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Respiratory allergies in childhood: recent advances and future challenges

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Abstract

The burden of allergic airway diseases still represents a major health problem in childhood. Despite many different options are currently available for the diagnostic work-up and management, the overall disease control in terms of impact on quality of life, morbidity and mortality, is not yet satisfactory. The extreme variability of individual risk factors and severity determinants may account for it. On the other side the knowledge of the multifaceted allergy background could pave the way to primary prevention, early intervention and disease course modification. In fact, most of current research is focusing on the identification of biological and clinical predictive markers of allergy and asthma onset. This review aims at summarizing the latest achievements concerning the complex interrelation between genetic predisposition and environmental factors, and their impact on prevention strategies and early identification of at risk subjects. An update on the diagnostic and monitoring tools as well as an insight into the newest treatments options is also provided.

Key words: airway; allergy; biomarkers; childhood; diagnostics; environment; life quality; prediction; risk factors; therapy

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Allergic airway diseases in childhood – a multifaceted enemy

Allergic diseases are the most common chronic diseases in children and no complete agreement on effective measures for primary prevention is available. The growing worldwide burden of allergy diseases is properly defined as the “allergy epidemic”. Allergy is common in children, adolescents and adults. The German epidemiological Multicentre Allergy Study (MAS) showed age-related typical manifestations of atopic and allergic diseases that are usually summarized in the “atopic march” concept, where infantile eczema and food allergy could precede the onset of allergic airway diseases (rhinitis and asthma) (1). Different from many other complex chronic diseases (diabetes mellitus or hypertension) allergic diseases generally start early in life, presumably even prenatal. The incidence of asthma is the highest in the preschool and early school-age children with the improvement of symptoms and prevalence decrease during the time. It is well known that allergic diseases are multifactorial with the complex influence of both gene and environmental factors. Identifying prenatal and early-life risk factors may represent an opportunity for a prompt prevention. The problem is even more complex as we know that there are many different asthma phenotypes and patient’s needs (2). The knowledge from different birth cohorts indicates that food sensitisation is one of the most important risks for asthma development (3). The awareness of age-related differences in schoolchildren’s asthma control has significant clinical implications for management and treatment, as well as for assessment of asthma control in relation to clinical research (4).

The focus of this review is to summarize the latest achievements concerning risk factors and preventive strategies moving from the complex interrelation of genetic predisposition and environmental factors, as well as to give insight into the newest diagnostic tools and treatments options.

Prenatal and early postnatal risk factors

Modern environmental changes have been related to a number of adverse effects on human health, increasing the risk of many inflammatory non-communicable diseases (NCDs). Most of the “modern life” diseases (asthma, allergies, heart disease, diabetes and obesity) are associated with similar modern environment. Due to the particular vulnerability of a developing immune system to environmental triggers, allergies are the earliest onset NCD and they usually begin in the first months of infancy. Environmental-driven changes begin in pregnancy, with emergent differences in immune function detectable at birth. Maternal diet, microbial exposure and toxic exposures in pregnancy are considered to be the most relevant prenatal and early postnatal risk factors (5, 6). Many data suggest that maternal smoking increases the risk of respiratory symptoms in children. A recent study highlighted the relationship between glutathione S-transferases (GSTs) detoxify xenobiotic from tobacco smoke and functional polymorphism in GST gene(s), that could predispose children to the detrimental effects of maternal smoking (7).

Other studies illustrated the link between maternal drug use during pregnancy and childhood asthma. The two most likely associations concern drugs for treatment of gastro oesophageal reflux disease (GERD) and opioids, but further studies are needed to verify or reject the associations. The authors found little evidence for an effect of paracetamol on childhood asthma risk, which agrees with a recent publication (8) also based on prospectively collected data. Many studies have already documented the influence of stressful events on asthma onset and development; however recent data also suggested that maternal stress (divorce, loss of her/his job etc.) during the pregnancy might increase the possibility of having wheezing, asthma, eczema and allergic rhinitis in offspring during childhood (9). According to multiple studies the mode of delivery is marked as one of the important risk factors for the development of allergic diseases. The caesarean section has been described as a major risk factor, being allergic diseases more prevalent in children born in that way.

