental role in its functioning, e.g. through interactions with epithelial/epidermal cells and the immune system of the effector organ that constitutes a niche for a given ecosystem. Intestinal or skin microbiota is very numerous and relatively well known, and its impact on the functioning of the respiratory system is a widely discussed issue. New sequencing techniques have allowed for a broader and more accurate analysis of the composition of the microbial ecosystem in the respiratory tract, which in turn enables work on determining the impact of **disturbances in the composition of the microbiota**, i.e. **dysbiosis**, on the pathomechanism of local chronic diseases. More and more attention is being paid to the involvement of dysbiosis in the initiation and/or persistence of the inflammatory processes underlying diseases such as CRS[1,2].

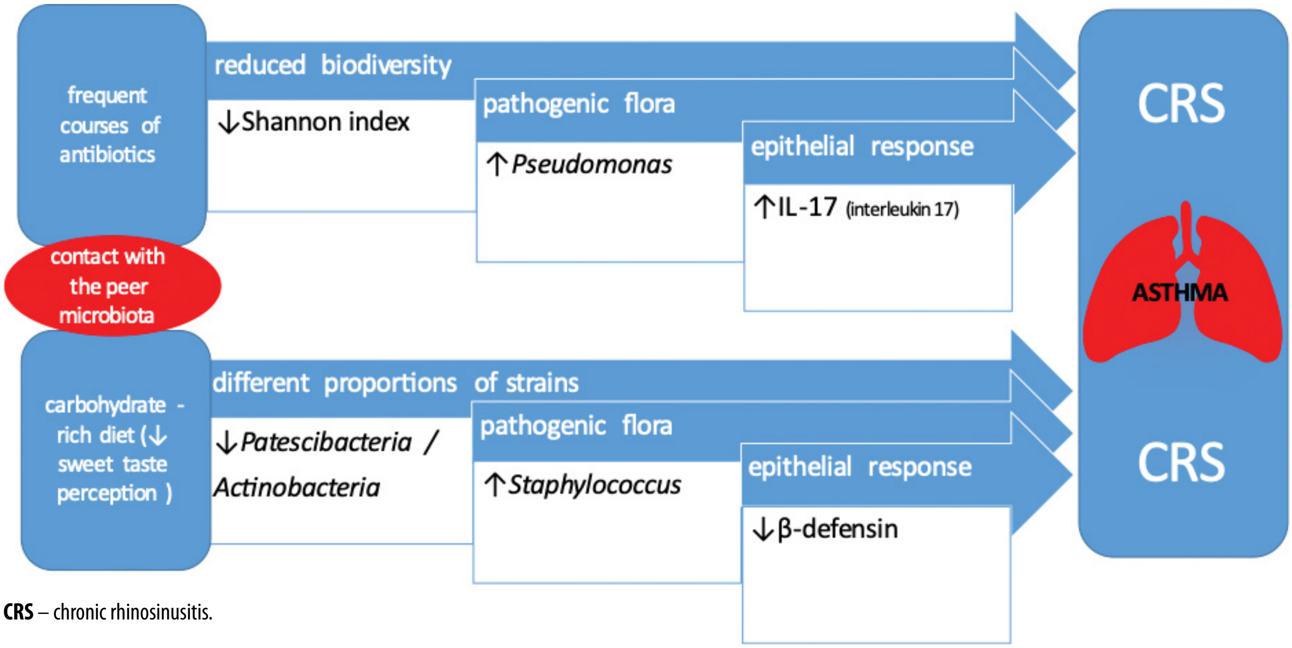
"VICIOUS CIRCLE" MECHANISM

Disturbances of the microbial ecosystem in the human body may be caused primarily by an abnormal composition of the microbiota dependent on changes in the external environment, e.g. preschool initiation, changes in diet or season, but they may also be a result of infectious and systemic diseases or local immune dysregulation leading to disturbances in the functioning of the MALT (mucosa-associated lymphoid tissue) system. Both of these causes interact with each other, and their interactions form a basis for considerations regarding the "vicious circle" between inflammation in the airways and local dysbiosis. It is obvious that each qualitative and quantitative dysfunction in the composition of the microbiota is associated with a change in the biochemical composition of the local ecosystem, which affects the activity of the MALT system. The development of dysbiosis, which is recognised as a pro-inflammatory factor, will occur if the situation persists for a long time and is additionally accompanied by a decrease in biodiversity and/or the emergence of pathogenic strains. In the case of the opposite phenomenon, in which the functioning of the MALT system changes initially (e.g. in allergies), one can expect a secondary change in the composition of the microbiota. The clinical implications of this "vicious circle" can be very serious, especially if the dysbiosis persists for a long time and is accompanied by chronic inflammation leading to remodelling, which can perpetuate the dysfunction of the microbiota, making it much more difficult and sometimes even impossible to eradicate[3].

