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Biologicals in childhood severe asthma: the European PERMEABLE survey on the *status quo*

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Shareable abstract (@ERSpublications)
This study reveals enormous differences in therapy with biologicals for childhood severe asthma across Europe, and demonstrates the urgent need for harmonisation in medication choice, definition of therapy success and how/when to discontinue treatment https://bit.ly/3tnJMTY

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Abstract

Introduction Severe asthma is a rare disease in children, for which three biologicals, anti-immunoglobulin E, anti-interleukin-5 and anti-IL4RA antibodies, are available in European countries. While global guidelines exist on who should receive biologicals, knowledge is lacking on how those guidelines are implemented in real life and which unmet needs exist in the field. In this survey, we aimed to investigate the *status quo* and identify open questions in biological therapy of childhood asthma across Europe.

Methods Structured interviews regarding experience with biologicals, regulations on access to the different treatment options, drug selection, therapy success and discontinuation of therapy were performed. Content analysis was used to analyse data.

Results We interviewed 37 experts from 25 European countries and Turkey and found a considerable range in the number of children treated with biologicals per centre. All participating countries provide public access to at least one biological. Most countries allow different medical disciplines to prescribe biologicals to children with asthma, and only a few restrict therapy to specialised centres. We observed significant variation in the time point at which treatment success is assessed, in therapy duration and in the success rate of discontinuation. Most participating centres intend to apply a personalised medicine approach in the future to match patients *a priori* to available biologicals.

Conclusion Substantial differences exist in the management of childhood severe asthma across Europe, and the need for further studies on biomarkers supporting selection of biologicals, on criteria to assess therapy response and on how/when to end therapy in stable patients is evident.

Introduction

Severe asthma in children is a rare disease affecting <5% of young asthma patients [1, 2]. In those that are not stable despite treatment with high dose of inhaled steroids and long-acting β_2-agonists or need recurrent oral steroids, therapy with biologicals has become an option in the last decade [3]. Until 2013, only the anti-immunoglobulin E (IgE) antibody omalizumab was available for treatment of severe childhood asthma, but recently, the European Medicines Agency (EMA) authorised the use of anti-interleukin (IL)-5 (mepolizumab and reslizumab) and anti-IL-4 receptor α (dupilumab) antibodies for children in some countries [4]. Owing to the low numbers of children with severe asthma, even large paediatric pneumonology/allergy centres across Europe have limited experience with these drugs. As asthma in children differs substantially from adults in many aspects (management needs and treatment response for example), a simple transfer of experience and rules from adults is not sufficient. Despite efforts to harmonise diagnosis and treatment of children with severe asthma [5], a number of unmet needs still exist in the field.

Based on the experience that even within a single country such as Germany access to biologicals for children is unevenly distributed depending on where a patient lives (*e.g.* rural areas *versus* metropolitan regions) and on the experience and approach the attending doctor has with biologicals, we hypothesised that access to biologicals for children with severe asthma may be even more variable on the European level. In the PERMEABLE project (PERsonalised MEdicine Approach for Asthma and Allergy Biologicals SeLEction) [6], we addressed this issue by performing the first comprehensive survey across Europe to investigate the current real-life situation and unmet needs in biological therapy of childhood asthma.

Methods

Study centres

Paediatric pneumonology/allergy centres across Europe that were either: 1) involved in research activity on severe asthma; or 2) national centres for the disease, based either on their involvement in European Respiratory Society (ERS) and/or European Academy of Allergy and Clinical Immunology (EAACI) activities on severe asthma or their reputation (*i.e.* publication record), were approached for this study. Between September 2019 and July 2020 we contacted these centres in all major countries of the European Union (with a population of over 500 000 inhabitants) by e-mail or individual phone calls. All centres that responded to the initial invitation and follow-up contacts were invited to participate in the survey. Centres in non-member countries associated with the European Union (*i.e.* Switzerland, Norway, Iceland, Turkey and Serbia) were also contacted. The ethics committee of the University of Regensburg waived ethical approval for this study.

