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Recent advances in diagnosis and therapy of allergic rhinitis and asthma in childhood

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SUMMARY

Some of the most recent advances in the diagnosis and treatment of childhood asthma and allergies are here reviewed. New perspectives have been opened by in vitro diagnostic tests for allergies based on a molecular approach and novel approaches to in vivo tests (SPT or FENO). A better characterization of the patients is opening new classifications of allergic asthma and rhinitis phenotypes, which allow personalizing management disease programs and targeting pharmacotherapy. Educational programs and better communication are improving awareness and compliance with medical prescriptions and adherence to guidelines. Increasing information is being acquired on the mechanisms, efficacy and safety profiles of anti-asthma and anti-allergic drugs, including antihistamines, inhaled corticosteroids, long acting beta agonists, antibiotics, anti-IgE antibodies. Progress in biotechnologies is fostering new approaches to allergen-specific immunotherapy (subcutaneous, sublingual) concerning the quality, mechanisms, efficacy and safety of allergen products.

Abbreviations

AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma & Immunology
ARIA: Allergic Rhinitis and its impact on Asthma
ASMA: Asthma Self-Management for Adolescents
ATS: American Thoracic Society
EAACI: European Academy of Allergy and Clinical Immunology
EIA: Exercise-induced asthma
ERS: European Respiratory Society
FENO: fractional NO in exhaled breath
FOXP3⁺CD4⁺CD25⁺ T_{reg}: Forkhead box protein 3-positive CD4⁺CD25⁺ Treg cells
GA²LEN: Global Allergy and the Asthma European Network
iCAALL: International Collaboration in Asthma, Allergy and Immunology
ICS: Inhaled corticosteroids

IP: Interferon gamma-inducible protein
LABAs: Long-acting β_2 agonists
NAEPP: National Asthma Education and prevention Program
NCS: Nasal corticosteroids
NO: Nitric oxide
PIAMA: Prevention and Incidence of Asthma and Mite Allergy
QoL: Quality of life
RANTES: Regulated on activation, normal T expressed and secreted
RCT: Randomized Controlled Trial
SARP: Severe Asthma Research Program
SCIT: Subcutaneous Immunotherapy
SIT: Allergen specific immunotherapy
SIP: Allergen specific immunoprophylaxis
SLIT: Sublingual Immunotherapy
SPT: skin prick test
WAO: World Allergy Organization

Introduction

The burden of respiratory allergic disease has dramatically increased during the last century: nowadays the prevalence of asthma is estimated to be from 8% to 12%, and allergic rhinitis affects from 20% to 25% of the developed world population (1). The urgency of this epidemiologic trend has been shown by the “calling for iCAALL” (International Collaboration in Asthma, Allergy and Immunology), an outreach program developed in 2012 by the AAAAI, the ACAAI, the EAACI and the WAO with the aim to ameliorate the communication of information about allergic diseases worldwide (1). Furthermore during the last years, the attention on allergic diseases has been focused overall on the pediatric field, as proven by an enormous amount of publications updating on childhood asthma and allergic rhinitis not only in pediatric allergy journals, but even in the most relevant asthma and allergy international journals (2-5). This review will focus on a few examples of the most recent advances in the diagnosis and treatment of childhood asthma and allergic rhinitis and will focus mostly on the new perspectives opened by *in vitro* diagnostic tests for allergies based on a molecular approach, novel approaches to *in vivo* tests [skin prick test (SPT) or measurement of fractional NO in exhaled breath (FENO)], new concepts on allergic asthma and rhinitis phenotypes, educational programs and adherence to guidelines, and on the mechanisms, efficacy and safety profiles of anti-asthma and anti-allergic drugs as well as of subcutaneous and sublingual allergen-specific immunotherapy.

Diagnosis

A general overview of all the new advances in *in-vivo* and *in-vitro* tests most frequently used in the diagnosis of allergic rhinoconjunctivitis and asthma falls beyond the possibilities of this review. We shall focus therefore only on some selected aspects of skin prick tests, IgE tests, and measurement of FENO.

