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The gut microbiome alterations in allergic and inflammatory skin diseases – an update

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Abstract (max 300 words)

The human microbiome is a wide range of microorganisms residing in and on our body. The homeostasis between host immune system and the microbial environment allows mutual benefits and protection. Physiological bacterial colonization is essential for the establishment of organism immunity. The human microbiota ecosystem can be divided into several compartments, out of which intestinal flora strongly affects our health and plays a crucial role in the pathophysiology of many diseases. The gastrointestinal tract, being a major guardian of the immune system, maintains the homeostasis with the commensal microorganisms by tolerating the typical flora antigens. The dysbiosis may trigger an inflammatory response followed by tissue damage or autoimmune processes. The gut microbiome alterations are linked to the pathogenesis of the allergic, cardiovascular, gastrointestinal, metabolic, neurodevelopmental, psychiatric and neurodegenerative diseases and cancer. Moreover, there is increasing evidence connecting the skin condition with the gastrointestinal microbiome, which has been described as the skin-gut axis. The aim of this study was to review the literature regarding the role of the gut microbiome alterations in the pathogenesis of selected allergic and inflammatory skin diseases.

Introduction

The human microbiome is a wide range of numerous bacteria and other microorganisms residing in and on our body. The homeostasis between the host immune system and the microbial environment allows mutual benefits and protection. Humans have up to 100 trillion bacteria and microbial cells and around 3.3 million microbial genes.¹⁻³ Physiological bacterial colonization is essential for the establishment of immunity. Already in the postpartum and early infancy period factors such as delivery mode and breastfeeding play a fundamental role in the bacterial flora acquisition and have a huge impact on the development of gut microbiome.^{2,4-6} The process of bacterial colonisation is vital to determine the newborn's immune response away from the allergy-favouring Type-2 response towards a Type-1 response, which is essential for pathogen elimination. The imbalance between Type 1 and Type 2 responses can promote autoimmunity.⁷⁻⁸ Nevertheless, also adult individuals are prone to complications caused by dysbiosis. Factors involved in bacterial imbalance include psychosocial stress, social relationships, environmental factors, health behaviours, nutrition, tobacco and alcohol intake, prescription drug use as well as socioeconomic status.⁹ A significant issue is also the extensive use of probiotics and antibiotics. Probiotics' impact on intestinal flora and gut-associated lymphoid tissue (GALT) is caused by both whole bacteria as well as their soluble factors, which act through pattern recognition receptors (PRRs) belonging to Toll-like receptors family on the surface of enterocytes, what results in TGF- β and interleukin 8 production and immune response modulation.¹⁰ The common overuse of antibiotics may trigger a significant imbalance in human microflora resulting in pathogenic bacteria overgrowth and infection, decrease in beneficial flora, immune system disruption and bacterial resistance.¹¹⁻¹²

The human microbiota ecosystem can be divided into several compartments, out of which intestinal flora may strongly affect our health.³ The gastrointestinal tract, being a major guardian of the immune system, maintains the homeostasis with the commensal microorganisms by tolerating typical flora antigens. Any quantitative or qualitative changes to the intestinal microbiome may trigger inflammatory response followed by tissue damage or autoimmune processes.⁵

The microorganisms diversely inhabit the gastrointestinal tract. The oral cavity shelters *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria* and *Fusobacteria*. In stomach *Actinobacteria* and *Helicobacter* may be encountered. The intestinal microbiome is composed in around 90% of *Bacteroidetes* and *Firmicutes* with lower levels of *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*. The small intestine microbiome resembles the large intestine flora qualitatively, but not quantitatively.^{3,7,13-14} The proximal small intestine consists of a minor number of bacteria, estimated at the maximum of 10³ CFU/ml (colony forming units), whereas in the large intestine the number of bacteria reaches 10⁴ CFU/ml. The increase in the number of bacteria to over 10⁵ CFU/ml or the presence of atypical flora is defined as the small intestinal bacterial overgrowth (SIBO).¹⁵⁻¹⁶ The imbalance of specific defence mechanisms, anatomical abnormalities or intestinal motility disorders may lead to SIBO development. Some of the most common SIBO manifestations include flatulence, diarrhoea, steatorrhoea, fat-soluble vitamins deficiency symptoms, neurological and psychiatric symptoms of malignant anaemia, malabsorption syndrome symptoms, systemic disorders (such as glomerulonephritis, hepatitis, fatty liver disease, arthritis, tendonitis) and cutaneous lesions.¹⁵⁻¹⁹ In colon, nine major types of bacteria are observed with the predominance of *Firmicutes* and *Bacteroidetes*.²⁰

