Editorial
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Asthma and Allergies: From Diagnosis-Based Approach towards Personalised Treatments

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Asthma and allergic diseases are amongst the most common chronic disorders worldwide (1). The articles in this issue of the journal are describing various aspects related to this modern "epidemics", starting with a practical guidance on how to deal with patients with severe asthma (2, 3), highlighting the advances related to virus-induced asthma exacerbations (4) and protective factors and mechanisms underpinning resistance to asthma (5, 6), then moving on to a fascinating discussion on the importance of a healthy immune status and the development thereof (7). A particular emphasis has been given to the challenges facing the low- and middle-income countries (8, 9). Finally, the focus shifts from respiratory diseases to the 'third wave' of the allergy epidemic (after increases in hay fever and asthma) – that of food (specifically peanut) allergy (10). What links them all is the need to move away from the current one-size-fits all approach to management, towards personalised treatment and prevention strategies (11, 12).

Asthma and allergic diseases encompasses a range of linked conditions which are complex and multifactorial, and may be caused by several different mechanisms which cause multiple heterogeneous clinical phenotypes (12, 13). For example, while some patients have symptoms affecting a single organ (e.g. lungs), others have symptoms encompassing multiple organs (e.g. skin, upper and lower airways) (14). The pathological mechanisms which underlie this heterogeneity are largely unknown (15, 16). The current approach to management is focused on treating the diagnosis, rather than directing a strategy towards pathological mechanisms which cause symptoms in an individual patient (17). Although there is clear evidence that asthma is not a single disease (18-22), but a spectrum of disorders which are underpinned by both common and idiosyncratic mechanisms (often called asthma endotypes (23)), the management guidelines approach is as if it is a homogeneous disease entity (12). As a result, patients from several distinct disease subtypes, caused by different mechanisms, are forced into a single group for a "trial and error" treatment (11). This diagnosis-based approach to asthma management is suboptimal for 21st century medicine (24), and there is an important cautionary lesson to be learnt from history.

We now take for granted that corticosteroids are the first-line treatment for asthma. Following the early observations of potential benefits of corticosteroids in asthma which date from the early 1950s (25), the UK Medical Research Council conducted a double-blind randomized placebo-controlled trial to formally assess their efficacy and provide evidence for their use in clinical practice (26). The results were clear and unequivocal, but

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from today's perspective very surprising - corticosteroid treatment was shown to have no advantage in asthma management over placebo (26). Intrigued and surprised by these findings which he could not reconcile with his clinical experience, Dr Harry Morrow Brown (1917-2013) single-handedly conducted a trial in which he tested his hypothesis that the presence of eosinophils in nasal secretions may be a marker of positive response to corticosteroids (27). He developed a rapid consulting-room method for sputum collection, and noted that "much encouragement was often needed" for patients to produce a specimen (a sentiment shared nowadays by many of those using induced sputum to guide asthma treatment). The results of his study were striking: oral prednisolone was very effective in the treatment of asthma – but only if the sputum of the patient contained eosinophils (27). In a marked contrast, amongst patients who did not have eosinophils in their sputum, prednisolone did not improve asthma control, and Morrow Brown concluded that in these patients, the use of corticosteroids may be contraindicated (27). This extraordinary study published more than 60 years ago (and in our opinion one of the most important, if not *the* most important randomized controlled trial in asthma), was the first controlled trail in which a biomarker (sputum eosinophils) was used for stratification of patients with the doctor diagnosis of asthma to predict treatment response. Morrow Brown provided a clear and unequivocal evidence that corticosteroids are effective only for a subgroup of patients with the diagnosis of asthma, i.e. that they are not a "silver bullet" appropriate for every patient. It is clear that the prescription of corticosteroids for asthma should be based on the mechanism which gives rise to a clinical manifestation (eosinophilic airway inflammation), rather than on a simple doctor diagnosis of a symptom-based phenotype (28).

