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The “Obese Asthma” in Children as a Distinct Clinical Phenotype: Review

Andjelka Stojkovic, Aleksandra Simovic,
Vesna Velickovic and Katerina Dajic

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Abstract

Asthma, obesity, and irrational use of antibiotics early in a life can be considered to be the three epidemics of modern times, which encourage one another and whose base is the loss of bioavailability. Disruption of the intestinal microbiome early in the life is the basis for the development of metabolic diseases, allergic immunological diseases, and high mortality rate due to infection with resistant strains of bacteria. During the irrational use of penicillin and macrolides postnatally, the composition of the intestinal microbiota and its functions change 12–24 months after the antibiotics treatment, the settlement of advantage intestinal flora with probiotic microorganisms is delayed, the maturation of the intestinal mucosa is compromised. Respiratory and systemic inflammation is strongly influenced by the rich adipocyte metabolism so that the treatment of these children is complex, and their asthma often remains only partially controlled. The phenotype “obese asthma” is characterized by a steroid and bronchodilator resistance. Therapeutic solution could be the body weight reducing, vitamin D3 substitution, and antileukotriene application. The prophylactic therapy of this asthma, using macrolides for a long time, should be supported, mandatory, with the substitution of probiotic/synbiotic during, and at least 6–9 months after discontinuation of therapy with macrolide.

Keywords: asthma, overweight, macrolide, prophylaxis, probiotic

1. Introduction

Pediatricians are nowadays increasingly more convinced by the data reported in the medical literature that the crucial time for the inception of asthma and obesity is during the childhood. What is it that happens during the 1st years of a child's life that produces changes in the lung and immune system, which predisposes the child to a lifetime of chronic symptoms related

to the “obese asthma” phenotype? This phenotype has previously been discussed [1, 2] as a unique, but today we are closer to the opinion that there is a distinct phenotype. Each of these diseases, asthma and obesity, is complex per se, modified by multiple factors, followed by complex inflammatory and immunological interactions, and often shared comorbidities; and, both diseases share similar lifestyle factors [1]. Until recently, many authors have explored a number of hypotheses about the mechanisms of their association including inflammation, gastro-esophageal reflux, and mechanical factors. Nowadays, we can consider the one more mechanism to be responsible for their association, i.e., the significant influence of irrational use of antibiotics (penicillin, macrolides) in the youngest children under 3 years of age [3, 4]. It is known that children of this age predominantly suffer from viral and atypical respiratory infection, which is, in practice, often treated with macrolides.

Macrolides, particularly, modify the microbiota and their functions, as well as the antibiotic resistance of the intestinal microbiota, and they are the strongest drive of interindividual differences in microbiota composition even 12–24 months after the course, as well as the drive of microbiota richness and maturity [4]. The recent study [4] has shown that, in all macrolide users, some advantage orders of germs (*Lactobacillus*, *Bifidobacterium*, *Collinsella*, *Anaerostipes*, unassigned *Coriobacteriaceae*) were reduced within 12–24 months while the number of side/undesirable orders of germs increased (*Lactobacillales*, *Bacteroides*, *Parabacteroides*, *Proteobacteria*, *Enterobacteriaceae*, *Eubacterium*, *Clostridium*, *Dorea*). It is known that the depletion of *Lactobacillus* and *Bifidobacterium* with intestinal microbiota deviations and low biodiversity, in early life, contributes to an increased risk of the allergic disease [5]. The composition of CD4 T lymphocytes and responsiveness of invariant natural killer T (iNKT) cells on many inflammatory cytokines in the intestinal mucosa affect the composition and diversity of the gut microbiota [6], especially during early life, and this may influence susceptibility to asthma later in life [7]. The commensal microbiota, achieving two mechanisms (positive-antigenic drive and negative-cytolytic depletion by CD8+T cells) profoundly depletes the iNKT cell compartment [7], plays an important epigenetic role in distinguishing individuals throughout life and contributes to the host immune status. The restricted gut flora followed with decreased microbial stimulation leads to the delayed immune maturation (Th2 and T regulatory) and impaired immune regulation with Th2-skewing early in life, which precedes asthma at school age [8]. The infant microbiome (gut microbiota and its corresponding genes) is undergone dynamic changes during the first 3 years of life when an adult-like microbiome is reached [9]. In the research with mice, it was found that the penicillin, also, led to the ileal atrophy associated with the generally decreased expression of genes involved in intestinal immune responses, with numerous consistencies across gender, i.e., reducing population of CD4 IL17 or IL22 in the ileum and colon [10].

Besides this, poor intestinal microbiota cannot provide adequate activity of the bile-salt hydrolase so there is no reduction in the host body weight, insulin resistance, and blood cholesterol [4].

2. The mechanisms of association between asthma and obesity

The pathogenesis of asthma in obese children and, vice versa, the obesity in asthmatics are poorly understood and, until recently, labeled as a pathogenesis of “obese asthmatics” [2].

Today, we know that the obesity had its origin in utero [1, 8]. Suboptimal nutrition in utero during the first two trimesters (despite normal postnatal nutrition and followed by catch-up growth in the first several years of life) causes obesity and consequently metabolic syndrome in children [8, 11]. Frey et al. [12] concluded that the children born with a low and high birth weight have an almost same increased risk of obesity later in life.

