Expert meeting report: towards a joint European roadmap to address the unmet needs and priorities of paediatric asthma patients on biologic therapy

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A digital multidisciplinary European expert meeting took place on the 9 July 2020 to identify the unmet needs of paediatric severe asthma patients, and set the priorities for clinical and research activities ahead https://bit.ly/3CeLBHB

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Biologics use in severe paediatric asthma

The global prevalence of severe asthma among adolescents ranges from 4% to 11%; and up to 7% of children with asthma display an uncontrolled and severe form that is often associated with a substantial burden on the quality of life of patients and their families, and increasing costs of healthcare [1, 2]. "Childhood asthma" is an umbrella term describing a heterogeneous disease comprising different phenotypes and a wide range of symptoms [3–5].

Despite decades of basic and clinical research, tailored strategies to modify the natural course of asthma, prevent severe exacerbations and inhibit lung function decline are still lacking. In addition, clinical phenotypes are only moderately reliable in the prediction of treatment responses and our current understanding of asthma endotypes is limited. Most asthma endotypes involve concomitant inflammatory pathways and distorted immune parameters. Advances in understanding severe paediatric asthma pathophysiological mechanisms and immunological pathways mediating the airway inflammation would allow better characterisation of these patients as well as optimised intervention, guided by treatable traits and biomarkers [6, 7].

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Recent studies have demonstrated the effectiveness of monoclonal antibodies (mAbs), also known as biologics, targeting type 2 inflammation in controlling the symptoms of severe asthma. Currently, four human mAbs are approved for use in children: mAbs that target interleukin (IL)-5 or IL-5 receptor (R) (mepolizumab and benralizumab), mAbs that target IL-4R (dupilumab), and mAbs that target immunoglobulin E (omalizumab). Omalizumab was the first biologic approved to treat moderate-to-severe allergic asthma (⩾6 years of age). Mepolizumab and dupilumab have been approved for severe eosinophilic asthma (⩾6 and ⩾12 years of age, respectively), while benralizumab has been approved in the USA to treat children (⩾12 years of age) with severe eosinophilic asthma [8–13].

The introduction of mAb agents in asthma treatment is a milestone in the application of personalised medicine. However, comparative studies and standardised algorithms for the management of paediatric severe asthma to guide the best therapeutic option for paediatric patients with severe asthma are lacking [14]. More personalised medicine approaches may benefit the patient by better matching patients with the most appropriate therapy. Risk stratification, remote monitoring and the integration of multiple data sources could help tailor management for the individual child with severe asthma.

A digital multidisciplinary European expert meeting took place on 9 July 2020. In this workshop, we brought together European respiratory/allergy paediatricians, immunologists, epidemiologists and basic scientists to identify the unmet needs of paediatric severe asthma patients, and set the priorities for clinical and research activities ahead. The participants discussed ongoing initiatives and knowledge gaps, and formulated proposals on how to address these challenges. In this report, we describe the main findings of this expert meeting.

Current knowledge gaps and challenges

Except for omalizumab, a major constraint to the optimal and consistent use of biologics in paediatric severe asthmatic is the limited evidence regarding the safety and efficacy of biologics in children [15, 16] (table S1). This especially holds true for biologics that entered the market recently. In the large phase 3 trials of these treatments, children were underrepresented and constituted only 1–6% of included patients [10, 17–20]. Although it might be challenging to recruit paediatric patients, assessing efficacy and safety in this population is essential since their immune system is under development and asthma progression is related to age and sex [21]. Studies that assessed the safety of omalizumab or mepolizumab in severe asthmatic children after 52 weeks of treatment did not observe any treatment-related severe adverse events [9, 22] but potential long-term effects remain unclear. Furthermore, the mepolizumab studies included very few children and adolescents. Finally, there are, to date, no data on biologics in the preschool-age severe asthma. How these treatments might impact underlying disease mechanisms is only partly clear and potential disease-modifying effects are not well understood. Since these expensive drugs may require lifelong administration [23], careful consideration is needed to assess which child is eligible for which biologic. A better understanding of paediatric asthma endotypes that can evolve over time might also lead to novel insights into whether biologics that previously showed no efficacy in adults could still be promising candidates for children [24].