Unfortunately, these astonishing results attracted very little interest and were largely overlooked (29). Sixty years later, the Individualized Therapy for Asthma in Toddlers (INFANT) trial (30) provided more evidence that fundamentally different mechanisms often underpin the same diagnosis in different paediatric patients. In pre-school children aged 12 months to 5 years with a doctor-diagnosed asthma, daily use of inhaled corticosteroids (ICS) preferentially benefitted children who were sensitised to inhalant allergen and had blood eosinophil count ≥300/μ (30). Unfortunately, most young children with doctor-diagnosed asthma or recurrent wheezing, particularly on the severe end of the spectrum, are prescribed ICS based on clinical history alone, without carrying any investigations (31). For example, the European Respiratory Society Task Force recommended that preschool wheezing should be managed according to the clinical phenotype, in that the Episodic viral wheeze (EVW) should be treated with as required short-acting bronchodilators, while ICS should be the first-line treatment for the multiple-trigger wheeze (MTW), but may also be considered in all patients with frequent or severe episodes of wheezing (32, 33). Although recommendations include discontinuing treatment if there is no benefit (33), this is rarely implemented in clinical practice (31). However, a clear distinction between EVW and MTW is difficult in many patients (33) and phenotypes in individual patients often changes over time (34, 35), making this phenotyping based only on anamnesis of limited value for treatment decision making. Two randomised placebo-controlled trials in infants who were mostly non-atopic did not show significant benefits of ICS for children in the first year of life with recurrent wheeze, but have indirectly suggested potential adverse outcomes for those in the ICS arm, including diminished lung function by school age (36), and a non-significant trend towards more symptoms (37). Diligence is therefore needed before ICS prescription in pre-school children, especially in non-atopic children in the first year of life, even if they have relatively severe symptoms. Full blood count (FBC) and skin tests to assess allergic sensitisation are simple and relatively cheap procedures, and although these two biomarkers clearly do not explain the complexity of pre-school wheezing, we would suggest that every preschool child who is considered for a treatment with ICS should have these two biomarkers objectively assessed before

commencing the treatment (38). If positive, ICS treatment should be commenced. However, if both are negative, ICS are unlikely to be of benefit, and alternative management strategies should be considered (including bronchodilators and/or muscarinic antagonists (39), or perhaps macrolide antibiotics (40)). However, biomarkers for targeted treatment among non-atopic pre-school wheezers remain elusive.

Severe asthma continues to pose one the greatest challenges faced by front-line clinicians (41). Andrew Bush describes a systematic approach to the management of a child with problematic severe asthma (PSA) who is not responding to the prescribed treatment (2), with a key message for those managing such patients: Do not rush into prescribing more treatments, but first ask 'What is it about this child which is making him/her non-responsive to standard therapies?'. Most severe asthma is associated with extrapulmonary comorbidities and social/environmental factors, rather than a genuinely therapy-resistant disease, and it is of critical importance to get the basics of management right before escalating the treatment (2). This includes ascertainment of co-morbidities (including obesity, exercise induced laryngeal obstruction, rhinitis etc), and environmental and lifestyle factors (including but not limited to adherence with treatment, exposure to allergens to which the child is sensitised, active and passive tobacco smoke exposure, etc.).

Understanding that one-size-fits-all approach patients with severe asthma is suboptimal, Scotney and Saglani outline a framework for an evidence-based approach for the diagnosis and management of children with PSA, who have uncontrolled asthma symptoms, despite maximal prescribed asthma treatment (3). The protocol has been developed and is continuously updated by the multidisciplinary team (MDT) at the Royal Brompton Hospital, London, and is of great value for all colleagues who carry out specialist respiratory assessment of children with troublesome asthma. The first step is confirming the diagnosis using *objective evidence*, which should include lung function tests (spirometry, bronchodilator reversibility and/or peak expiratory flow variability), assessment of airway inflammation (by FeNO measurement) and airway hyper-responsiveness (e.g. by direct methacholine or histamine challenge, or indirect airway challenge using exercise, mannitol or hypertonic saline). Assessment of adherence with ICS treatment is the crucially important next step. A multidisciplinary team (MDT) approach is essential to identify patients with initial diagnosis of PSA who have uncontrolled symptoms due to factors which can be modified, including poor treatment adherence, poor inhaler technique, exposure to environmental allergens or tobacco smoke, and/or treatable co-morbid conditions and psycho-social factors (2, 3). These patients with modifiable risk factors comprise ~80% of patients with troublesome asthma. However, there remains ~20% of children with PSA who have a genuinely severe therapy resistant asthma (STRA), and have poor symptom control despite good treatment adherence and correction of modifiable factors (3). Further investigation of children with STRA should include an assessment of systemic steroid responsiveness (e.g. by giving a single dose of intramuscular triamcinolone and measuring a change in asthma symptoms and objective markers such as lung function). This step is important for confirming the diagnosis of STRA, and guiding the choice of additional treatment with expensive biologics (3).