According to one hypothesis, the first risk factors for obesity in childhood asthma and "non-pure eosinophilic childhood asthma" [1, 13] are younger gestational age at birth and higher infant weight gain. For the "obese asthma," there is no sufficient evidence of a noneosinophilic pattern of inflammation, with subgroup of asthmatics demonstrating IL8-driven neutrophilic airway inflammation [13]. In such cases, there is a high mitogen-activated protein kinase (MAPK) and 8-isoprostane level, which all together correlate with increased leptin, increased Th 1 cytokines (IL2, tumor necrosis factor (TNF)-alpha, IL6, INF-gamma, and IL1-beta, IL8), increased tryptase, expressed leptin and adiponectin receptors in bronchial and alveolar epithelial cells, and simultaneously, they correlate with low adiponectin, decreased Th2 cytokines (IL4, IL5, and IL13), decreased Treg cells, decreased eosinophils, and decreased M2 macrophages [14]. Leptin and TNF-alpha establish a positive feedback mechanism. Leptin promotes activation toward Th1 phenotype, increases production of interferon (INF)-gamma, and promotes monocytes and alveolar macrophage activation, but decreases Th2 cytokines production. Simultaneously, leptin exhibits antiapoptotic properties on neutrophils via NF-kB and MEK1/2 MAPK pathway, and so it promotes neutrophil survival. These, all together, immunological occasions could modify airway function and lead to asthma with special airway inflammation [1, 13], accompanied, in the same time, with a low-level chronic systemic inflammation [14]. The systemic inflammation in obesity upregulates the asthmatic pathway, and this is modified by adipokines and other systemic inflammatory markers [14]. Increased TNF-alpha is responsible for airway hyperresponsiveness although data suggest little association with obesity [15]. However, other authors [16] consider that the adipocytes diameter is in a positive correlation with TNF-alpha. The subcutaneous adipocytes may be more important for glucose/insulin regulation than visceral fat in obese children and women [6, 16, 17]. The low insulin sensitivity is followed by high exhaled breath condensate levels of malondialdehyde, high exhaled nitric oxide, and low glutathione, which are some asthma markers [18, 19].

At the same time, leptin promotes angiogenesis and airway remodeling via vascular endothelial growth factor (VEGF) (released from airway muscle cells). However, metabolism of leptin can only partly explain the relationship that exists in the phenotype of asthma in obese children [13]. The next adipokine, called adiponectin, decreases in the obese, increases with weight loss, i.e., inversely correlates with body mass index (BMI), and can inhibit the production of pro-inflammatory cytokines (IL6, TNF-alpha), can promote the production of anti-inflammatory cytokine IL1 receptor antagonist and IL10, and so can attenuate allergen-induced airway inflammation [13].

Furthermore, some researchers observed the intergeneration aggregation (transgeneration transmission) of obesity and metabolic dysfunction [11, 12]. The gestational programming with metabolic abnormalities leads to the changes to the epigenomics and shifts toward obesity and metabolic syndrome. This should be taken with caution because the epigenetic gene modifications may be reversible [11, 12]. Surely, the epigenetic alterations are induced by suboptimal maternal nutrition/endocrine factors and include several factors (deoxyribonucleic

acid (DNA) methylation, histone modifications, chromatin remodeling, and/or regulatory feedback by microRNAs) that have the ability to modulate gene expression and promote the metabolic syndrome phenotype [13]. DNA methylation prevents gene access to transcription factors into mRNA and promotes other epigenetic changes. Epigenetic modification of genes in immune cells responsible for disease/disorder is launched by diet, microbiome, and environmental exposures, and can have long-lasting effects on immune responses related to allergic disease. We should not forget that prenatal exposures can have the potential to modify the development of atopic diseases during childhood.

Moreover, the possible reason for obesity in early childhood is a genetic polymorphism (Arg16, Gln 27, 308-G/A, and NR3C1) [13]. Polymorphism of gene Gln27 for beta-2-adrenergic receptors is associated with obesity and poor bronchodilator response. Polymorphism of 308-G/A of gene for TNF-alpha is also associated with both obesity and asthma. Gene ADRB2 codes the activity of adrenergic beta-2-receptor and is located on chromosome 5q31-q32. Thus, Arg16 polymorphism of this receptor may be associated with some asthma phenotypes (nocturnal, response to long-acting beta-2-agonists). Polymorphism of gene NR3C1 is followed by the resistance of glucocorticoid receptors and difficult-to-control asthma. Polymorphism of gene on chromosome 11q13 contributes to variation of obesity phenotypes in general population. Moreover, it is known that single nucleotide polymorphisms within several genes influence the development of both obesity and asthma at the genetic level [13]. We should not forget that chromosome 12q contains genes (12q13) for variants in vitamin D receptors and inflammatory cytokines in obese asthmatics [13, 14].

Atopy significantly mediates the effect of adiposity on asthma outcomes (**Figure 1**). However, the exact role of atopy or allergic airway inflammation in the “obese asthmatic” phenotype is currently unclear [13]. Periyalil et al. [14] found that adipocytes, macrophages, and mast cells secrete inflammatory cytokines, which in turn lead to systemic inflammation and negative effects of target organs. Allergic asthma may be followed by obesity when the children are

Figure 1. Associations among asthma, obesity, irrational use of antibiotics and effects of probiotics/synbiotics. The solid arrows indicate undesirable effects. The dashed-line arrows indicate desirable effects.

younger than 12 years and suffer from early-onset asthma and/or atopic eczema and/or food allergy in infants, that all together lead to excessive consumption of food and to modified asthma phenotype called "obese asthmatic" phenotype [13]. As the metabolism of adipocytes is rich, and the estrogen enhances eosinophil function and modulates IL4 and IL13 production by monocytes, the "obese asthma" phenotype is noted predominantly in prepubertal boys and girls, and premenopausal women, established the sex and age dependency [15–17].