However, novel data implicated that there is only connection between urgent caesarean section and allergic disease development (10).

According to the multiple investigations that have been ongoing for decades, infantile exposure in early life could conceivably 'program' the structure and function of particular tissues, thereby protecting from or predisposing to future morbidities. Environmental exposure may be an instrument in shaping infants immune system. In keeping with those data, breastfeeding has a prominent role in the regulation of neonatal innate immune responses (11). Breastfeeding has been considered as one of the most important factors in allergies prevention. Over the last decades a new concept has been established: the heterogeneous nature of breastfeeding effects suggests it may influence systemic immune inflammatory function at several different levels. Recent data suggest that human milk contains a small amount of proteins that may influence the expression of inflammatory symptoms associated with respiratory infections and atopy in early life, even though these effects appear to be inconsistent and transient (11,12). Evidence from several observational studies suggest an important influence of vitamin A, D, E, zinc, the Mediterranean diet, and timing and diversity of infant feeding on the allergic disease development and exacerbation. These findings need to be confirmed through large, definitive primary prevention trials for studying the outcomes over many years (13,14). Overall, there is neither special dietary recommendation during pregnancy nor during the lactation period for infants at high risk for atopy. Irrespective of atopic risk, solid food introduction is recommended according to normal standard weaning practice and nutritional guidelines (15). The early introduction of fish reduced the risk, while treatment with broad-spectrum antibiotics during the first weeks of life increased the risk of doctor-diagnosed asthma at 8 years of age (16). The associations were significant for children with atopic asthma but not for non-atopic asthma. The effect on atopic asthma is of major clinical importance and is suggestive of an effect mediated via the immune system. According to many data, preterm birth is associated with the increased risk of infectious as well as the risk of severe asthma. One study confirmed that, though

suggested a decreased risk of severe atopic dermatitis in preterm babies (17). Identification of risk and protective factors in a prenatal and perinatal period may lead to novel approaches in the prevention and treatment of atopic diseases. Respiratory tract infections particularly by viruses in early life represent an important environmental factor for asthma development demonstrated in multiple studies (18, 19). Early respiratory syncytial virus (RSV) infections have been documented to influence asthma development (20) whereas the latest data showed the significant influence of the infectious of human rhinovirus (HRVs) in the asthma development (21). These findings open new perspectives for asthma treatment and prevention through the use of vaccination and direct antivirals, or indirect means of enhancing the immune response in high-risk individuals. Studies focusing on early prevention, such as the case with palivizumab and RSV, are encouraging in demonstrating that early intervention may modify subsequent risk and morbidity from recurrent wheezing illnesses (22).

These findings foreshadow the potential therapeutic and preventative role for strategies against other respiratory pathogens, notably HRV. The relationships among infections, host responses, and asthma inception remain complex and represent an important area for future study.

Further investigations are also needed about the correlation between antibiotic use in infancy and the predisposition to develop allergic diseases. One of the involved mechanisms seems to be the disruption of gut microflora during a critical period for the immune system development. A longitudinal birth cohort reported a dose-dependent association between the use of antibiotics in the first 2 years of life and the development of asthma, eczema or hay fever by the age of 7.5 (23).

Evolution, genes and the environment

The development and phenotypic expression of allergic diseases depends mostly on the interaction between genetic and environmental factors (such as exposure to allergens together with risk and protective factors). Positive family history of allergic diseases in the first-degree relatives is a well-

known risk factor. Nevertheless, the identification of genes that are responsible for allergic diseases is still in progress. The data from several genome studies suggest that polymorphisms of gene that coded FCER1A not only drive IgE levels in the general population but that specific polymorphisms may also influence IgE in association with asthma, suggesting a possible IgE-regulation by disease-specific mechanisms (24). A possible role in childhood asthma might be played by other genes, such as intercellular adhesion molecule 1 (25). Significant interactions has been found between polymorphisms in 20p13-p12 and early-life environmental tobacco smoke exposure with asthma presence and, amongst asthmatics, a significant association with the severity of their disease (26).