Asthma exacerbations (asthma attacks) are another domain of the disease which is associated with worse health-related quality of life, and a marked increases in healthcare-related expenditure for both patients and healthcare systems (42, 43). Children with frequent severe exacerbations have poorer long-term outcomes, including loss of lung function during school-age years and a diminished lung function in early adulthood (44-46). Therefore, the prediction, prevention and treatment of asthma attacks remain the key unmet needs (47, 48). However, preventing asthma attacks remains difficult (49), and large randomised controlled trial in school-age children has conclusively shown that commonly used strategy of increasing the dose of ICS at the early signs of loss of asthma control (in this case quintupling the dose)

did not prevent subsequent exacerbation (50). When discussing causation and mechanisms of asthma attacks, the focus is usually on virus infections. Kumar et al. (4) discuss the latest developments in research relating to virus-induced asthma exacerbations, including recent advances in treatment options. A substantial body of evidence suggests that deficiencies in the host innate immune response to some (but not all) viruses may predispose many asthma patients to virus-induced exacerbations. There have been several recent advances in our understanding of the mechanisms underlying virus-induced airway inflammation in asthma, including growing evidence around the interaction between viruses and bacterial infections, the role of pro-inflammatory cytokines such as IL-33, neutrophil extracellular traps (NETs) s, and eosinophils, which led to identification of novel therapeutic targets for more efficacious therapies to prevent and treat virus-induced asthma attacks (4).

While rhinovirus infections are undoubtedly important (and Kumar et al. provide an excellent overview of the role of viruses in asthma attacks) (4), they are not the only trigger of asthma attacks. We have described two peaks of acute asthma attack leading to hospital admission in Manchester, UK: one, occurring in September associated with rhinovirus infections, and a second peak in June/July, which coincided with high grass pollen level (51). The risk factors among children admitted to hospital during these two peaks of hospitalisations were fundamentally different, with most acute asthma attacks in summer occurring in children sensitized to pollen who were not using preventative treatment with ICS. We would argue that children admitted to hospital during the June/July have a different type of asthma than those who experience exacerbation in autumn, yet both have the same diagnosis and are labelled the same way. The Melbourne epidemic thunderstorm asthma which occurred on 21st November 2016 is a fascinating natural experiment which offers clues about asthma endotypes. Over a 30-hour period, there was a huge 7-fold increase in respiratory presentations to public hospitals, 476 excess asthma-related hospital admissions, and tragically 10 deaths (52). However, more than half of patients admitted to hospitals with asthma attacks had not have a prior asthma diagnosis, although most had a history of rhinitis (53). It is very likely that the thunderstorm gust front coupled with extremely high airborne ryegrass pollen concentrations created conditions for pollen grains to absorb moisture and burst into much smaller particles which can reach into the lower airways and cause allergic reaction (53). Fascinating post-hoc analysis of the open-label study of sublingual immunotherapy for ryegrass pollen sensitized patients with seasonal allergic rhinitis reported that none of the 17 participants who had completed 2-3 years of treatment and were exposed to the thunderstorm experienced an asthma attack (54). In a marked contrast, 7 of 17 (41%) control patients with allergic rhinitis who used pharmacotherapy only, had asthma attack (54). This extraordinary natural experiment offers many important learning points (53), among them the fact that most patients who were hospitalized with severe asthma attack did not have prior diagnosis of asthma, and that allergen-specific immunotherapy appeared to offer protection. Did these patients have several co-morbid conditions (seasonal asthma, seasonal allergic rhinitis and/seasonal conjunctivitis, or did they suffer from a single condition? We would argue that for most patients admitted to hospital during the thunderstorm asthma episode has a single disease with a clearly defined mechanism (ryegrass pollen IgE-mediated airways disease), that this disease has a biomarker for treatment stratification (specific IgE to ryegrass pollen), and that a mechanism-based treatment is available (specific immunotherapy for ryegrass pollen). We therefore proposed that this may be one clearly defined asthma endotype (17). This, however, is a very different disease compared to that seen in patients with recurrent attacks caused by rhinovirus, in whom very different mechanisms lead to asthma attack.

There are potential biomarkers of interest which may help differentiate virus-induced asthma attacks from non-viral exacerbations. For example, in steroid-naïve asthmatics, serum IFN-

γ-induced protein 10 (IP-10; CXCL10) levels are higher among patients with virus-induced asthma attacks compared to those with non-viral attacks, and serum IP-10 levels have been shown to have a sensitivity of 95% and specificity of 70% for virus-induced asthma (55). Ultimately, only through better understanding of the mechanisms underlying the interactions between respiratory viruses and the immune system will we be able to develop novel mechanism-based treatments to prevent and/or treat virus-induced asthma attacks (4).