The gut microbiome alterations are linked to the pathogenesis of the allergic, cardiovascular, neurodevelopmental, psychiatric and neurodegenerative diseases, cancer, diabetes mellitus, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, kwashiorkor, liver diseases, metabolic syndrome and obesity.²¹ Moreover, there is increasing evidence connecting the skin condition with the gastrointestinal microbiome, what has been described as skin-gut axis.²² The aim of this study was to review the literature regarding the role of the gut microbiome alterations in the pathogenesis of selected allergic and inflammatory skin diseases.

Materials and Methods

The review of the literature was performed on MEDLINE database from January 2009 to January 2019 complementary to PRISMA protocol. The database was searched using the relevant MeSH terms including all sub-headings. The studies reporting the role of gastrointestinal microflora (especially small intestinal bacterial overgrowth syndrome) in the development of selected allergic and inflammatory skin diseases were identified from the database by utilizing the search terms 'enteric bacteria' OR 'gastrointestinal flora' OR 'gastrointestinal microbiota' OR 'gastrointestinal microflora' OR 'gut flora' OR 'gut microbiome' OR 'gut microbiota' OR 'gut microflora' OR 'intestinal flora' OR 'intestinal microbiome' OR 'intestinal microbiota' OR 'intestinal microflora' OR 'small intestinal bacterial overgrowth' OR 'small intestine bacterial overgrowth' OR 'SIBO' OR 'small bowel

bacterial overgrowth' OR 'small intestine overgrowth' OR 'small intestinal overgrowth' OR 'small bowel overgrowth' OR 'small gut overgrowth' OR 'small bowel bacterial overgrowth' OR 'small gut bacterial overgrowth' AND 'psoriasis arthropathica' OR 'arthritic psoriasis' OR 'psoriatic arthritis' OR 'psoriatic arthropathy' OR 'psoriasis' OR 'palmoplantar pustulosis' OR 'acne' OR 'acne vulgaris' OR 'hidradenitis suppurativa' OR 'acne inversa' OR 'hidradenitis' OR 'suppurative hidradenitis' OR 'rosacea' OR 'atopic dermatitis' OR 'atopic eczema' OR 'infantile eczema' OR 'atopic neurodermatitis' OR 'disseminated neurodermatitis' OR 'alopecia' OR 'alopecia areata' OR 'alopecia universalis' OR 'alopecia totalis' OR 'alopecia circumscripta'. The initial search revealed 301 results. After applying additional criteria (English language publications) the database search revealed 286 (195 when human studies applied) records. After screening the records we chose 154 articles. After full-text article assessment, we chose the most representative (most insightful, explaining or suggesting the pathophysiology of the described conditions) studies eventually obtaining 131 results.

Gut microbiome and immunity

The intestinal flora is involved in the development of host immune response, in the structural modification of intestinal mucosa, endocrine and metabolic mechanisms as well as neurological transmission and vitamin K production.¹⁴

A large area of intestinal absorption makes the gastrointestinal tract exposed and vulnerable to external antigens influence. There is a variety of defence mechanisms preventing from harmful bacterial invasion including low pH of gastric acid, proteolytic enzymes, lysozyme and lactoferrin. The fundamental role of all mucosa-associated lymphoid tissues (MALT) is the production of secretory-IgA (s-IgA) with the ability to neutralize foreign microorganisms and bacterial toxins. In the intestinal area, the adherent epithelial barrier with the help of defensins, cathelicidins and C-type lectins comprise the first-line protection strategy from microbial antigens.¹² GALT is one of the major immunological structures in our body. It is built up of epithelial layer, Peyer patches, lamina propria (containing macrophages, dendritic cells, T- and B- lymphocytes alongside with immunoglobulins especially s-IgA) and mesenteric lymph nodes.¹⁰ The macromolecules and microorganisms captured in Peyer patches are presented via dendritic cells to T- and B-cells provoking the production of plasma cells precursors. Through lymphatic vessels, the plasmablasts reach mesenteric lymph nodes and then migrate with the bloodstream to other sites of MALT. The MALT repopulation by the lymphocytes is promoted by the presence of certain integrins and addressins.¹²