In birth cohorts, environmental exposure can be measured to allow analysing complex gene-environment interaction. Most of the other studies have been focused on the influence of environmental factors (27), such as early feeding (breastfeeding vs cow's milk formula) (11), diet/nutrients (28, 29), postnatal growth (30) and obesity (31, 32) and exposure to allergens (33-35), tobacco smoking, pollution, farm vs urban environment and infectious load. Regarding the environmental exposure many hypotheses have been proposed, most of them with contrasting results. Hygiene hypothesis has been extensively investigated. An early exposure to common bacterial triggers (endotoxins, LPS, or helminthic) might have protective effects. The strongest association has been documented between the exposure to allergen, IgE sensitization and the development of allergic diseases. According to recent studies exposure to food comes first, followed by sensitization to indoor allergens like house dust mite, pets and later to outdoor allergens (pollens, mould) (36, 37). The area of hygiene hypothesis is nowadays redefined as "biodiversity hypothesis" and is supported in several epidemiological studies that are suggesting the following: 1) respiratory allergies are inversely related to the number of different foodborne infectious; 2) atopic eczema is associated with lower diversity of gut microbial flora in the first weeks of life, with less probability of asthma development in farming children. High "antigen burden" in early life provided mostly by infection and nutrition exposure is necessary for adequate "education" of immune system. Although

several studies investigated protective effects of probiotics for pregnant women to infants, there are still no univocal results about. Other strategies like administration of oral or intranasal bacterial extracts and early food introduction are still under investigation (38,39).

Diagnostic tools and monitoring

Airway allergic disease diagnosis still represents a challenge, especially in pre-school children (40,41). From a clinical point of view the distinction among asthma, transient wheezing and infectious disease remains quite difficult (40). Some clinical features have been identified as markers of asthma. Rancier et al (42) described the “cough phenotype” as a hallmark of allergic airway disease while the “dyspnoea phenotype” is mainly associated with infections. Oren et al recently demonstrated that children with prolonged cough (more than 28 days) in infancy and cough without cold are more likely to develop asthma, independent of infant wheeze, total IgE level and specific IgE to aeroallergens (43).

A standard method to easily assess pulmonary function in very young children is still lacking. In fact, although current guidelines identify spirometry as the primary method to detect the airflow limitation associated with asthma in children older than 5 years (44, 45), it's not always a feasible assessment instrument (44, 46). It is particularly true in pre-school children, as controversial reports on their technical ability to perform spirometry have been recently published and acceptability rates of the test seem to significantly correlate with age (46). However, lung function assessment in children is difficult and time-consuming. Furthermore, according to recent evidence spirometry did not always prove to be a useful test to identify children with asthma and did not correlate with other objective measures of asthma control (47). Bronchial obstruction appears episodically in children with asthma and it is rarely detected, which decreases the clinical value of such findings. The value of bronchial provocation test is still debated in children older than 5 years because in clinical practice it may arise some concerns regarding safety and applicability for technical reasons (44, 48). In

children who failed to perform forced expiratory manoeuvres impulse oscillometry (IOS) has been recently suggested as a reliable test, due to its highly significant association with spirometry indices and reversibility testing (49).

Total specific airway resistance (sR_{tot}) measured by body plethysmography deserves increasing interest as it is non-invasive, easy to perform, and requires only minimal patient cooperation. A recent study has shown its high sensitivity and sensibility in identifying children with reversible obstruction (50).