According to another hypothesis, both asthma and obesity are associated with the increased airway oxidative stress and systemic inflammation, which is followed by lung restriction, reduced tidal volume (V_t), reduced cyclic loading and unloading impulses, less production of adenosine triphosphate (ATP) for uncoupling, i.e., unlocking of actin-myosin latch so that the airway smooth muscles are in stiff state, the bronchoconstriction is very strong and without bronchodilator response [19, 20]. This is accompanied with changes in the mechanics of breathing [21] with low volume at end of normal expiration (FRC), especially when in supine position, and low the expiratory reserve volume (if BMI higher than 35), the tidal volume (V_t) closed to residual volume. Low forced expiratory volume in 1 second (FEV1), low forced vital capacity (FVC), and the ventilation/perfusion ratio mismatch are followed by barrelhocked chest and possible atelectasis; lung compliance is reduced, and the airway resistance rises so that oxygen uptake is greater (VO_2) with high respiratory rate and work of breathing. Recent research study [21] has found that, within obese patients in supine position, the airway resistance during tidal breathing increases, but there is a difference between those with and without ventilatory failure. This change is mostly correlated with the visceral adipose tissue mass and the small airways. In effect, the authors [21, 22] argue that mass loading affects respiratory mechanics by other mechanisms such as altering chest wall compliance directly by restricting expansion and causing the respiratory system to operate on a less compliant part of the pressure-volume curve.

According to the third hypothesis, the obese children often have gastroesophageal reflux disease [23], which can worsen their asthma and vice versa. The stomach acid goes back into the esophagus, spills over the larynx, causes injury to the lining of the throat, airways, and lungs, which makes inhalation difficult and often causes a persistent cough on extraneous content, or acid enters the esophagus, triggers the afferent nerve reflex of coughing, causes the narrowing of airways in order to prevent the acid from entering, and the consequence is the shortness of breath [24]. Neural connections between esophagus and airway through the transient receptor potential may contribute to that [24]. Microaspirations of small amounts of acidic content, over time, contribute to chronic cough and reduce laryngeal mechanosensitivity to air stimuli, increasing the risk of aspiration thereby, as in a vicious circle [24].

3. The pathogenesis of asthma in children who are not obese

Unlike the obese children suffering from asthma, the asthmatic children with normal body weight (nBW) have a different immunopathogenesis of asthma. Asthma in children with nBW is predominantly allergic, especially if it is associated with eczema, food allergy, and allergic rhinitis. Allergic asthma can begin during the 1st year and disappear by the 3rd year of life. In this

case, it is called infantile asthma. Immunopathogenesis of infantile allergic asthma [25] often is not typical (mediated by increased immunoglobulin E (IgE) production of IgE and eosinophilic airway inflammation). Postnatal sensitization to perennial inhalant allergens and frequent viral infections of the lower respiratory tract occur in this age. The most common trigger factors of the asthmatic attacks are viruses and atypical bacteria, so the asthma is accompanied by mixed (eosinophil/neutrophil) inflammation of the airways. In children older than 3 years with nBW, allergic asthma usually has a typical immunopathogenesis, with the increased IgE production, eosinophilic inflammation of the airways, and type I hypersensitivity response.

Certainly, in children suffering from asthma with nBW, undermined tissues integrity of the airways and/or defective function of the respiratory epithelial barrier allow penetration of allergens, viruses, bacterial toxins, and other harmful noxae, which activate the immune system (**Figure 2**) and direct toward chronic airway inflammation [25, 26]. Activation of epithelial cells and the release of pro-inflammatory cytokines and chemokines (TNF-alpha, IL13, thymic stromal lymphopoietin (TSLP), IL31, and IL33) lead to Th2 cell response (IVb type immune response). After that the apoptosis of the epithelial cells and their peeling with a supporting release of IFN-gamma, TNF-alpha, and IL32 follow. Chemokines attract inflammatory cells that interact with the target tissue cells. Akdis found that innate lymphoid cell type 2 (ILC2) plays a key role in the activation and collection of T and B cells, i.e., they are early providers of Th2 immune response followed by the release of IL5, IL9, and IL13 when stimulated with IL25, IL33, and TSLP (released from epithelial cells of mucous membranes in response to protease allergens) [25, 26].

Figure 2. Pathogenic mechanisms in asthma.

It is known that certain interleukins (IL5, IL25, and IL33) induce eosinophilia and eosinophilic airway inflammation, and other interleukins (IL4 and IL13) induce local and systemic IgE production [25, 26]. In the phase of sensitization of a patient, FcεRI binds the allergen-specific IgE [25] on the surface of mast cells and basophil cells. During the repeated contact with the same allergen, subsequent degranulation of mast cells and basophils, which release the mediators of type I hypersensitivity reactions (histamine, prostaglandin D2 (PGD2), PAF, LTC4, LTD4, LTE4, IL3, IL4, IL5, IL13, chemokines), occurs. Effector T cell subpopulations (TH9, Th17, and TH22) play a partial role in inflammation, mucus production, and the tissue healing. Bronchial hyperreactivity, smooth muscle spasm, and activation of myofibroblasts are controlled by a number of cytokines (IL4, IL9, IL13, IL25, and IL33). Subsequently, collection of inflammatory cells and increased inflammatory cascade are induced by chemokines and the molecules of the metabolic pathway of arachidonic acid. Angiogenesis is a sign of chronic inflammation and is accompanied by an increased production of VEGF and IL32. Survival, reactivation of migratory inflammatory cells and their interaction with tissue cells are mediated by IL2 and IL4 [26]. The type 2 innate lymphoid cells also produce amphiregulin to induce airway remodeling (**Figure 2**).