SPT – During 2012 a new practical guide on recommendations on SPTs use in asthma and allergic rhinoconjunctivitis has been produced by the Global Allergy and the Asthma European Network (GA²LEN) together with the Allergic Rhinitis and its impact on Asthma (ARIA) task force (6). A pocket guide has condensed the indications in clinical practice and focused in particular on the need that tests are performed using high quality and stan-

dardized allergen products; interestingly, the guidelines concluded that native and recombinant allergens molecules show similar diagnostic value (6). In keeping with this conclusion, SPTs performed with a recombinant hybrid molecule containing the 4 major timothy grass major pollens (Phl p 1, Phl p 2, Phl p 5 and Phl p 6) were sensitive and specific in diagnosing hay fever due to grass pollen allergy (7). In addition, two groups have shown that SPTs even in the early age can be useful in the wheezing child to identify an airborne allergen sensitization, a major criterion in predicting asthma development (8, 9). These advantages are balanced by a not negligible risk of adverse generalized reactions when SPT are performed by not specialists (10). This risk is downgraded to zero when primary care pediatrician use *in vitro* tests specifically designed to screen for atopy in childhood, a test used to predict future sensitization and allergic symptoms in pre-school children (11).

IgE tests – The advantage of using *in vitro* tests to diagnose atopy in children is being increased by the availability of a wide array of molecules for *in vitro* diagnostic purposes. *In vitro* IgE microarrays based on allergenic molecules allow identifying whether the sensitization detected by extracts is primary (species specific) or a result of cross-reactivity to similar proteins present in unrelated allergenic sources (12). This aspect is particularly useful in the so-called multiple pollen syndrome and is necessary to better address specific immunotherapy (13, 14). On the other hand, the molecular analysis is highlighting that the IgE response toward an allergenic source is very complex and heterogeneous when seen at a molecular level. Accordingly, hay fever and a multi-systemic allergic phenotype were associated to more complex sensitization profile in grass pollen and mite allergic children, respectively (15-17). Other *in vitro* technologies, such as a new microfluidic immunoassay cartridge have been also recently investigated and validated in clinical settings, and may be applied to molecular allergology in the future (18).

FENO – Nitric oxide (NO) is as an important marker of eosinophilic airway inflammation, produced by nitric oxide synthase enzyme of the human airway epithelial cells. The measurement of fractional NO in exhaled breath has been longtime recognized as a safe and noninvasive method in supporting diagnosis, monitoring and assessing responsiveness to corticosteroids therapy in allergic respiratory diseases with a particular regard to allergic asthma, and its feasibility even in childhood age has been largely proven. In 2011 the American Thoracic Society (ATS) developed a practice guideline for the interpretation and

clinical applications of FE_{NO} (19). ATS guidelines recommend that FE_{NO} cutoff values for normality are different between children and adults, as the patient's height and age is a relevant confounding factor especially in children younger than 12 years (19). According to previous ATS/ERS guidelines, FE_{NO} levels can be assessed in children from the age of four using a chemiluminescence analyzer (20). In a recent interesting study on wheezing infants younger than 3 years, exhaled air was collected through a facemask with a two-way non-rebreathing valve and then analyzed. This method has given strongly reproducible values on two measurements ($r = 0.95$, $p < 0.0001$) (21). In addition, a good feasibility and linearity of FE_{NO} measurements has been reported in children aged 6–12 years with moderate-persistent asthma at different flow rates performed on three occasions 3 months apart (22). This study showed also a significant “learning effect” with an increasing feasibility from 67% to 95% within 6 months. Testing FE_{NO} has been proven to be useful also for asthma prediction. Measuring FE_{NO} at 4 years of age significantly predicted asthma at the age of 8 [OR 1.6 (95% CI 1.1 to 2.2)] in a group of 306 wheezing children recruited by the PIAMA birth cohort (23). Similarly, among 331 ten-years old children recruited in the Environment and Childhood asthma Study, those with asthma showed a significantly higher FE_{NO} levels than their healthy peers (9.6 ppb *vs.* 5.8 ppb, $p < 0.001$). Interestingly, no differences were found by comparing FE_{NO} levels of the non-allergic asthmatic children subgroup to the healthy children group (24). The ATS guidelines state that testing FE_{NO} levels are useful to monitor airway inflammation and assess the patient's responsiveness to anti-inflammatory therapy. A recent study measured significantly higher levels of FE_{NO} in 40 infants aged ≤ 3 years with uncontrolled wheezing compared with 40 age-matched infants with well controlled wheezing (19.8 ppb *vs.* 7.7 ppb, $p < 0.0001$) (21). This relevance is extended to exercise-induced asthma (EIA). Both bronchial and alveolar NO levels were found significantly higher in 18 asthmatic children and adolescents with EIA, compared to 12 asthmatic children without EIB and to healthy controls ($p < 0.001$) (25).