In children with recurrent respiratory symptoms, once that clinical and functional assessment has been performed, allergic sensitization should always be investigated, as it has been associated with increased bronchial hyper-responsiveness and airway inflammation (51, 52). Particularly, together with clinical history, poly-sensitization and high specific IgE levels have been related to more severe clinical profiles (51,53). Skin prick testing may be time-consuming especially in small children and provide information about the sensitization source only. Molecular-based allergy diagnosis, though implying blood sampling, deserves increasing interest as it offers the opportunity for a complete sensitization profile assessment. Furthermore differently from other serologic tests the microarray technique requires a very small serum amount (54). A new microarray chip has been recently developed within the EU-funded MeDALL project. It includes more allergen components than the ISAC-chip test (55). The preliminary results suggest that the MeDALL- chip may identify allergic sensitization at an earlier stage in the allergic sensitization process than SPT and ISAC. However its clinical usefulness and predictive value needs further investigations.

Optimal monitoring of children with asthma should include regular assessment of symptoms, lung function, bronchial hyper responsiveness and inflammation, but the evidence on how to integrate all these variables is still limited (44, 56). Furthermore a number of other determinants have been shown to be significantly related to a higher risk of uncontrolled asthma. A large web-based survey

involving 49,096 children has recently confirmed maternal smoking, pet ownership during infancy, obesity, concomitant rhinitis and history of eczema and food allergy as independent risk factors for poorly controlled disease (57).

Composite asthma control scores are increasingly being used in paediatric asthma management, as they are easy to perform, cost-effective and allow to involve the primary care (GPs and pharmacists) in the asthma management action plan (44). However their use has not been univocally shown to improve asthma outcome and QoL measures (44, 58).

Recently, two new composite asthma control scores have been developed: the Test for Respiratory and Asthma Control in Kids (TRACK) and the Composite Asthma Severity Index (CASI) (59, 60). Differently from Childhood Asthma Control Test (C-ACT), and the Asthma Control Questionnaire (ACQ), they also include exacerbations, allowing a more reliable evaluation on future risk as well.

Different authors have recently investigated the use of web-based tools for home monitoring, showing controversial results. One study demonstrated that a home monitoring device was able to detect more cases poorly controlled asthma than retrospective assessment through the ACQ (61). On the opposite Voorend-van Bergen et al (62) did not find significant differences in terms of symptom-free days in asthmatic children, by using web-based monitoring in comparison with standard care.

Quality of life in children with respiratory allergies

Quality of life (QoL) is now recognized as a crucial aspect of the complex allergic airway diseases clinical frame. Its assessment is recommended as part of the diagnostic work up as well as an outcome measure in patients suffering from respiratory allergy (44). It has been recently demonstrated that dealing with the impact of the disease on patients' everyday physical, social,

emotional and school functioning is particularly relevant in adolescents, due to the unique physiological and psychological changes specifically related to that life period (63, 64).

Measuring perceptions (necessity and concerns) and knowledge about the asthma and asthma treatment, as well as satisfaction and expectation with the asthma management is of major importance to ensure optimal disease management, treatment adherence and adequate health care utilization by the patient.

Questionnaires are the most common instrumental tools to evaluate health related quality of life (HRQoL) recommended by international guidelines (44). During the last years, several questionnaires were developed and validated for measuring HRQoL in patients with rhinitis or asthma, and some of these were specifically addressed for children (65). Recently the first quality of life tool for adolescents with respiratory allergies has been created (66). It is a simple tool, able to discriminate the disease severity level and evaluate the impact of nasal comorbidity on asthma control. It showed an optimal sensitivity in detecting individual changes as well as the burden of the disease in patient's everyday life. In this context, the RHINASTHMA Adolescents could be useful as in clinical trial as in routine medical practice to better manage respiratory allergy in adolescents.