Another important defence mechanism is the physiological intestinal microbiome, which prevents extensive development of potentially pathogenic bacteria and stimulates immune defence. Normal intestinal flora competes with the invaders for nutrients and binding receptors at the surface of enterocytes and has the ability to produce bactericidal bacteriocins. Apart from that, in the process of non-digestible carbohydrates fermentation bacteria inhabiting our intestines produce short-chain fatty acids (SCFA), which act as

immune modulators. SCFAs metabolites influence T-cell differentiation, e.g. butyrate increases T_{reg} cells percentage as well as interleukin 10 and 12 levels with the simultaneous decrease of interleukin 17 and 23 levels.^{12,23} Taking part in tryptophan catabolism, gastrointestinal microbiota stimulates the production of anti-inflammatory interleukin 22, which enhances the expression of antimicrobial peptides at the mucosal surfaces.^{12,24} The beneficial anti-inflammatory effects of *Bacteroides fragilis* have been observed within multiple organs, including intestines. Their role in immune response regulation was observed in terms of interleukin 10, T_{reg} cells subpopulation, T_{H1}/T_{H2} balance and sIgA production promotion as well as lipopolysaccharide responsiveness decrease during infancy.^{5,12,25} Segmented filamentous bacteria turned out to stimulate T_{H17} response and T_{reg} cells number.^{5,26} The protective role of *Clostridia* has been also investigated in the pathogenesis of inflammatory bowel diseases. *Clostridium coccoides* and *Clostridium leprum* stimulate interleukin 10 and T_{reg} cells subpopulation.⁵ The role of gut microbiome alterations in the pathophysiology of selected skin diseases was summarized in Fig. 1.

The gut-skin axis

Indisputable interaction between gut and skin has been observed in many dermatoses coexisting with gastrointestinal comorbidities. Intestine and skin share many common features and functions. They are critical immunological barriers and constitute the environment for physiological microflora. The interaction of both organs has been well-established in case of inflammatory bowel diseases, rosacea, gastrointestinal malignancies and Peutz-Jeghers syndrome.²⁷ Inflammatory bowel diseases (IBD) are autoimmune disorders commonly associated with extraintestinal manifestations, which may affect the skin as psoriatic lesions, erythema nodosum and pyoderma gangrenosum. Satta et al. observed lower skin lesions incidence in IBD patients, who underwent probiotic supplementation. The risk of developing at least one skin lesion was 1.40 versus 0.3 for probiotic use between respectively 5–19% or 50% of disease duration.²⁸ Probiotics supplementation is believed to prevent pathological intestinal flora colonization, improve intestinal barrier mechanisms, modulate immune system towards anti-inflammatory response and synthesize beneficial anti-inflammatory metabolites.²⁹ Probiotic-fed mice exhibited increased dermal thickness, improved folliculogenesis and increased sebocyte production resulting in thicker and shinier fur.³⁰ Furthermore, in other studies, probiotic supplementation decreased cutaneous arterial sympathetic nerve tone and transepidermal water loss, increased cutaneous blood flow and skin hydration as well as TGF- β levels.^{22,30-32} The beneficial role of *Lactobacillus johnsonii* has been also observed in the restoration of UV-radiation damaged skin.³³ Children supplemented with probiotics in postneonatal life were found to be at much lower risk of developing atopic dermatitis.³⁴ Antibiotics use during pregnancy contributes to the atopic march and eczema in children.^{7,35} One of the favourable mechanism is promoting Th_1 response in atopic patients.²⁹ The role of microbiota has been also observed in oxazolone-induced mouse model of atopic dermatitis, where atopic dermatitis phenotype correlated with the gut microbiota transfer.³⁶ Potential

beneficial role of probiotic supplementation may also modulate the inflammatory processes in the course of psoriasis by the suppression of interleukin 23 and Th₁₇ axis.³⁷ The perinatal antibiotic therapy in imiquimod-induced psoriasis resulted in gut dysbiosis and skin lesion aggravation.³⁸