Disease phenotypes

Increasing attention is being devoted to the very heterogeneous factors underlying the natural course of allergic respiratory disorders and especially of steroid resistant asthma.

Although the morbidity of “uncontrolled” asthma is relevant, the definition of asthma “control” is still controversial (26). Among 115 asthmatic schoolchildren, those with severe and persistent asthma had a reduced lung function, higher IgE levels and reduced quality of life (QoL) when compared to patients remaining asymptomatic even during phases of disease activity, suggesting that these groups represent different disease phenotypes (27). Moreover many heterogeneous factors, such as psychogenic and functional breathing symptoms can make a correct diagnosis difficult and interfere with the assessment of severe asthma (28). The analysis of the heterogeneous “asthma phenotypes” is therefore highlighted in more and more studies and reviews aimed at discussing a better control of asthma (2, 29). The Severe Asthma Research Program (SARP) examined with the cluster analysis 161 asthmatic children and permitted the identification of four novel asthma clusters, characterized according to asthma duration, baseline lung function and use of controller medications. Interestingly, the authors concluded that none of the four clusters corresponded to the definition of “severe asthma” proposed by the ATS, the Global Initiative for Asthma and the National Asthma Education and prevention Program (NAEPP) guidelines (26). In this context, the concept of “personalized medicine”, fosters a greater attention to the biological mechanisms underlying different asthma phenotypes, the so-called “asthma endotypes” (29). This trend will generate more specific predictive and preventive strategies, especially in early life, based on the discrimination of risk factors and pathophysiologic mechanisms characteristic of different asthma phenotypes (30). An example of this approach is given by the differentiation of a “cough phenotype” of asthma, more frequently characterized by atopic features, from a “dyspnoea phenotype”, more frequently linked to infectious agents (31). Severe asthma can therefore be considered not just as a single disease, but as an extremely complex disorder characterized by heterogeneous phenotypes and pathophysiological mechanisms (e.g the IL-13 pathway) that may become as a target for new personalized therapies (30, 32–34). Much less is known about different childhood rhinitis phenotypes. The link between allergic rhino-conjunctivitis and asthma is well known and the concept of “united airway disease” is based on their common atopic background (35); nevertheless, doctors should be aware of the risk of mistaking allergic rhino-conjunctivitis and its co-morbidities with other less common but severe conditions like primary ciliary dyskinesia and cystic fibrosis. These conditions can mimic allergic rhinitis very well, as described in recent case reports (36).

Disease management

The improvement of diagnostic and therapeutic tools for allergies and asthma in childhood has little impact on the patients if these tools are not widely and correctly used. More and more attention is being focused therefore on guidelines, disease management programs and their implementation in clinical practice (2-4, 37). Recently, a stepwise asthma management plan has been based on three strategies: A) a step-up "long-term" for patients whose control is persistently difficult; B) a step-up "short-term" plan for patients whose asthma control is only occasionally difficult; C) a step-up "intermittent" plan for patients with only mild symptoms and relatively good control (38). This approach has been considered excellent to take guidelines closer to the personal needs of each patient, in keeping with a more "personalized" concept of medicine (39, 40). On the other hand, achieving the best disease control with the lowest medication is not an easy target. Recent surveys on asthma prescription patterns have shown that up to 30%-40% asthmatic children are "undertreated" and, surprisingly, up to 50% are "overtreated", even for long periods (23, 41, 42). Overtreatment and use of inadequate therapies such as sedating antihistamines are common practices even in patients with allergic rhinitis, mainly due to self-medication (43, 44). A preliminary diagnostic assessment of the allergic patients, especially in those with severe asthma, is an essential step towards the best treatment strategy (45, 46). Regrettably, although composite scores of disease control, clinical diaries and quality of life questionnaires have been increasingly proposed both for asthma and allergic rhinitis, only a few of them have been validated for children (47-51). Moreover, a careful diagnostic and monitoring plan must be accompanied by an appropriate treatment strategy supported by self-management programs. For example, this approach recently allowed reducing emergency care visits, hospitalization, missing school and shorter time in achieving asthma control among children and adolescents in the ASMA program in the United States (52, 53); similarly, written action plans also improve adherence to therapy and asthma control (54). Increasing attention has been recently given to the determinant role of the family setting in achieving and maintaining asthma control both for children and adolescents. A low level of education, a distorted perception towards medications and the gap in communications, can induce parents to underestimate the real burden of their children disease; a better understanding of asthma within the whole family contributes in maintaining asthma under control (55, 56). The psychological impact of

asthma on children's caregivers is quite relevant, and can even produce depressive symptoms (57).