IL33 is a cytokine and a biomarker of innate immune response. It is expressed by epithelial cells, endothelial cells, eosinophils, smooth muscle, myofibroblasts, dendritic cells (DC), macrophages, and mast cells, and contributes to Th2 inflammation and bronchial hyperreactivity in asthma, and involves in T cell differentiation. IL33 is one of the sensing cytokines, thus signals to the allergen-presenting dendritic cells to take up incoming allergens and bring them to lymph nodes.

In the course of the immune response to a viral antigen, the signaling of factor 3 of the interferon gene regulation is defective in a child suffering from allergic asthma, which is accompanied by a reduced or absent INF-beta production, causing the absence of apoptosis and inhibition of the virus replication [25–27]. Since the cellular immunity is defective, viral nucleic acid cannot activate the toll-like receptors (TLR3, TLR5, and TLR7) that lead to the virus survival, its replication, and the cytotoxic destruction of epithelial cells, which release the mediators that cause the exacerbations with mixed neutrophil/eosinophilic inflammation. The final result of INF-beta deficiency is an increase of transforming growth factor (TGF)-beta, which contributes to the deregulation of Treg lymphocytes, an early proliferation and remodeling of the airways [27]. At the same time, FcεRI action on the precursors of dendritic cells is amplified, so the virus can be easily attached via a light chain of the Fab fragment of IgE. Recent research findings suggest that the iNKT cells promote sensitization to ubiquitous inhalant allergens [28], contribute to *in vivo* Th2 inflammatory response of the airways facilitating the activity of dendritic cells, i.e., acting as adjuvants for the enhance of Th2 inflammatory cell response [29] and thereby contribute to the development of asthma and other allergic diseases. What else, activated DCs traffic to lymphoid organs to initiate T cell responses to the viruses or allergens and so contribute to further disease pathogenesis.

Th2 molecular asthma phenotypes are determined by identifying the clinical characteristics and biomarkers (eosinophilia and serum periostin, the concentration of exhaled nitric oxide) and sometimes by identifying specific molecular pathways [30]. However, non-Th2 phenotypes of asthma, often asthma in obese children and sometimes infantile asthma, are still

poorly defined and their biomarkers (modified natural inhibitor of inducible nitric oxide synthase, asymmetric dimethylarginine in the blood) are still not routinely measured. Identifying phenotypes of asthma in children and adults is important so we could provide the appropriate treatment. Most children suffering from allergic asthma with nBW are successfully treated according to the recommendations of the Global Initiative for Asthma [31]. Most children suffering from the asthma with the nBW have a good response to inhaled steroids (ICS) and/or antileukotrienes. In a small number of children, asthma is severe and requires the treatment with high-dose of ICS. Poor response to ICS can have children with difficult to treat asthma, asthma induced by viruses and “obese” asthma so the treatment of these patients is complicated.

4. The obese and asthmatic children treated with antibiotics

The children of the youngest age predominantly suffer from viral and atypical respiratory infection, which is, often, mistakenly treated with antibiotics, actually, very often with macrolides. This applies, furthermore, in the children suffering from asthma with accompanying obesity because their asthma exacerbation, very often, triggered with virus and followed by the fever, is often considered to be a respiratory infection with bronchial obstruction and is hitherto mistakenly treated with antibiotics.

The overweight cases, the asthmatics, and the children treated with penicillin or macrolide (one or more times) have the microbiota with the abundance of side bacteria and long-term reduction in microbial richness [4] (**Figure 1**). For example, one of the macrolides, the azithromycin, reduces biomarkers of not only environmental enteropathy and pathogenic intestinal bacteria [32, 33], but also commensal and advantage bacteria, which makes restricted (poor) flora. The gut microbiota with restricted flora is mediated by cytolytic CD8⁺ T cells with depleted iNKT cells that contribute to epigenetically modulating of specific host immune traits (defense and immunoregulation) [6]. It is known that CD8⁺ T cell responses are elicited by certain microbiota, including *Listeria* and *Salmonella* and followed by the local enteric mucosal stress response, which is associated with striking increases in certain chronic inflammatory and autoimmune diseases [6]. Besides that azithromycin inhibits ribosomal translocation, leading to the inhibition of bacterial protein synthesis, acts bacteriostatic but may be bactericidal at high concentrations, modulates differentiation and lipopolysaccharide (LPS) induces maturation in dendritic cells but decreases transcription and activity of histone deacetylation-2 promoter, which results in gene repression [32]. After macrolide [3, 4, 32, 33], the microbiota slowly recovers so that it establishes persistence of the antibiotic-associated microbiota composition, which contributes to the persistence of metabolic changes and compromises the development of a healthy immune system, so that the consequences are early manifestations of asthma and obesity. The mentioned effect of macrolides is not dependent on the age of the child [4].