That prevention is better than cure is not a new idea – it is attributed to the great Dutch philosopher and scholar Erasmus. The reduction of the burden of persistent asthma via prevention of early disease onset remains an important, but as yet elusive goal. Seminal epidemiological studies, to a large extent led by Erika von Mutius, have conclusively shown that prevalence of asthma is low amongst children in the traditional farming families. In this issue of the journal, Pechlivanis and von Mutius summarise the main finding of 27 studies which investigated the effect of farming on the risk of asthma in children (5), and discuss potential mechanisms which lead to this "acquired" asthma-resistant phenotype. The protection appears associated with prolonged exposure, not only postnatally but also antenatally, to microbial products derived from farming-related activities (5). The strongest protective effect was observed for the contact with farm animals and intake of unprocessed farm milk (56). Both of these protective exposures are associated with high and diverse microbial content (e.g. the effect of unprocessed milk consumption is abrogated by heating (57)). The epidemiological observation of prenatal protective effects of farming have been triangulated in experimental mechanistic studies in neonatal mouse models which confirmed the protective effect of exposures to a variety of microbial extracts including that from barn dust, giving us confidence that novel strategies to prevent asthma could be developed (5). Overall, the evidence to date is consistent with the proposal that microbial diversity is a hallmark of farm homes and contributes to the reduced asthma risk, and that similar farm-like microbial composition in non-farm homes also offers protection (58). In such microbe-rich environments, exposure to microorganisms from different sources can occur *via* skin, respiratory tract or gut, and this environmental microbiome shapes the host microbiome to modulate innate immune response and impact upon the risk of disease (59, 60). The current evidence on host microbiome, and its relationship with asthma in children has been summarised by Dick and Turner (6). The route of exposure may be important, but it remains unclear what is the relative contribution of the microbiome of the upper and lower airways, the gut and the skin, to immune tolerance, asthma and allergy (6). For example, some studies have suggested that nasal, but not throat microbiome is associated with reduced risk of asthma (59). A recent study from Pozega County in Croatia indirectly supports the potential important role of the gut microbiome (61). Children living in homes with drinking water supply from individual wells had a reduced risk of allergic diseases when compared to those living in homes with a public mains water supply (61). The study team capitalized on availability of data on microbial content of water during each child's first year of life to demonstrate that the risk of allergic diseases decreased with increasing bacterial content in drinking water a dose-response manner, suggesting a possible causal relationship (61). Importantly, the information gleaned from these naturally *asthma-resistant* populations and subsequent mechanistic studies offers potential pathways towards translation into the primary prevention strategies (62).

The idea of primary prevention puts emphasis to strategies for promoting health, rather than focussing on the disease. In this context, there is a common misconception that having a "strong" immune system is beneficial for health in general. However, a healthy immune status requires effective responses against pathogenic microbes and cancer cells, while at the same time it needs to tolerate self-tissues, commensal microorganisms and harmless environmental antigens, or, as a Kucuksezer et al. put it forward, the 'balanced tolerance' is essential for the survival (7). Allergic diseases,

along with autoimmune disorders and transplant rejection are examples of the consequences of the loss of immune tolerance. Therefore, understanding the mechanisms of peripheral immune tolerance is critically important, as both excessive and deficient immune tolerance lead to potentially unwanted and adverse outcomes (7). Kucuksezer et al. describe how the balance between reactivity (effector functions) and non-reactivity (tolerance) can be established for a healthy state, and argue that understanding of the relationship between innate immunity and immune tolerance, and development of biomarkers of the tolerance status are key factors for the development of novel therapeutic targets for personalized approach (7).

The focus of this special issue of the journal then moves on to the issues relevant to low- and middle-income countries (LMICs) (8, 9). Soto-Martinez et al. review the obstacles for achieving asthma control in LMICs, which include social, financial, cultural and healthcare barriers (8). There is no doubt that global asthma guidelines have played an important role in raising the awareness and improving diagnosis and management of asthma in LMICs. However, the generic guidelines are often difficult to implement in the healthcare systems overstretched by the pressure of communicable diseases. This can be in part addressed through the development and implementation of national asthma guidelines tailored to local needs, and, given the sharp increase in asthma prevalence in LMICs, this should be a public health priority in these areas (8). There are notable examples of success of such approach – for example, the implementation of the National Asthma Plan in Costa Rica, which included the provision of beclomethasone as an affordable preventive medication for all patients, has resulted in a marked decrease in hospital admissions (by 53%) and mortality (by 80%) in the country (63). Given that the main reasons for inadequate asthma control in these underserved populations include weak infrastructure of health services, low accessibility of controller medications, poor adherence, lack of education, adverse environmental exposures and social, cultural and language barriers, the emphasis and concerted effort should be focussed on improving education and access to care, including better access to effective treatments (for example, having basic preventer asthma medicines and spacers available free of charge). This, however, can be achieved only through governmental commitment (8, 63).