The American Thoracic Society and the European Respiratory Society (ERS) define severe asthma as asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming “uncontrolled” or “which remains uncontrolled despite this therapy” [25]. Application of adult definitions and treatment guidelines may not always be appropriate; children with severe asthma have more atopy, less airflow limitation and less association with obesity [26]. The lack of clear definitions of “paediatric severe asthma” and “treatment response” were also identified as important hurdles. Moreover, there is an urgent need to formulate a definition of severe preschool asthma/wheeze. A consensus is needed both for research on biologics in the paediatric population as well as for uniform clinical management across Europe, in accordance with the Paediatric Investigational Plans of the European Medicines Agency. Moreover, the lack of research funding for paediatric studies on biologics and lack of scientific collaboration with other inflammatory disease areas where biologics have been applied in the paediatric population were identified as important challenges.

Lastly, the COVID-19 era has led to significant changes in how healthcare is accessed and provided [27]. This brings new challenges, as well as opportunities, for the management of children on biologics. There is now a stronger focus on remote care and monitoring, on the use and development of digital tools that might help with this, and on possible home administration of biologics. Self- or caregiver-administered injections make it possible for patients that live further away from a clinic to receive treatment more consistently, but also requires proper training, as well as careful remote monitoring for complications and to ensure good adherence [28].

Ongoing initiatives: bringing European experts together

The high socioeconomic burden of uncontrolled disease, and the lack of clear indicators for treatment choice and responses to administrated treatment, especially for biologics, underline the need for better characterisation of paediatric asthma phenotypes/endotypes and novel therapeutic options. Several ongoing studies and initiatives within European consortia address those needs (table S2). Hurdles in recruitment and underrepresentation of children in severe asthma studies provide an urgent need for collaborative efforts between European medical centres. Therefore, bringing together the data that are already available from existing consortia may be the first step towards more efficient characterisation of the disease and treatment options. Pan-European standardisation of inclusion and exclusion criteria for study participants and operating protocols, as well as an agreement on sample and data collection, would further provide better validity of outcomes and enable access to large biobanks.

There was consensus on the need for new collaborative trials, real-life cohorts and *in vitro* pre-clinical models with standardised protocols on applicable paediatric antiasthmatic drugs. An urgent update and uniformisation of treatment guidelines that take into account switching from one biologic to another, compatibility of more than one biologic, dose adjustment and long-term (side-)effects of these therapies was considered essential. This requires a development of specific paediatric tools for evaluating severity, level of control and response to treatment, and as well as data harmonisation.

Identified research priorities

Seven priority research areas were identified: 1) early identification of young asthma patients, including preschoolers, with a high risk of progression to severe disease; 2) exploring molecular mechanisms underlying poor response to treatment; 3) prediction of response to biologics; 4) understanding mechanistic differences underlying paediatric and adult severe asthma phenotypes; 5) long-term efficacy and safety; 6) understanding patient and caregiver perspectives on biologics use; and 7) harmonising (access to) biologics for asthmatic children treatment across Europe (table 1).

The early identification of asthmatic children at greatest risk of progression to severe disease requires longitudinal follow-up combined with in-depth pheno-endotyping [29]. Since various European initiatives are ongoing in this area, connecting different paediatric initiatives was identified as an important next step, in addition to linking with other ERS Clinical Research Collaborations with an adult focus, such as SHARP (focusing on severe asthma in adults) [30] and CADSET (focusing on lung function trajectories).

To predict which patients will respond to which biologics, ideally, comparative crossover clinical trials are needed. However, these kinds of trials are likely to be very challenging. Pragmatic and noninferiority trials, such as the recently initiated TREAT trial in the UK, which aims to compare the efficacy of mepolizumab *versus* omalizumab in reducing asthma attacks in children, might be more feasible [31]. Real-life efficacy data, combined with prospectively collected biomarkers, have the potential to provide additional valuable information [32, 33]. International and multidisciplinary collaboration is critical to reaching a consensus on response definitions (as is currently ongoing with the 3TR consortium), to recruit enough patients and to harmonise research protocols.