The impression is that use of antibiotics during early life, linked with poor gut microbial diversity, drive to “preponderance” of side over advantage effects of antibiotics (macrolides and penicillin) [3, 4, 32, 33]. Pronouncedly, in the case of irrational use of antibiotics during early life, the restricted gut flora is followed by a decreased microbial stimulation, which

leads to the delayed immune maturation (Th2 and T regulatory) and the impaired immune regulation with Th2-skewing early in life, which precedes asthma at school age [3, 4, 8] and obesity early in life [10, 11, 14]. This consideration has no intention of diminishing the desired effects of azithromycin (attenuates Th-1 responses following LPS or INF-gamma stimulation of macrophages, shifting polarization of activated macrophages toward the alternative/anti-inflammatory M2-phenotype (which plays a role in directing Th-2 responses), inhibits IL17-induced IL8 and 8-isoprostane release)—but pointing out the need for its rational application, the “balanced” therapy, new therapeutic modality, especially in the children suffering from wheezing, respiratory infections and obesity.

In the mentioned period of 12–24 months, the macrolide use is associated with the increased risk of asthma and it predisposes children to the antibiotic-associated weight gain. The macrolides impact on the intestinal microbiota should be considered with mandatory prescribing probiotics [4], which would prevent compromising of a healthy immune system and metabolism development. It has been proven that “good” probiotic bacteria and “good” probiotic fungi in the mouth and intestines, sufficiently represented, are necessary to compensate destroyed intestinal flora during and after antibiotic therapy and for the health of children [5] (**Figure 1**). We have, also, confirmed that the use of synbiotics in the optimal period of time of 3–6 months can achieve adequate control of respiratory infection and allergic wheezing diseases in children younger than 5 years [34]. Nevertheless, we have found that the time necessary for the restitution of the immune balance between immunoglobulin A and immunoglobulin E was 9 months in the youngest children [34]. Now, we can add a logical setting as hypothesis that should have been assessed in clinical trials, that the everyday application of synbiotic (during several months) after antibiotic using would likely prevent the obesity.

In favor of this Million's findings [35], the probiotics affect the microbiota directly by modulating its bacterial content and indirectly through bacteriocins produced by the probiotic bacteria, as well as, *L. plantarum* and *Lactobacillus gasseri* (formerly named *L. acidophilus*) strains, which has an anti-obesity effect in overweight/obese people in terms of reductions in abdominal adiposity, body weight, and other measures. Adding a probiotic strain Bacteroidetes can be essential for the body weight loss in obese patients, because Bacteroidetes overgrows the undesirable gut strain named Firmicutes [35].

It is known that the trillions of the side microbial cells in the intestinal microbiota can contribute to obesity by increasing energy extraction or by altering metabolic signaling and inflammation [36], and thus occupy a central role in the pathogenesis of, so far seemingly unrelated systemic auto-inflammatory and metabolic disorders. As a matter of fact that the condition of basal immune and metabolic homeostasis is mainly controlled by the bacterial microbiome.

5. The inflammation in the “obese asthma” phenotype and the possibility of the treatment

Inflammation is the goal in the treating of childhood asthma accompanied by obesity, but here, inflammation is neutrophilic, with elevated leptin levels in the plasma and airways, predominately Th-1-related inflammation (IL8 driven) [13, 21], potential and IL-17-related

inflammation, enhanced inflammatory/oxidative response to leptin and decreased airway eosinophils. The high level of leptin stimulates the synthesis of TNF- α , IL6, and prostaglandins, which is the basis for a low-grade inflammatory process that leads to the atherogenesis process and early development of metabolic syndrome. The leptin receptors are reduced in the airways but they are represented in the visceral fat, which enables metabolic influence on bronchial hyperreactivity [20, 37]. Increased oxidative stress and decreased physiologic nitric oxide are due to low L-arginine/asymmetric dimethylarginine ratio, which overall contributes to bronchoconstriction [20, 21, 38, 39]. This metabolic function of smooth muscle in the airways contributes to a poor response to bronchodilators, poor asthma control, and low pulmonary function. In the “obese asthma” phenotype, increased airway oxidative stress and systemic inflammation are followed by reduced cycling loading and unloading impulses, the less production of adenosine triphosphate for uncoupling, i.e., unlocking of actin-myosin latch [19, 20], so that the smooth muscles airways are in a stiff state, the bronchoconstriction is very strong and without bronchodilator response, i.e., the resistance to short-acting beta-agonists exists.

Both conditions, asthma and obesity, associated, act to aggravate the degree of bronchodilatation after a deep inhalation, which is a mechanical airway dysfunction [37]. The mechanical airway dysfunction in an “obese asthma” phenotype is a consequence of restriction or reduced the total lung capacity, decreased expiratory reserve volume and there is a ventilation/perfusion mismatch. In obese asthmatics, it is associated with increased airway inflammation indices. At the same time, body mass index (BMI) more than 30 was associated with a 10-fold increase in odds for developing methacholine responsiveness [37, 38]. Anyhow, early onset of asthma is a potential risk factor for the weight gain. In the early onset category, BMI increased linearly for every year of having asthma since diagnosis [37]. It is still not clear whether obesity, preceding or following asthma, influences the severity of asthma and asthma control.