Manzhali et al. observed in 89% patients with acne, papular-pustular rosacea and seborrheic dermatitis satisfactory response to *Escherichia coli* Nissle therapy resulting in significant amelioration or complete recovery of skin lesions in contrast to 56% in the control group. *Escherichia coli* Nissle plays a protective role by promoting favourable gut microbiota leading to clinical improvement of intestinal borne dermatoses.³⁹ On the other hand, the overgrowth of the atypical flora or excessive physiological flora colonization may result in skin lesions exacerbation as in case of small intestinal overgrowth in rosacea patients.⁴⁰ Dysbiosis and factors interfering gut microbiota has been also widely associated with atopic dermatitis.⁴¹⁻⁴² Another proof of existing gut-skin axis is the beneficial role of appropriate diet in certain skin conditions. High-glycaemic diet is a well-established aggravating factor in acne vulgaris.⁴³ Moreover, significant changes observed in gut microbiome composition in the course of selected skin diseases are summarized in Table 1.

Psoriasis and psoriatic arthritis

Psoriasis is a common inflammatory disease affecting around 2-3% of the adult population.⁴⁴ It can present itself at any age in the form of papulosquamous skin lesions of variable morphology, distribution, severity, and course.⁴⁵ Metabolic syndrome, abdominal obesity, hypertension, atherogenic dyslipidaemia, type 2 diabetes, insulin resistance and non-alcoholic fatty liver disease are common psoriasis comorbidities.⁴⁶ A common clinical extracutaneous manifestation of the disease is psoriatic arthritis (PsA) affecting around one-third of psoriatic patients.⁴⁷ Psoriasis is a multifactorial disease and may develop in genetically predisposed individuals under certain environmental factors including gut microbiome changes.⁴⁸

The strong correlation of skin condition and bowel involvement has been noticed in psoriatic patients with IBD. It has been observed that psoriatic patients are at 3-times higher risk of developing Crohn's disease (CD) and contrariwise patients with CD have 7-times higher risk of psoriatic lesions development.⁴⁹ The pathophysiological role of Th₁₇ cells and Th₁₇ cytokine profile (interleukin 17, 22 and 23) in psoriasis is also a linking mechanism with the IBD pathophysiology.⁵⁰ Recent studies demonstrate the role of intestinal flora in Th₁₇ cells regulation.¹²

Recent studies underline the role of intestinal microbiota in psoriasis. Huang et al. investigated the faecal samples of psoriatic patients and observed significant disturbances in microbiota profiles and dysbiosis associated with psoriasis. Psoriatic patients had increased abundance of *Bacteroidetes* and decreased levels of *Firmicutes*, *Proteobacteria*, *Actinobacteria*. No relevant microbial diversity was observed among psoriasis subtypes, nevertheless the severity of the disease correlated with more frequent microbiota alterations.⁵¹ Significantly reduced abundance of *Akkermansia muciniphila* was observed among psoriatic patients. Similar observations have been made in case of IBD and obesity, which also share a common pathological background with psoriasis including Th₁₇, Th₁ and

T_{reg} role in immune response.⁵² Moreover it has been suggested that gut microbiota control imiquimod-induced murine model of psoriasis skin lesions by altering the T cells response.³⁷

Another study inspecting psoriasis patients faecal microflora composition showed an increased abundance of phylum *Firmicutes* and decreased abundance of phylum *Bacteroidetes*. The observations also suggested that the characteristic psoriatic microbial composition might be associated with altered transport of carbohydrate, cobalamin and iron, as well as chemotaxis.⁵³ In accordance with these reports remains the term 'psoriatic core intestinal microbiome', which has been proved to show distinct changes of gut microbiome pattern in comparison with healthy individuals.⁵⁴ As already mentioned Zanvit et al. have demonstrated that mice treated with antibiotics in neonatal life developed exacerbated imiquimod-induced psoriasis in the adulthood and provoked gut and skin microbiota dysfunction in adults, which was associated with increased susceptibility to experimental psoriasis.³⁸ Alterations in gut microflora may also lead to intestinal barrier disintegration. Higher levels of claudin-3 and intestinal fatty acid binding protein, the markers of intestinal barrier damage, were noticed among psoriatic patients.⁵⁵