CLINICAL IMPLICATIONS OF ALLERGY AND DYSBIOSIS IN CHILDREN

The induction of allergic processes in children is often accompanied by a tendency to frequent respiratory tract infections combined with an increased likelihood of frequent courses of antibiotic therapy. In the context of previous considerations, in young patients with allergies and frequent cycles of antibiotic therapy, one can expect features of dysbiosis in the microbiota inhabiting the respiratory tract. Such observations were made in a study of a total of 111 Polish children aged 4–8 years, diagnosed with mild or moderate CRS with or without concomitant asthma. The target groups were characterised before the coronavirus disease 2019 (COVID-19) pandemic, while the last follow-up visit – in the form of a teleconsultation – took place during the pandemic isolation. Sensitisation to house dust mites (HDM) allergens was shown to increase the risk of moderate CRS almost fourfold. Another, independent, factor was the baseline number of courses of antibiotic therapy, as each subsequent cycle increased the risk of moderate CRS in young children by more than 40%. In addition, sensitisation to HDM was associated with a decrease in the Shannon index (an index of reduced biodiversity), which is one of the hallmarks of dysbiosis. Interestingly, before the pandemic, such significant interactions between the aforementioned factors were not recorded, but the pandemic isolation revealed the clinical consequences of allergies and persistent dysbiosis. During this specific time of isolation from peers, only the group of children allergic to house dust mite allergens and children with permanent dysbiosis (secondary to frequent courses of antibiotic therapy) exhibited moderate symptoms of CRS with all clinical consequences[4]. The results of this study also suggest that the interaction between allergic and dysbiotic processes, from a clinical perspective, is synergistic with typical amplification of symptoms and long-term sequelae.

In this context, the results of another study conducted in the same cohort seem interesting. A group of 133 children aged 4–8 years, with CRS and concomitant asthma (62% of patients), was included in the analysis. It was shown that people with bronchial asthma have a specific dysbiosis in the upper respiratory tract. It is characterised by altered proportions of the main types of bacteria and is expressed by a reduced ratio of *Patescibacteria/Actinobacteria*. In the nasopharynx of asthmatic patients, compared to non-asthmatic children, a lower frequency of *Patescibacteria* was observed, with an increase in the frequency of *Actinobacteria* and secondary colonisation of *Staphylococcus*. It was this



CRS – chronic rhinosinusitis.

Fig. 1. Visualisation of dysbiotic processes in children with chronic rhinosinusitis (CRS)

type of dysbiosis, independent of atopy, that was associated with asthma risk. This type of dysbiosis was also shown to be associated with increased consumption of sweets and lower perception of the sweet taste. Moreover, lower expression of beta-defensins was noted in the nasal epithelium of these children. The same analysis identified a distinct type of dysbiosis with different risk factors and other immunological consequences. It was shown that the reduction in biodiversity of the microbiota of the upper respiratory tract attributed to frequent courses of antibiotic therapy was associated with an increase in the expression of interleukin 17 (IL-17), which is a marker of type 3 inflammation. These results lead to the conclusion that dysbiosis as a pro-inflammatory stimulus is a complex mechanism, with multiple causes and consequences[5]. A visualisation of the above-mentioned aspects of dysbiosis is shown in Fig. 1.

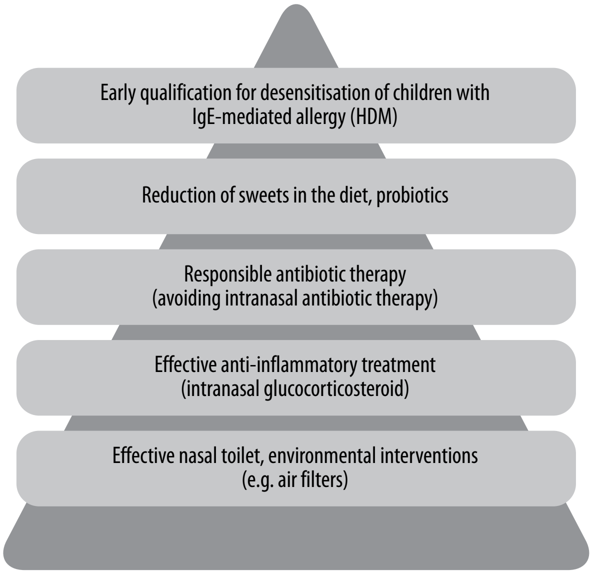
The results of both of these analyses underline the well-known fact that in young children, the lack of control of inflammation in the upper respiratory tract is an important cause of the induction and persistence of bronchial asthma symptoms. This fact, in accordance with the applicable recommendations included in the EPOS (*European position paper on rhinosinusitis and nasal polyps*)[6] and GINA (Global Initiative for Asthma)[7], should influence the paediatrician's specific therapeutic decisions.