Therapy of allergic airway disease in childhood

Recent research on traditional pharmacological treatments has mainly addressed the potential preventive role of early intervention with drugs. It is well known that cysteinyl leukotrienes (cysLTs), released during RSV infection, are implicated in the pathogenesis of airways allergic inflammation (67). A recent systematic review (67), concluded that montelukast is safe and effective in reducing the frequency of post-bronchiolitic wheezing, but the evidence of its role in decreasing the incidence of recurrent wheezing, symptom-free days, or the need for oral corticosteroid in post-bronchiolitis patients is still weak. A 7-years follow-up randomized study on the efficacy of oral prednisolone as a treatment for viral respiratory infections showed no overall efficacy of the treatment in reducing

recurrent wheezing but was associated with less recurrent wheezing in HRV-affected children (68). It is probably due to the increased susceptibility to lower airway HRV infections in subjects with clear atopic characteristics.

A number of studies have recently addressed how to optimizing the management of currently available inhaled drugs in the treatment of paediatric chronic asthma. A Cochrane review (69) explored the efficacy and safety of stepping down to inhaled corticosteroids (ICS)-only versus continuing ICS plus LABA in children whose asthma is well controlled on combined ICS and LABA therapy and concluded that there is a substantial lack of data on the topic. The authors raised the urgent need for randomised trials. van Aalderen (70) and colleagues recently investigated the effectiveness of ICS dose step-up using small-particle ICS in comparison with adding long- acting β_2 -agonist (LABA) to the ICS. They studied two cohorts involving 797 children each and demonstrated that initiating or stepping up the ICS dose with small-particle ICS rather than with standard size particle ICS is more effective in terms of severe exacerbations and rescue medications use, and shows similar effectiveness to add-on LABA in childhood asthma.

However, as in real world clinical settings inhaled drugs are often used at irregular intervals by patients, a recently published Cochrane aimed at comparing the efficacy and safety profile of intermittent ICS versus placebo. Although data are poor and weak, studies have shown that the use of intermittent ICS at the time of exacerbation reduced the chances of needing oral corticosteroids by half (71).

Allergen specific immunotherapy (AIT) still represents the only treatment potentially able to modify the natural history of allergic respiratory disease and to prevent the onset of new sensitizations (72-74). This achievement provided the background for conceiving the so-called “specific immunoprophylaxis” (75). It consists in the early administration of specific kind of immunotherapy to healthy pre-school children with serum specific IgE and familiar history of respiratory allergy. It

would prevent or delay allergic rhinitis onset and stop the disease progression to asthma. Further research is certainly needed but this approach would open the door to a kind of secondary prevention of respiratory allergy.

Unless extensively underused (72), it is well known that both sublingual (SLIT) and subcutaneous immunotherapy (SCIT) is effective as a target treatment on allergic rhinitis and conjunctivitis and that SLIT has an optimal safety and tolerability profile (72), although rare cases of anaphylactic reactions have been linked to this type of treatment (76,77). Recently a first large real life study on 5-grass pollen sublingual tablet evaluated its safety and tolerability in more than eight hundreds children and adolescents (78). According to the safety analysis 27.4% of patients reported at least one adverse reaction (ADR), most of them local. Of note 9.2% of children discontinued SLIT due to ADRs. It suggests once more that providing treated patients with comprehensive information on recognizing and dealing with ADRs is of utmost importance. In fact it has already been demonstrated that severity, persistence or simply poor awareness of even local reactions increase the risk of treatment discontinuation, despite its efficacy (79).

The impact of immunotherapy on allergic asthma is still matter of debate. A recently published Cochrane review on SLIT (80) specifically addressed the topic and highlighted the lack of data for important asthma-related outcomes such as exacerbations and quality of life; furthermore the use of different un-validated symptom and medication scores has been pointed out. For these reasons up to now a clinically useful conclusion on the topic cannot be reached. The European Medicines Agency (EMA) as well within the paediatric investigations plan requests further well-designed and well-powered studies in children, with a particular emphasis on long-term efficacy (72).

Although severe asthma still represents a contraindication to AIT, pre-treatment with Omalizumab seems to make AIT possible even in patients suffering from that condition. Lambert et al reported an experience with six patients, aged 11–21 years, suggesting that omalizumab “premedication” improved tolerability (during and after discontinuation of omalizumab) and efficacy of SCIT (81). Further confirmation by prospective double blind studies is required.