Understanding molecular mechanisms and immunological pathways are essential for the assessment of biomarker candidates for treatment response as well as an acceleration of the development of novel therapeutics. Successful modern research collaborations increasingly include scientists and clinicians of different expertise. Today, *ex vivo* translational models, including monolayer cultures, coculture systems or organ-on-chip lung models, provide an unprecedented opportunity to study *in vitro* effects of promising drugs. Introduction of novel technologies, *i.e.* single-cell sequencing or CRISPR-Cas9, enable a functional validation of potential biomarkers predicted by genome-wide association studies in *ex vivo* airway cell/tissue models [34, 35].

Knowledge as to which asthmatic patients progress into severe adult asthma is lacking, although risk factors like atopy, multiple allergic comorbidities, impaired lung function, obesity and environmental exposures are well-described [29]. Severe disease may differ substantially between children and adults. For example, blood eosinophils or airway eosinophils might not equal T2 inflammation in children, while they often do in adults [36]. Upcoming results from initiatives and consortia such as VIRASTHMA2, COBRAPed, UBIOPRED paediatric cohorts and SysPharmPediA might be able to shed more light on paediatric endotypes of severe disease.

The patient and caregiver perspectives must also be heard, as beliefs about treatment are known to influence treatment satisfaction and adherence [37]. Qualitative studies and active collaborations between

TABLE 1 Identified research priorities

Research priority	Action steps
Identifying young patients at highest risk for progression to severe disease	Establish a European real-world paediatric severe asthma cohort with longitudinal follow-up (into adulthood), building on existing initiatives and infrastructures (*e.g.* SPACE, UBIOPRED, GAN, PERMEABLE, COBRAPed, VIRASTHMA2 and the Danish National Database for Severe Asthma)
Identifying paediatric responders and nonresponders to biologicals	Standardise a definition of a responder/nonresponder Large-scale collaboration to include paediatric patients with severe asthma/allergy Collaborative study efforts using joint research/clinical protocols (*e.g.* pragmatic real-world studies and comparative studies with biologics) Assess whether incorporation of identified predictive biomarkers in clinical decision-making models improve clinical outcomes and are cost-effective
Understanding phenotypes of severe disease, and differences between adult and paediatric severe disease phenotypes	In-depth phenotyping of severe asthma/allergy patients combining clinical characteristics and -omics data (*e.g.* UBIOPRED, COBRAPed, SysPharmPediA, SPACE, PERMEABLE and VIRASTHMA2) in combination with validation in adult cohorts (*e.g.* SHARP and UBIOPRED) Long-term follow-up of severe paediatric asthma into adulthood
Long-term efficacy and safety of biologics use	Establish a European real-world paediatric cohort with patients on biologics of choice and/or switchers with longitudinal follow-up (assess the maintenance dosage, long-term follow-up on overall health and QoL of patients)
Understanding molecular mechanisms to accelerate drug development using *ex vivo* translational models	Establish collaborations with immunologists and molecular biologists to ensure hypothesis/outcome validation in preclinical disease models Implement the latest molecular biology techniques (*i.e.* CRISPR-Cas9 and single-cell sequencing assays) both to validate existing outcomes based on associations and to discover novel cell (sub)types that mediate underlying inflammatory processes Develop noninvasive techniques to explore pathophysiological mechanisms
Understanding patient and caregiver perspectives on biologics use	Perform qualitative studies on patient and caregiver experiences Establish a European patient and caregiver advisory board specific for biologics use (in collaboration with European Lung Foundation and national patient organisations) Develop and apply a platform for children and parents' involvement
Harmonising treatment protocols across Europe	Systematically assess which differences exist within the European countries Develop online educational programmes and regularly update these programmes based on novel scientific evidence
Applying a precision medicine approach in severe paediatric asthma	Evaluate the added value of biomarker and -omics data for individual treatment selection Combine disease history data, clinical measures, and biomarker data into useful disease score models