A special problem in the treatment of this asthma phenotype is the steroid resistance. The response to inhaled steroids is different according to BMI categories [39]. The oxidative stress contributes to the activation of MAPK, baseline TNF- α in peripheral blood mononuclear cells and bronchoalveolar lavage cells, so that the response, for example, to dexamethasone is poor or does not exist. The TNF- α is in a positive correlation with the adipocyte diameter, with which metabolism is rich. Doubtless, we can always try to treat this asthma phenotype in the form of fixed combinations of low doses of inhaled steroid and long-acting beta 2 agonist.

The second reason for the steroid resistance in the “obese asthma” phenotype is, often, a low vitamin D level that is inversely related to BMI [40, 41]. Vitamin D performs the upregulation of IL-10 by CD4 Treg lymphocytes, thus it exceeds steroid resistance [37] and inhibits the activity of DCs across the decreased LPS activation, inhibits the proliferation and fibroblasts activation and inhibits the inflammatory cytokines and the airway remodeling mediators secretion by the smooth muscle cells in airway, reduces the secretion of extracellular matrix, acts anti-proliferatively on smooth muscles, improves the immune function in the lungs, upregulates the antimicrobial proteins (cathelicidin, beta-defensin), acts anti-inflammatory, reduces the pulmonary hyperplasia, inhibits the eosinophils recruitment, promotes the immune tolerance [41], and reduces the IL-17A and IL-22 cytokine levels [42].

The antileukotriene treatment can be successful at the certain asthmatics with the phenotype “obese asthma” because it controls the release of INF-gamma and producing of myofibroblasts types I and II well [31].

The antineutrophil drugs, such as macrolides and dapsons (diaminodiphenyl sulfone), did not give the expected results for the “obese asthma” phenotype control [31]. Furthermore, the advantage of anti-inflammatory role of macrolides is in conflict with its side, already commented, effects on intestinal mucosa in young children. Because of this, we must find other drugs to treat the “obese asthma” phenotype in the youngest children, such as, perhaps, anti-cytokines or biological agent [12]. However, the anti-TNF-alpha therapies have not yet been approved for children, but only for adults [38]. The bariatric surgery is the only aggressive attempt.

6. Conclusion

Well-known and safe recommendations for the “obese asthma” phenotype control are, without doubt, the cutoff of the vicious cycle of childhood obesity/asthma, which should be reached with more physical activity and less desire for food [43, 44]. Afterward, the substitution of D3 vitamin may be decisive in the treatment of the asthma with a distinct phenotype “obese asthma.” The treatment of this asthma phenotype in children, always, involves an attempt with antileukotriene or/and a fixed combination of low dose of inhaled steroid and long-acting beta 2 agonist. The current use of some macrolides, as an anti-inflammatory drug for asthma, is under question now, because it is necessary to make a new assessment of benefit and harm, or establish a new treatment modality with a combination of macrolides and probiotics/synbiotics.

We expect that, in the future, the indications for macrolides, as an anti-inflammatory drug (e.g., for infantile and asthma in childhood), will be accompanied by a recommendation on mandatory, simultaneous, and the concomitant application of probiotics or synbiotics, especially in the youngest children (**Figure 1**). The duration of substitution with probiotics or synbiotics during and after discontinuation of macrolides should be determined in future studies. From our current perspective and findings, and bearing in mind the long-term disruption (24 months) of the intestinal microbiota, we suggest a period of, at least, 9 months of probiotics or synbiotics supplementation, which is necessary time for the restitution of immune balance between immunoglobulin A and E, in the youngest children [34, 44]. We join the recommendation, to avoid all antibiotics, in particular macrolides, for the “irresponsible” treatment of viral infections in the youngest children, or several times a year, or longer than the prescribed time and doses for macrolides [45] and penicillin [46]. All antibiotics should be avoided for one more reason—it is the exclusive way to avoid the intestinal microbiota disruption, disorder of the genetic material within the intestinal microbial niches (microbiome), metabolic alterations, obesity, immunological imbalance, and early onset of asthma.

We and many other authors worldwide did not end the research for the treatment of asthma in obese children, for the “balanced” treatment of the youngest children during respiratory

infections, for the overcoming the side effects of some antibiotics in early childhood, for a new therapeutic modality, especially in children suffering from wheezing/asthma, respiratory infections and obesity, simultaneously, but this is our future research goal.

Abbreviations

iNKT	invariant natural killer T cells
Th	T helper cells
IL	interleukin
TNF-alpha	tumor necrosis factor-alpha
INF	interferon
nBW	normal body weight
TSLP	thymic stromal lymphopoietin
ILC2	innate lymphoid cells type 2
DC	dendritic cell
IgE	immunoglobulin E
FcεRI	Fc epsilon RI, the high-affinity receptor for the Fc region of IgE
PGD2	prostaglandin D2
PAF	platelet-activating factor
TGF	transforming growth factor
MAPK	mitogen-activated protein kinase
MEK1	mitogen-activated protein kinase kinase 1
MEK2	mitogen-activated protein kinase kinase 2
NF-κB	nuclear factor kappa B
VEGF	vascular endothelial growth factor
Areg	amphiregulin
mRNA	messenger RNA
DNA	deoxyribonucleic acid
RNA	ribonucleic acid
TLR	toll-like receptor

ICS	inhaled steroids
V _t	tidal volume
ATP	adenosine triphosphate
FRC	functional residual capacity
FEV ₁	forced expiratory volume in 1 second
FVC	forced vital capacity
VO ₂	oxygen consumption
LPS	lipopolysaccharide

Author details

Andjelka Stojkovic^{1,2*}, Aleksandra Simovic^{1,2}, Vesna Velickovic² and Katerina Dajic²