The studies concerning the coexistence of SIBO with psoriasis remain contradictory. Nevertheless, SIBO eradication has been associated with cutaneous lesions amelioration.⁵⁶⁻⁵⁷ Moreover, there are accounts of SIBO eradication effectiveness when it comes to oral psoriasis manifestations (geographic and fissured tongue) treatment.⁵⁸

Physiological intestinal microflora modulates the balance in Th₁, Th₂, and Th₁₇ cells subpopulations. Gut colonization alterations may trigger chronic inflammation not only within the skin and intestines but also affecting the joints.^{59,60} While the joint environment was thought to be sterile, some bacterial modules, presumably originating from GALT, were detected in synovial fluid of rheumatoid arthritis patients.⁶¹ The characteristic pattern of intestinal flora in the course of PsA has been well-established by Sacher et al. The gene analysis used to assess the gut microbiota composition revealed that PsA patients have lower abundance of *Firmicutes*, *Clostridiales*, *Verrucomicrobiales* and higher *Bacteroidetes* in comparison with patients demonstrating an isolated cutaneous form of the disease. In comparison with the healthy control group, PsA patients had lower *Akkermansia*, *Ruminococcus* and *Pseudobutyrvibrio* abundances. In comparison with healthy controls, both psoriasis and PsA group showed lower intestinal flora diversity, especially concerning beneficial taxa, which resembled the dysbiosis observed in the course of IBD.⁶²⁻⁶³ The importance of intestinal flora is yet to be investigated in a randomised, placebo-controlled trial of faecal microbiota transplantation infused in the small intestine in PsA patients unresponsive to methotrexate treatment.⁶⁴

Acne vulgaris

Acne vulgaris is a chronic inflammatory dermatosis with an 85% prevalence rate in individuals aged 12–24 years. The disease is characterized by the presence of noninflammatory comedones and inflammatory skin lesions such as papules and pustules.⁶⁵ The existence of the gut-brain-skin axis has been postulated since the 1930's, when researchers linked emotional and psychological well-being with the gastrointestinal microflora alterations, intestinal permeability as well as local and systemic inflammation.⁶⁶⁻⁶⁷ The beneficial role of *Lactobacilli* supplementation has been already noticed by then.⁶⁸ Recent studies prove the existence of gut alterations in patients with moderate to severe acne vulgaris. Yan et al. observed decreased levels of *Actinobacteria*, *Bifidobacterium*,

Butyricoccus, *Coprobacillus*, *Lactobacillus* and increased amounts of *Proteobacteria* in patients suffering from acne.⁶⁹ According to Deng observations, acne patients encounter lower *Firmicutes* abundance and increased *Bacteroides* abundance. Furthermore, the potentially beneficial taxa are depleted.⁷⁰ The skin condition of acne patients has been observed to improve after *Escherichia coli* Nissle therapy.³⁹ The beneficial microflora is linked to skin changes amelioration by its influence on T_{reg} cells population and hyporesponsiveness of B and T_h cells with inflammatory cytokine suppression, promotion of sIgA production and production of anti-inflammatory butyrate.⁶⁹

Despite the unclear role of *Propionibacterium acnes* in the pathogenesis of the disease, antibiotics remain one of the first-line treatments of acne vulgaris regardless of their potential adverse effects on the gastrointestinal tract. Antibiotic therapies introduced in patients with IBD may result in increased disease activity or cause IBD in previously healthy individuals.^{71,72} The influence of certain antibiotics and isotretinoin on gut microbiome was examined by Becker et al. The faecal microbiota assessment showed that doxycycline had modest, but persistent effect on intestinal bacteria diversity, whereas metronidazole affected the gut microbiota only transitorily and isotretinoin influence remained irrelevant.⁷³

The dietary habits role in the course of acne vulgaris supports the existence of gut-skin axis. Low-glycaemic diet is associated with skin lesions improvement and lower levels of insulin.⁷⁴ Whereas hyperinsulinemia boosts serum levels of insulin-like growth factor-1, which enhances keratinocyte proliferation and hormone production resulting in acne flares.⁷⁵ Gut microbiota alterations may also contribute to insulin resistance and thus higher insulin serum levels.⁷⁶⁻⁷⁷

Patients with decreased gastric acid secretion may suffer from the disruption of the defence mechanisms preventing the excessive bacterial colonization of small bowel. Commonly administered proton pump inhibitors contribute to this disturbances. Already, in the 1930's researchers noticed the higher incidence of hypochlorhydria among patients with acne vulgaris and susceptibility gut microbiome alterations.^{16,66-67} Although the connection and prevalence of SIBO in acne vulgaris are yet to be examined, abovementioned facts allow hypothesizing that there is a bridge linking these two entities.