SPACE: Severe Paediatric Asthma Collaborative in Europe; UBIOPRED: Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes; GAN: Global Asthma Network; PERMEABLE: Personalized Medicine Approach for Asthma and Allergy Biologicals Selection; VIRASTHMA2: Inflammatory and Immune Profiles During a Severe Exacerbation in Preschool Asthmatic Children; COBRAPed: Pediatric Cohort of Bronchial Obstruction and Asthma; SysPharmPedia: Systems Pharmacology Approach to Difficult-to-Treat Pediatric Asthma; SHARP: Severe Heterogeneous Asthma Registry, Patient-Oriented; QoL: quality of life.

researchers and patient representatives [38, 39] are needed to address the needs and beliefs of patients and their caregivers. A young patient working group, as currently being established within 3TR, is a great first step to including the patients' voice in treatment considerations.

Next steps

Collaboration is essential to address the unmet clinical needs and priorities of paediatric severe asthma patients. Joining forces will help bring the field forward and pave the way for a new joint effort to optimise treatment for this vulnerable patient population. This requires a broad engagement to represent all stakeholders and involvement of national respiratory societies and patients to ensure optimal implementation of the research findings into clinical practice. As such, we aim to establish a European working group on joint research and clinical protocols, establish a common European database for paediatric asthma patients, and obtain research funding together. Discussions are ongoing, and we are now reaching out to clinicians, scientists, technology, regulators, healthcare providers and, most importantly, patients into collaborative efforts. This initiative is open for new collaborators to help lead the way for precision medicine of severe paediatric asthma.

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References

1 Odling M, Andersson N, Ekstrom S, *et al.* Characterization of asthma in the adolescent population. *Allergy* 2018; 73: 1744–1746.
2 Lai CKW, Beasley R, Crane J, *et al.* Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; 64: 476–483.
3 Vijverberg SJH, Brinkman P, Rutjes NWP, *et al.* Precision medicine in severe pediatric asthma: opportunities and challenges. *Curr Opin Pulm Med* 2020; 26: 77–83.
4 Golebski K, Kabesch M, Melen E, *et al.* Childhood asthma in the new omics era: challenges and perspectives. *Curr Opin Allergy Clin Immunol* 2020; 20: 155–161.
5 Pavord ID, Beasley R, Agusti A, *et al.* After asthma: redefining airways diseases. *Lancet* 2018; 391: 350–400.
6 Pijnenburg MW, Fleming L. Advances in understanding and reducing the burden of severe asthma in children. *Lancet Respir Med* 2020; 8: 1032–1044.
7 Lejeune S, Deschildre A, Le Rouzic O, *et al.* Childhood asthma heterogeneity at the era of precision medicine: Modulating the immune response or the microbiota for the management of asthma attack. *Biochem Pharmacol* 2020; 179: 114046.
8 Corren J, Kavati A, Ortiz B, *et al.* Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: A systematic literature review. *Allergy Asthma Proc* 2017; 38: 250–263.
9 Gupta A, Ikeda M, Geng B, *et al.* Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol* 2019; 144: 1336–1342.
10 Bleecker ER, Wechsler ME, FitzGerald JM, *et al.* Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J* 2018; 52: 190936.
11 Agache I, Beltran J, Akdis C, *et al.* Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. *Allergy* 2020; 75: 1023–1042.
12 Henriksen DP, Bodtger U, Sidenius K, *et al.* Efficacy of omalizumab in children, adolescents, and adults with severe allergic asthma: a systematic review, meta-analysis, and call for new trials using current guidelines for assessment of severe asthma. *Allergy Asthma Clin Immunol* 2020; 16: 49.
13 Chipps BE, Lanier B, Milgrom H, *et al.* Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017; 139: 1431–1444.