Pharmacotherapy

Clinical studies on the efficacy and safety of many categories of drugs, including ICS, LABA, macrolides, monoclonal anti-IgE antibodies, and anti-histamines are worthwhile to be mentioned in this review.

Inhaled corticosteroids

Although inhaled corticosteroids (ICS) have been confirmed as a very effective treatment in childhood asthma, some recent studies questioned unclear aspects both in their efficacy and safety (58). Controversies in the treatment of preschool wheezing children were highlighted and ICS treatment in wheezing infants had no long-term influence on their lung function at 10 years (59-61). Nevertheless, ICS have been confirmed as effective treatment in children and adolescents with mild persistent asthma (62). Interestingly, no significant benefits were found in ICS at doubling dose when compared to the combination of ICS at normal dose with long-acting β_2 agonists (LABAs) (63, 64). Increasing attention is being focused on ICS safety and its evaluation. The morning serum ACTH level has been recently suggested as a valuable screening test to detect hypothalamic-pituitary-adrenal axis suppression (65). Actually, both short- and long-term growth seem to be affected by ICS (66-69). Nevertheless, new ICS molecules may have a safer profile, as they had no significant effects on short term lower-leg growth rate and they had a lower suppressive action on hypothalamic-pituitary-adrenal axis function (67). Additional favorable information on ICS came from studies showing that they may prevent DNA mutations in asthmatic children and that they do not increase the risk of pneumonia (70, 71).

Long-Acting Beta-2 Agonists

A Cochrane document assessed that, differently from adults, the safety and efficacy of the LABAs 'add-on' therapy in children remain still uncertain (54, 72). A controlled trial showed that prolonged treatment with LABA induced a significant decrease in bronchoprotective effect and in salbutamol responsiveness (73). On the other hand, both long and short-acting β_2 agonists exerted a suppressive role on chemokine expressions (e.g. RANTES, IP-10, eotaxin-1) in bronchial epithelial cells (74).

Macrolides

New interest has been aroused on the role of macrolides in the treatment of asthma. A 3 weeks course of clarithromycin was found to increase disease control, while low dose of erythromycin has been demonstrated to induce antiinflammatory effects, and to improve symptoms in severe asthma (75, 76).

Anti-IgE MoAb

In 2012, PRACTALL guidelines (a joint initiative from AAAAI and EAACI) highlighted the emerging role of immune-modulators in asthma treatment. The document focused the attention also on Omalizumab (the anti-IgE monoclonal antibody) (77). Omalizumab is an effective and safe therapy in children with moderate-severe asthma reducing up to 24% the days with exacerbations and drug consumption (77-80). Omalizumab has been recently considered also in the treatment plans of allergic rhinitis. In case of moderate-severe allergic rhinitis, Omalizumab is confirmed to be an effective and safe treatment in patients with seasonal symptoms (79). Moreover the combination of Omalizumab with allergen specific immunotherapy (SIT) was found to play a protective effect against SIT-related severe side effects and improve SIT efficacy (81). Finally, no increased incidence of malignancy was documented in a recent pooled analysis on 32 DBPC trials with Omalizumab (82).

H1-antihistamine drugs and nasal corticosteroids

Last generation of H1-antihistamines are still considered as the first line therapy for allergic rhinitis and their long term safety has been documented in RCT both in adults and children and infants after the age of 1 (83). Nasal antihistamines seem to be more rapid and effective than oral formulations (83). Comparing to H1-antihistamines, nasal corticosteroids (NCS) have a higher efficacy in the treatment of allergic rhinitis (84, 85). However a recent survey documented a low compliance with nasal corticosteroids in up to 25% of children with allergic rhinitis, above all among young children (86). In addition, children suffering from otitis media with effusion seem benefit from NCS treatment and this may be correlated with a higher prevalence of allergic rhinitis in this group of patients (87).