*Address all correspondence to: andja410@mts.rs

1 Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

2 Paediatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia

References

- [1] Stojkovic A, Velickovic V. The clinical implications of asthma in obese children: Review. *Pediatru.ro*. 2015;**39**(3):18-20
- [2] Papadopoulos NG, Arakawa H, Carlsen K-H, Custovic A, Gern J, Lemanske R, et al. International consensus on (icon) pediatric asthma. *Allergy* 2012; DOI: 10.1111/j.1398-9995.2012.02865.x
- [3] Nobel RY, Cox ML, Kirgin FF, Bokulich AN, Yamanishu S, Teitler I, et al. Metabolic and metagenomic outcomes from early-life pulsed antibiotic treatment. *Nature Communications*. 2015;**6**:74-86. DOI: 10.1038/ncomms8486
- [4] Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, Bork P, de Vos WM. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nature Communications*. 2016;**7**:10410. DOI: 10.1038/ncomms10410
- [5] Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, et al. The biodiversity hypothesis and allergic disease: World allergy organization position statement. *World Allergy Organization Journal*. 2013;**6**:3-41. DOI: 10.1186/1939-4551-6-3
- [6] Wingender G, Stepniak D, Krebs P, Lin L, McBrides S, Wei B, et al. Intestinal microbes affect phenotypes and functions of invariant natural killer T cells in mice. *Gastroenterology*. 2012;**143**(2):418-428. DOI: 10.1053/j.gastro.2012.04.017

- [7] Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. *Science*. 2016;**352**(6285):539-544. DOI: 10.1126/science.aad9378
- [8] Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical & Experimental Allergy*. 2014;**44**(6):842-850. DOI: 10.1111/cea.12253
- [9] Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;**486**:222-227. DOI: 10.1038/nature11053
- [10] Cox ML, Yamanishi S, Sohn J, Alekseyenko VA, Leung MJ, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell*. 2014;**158**(4):705-721. DOI: 10.1016/j.cell.2014.05.052
- [11] Desai M, Jellyman JK, Ross MG. Epigenomics, gestational programming and risk of metabolic syndrome. *International Journal of Obesity*. 2015;**39**(4):633-641. DOI:10.1038/ijo.2015.13
- [12] Frey U, Latzin P, Usemann J, Maccora J, Zumsteg U, Kriemler S. Asthma and obesity in children: Current evidence and potential systems biology approaches. *Allergy*. 2015;**70**:26-40. DOI:10.1111/all.12525
- [13] Ali Z, Ulrik SC. Obesity and Asthma: A coincidence or a causal relationship? A systemic review. *Respiratory Medicine*. 2013;**107**(9):1287-1300. DOI: 10.1016/j.rmed.2013.03.019
- [14] Periyalil AH, Gibson GP, Wood GL. Immunometabolism in obese asthmatics: are we there yet? *Nutrients*. 2013;**5**:3506-3530. DOI: 10.3390/nu5093506
- [15] Maffei C, Manfredi R, Trombetta M, Sordelli S, Storti M, Benuzzi T, et al. Insulin sensitivity is correlated with subcutaneous but not visceral body fat in overweight and obese prepubertal children. *The Journal of Clinical Endocrinology & Metabolism*. 2008;**93**(6):2122-2128. DOI: 10.1210/JC.2007-2089
- [16] Boulet LP. Asthma and obesity. *Clinical & Experimental Allergy*. 2013;**43**(1):8-21. DOI: 10.1111/j.1365-2222.2012.04040.x
- [17] Vieira VJ, Ronan AM, Windt MR, Tagliaferro AR. Elevated atopy in healthy obese women. *The American Journal of Clinical Nutrition*. 2005;**82**(3):504-509 [PubMed: 16155260]
- [18] Forno E, Acosta-Pérez E, Brehm JM, Han YY, Alvarez M, Colón-Semidey A, Canino G, Celedón JC. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. *Journal of Allergy and Clinical Immunology*. 2014;**133**(5):1308-1314. DOI: 10.1016/j.jaci.2013.09.041
- [19] Jimenez SJ, Espinet HJF, Garrido MMJ, Antonio RJ, Mayor PS, Boira PdelMM, Comas RA, Martinez BA. Asthma and insulin resistance in obese children and adolescents. *Pediatric Allergy and Immunology*. 2015;**25**:699-705. DOI: 10.1111/pai.12294
- [20] Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calboun WJ, et al. Effect of beta2-adrenergic receptor polymorphism on response to long acting beta2