14 Makhecha S, Jamalzadeh A, Irving S, *et al.* Paediatric severe asthma biologics service: from hospital to home. *Arch Dis Child* 2021; 106: 900–902.
15 Just J, Deschildre A, Lejeune S, *et al.* New perspectives of childhood asthma treatment with biologics. *Pediatr Allergy Immunol* 2019; 30: 159–171.
16 Papadopoulos NG, Custovic A, Cabana MD, *et al.* Pediatric asthma: an unmet need for more effective, focused treatments. *Pediatr Allergy Immunol* 2019; 30: 7–16.
17 Lovinsky-Desir S. The use of biologic therapies for the management of pediatric asthma. *Pediatr Pulmonol* 2020; 55: 803–808.
18 Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378: 2486–2496.
19 Rabe KF, Nair P, Brusselle G, *et al.* Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378: 2475–2485.
20 Yancey SW, Ortega HG, Keene ON, *et al.* Efficacy of add-on mepolizumab in adolescents with severe eosinophilic asthma. *Allergy Asthma Clin Immunol* 2019; 15: 53.
21 Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci* 2015; 282: 20143085.
22 Berger W, Gupta N, McAlary M, *et al.* Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003; 91: 182–188.
23 Ortega H, Lemiere C, Llanos JP, *et al.* Outcomes following mepolizumab treatment discontinuation: real-world experience from an open-label trial. *Allergy Asthma Clin Immunol* 2019; 15: 37.
24 Holguin F, Cardet JC, Chung KF, *et al.* Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020; 55: 1900588.
25 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2015; 43: 343–373.
26 Phipatanakul W, Mauger DT, Sorkness RL, *et al.* Effects of age and disease severity on systemic corticosteroid responses in asthma. *Am J Respir Crit Care Med* 2017; 195: 1439–1448.
27 Papadopoulos NG, Custovic A, Deschildre A, *et al.* Impact of COVID-19 on pediatric asthma: practice adjustments and disease burden. *J Allergy Clin Immunol Pract* 2020; 8: 2592–9.e3.
28 Shaker M, Briggs A, Dbouk A, *et al.* Estimation of health and economic benefits of clinic *versus* home administration of omalizumab and mepolizumab. *J Allergy Clin Immunol Pract* 2020; 8: 565–572.
29 Melen E, Guerra S, Hallberg J, *et al.* Linking COPD epidemiology with pediatric asthma care: implications for the patient and the physician. *Pediatr Allergy Immunol* 2019; 30: 589–597.
30 van Bragt J, Adcock IM, Bel EHD, *et al.* Characteristics and treatment regimens across ERS SHARP severe asthma registries. *Eur Respir J* 2020; 55: 1901163.
31 Saglani S, Bush A, Carroll W, *et al.* Biologics for paediatric severe asthma: trick or TREAT? *Lancet Respir Med* 2019; 7: 294–296.
32 Eger K, Kroes JA, Ten Brinke A, *et al.* Long-term therapy response to anti-IL-5 biologics in severe asthma-A real-life evaluation. *J Allergy Clin Immunol Pract* 2021; 9: 1194–1200.
33 Liu NM, Carlsen KCL, Cunningham S, *et al.* First analysis of the Severe Paediatric Asthma Collaborative in Europe registry. *ERJ Open Res* 2020; 6: 00566-2020.
34 Jackson ND, Everman JL, Chioccioli M, *et al.* Single-cell and population transcriptomics reveal pan-epithelial remodeling in type 2-high asthma. *Cell Rep* 2020; 32: 107872.
35 Goodman MA, Moradi Manesh D, Malik P, *et al.* CRISPR/Cas9 in allergic and immunologic diseases. *Expert Rev Clin Immunol* 2017; 13: 5–9.
36 Bush A. Pathophysiological mechanisms of asthma. *Front Pediatr* 2019; 7: 68.
37 Santus P, Ferrando M, Baiardini I, *et al.* Patients beliefs on intravenous and subcutaneous routes of administration of biologics for severe asthma treatment: a cross-sectional observational survey study. *World Allergy Organ J* 2019; 12: 100030.
38 Groot B, Dedding C, Slob E, *et al.* Adolescents' experiences with patient engagement in respiratory medicine. *Pediatr Pulmonol* 2021; 56: 211–216.
39 Supple D, Roberts A, Hudson V, *et al.* From tokenism to meaningful engagement: best practices in patient involvement in an EU project. *Res Involv Engagem* 2015; 1: 5.