The relevance of Omalizumab treatment in paediatric moderate-to-severe asthma uncontrolled with the recommended inhaled steroid treatment has been recently confirmed by some systematic reviews (82, 83). Omalizumab provides an acceptable safety and tolerability profile and is effective in reducing asthma exacerbations and hospitalisations as an adjunctive therapy to inhaled steroids. Its oral steroids-sparing effect needs further assessment. Some new data coming from a two-years follow-up of 92 children under Omalizumab treatment have been provided by a real-life experience study (84). In comparison with 1-year treatment outcomes, authors have observed a persistent positive effect on the severe exacerbation rate, and a modest effect on asthma control in the children who continued omalizumab for two years. No further lung function improvement was recorded, despite a persistent moderate to high ICS dose treatment. The authors also highlighted a high omalizumab discontinuation rate (20.7%) during the second year, mainly due to poor clinical response, patients’ own decisions and loss to follow-up. 8% of the patients stopped omalizumab because of side-effects, 75% of which were fatigue following injection.

The duration of omalizumab treatment and its long-term effect is still under discussion. According to Molimard et al (85), control was maintained for at least 6 months after discontinuation in 57% of the children undergoing omalizumab treatment for 23 months on average. Baena-Cagnani et al (86) recently reported the results of a 4-year follow-up after a 52 weeks long treatment discontinuation. During the first 3 years of follow-up, children were completely free of asthma symptoms without any

need of ICS or rescue medication. Besides biologicals in asthma, immunomodulation is one of the new frontiers.

The role of probiotics or bacterial lysate assumption is currently under investigation not only in allergic diseases prophylaxis (87, 88) but also in asthma therapy (89).

Biomarkers and prediction

The extreme variability of asthma in terms of individual risk factors and severity determinants hampers the identification of predictive markers of asthma onset. On the other side such knowledge could pave the way to primary prevention, early intervention and disease course modification (90).

Currently reliable tools that can adequately predict which children will develop asthma are still lacking (91).

Most of recent clinical research has focused on pre-school wheezing. The appropriate management and careful evaluation of this very common condition in the frame of other relevant risk factors related to asthma development can make the difference in terms of disease natural history (18, 91-93). According to the most recent evidence the recurrence of respiratory infections, particularly viral infections, can be interpreted in the light of the complex interaction between genetic predisposition, allergic sensitization, antiviral immune responses, the airway microbiome, and environmental exposures (90). It has been recently demonstrated that allergic sensitization but also exposure to parental smoking may account for impaired antiviral immunity, enhanced viral (particularly Rhinovirus) susceptibility and airway responsiveness, impaired barrier function, and increased mucous secretion (91). The evidence that allergic sensitisation precedes wheezing illness induced by human rhinovirus (HRV) in genetically predisposed children who subsequently develop asthma has led to speculate that prevention of RSV infection could potentially reduce asthma outcomes (18, 90). The topic is still matter of debate.

Independently of infection component, the relevance of atopic state assessment in the prediction of asthma development has been recently reviewed. A study involving among 820 children from the German Multicenter Allergy Study cohort demonstrated that increased specific IgE to grass or birch pollen level is a strong preclinical factor and may predict the future onset of seasonal allergic rhinitis (94). Furthermore recent clinical and experimental evidence has suggested a role of specific FCER1A polymorphisms in the pathogenesis of atopic asthma (24).

Under the clinical perspective the childhood asthma-predictive phenotype approach has been recently re-evaluated as a practical tool useful in discriminating between transient wheezing children and persistent wheezers prone to develop asthma (95). The typical childhood asthma-predictive phenotype is characterized by: male gender; a history of wheezing, with lower respiratory tract recurrent infections; history of parental asthma; history of atopic dermatitis; eosinophilia; early sensitization to food or aeroallergens; lower lung function in early life. A gender-specific predictive model for early childhood asthma recently studied on a population of 19,192 children has highlighted parental socio economic status, parental history of atopic disease, place of residence (i.e., urban vs. rural area), indoor mold or painting/renovations during pregnancy, maternal postpartum depression, and onset of physician-diagnosed AD before the age of 6 months as important predictors of asthma risk in 5-yr-old children (96).