Rosacea

Rosacea is a chronic relapsing inflammatory skin disease affecting approximately 10% of the population, mostly individuals aged 30-60. The disease may present itself in the form of persisting erythema, telangiectasia, papules, pustules, excessive fibrous tissue overgrowth, rhinophyma as well as periocular changes.⁷⁸ The role of the dietary habits emphasizes the importance of the gastrointestinal tract in the rosacea pathogenesis.⁷⁹ Also specific microbiome changes are contributed to Toll-like receptors abnormal activation observed in rosacea patients.⁸⁰ Rosacea is reported to coincide with gastrointestinal comorbidities and certain studies link this coexistence to gut microbiome changes. Hitherto, conducted studies confirm a significant bi-directional association in the occurrence of IBD

and rosacea.⁸¹ Other examples of concomitant gastrointestinal conditions are celiac disease, gastrointestinal flora alterations as well as metabolic conditions such as obesity and insulin resistance.⁸²⁻⁸⁴ Nam et al. revealed reduced abundance of *Peptococcaceae*, *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter* and *Desulfovibrio* and increased abundance of *Acidaminococcus*, *Megasphaera* and *Lactobacillales*.⁸⁵

Egeberg et al. confirm common rosacea and gastrointestinal disorders coexistence, also with reference to regarding *Helicobacter pylori* infection and SIBO.⁸⁶ Further studies show positive SIBO results in around 46-51% of rosacea patients and estimate the risk of SIBO development in this group 13-times higher than in healthy individuals. Another observation of high clinical value is the improvement of skin condition among patients, who successfully underwent eradication therapy.^{40,87-89} Nevertheless, some studies report contradictory conclusions, e.g. Gravina et al. observed no significant differences between SIBO prevalence in rosacea patients and healthy controls.⁹⁰

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease affecting hair follicles in intertriginous areas with the reported prevalence ranging from 0.03 to 4.1%.⁹¹ HS and acne vulgaris share some characteristic features such as the adverse impact of high-glycaemic diet and dietary consumption as well as common IBD and metabolic syndrome concomitance. This suggests the possible role of gut microbiome disruption role in HS pathology.⁹²⁻⁹³ Deckers et al. report 4-times higher prevalence of IBD among HS patients than in healthy controls.⁹⁴ *Faecalibacterium prausnitzii* depletion and *Escherichia coli* increase is well-documented among patients with IBD. However, in patients with HS and no concomitant bowel disease, no meaningful difference in *F. prausnitzii* or *E. coli* abundance was found.⁹⁵ Bacteria seem to play a significant role in the development of HS. The majority of literature evidence points out the antibiotics as first-line HS treatment option. The modulation of gut microbiota is a potential therapeutic target in IBD. Therefore metronidazole and ciprofloxacin found to be useful in certain IBD clinical subtypes. Nevertheless, tetracyclines, antibiotics widely used for HS, showed a higher risk for developing IBD.^{93,96} Brewer's yeast elimination in the dietary products after the completion of HS surgery was associated with stabilization and eventual regression of HS.⁹⁷ Smoking is another factor that may contribute to microbiota alterations - *Firmicutes* and *Actinobacteria* reduction and *Proteobacteria* and *Bacteroides* increase, what correlates with HS flares.⁹⁸⁻⁹⁹

Atopic dermatitis (AD)