- agonist in asthma (LARGE trial): A genotype-stratified, randomised, placebo-controlled, crossover trial. *Lancet*. 2009;**374**(9703):1754-1764. DOI: 10.1016/S0140-6736(09)61492-6
- [21] Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. 2006;**130**(3):827-833 [PMID: 16963682]
- [22] Dattani RS, Swerner CB, Stradling JR, et al. Exploratory study into the effect of abdominal mass loading on airways resistance and ventilatory failure. *BMJ Open Respiratory Research*. 2016;**3**:e000138. DOI: 10.1136/bmjresp-2016000138
- [23] Gause SG. Pulmonary manifestations of gastroesophageal reflux disease. *Annals of Thoracic Medicine*. 2009;**4**(3):115-123. DOI: 10.4103/1817-1737.53347
- [24] Mitrovic S. Terminology, diagnostics and therapy of laryngopharyngeal reflux—A glimpse into the past. *Vojnosanitetski Pregled*. 2014;**71**(6):608-610. DOI: 10.2298/VSP1406608M
- [25] Akdis M. The pathogenesis of asthma. In: *Global Atlas of Asthma*. European Academy of Allergy and Clinical Immunology; 2013. pp. 28-30
- [26] Akdis CA. The underlying mechanisms in allergy. In: *Global Atlas of Allergy*. European Academy of Allergy and Clinical Immunology; 2014. pp. 39-42
- [27] Bordon Y. Asthma and allergy: TGF β —Too much of a good thing? *Nature Reviews Immunology*. 2013;**13**(9):618-619. DOI: 10.1038/nri3519
- [28] Wingender G, Rogers P, Batzer G, Lee MS, Bai D, Pei B, et al. Invariant NKT cells are required for airway inflammation induced by environmental antigens. *Journal of Experimental Medicine*. 2011;**208**(6):1151-1162. DOI: 10.1084/jem.20102229
- [29] Nie H, Yang Q, Zhang G, Wang A, He Q, Liu M, et al. Invariant NKT cells act as an adjuvant to enhance Th2 inflammatory response in an OVA-induced mouse model of asthma. *PLoS One*. 2015;**10**(4):e0119901. DOI: 10.1371/journal.pone.0119901
- [30] Wenzel S. Phenotypes & endotypes: Emerging concepts on asthma heterogeneity. In: *Global Atlas of Asthma*. European Academy of Allergy and Clinical Immunology; 2013. pp. 34-35
- [31] Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute, National Institute of Health. GINA Report. Global Strategy for Asthma Management and Prevention. Bethesda: National Institute of Health; Updated 2016. Available from: www.ginasthma.org
- [32] Parnham JM, Eraković Haber V, Giamarellos-Bourboulis JE, Perletti G, Verleden MG, Vos R. Azithromycin: Mechanisms of action and their relevance for clinical applications. *Pharmacology & Therapeutics*. 2014;**143**(2):225-245. DOI: 10.1016/j.pharmthera.2014.03.003
- [33] Bishai WR. Macrolide immunomodulatory effects and symptom resolution in acute exacerbation of chronic bronchitis and acute maxillary sinusitis: A focus on clarithromycin. *Expert Review of Anti-infective Therapy*. 2006;**4**(3):405-416. DOI: 10.1586/14787210.4.3.405

- [34] Stojkovic A, Simovic A, Bogdanovic Z, Bankovic D, Poskurica M. Optimal time period to achieve the effects on synbiotic-controlled wheezing and respiratory infections in young children. *Srpski Arhiv za Celokupno Lekarstvo*. 2016;**144**(1-2):38-45. DOI: 10.2298/SARH1602038S
- [35] Million M, Lagier C-J, Yahav D, Paul M. Gut bacterial microbiota and obesity. *Clinical Microbiology and Infection*. 2013;**19**:305-313. DOI: 10.1111/1469-0691.12172
- [36] Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal ZW, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature*. 2012;**482**:179-185. DOI: 10.1038/nature10809
- [37] Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with development of metacholine airway hyperresponsiveness in men: The normative aging study. *Thorax*. 2002;**57**(7):581-585. DOI:10.1136/thorax.57.7.581
- [38] Szeffler JS. Advances in pediatric asthma in 2014: Moving toward a population health perspective. *Journal of Allergy and Clinical Immunology*. 2015;**135**:644-652. DOI: <http://dx.doi.org/10.1016/j.jaci.2014.12.1921>
- [39] Baffi WC, Winnica ED, Holguin F. Asthma and obesity: Mechanisms and clinical implications. *Asthma Research and Practice*. 2015;**1**:1-7. DOI: 10.1186/s40733-015-0001-7
- [40] Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL10 secreting regulatory T cell in glucocorticoid resistant asthma patients. *Journal of Clinical Investigation*. 2006;**116**(1):146-155. DOI: 10.1172/JCI21759
- [41] Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, Saglani S. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *American Journal of Respiratory and Critical Care Medicine*. 2011;**184**:1342-1349. DOI: 10.1164/rccm.201107-1239OC
- [42] Nanzer MA, Chambers SE, Ryanna K, Richards D, Black C, Timms MP, et al. Enhanced production of IL-17A in patients with severe asthma inhibited by 1 α ,25-dihydroxyvitamin D3 in a glucocorticoid-independent fashion. *Journal of Allergy and Clinical Immunology*. 2013;**132**:297-304. DOI: 10.1016/j.jaci.2013.03.037
- [43] Moreira A, Bonini M, Garcia-Larsen V, Bonini S, Del Giacco RS, Agache I, Fonseca J, Papadopoulos GN, Carlsen HK, Delgado L, Haahtela T. Weight loss interventions in asthma: EAACI Evidence-based clinical practice guideline (part I). *Allergy*. 2013;**68**(4):425-439. DOI: 10.1111/all.12106
- [44] Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-Year follow-up of a randomised placebo-controlled trial. *Lancet*. 2003;**361**(9372):1869-1871. [PMID: 12788576]
- [45] Macrolides. BNF for Children 2014. Vol. 15. London, UK: BMJ Group, Pharmaceutical Press. pp. 283-286. Available from: www.bnf.org
- [46] Penicillins. BNF for Children 2014. Vol. 15. London, UK: BMJ Group, Pharmaceutical Press. pp. 261-269. Available from: www.bnf.org