Some scoring systems have been developed in the last years, in order to standardize this clinical approach (91). A common limitation of these tools is the lack of external validation that affects their predictive performance (90,91). Pescatore et al (97) have recently established a 10 items asthma prediction tool, mainly relying on indicative symptoms, and accounting for age, sex, comorbid eczema and parents' history of asthma/bronchitis. It has been externally validated in another population and has revealed to be a very promising tool (98).

Recent research has focused on identifying objective biomarkers, which can be helpful in early detection of subjects at risk of asthma development as well as in asthma management, from the diagnosis to follow-up, and in treatment tailoring (91, 99). Among blood biomarkers some chemokines, such as interferon-induced protein 10, thymus- and activation-regulated chemokine, and macrophage-derived chemokine represent a promising novelty in the research field (100). Increased plasma levels of these chemokines have been demonstrated only in wheezers at 3 years of age who later developed allergic asthma, but not in transient wheezers. Furthermore some preliminary results suggest the association between abnormal increase in the peripheral blood CD4+CD28 T cells and development and severity of children asthma (101).

Up to now FENO measurement is the only validated non-invasive method for assessing asthma-related eosinophilic inflammation in clinical practice (44). FeNO allows early discriminating asthmatic children from healthy controls and from non-asthmatic children with chronic cough, as it showed higher levels in atopic wheezers have than non-atopic ones (91, 99). It has also been suggested as a reliable predictor of exacerbations and steroid-responsiveness (44, 102). Nevertheless it is affected by various shortcomings and its clinical utility has now been reconsidered, particularly concerning the FeNO relevance as a marker for driving day-by-day therapy modulation (103). Many variables may influence FeNO values, such as steroid therapy, nasal eosinophilic inflammation, second hand-cigarette smoke, specific food intake. According to a recent longitudinal study (104) FeNO showed a poor correlation with symptoms and c-ACT-assessed asthma control; furthermore in children with no asthma or with well-controlled asthma the variability in FeNO value was dependent mostly on baseline value and interval between repeated measurements.

Interestingly accuracy of FeNO in early assessment of allergic airway disease could be improved by a combining more than one biomarker. Schulze et al. have recently highlighted the increased predictive values of the allergen-specific IgE, PD20-FEV₁ methacholine and eNO taken together, in the early detection of house dust mite allergy in 350 patients, independent of therapy with ICS (48).

Among the non-invasive methods for assessing airway inflammation, the evaluation of exhaled breath condensate (EBC) deserves increasing interest (99). A number of markers, such as 8-isoprostane and Hydrogen peroxide, can be isolated from the respiratory tract, providing useful information on the pathophysiology underlying asthma, risk of asthma development and asthma control (105). The lack of an appropriate standardization and reference values currently represents a limitation to a large use of EBC analysis in clinical practice.

A revolutionary approach comes from the ‘-omic’ sciences, particularly metabolomics (106, 107). The possibility to assess several mediators simultaneously without any a priori hypothesis is opening new horizons, by contributing to the characterization of a biomarker fingerprint with a potential relevance in paediatric asthma prediction or early diagnosis. It also may lead to effective personalized treatments based on each patient’s specific molecular phenotype. Under this perspective measuring the volatile organic compounds (VOCs) in exhaled breath (EB) seems to be particularly promising (108). Some preliminary results suggested VOCs as a tool for distinguishing between preschool children with and without recurrent wheeze (88), and for predicting asthma signatures in preschool wheezers (109). However up to now their use is limited to the research field. What recent advances suggest is that single biomarkers should be integrated in a composite model, in order to enhance their predictive value by better reflecting the complexity of asthma pathological processes.

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