In the past decades, we observed an increasing prevalence of allergic diseases. It is well-documented that the gut microbiome plays a crucial role in immune regulation and that the dysbiosis and low intestinal microbiota diversity can determine allergic diseases development. An elevated *Klebsiella/Bifidobacterium* ratio in early infancy can be a potential indicator of an increased risk of allergy development.¹⁰⁰⁻¹⁰¹ In the first days of life, the neonatal gastrointestinal tract becomes gradually inhabited by multiple microorganisms. This process is modulated by factors such as delivery mode, maternal microbiota and antibiotic therapy as well as milk source and probiotic supplementation. Any disruptions and

modifications of these factors may trigger impaired bacterial colonization. C-section delivery combined with prenatal antibiotic treatment is associated with significantly higher AD risk development. Lower intestinal bacterial diversity with higher levels of *Bacteroides*, *Clostridium*, *Enterobacteriaceae* and *Staphylococcus* early in life has been associated with an increased risk for atopic disease.¹⁰²⁻¹⁰⁴ Early innate immunity responses in the gut, including intestinal defensin secretion, are associated with the emergence of sensitization and atopic dermatitis later in childhood.¹⁰⁵

Apart from well-known skin microbiome alterations in AD pathophysiology, a strong influence of intestinal flora has been described. Decreased *Bifidobacterium* abundance has been detected in the gut of AD patients in comparison to healthy controls, and lower *Bifidobacterium* levels correlated with a more severe course of the disease.¹⁰⁶⁻¹⁰⁷ Infants with eczema have a higher abundance of *Escherichia/Shigella*, *Veillonella*, *Faecalibacterium*, *Lachnospiraceae incertae sedis* and *Clostridium XIVa*, as well as higher amounts of *Faecalibacterium prausnitzii* and *Ruminococcus gnavus*. Increased counts of *Akkermansia muciniphila* in AD infants might be responsible for intestinal barrier function loss and skin lesions exacerbation. *Akkermansia muciniphila* ability degrade polysaccharides into short-chain fatty acids leading to decreased microbial diversity.¹⁰⁸ Decreased amounts of anti-inflammatory *Bacteroides fragilis* and *Streptococcus salivarius* properties correlate with eczematous lesions.¹⁰⁸⁻¹¹⁰ Moreover, a decreased gut microbiome diversity in the neonatal period was associated with consecutive AD.¹¹¹

Multiple studies have shown beneficial role of probiotic supplementation in AD patients, e.g. *Lactobacillus sakei* WIKIM30 proved to ameliorate atopic-dermatitis skin lesions by T_{reg} cells induction and altering intestinal microbiota in mice, *Lactobacillus casei* variety *rhamnosus* alleviated mice model of induced atopic dermatitis by increasing *Bifidobacterium*, *Lactobacilli*, *Enterococcus* and *Bacteroides fragilis* levels and decreasing *Clostridium coccoides* amounts, attenuative effects on skin inflammation in mice was also observed in case of *Lactobacillus salivarius* LA307 and *Lactobacillus rhamnosus* LA305.¹¹²⁻¹¹⁵ Furthermore, probiotics have shown to present antipruritic effects in AD.¹¹⁶⁻¹¹⁷ The meta-analysis carried out by Chang et al. supported synbiotics in the AD therapy, especially among 1-year old and older children.¹¹⁸

Probiotics helpful role in AD treatment is based on their ability to balance the gut microflora, protecting intestinal barrier function and decreasing the synthesis of the pro-inflammatory cytokines. Additionally, there is a possible promoting effect of probiotics on Toll-like receptors, which can serve as pathogen-associated molecular patterns (PAMPs), recognize structures and therefore induce the differentiation of T cells and allergic reactions.¹¹⁹

Antibiotics are the most commonly prescribed drugs among children. Antibiotic therapy during the first 2 years of life is associated with an increased risk of AD development.¹²⁰ The recent study enrolling patients from over 20 countries proved the association between antibiotic intake in the first year of life and AD in children in the age of 6 to 7 years.¹²¹

Elevated levels of faecal calprotectin, a marker of intestinal inflammation commonly raised in the course of IBD, has been also detected among paediatric patients with AD and correlated with increased severity index scores. This underlines the role of intestinal barrier integrity impairment the AD.¹²²⁻¹²³

Reduced early amounts of *Escherichia coli* were shown to impair interleukin 10 regulation, which low levels were also associated with *Bifidobacterium* colonization and AD risk.¹²³⁻¹²⁴