Structured interview/questionnaire

We applied structured interviews and, if those were not possible (*e.g.* due to time restraints or language barrier), online questionnaires in the multilingual qnome system (www.qnome.de) were used to acquire data. All interviews were done by a single investigator (M. Kabesch) to avoid interobserver variation. The interview covered the following domains: experience of centres in the use of biologicals; access to different biologicals and national regulations on access; attitude towards selection of biologicals; evaluation of therapy success and treatment discontinuation. The questionnaire is publicly available on www.we-care.de/permeable

Qualitative data analyses

Content analysis was performed to summarise and tabulate the data obtained during the interviews. All data are displayed in descriptive terms and no statistical comparisons were performed as data are not representative. Median and mean values were calculated. When multiple answers were possible or questions were not applicable in certain centres, total numbers may not add up to 100%.

Results

Overall, 37 clinical experts on severe asthma in medical centres from 25 European countries and Turkey participated in the survey (figure 1). The number of children ever treated with biologicals for severe asthma varied considerably among centres, even though all centres applied the same or very similar criteria for induction of therapy (national guidelines based on GINA (Global Initiative for Asthma) and/or NICE (National Institute for Health and Care Excellence)). While a handful of centres had experience in treating 100 or more childhood cases with biologicals, most centres had considerably lower numbers of patients they had treated (colour coded in figure 1). Eight out of the 37 centres had treated less than five patients in total (Ankara, Turkey; Warsaw, Poland; Ljubljana, Slovenia; Budapest, Hungary; Porto, Portugal; Belgrade, Serbia; Msida, Malta; and Bucharest, Romania). The time point when biologicals were introduced into the market in the respective countries influenced the level of experience, and for the newer biologicals, targeting IL-5 and IL-4Rα, this was most pronounced. Whereas all centres (except Bulgaria where approval for therapy in children is still pending) had experience with anti-IgE (omalizumab), only 17 (47%) out of 36 treated children with anti-IL-5 (mepolizumab, reslizumab) and nine (25%) with IL-4Rα antagonist (dupilumab) leading to only 78 children currently treated with a biological other than omalizumab in the 37 centres included in the survey (figure 2).

Even though the health systems differ considerably among European countries, public access to at least one biological for severe asthma in children exists in theory in all countries that participated in the survey. However, major differences in national regulations and specific requirements for therapy in children were observed. In 15 countries biological therapy in children can only be prescribed by specialised centres, whereas in many other countries a range of practitioners and medical disciplines can prescribe biologicals to children with asthma (figure 3). Rules of reimbursement controlled by national health insurance systems had a strong influence on the access of children to biologicals in many countries, leading to severely limited numbers of children qualifying for therapy in some countries.

We also explored the approach of centres towards the present and future selection of therapy when different biologicals are available for the treatment of severe asthma. Overall, 29.7% of centres (11 out of 37) stated that they prefer a stepwise approach, always starting therapy with omalizumab as the biological for which the most experience in children exists and using other biologicals only as second-line therapy. Interestingly, 56.8% of the centres (21 out of 37) favoured an *a priori* personalised approach matching patients with the most suitable biological as the first-choice therapy. The remaining 13.5% of the centres (five out of 37) were undecided. However, during the interviews, it became clear that many clinicians who preferred a personalised approach identified a lack of biomarkers to support decision-making. Overall,