Lower respiratory tract illness (LRTI) caused by the respiratory syncytial virus (RSV) is a recognised risk factor for the development of asthma (64). The most hospitalisations and mortality from RSV-related diseases occur in LMICs, and Laudanno et al. review the disparities in burden and outcomes of RSV LTRI between industrialised and developing countries, and highlight the need to identify specific risk factors in different populations for a targeted RSV LRTI prevention (9). To this end, the article reviews the current state of development of several vaccines to prevent RSV infection and monoclonal antibodies to prevent severe disease, which are in the late phase of clinical trials (64). These new treatments may completely change the landscape of RSV infections in young infants globally by providing effective solutions against this important pathogen, but access to treatments needs to be secured for the areas of greatest need – namely, the low- and middle-income countries.

The final topic relates to peanut allergy, which was uncommon before the 1990s, but has risen sharply over the last two decades (65, 66), to the estimated prevalence of 2.5% among school-age children in the UK (67). Chong and Turner provide a thorough overview on the latest advances in the management and prevention of peanut allergy (10), which in recent years has firmly shifted from strict avoidance, prompt recognition of allergic reactions, and rapid initiation of adrenaline autoinjector, towards active management and prevention (68-70). The key evidence was provided by the Learning Early About Peanut (LEAP) study which demonstrated for that the early introduction of peanut into the infant diet (prior to 12 months of age) substantially reduces the risk of the subsequent development of peanut allergy (81 percent relative reduction in risk), while delayed introduction beyond 12 months increases risk (71). This

has led to the update in Guidelines for prevention of peanut allergy, which now advocate the early introduction of peanut-containing foods into the diets of infants (72). The practical information for clinicians can be found on https://www.niaid.nih.gov/sites/default/files/peanut-allergy-prevention-guidelines-clinician-summary.pdf. So, unlike in asthma where prevention is still elusive, in peanut allergy there is an emerging consensus that active preventative measures should be implemented for high-risk infants (those with severe eczema and/or egg allergy) by introducing peanut-containing foods as early as 4-6 months, but only after determining that it is safe to do so. Whether such active intervention would be appropriate for infants at moderate- or low-risk of developing peanut allergies, and/or for population-based recommendations, remains a matter of debate (70). Furthermore, the complexity of, and barriers to, effective implementation of such primary prevention interventions in resource-poor settings in LMICs cannot be underestimated (70).

For patients with established peanut allergy, approach is also gradually shifting from complete avoidance (with the provision of adrenaline auto-injectors) towards food immunotherapy as a form of *active* management. However, whether immunotherapy for food allergy is ready for the routine use in clinical practice is a subject of a considerable debate. For example, oral immunotherapy (OIT) for peanut is associated with a higher rate of allergic reactions compared to strict avoidance (73), and adverse events (which include anaphylaxis) are common and contribute to a treatment-failure/withdrawal rate of ~20% (74). A lack of data to inform safety and longer-term efficacy is a major gap in evaluating OIT for routine clinical use. A sustained unresponsiveness (i.e. an outcome of treatment in which *clinical non-reactivity to allergens persists once therapy has finished*) is a principal objective of food immunotherapy. However, the data available to date indicate that peanut OIT induces desensitisation (i.e. clinical non-reactivity *while patient is on treatment*), and consequently the majority of patients require ongoing long-term dosing (even life-long) to maintain the efficacy (74). Knowledge regarding the mechanisms of peanut OIT and the immune changes which maintain sustained unresponsiveness is limited, and addressing this knowledge gap could help identify biomarkers which could be used in treatment decisions to facilitate a personalised approach and improve safety and efficacy of food OIT (10). Therefore, before peanut immunotherapy can be considered the standard of care for peanut-allergic children, more data are needed to improve safety and longer-term outcomes (10).

The articles in this issue of AMA emphasise the need for improvements in access to care, and continuous education of physicians, patients and general public about the concept of personalised (precision or stratified) prevention and treatment strategies for common complex allergic diseases (75). We hope that this will help start the debate about these important issues tailored to local needs in Bosnia and Herzegovina.

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