Allergen specific immunotherapy

Allergen-specific immunotherapy (SIT) has just celebrated a century of life, it is still considered as the only curative treatment for allergic respiratory diseases (88). In the last years several updates and review papers highlighted the new steps done towards a better comprehension of mechanisms underlying SIT and its efficacy and safety in clinical practice (5, 89-91). An increasing attention has been therefore focused on the necessity to provide standardized recommendations through guidelines and consensus papers. These documents highlighted the efficacy and safety of SIT in children from the age of 5 years and confirmed its preventive effect towards asthma development (92-95).

The mechanisms of SIT efficacy are more and more clear (89, 96). Many studies have indeed confirmed the key role of T_{reg} and of its two subsets (FOXP3⁺CD4⁺CD25⁺ T_{reg} and T_{R1} cells) in inducing tolerance against antigens through secretion of suppressive cytokines (e.g. IL-10) and discussed the role of specific IgG4 (97-101).

The concept of "quality" and "standardization" of products used in SIT has been recently considered very relevant. Along this line, important progresses have been made in the area of molecularly designed SIT preparations (102, 103). Thanks to recombinant DNA technology new molecules (hypoallergenic variants) have been produced with high antigenicity but low IgE-reactivity (104). The debate on advantages and disadvantages of these new variants versus native molecules is still open (104, 105). Interestingly, it has been recently shown that the molecular profiles of IgE sensitization to allergenic sources are extremely heterogeneous in children and a debate has been opened on the implication of this diversity on allergen specific immunotherapy (15). Similarly, longitudinal analyses in birth cohorts have demonstrated a pre-clinical IgE response to allergenic sources: this response is weaker and directed against one or two molecules only, suggesting that an earlier, allergen-specific intervention (allergen specific immunoprophylaxis, SIP) (16).

Subcutaneous Immunotherapy (SCIT)

A RCT has recently shown a reduction in ICS use in 65 asthmatic children treated with a high dose of hypoallergenic mite SCIT preparation, when compared to the group receiving placebo ($p < 0.05$) (106). Similarly, a three years-long treatment with dust mite SCIT was sufficient

to significantly reduce rhinitis and asthma symptom scores (107). A very interesting study has investigated a new immunotherapy regimen, based on the combination of sublingual and subcutaneous routes, and showed a reduction of asthma attacks in patients treated with SCIT alone and SCIT plus SLIT, against SLIT group and pharmacotherapy group (108). On the same line, a comparison based on meta-analyses has shown that the relative efficacy of SCIT on seasonal allergic rhinitis symptoms is similar or even better than that of drugs already in the first season after SCIT initiation (91). The indications of SCIT are becoming broader: the treatment of polysensitized patients with SCIT is indeed controversial; nevertheless, new evidences suggested that multiallergen SIT (up to 2 allergens) could be effective in polysensitized patients (109). New administration schedules are also investigated: on one hand, ultra short course of SCIT with a pollen allergoid reduced the use of drugs and resulted well tolerated in most patients with rhinitis and/or asthma (110); on the other hand, SCIT proved to be very safe in association with anti-IgE treatment (111, 112).

Sublingual Immunotherapy (SLIT)

The efficacy and safety of SLIT in the treatment of allergic rhinitis in children ≥ 5 years has been confirmed in recent position papers and meta-analysis, even if further evaluations and well done RCT are needed (113-116). Many recent RCT on grass pollen SLIT confirmed the efficacy and tolerability in children even at high-dose regimen (117-122). The economic impact of SCIT and SLIT has been long time discussed: especially in childhood its long term effects may reduce direct and indirect medical costs (123-125). The role of administration schedule and setting has been the object of many trials: first, the safety of ultra-rush SLIT in tree-pollen allergic children with asthma has been clearly demonstrated, then a co-seasonal regimen for grass SLIT showed a better efficacy during the first season than continuous treatment (126, 127); last, SLIT didn't improve symptoms in house dust mite allergic children when administered in primary care (128).

Conclusion

The few examples of the most recent advances in the diagnosis and treatment of childhood asthma and allergic rhinitis summarized here give us an idea of how fast and

broad is clinical research in this area. These new diagnostic tools and therapeutic approaches will have to be integrated in guidelines and comprehensive disease management plans, whose implementation can be assured only in the context of appropriate public health programs.

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