Alopecia areata

Alopecia areata (AA) is a complex autoimmune disease characterized by nonscarring hair loss, which may present itself at any age in the form of oval hair loss patches as well as complete scalp and/or body hair loss.¹²³ Literature data provides specific evidence of gut microbiota role in proper hair maintenance. Probiotic-fed mice exhibit improved folliculogenesis and thicker and shinier fur.³⁰ The correlation of microbiome role in the autoimmune disease pathogenesis has been also contributed to microbial role immune mechanisms modulation. Several studies indicate that the loss of intestinal barrier integrity in local and systemic inflammation induction as well as autoimmunity.¹²⁶ Literature data on the gastrointestinal role in AA indicate a higher prevalence of AA in patients with ulcerative colitis than in general population.¹²⁷⁻¹²⁸ Contradictory results were presented by Kim et al., who observed no higher AA prevalence in the course of IBD.¹²⁹ Furthermore, some authors contribute SIBO role to the gastrointestinal flora alterations in patients, who later develop AA. Though pathogenetically this hypothesis has substantial implications, SIBO role in triggering AA is yet to be studied.¹²⁷ Experimental mice models with antibiotic-induced dysbiosis and *Lactobacillus murinus* overgrowth showed consecutive biotin deprivation and alopecia induction.¹³⁰ The meaning of microbiota in AA was observed in the course of *Clostridium difficile* infection successfully treated with faecal microbiota transplantation (FMT). Rebello et al. observed subsequent hair regrowth FMT for treatment of recurrent *C. difficile* infections in patients who suffered from alopecia universalis.¹³¹

Conclusions

Our understanding of gut microbiome role in the homeostasis of human organism has progressed in recent years. Growing evidence of microbiota role in immunity, defence mechanisms and organism well-being significantly contributed to defining its role in autoimmune and allergic diseases pathophysiology. It has also allowed us to connect certain skin conditions with gastrointestinal microbial structure alterations. Our review gives an insight into the gut microbiome alterations role in the pathogenesis of psoriasis, psoriatic arthritis, acne vulgaris, hidradenitis suppurativa, atopic dermatitis and alopecia areata. Various beneficial gut microbiome functions prevent pathological flora colonisation, sustain proper intestinal barrier integrity and function and take part in balancing and modulating the immune response.

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Tables

Table 1.

Disease	Observed changes
Psoriasis	↑ <i>Bacteroidetes</i> ↓ <i>Firmicutes</i> , <i>Proteobacteria</i> , <i>Actinobacteria</i> ⁵¹
Psoriatic arthritis	↓ <i>Akkermansia</i> , <i>Ruminococcus</i> , <i>Pseudobutyrvibrio</i>
Acne vulgaris	↑ <i>Proteobacteria</i> , <i>Bacteroides</i> ↓ <i>Actinobacteria</i> , <i>Bifidobacterium</i> , <i>Butyricicoccus</i> , <i>Coprobacillus</i> , <i>Lactobacillus</i> , <i>Firmicutes</i> ⁶⁹⁻⁷⁰
Rosacea	↑ <i>Acidaminococcus</i> , <i>Megasphaera</i> , <i>Lactobacillales</i> ↓ <i>Peptococcaceae</i> , <i>Methanobrevibacter</i> , <i>Slackia</i> , <i>Coprobacillus</i> , <i>Citrobacter</i> , <i>Desulfovibrio</i> ⁸⁵
Hidradenitis suppurativa	= <i>Faecalibacterium prausnitzii</i> , <i>Escherichia coli</i> ⁹⁵
Atopic dermatitis	↑ <i>Escherichia/Shigella</i> , <i>Veillonella</i> , <i>Faecalibacterium</i> , <i>Lachnospiraceae incertae sedis</i> , <i>Clostridium XIVa</i> , <i>Faecalibacterium prausnitzii</i> , <i>Ruminococcus gnavus</i> ↓ <i>Bifidobacterium</i> ¹⁰⁶⁻¹⁰⁷

Legends

Table 1. Changes observed in gut microbiome composition in the course of selected skin diseases.^{51,69,70,85,106,107}

Fig. 1. The interaction between gut microbiota alterations and immune mechanisms taking part in selected skin diseases pathophysiology.

Figures

Fig. 1.