POSSIBILITIES FOR THERAPEUTIC INTERVENTIONS

In the light of the presented research results, combating dysbiosis should be the clinician's primary therapeutic goal. From the beginning, however, the focus should be on effective anti-inflammatory treatment of the underlying disease entity which contributes to microbiota disorders through the associated inflammation. The phenomenon of secondary dysbiosis acts as a pro-inflammatory stimulus, making it difficult to achieve remission. At this point, the results of a randomised study published this year in "JAMA Pediatrics" should be quoted. The authors evaluated the effects of a 12-week treatment with intranasal glucocorticosteroids in children aged 4–8 years with CRS. It was shown that a significant reduction in CRS symptoms was associated with an increase in microbiota biodiversity indices and a decrease in type 3 inflammation assessed by the expression of type 3 lymphoid cells[8].

In the context of dysbiosis, supplementation with probiotics seems to be justified, with potential goals including restoration of the balance in the composition of the microbiota and displacement of pathogenic flora. Both assumptions remain debatable, though the latter found some validation in the studies of Bidossi et al., who observed the inhibition of *Staphylococcus aureus* and *Moraxella catarrhalis* biofilm formation under the influence of supplementation with *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a[9]. Unfortunately, despite a large number of publications on the use of various strains in specific clinical settings, it is difficult to unequivocally confirm the lasting clinical efficacy of this method. From the pathophysiological perspective, effective treatment or prevention of dysbiosis should involve personalised interventions. Therefore, an individual selection of the dose, strain and route of administration seems justified. This is the likely direction of further development of this therapeutic method.

It is reasonable to avert the development of dysbiosis through preventive measures to avoid CRS, such as effective nasal toilet, interventions decreasing exposure to allergens and



HDM – house dust mites.

Fig. 2. Therapeutic and preventive interventions conducive to the correction of dysbiotic processes in children suffering from chronic rhinosinusitis

environmental pollution (filters), decrease in the consumption of sweets[3,5], rational antibiotic therapy (according to the EPOS, there are no indications for intranasal antibiotics in the treatment of CRS in children), encouraging physical exercise[10] or early implementation of allergen immunotherapy. The latter strategy is of particular importance for children with CRS who are allergic to HDM, because the coexistence of the conditions is associated with an increased risk of developing asthma, regardless of sensitisation to other allergens. A similar trend was observed in the study by Mohan et al.[11], while analyses conducted in the Chinese paediatric population indicate that HDMs are the most common inhalant allergens in patients with perennial allergic rhinitis[12]. Even though the results of single studies suggesting a possible correction of dysbiosis under the influence of effective desensitisation to birch pollen have been published[13], there are still no research findings confirming the role of desensitisation in the treatment of CRS in children.

Chronic nasal obstruction secondary to adenoid hyperplasia remains an important problem in young children. Tonsil enlargement should be understood as a physiological response of the MALT system to microbial stimuli in preschool children with frequent respiratory infections. The process is fuelled even more by uncontrolled inflammation in the case of HDM allergy. Regardless of the primary cause, a "vicious circle" thus develops, sustained by a specific dysbiosis of the local microbiota[14]. There is still no data that would confirm that the surgical solution (adenotomy) corrects the disturbances in the composition of the local microbiota.

Therapeutic and preventive interventions that may contribute to the correction of dysbiotic processes in children suffering from CRS are summarised in Fig. 2.

ROLE OF INTERNATIONAL RECOMMENDATIONS

It should be emphasised that effective treatment of CRS promotes the development of normal microbiota. The best chances for long-term efficacy and safety (also microbiological) are related to the procedure in accordance with the applicable international recommendations (EPOS). In this context, it is important to remember that any child diagnosed with:

- complications of CRS (including bleeding);
- one-sided symptoms, nasal polyps;
- chronic nasal obstruction;
- sleep apnoea;
- symptoms of rhinitis present continuously from birth;
- lack of response to treatment (after verification of the drug application technique),

should be referred to a laryngologist.

SUMMARY

In the light of current research, it can be concluded that urbanisation and industrialisation of the environment in which children live contribute to an increase in the incidence of not only allergic diseases, but also chronic inflammatory conditions of the respiratory tract, including CRS[15]. The impact of microbiota on the epithelial and epidermal barrier as well as the MALT system contributes to inflammatory processes and, according to the hygiene hypothesis, under conditions of dysbiosis (decrease in the number of bacteria, reduced biodiversity) may trigger the development of allergies. Children in the nursery and preschool period experience an intense exposure to the microbiota of their peers. It is therefore in this age group that clinical interactions between complex dysbiotic processes and the induction of allergic disease are most clearly observed. Understanding these relationships is the basis for safe and effective clinical management.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could negatively affect the content of the publication and claim the right to publish it.

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