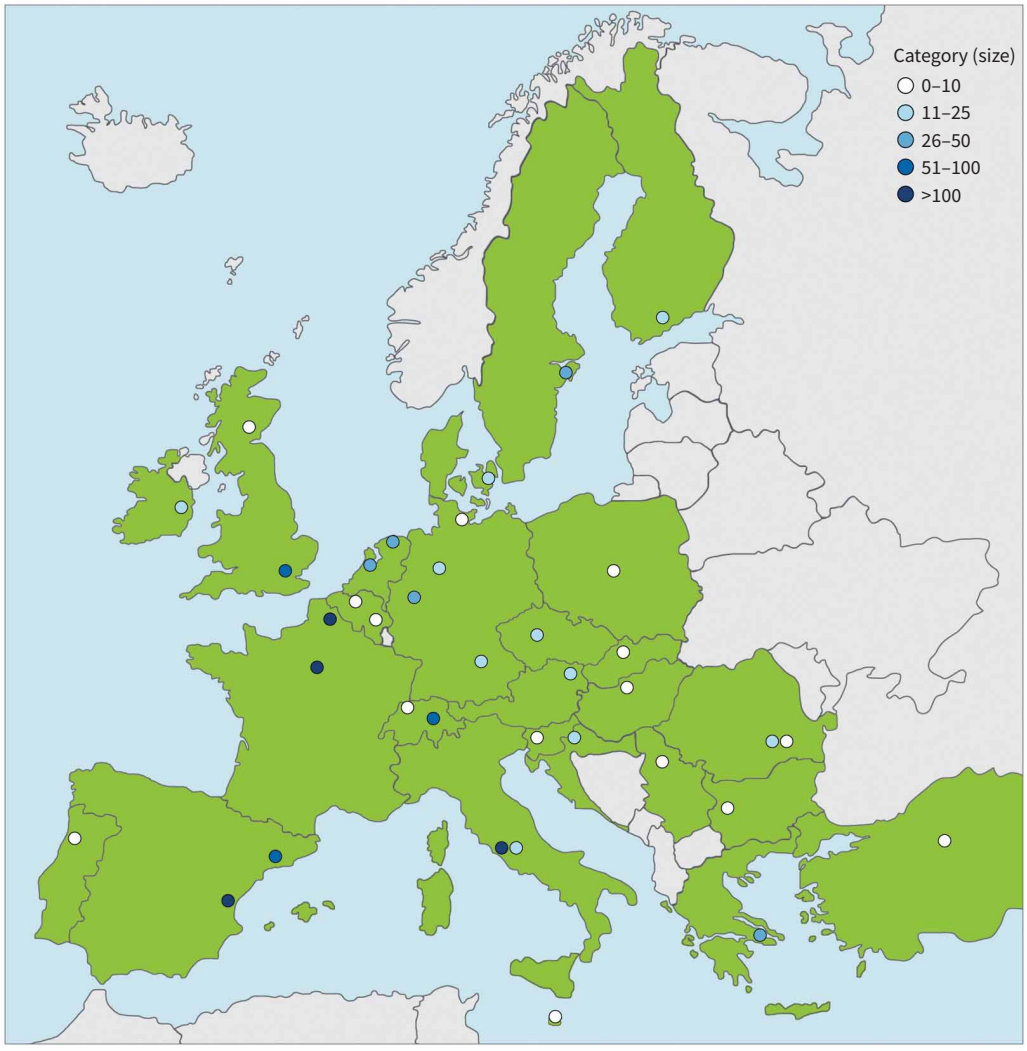

FIGURE 1 Map of Europe with location of centres contributing to the survey and centre size by colour code. Participating countries are depicted in green, and locations of survey centres are given. Colour codes for overall centre experience in biological treatment (number of children ever treated with biologicals) are shown according to five categories.

more small- to medium-sized centres (11 (73.3%) out of 15 *versus* 8 (66.7%) out of 12) tended towards a personalised approach currently or in the future and those from the south and east of Europe (10 (76.9%) out of 13) more than those from the west and north (16 (66.7%) out of 24).

We investigated how and when centres assess the response to treatment with biologicals in their patients. The usual time point for each centre after therapy induction, when the decision is made as to whether the biological should be continued long-term, varies from 2 months to 12 months (figure 4, green lines/areas). Major criteria for assessing therapy success in most centres are scores in the asthma control test, frequency of exacerbations and use of rescue medication (table 1).

The minimum duration of therapy before considering a trial for discontinuation is 6 months but ranges from 6 to 36 months among centres (figure 4, blue bars). Eight (27.6%) out of 29 centres stretch intervals of biological application before they stop therapy, while others (55.2%) stop immediately, and some do both on an individual basis (table 1). Discontinuation is considered successful when a patient stayed stable without relapsing into another course of biological treatment. The success rate of discontinuation varies considerably among centres, and many factors still to be explored beyond this survey in clinical studies may contribute to that.

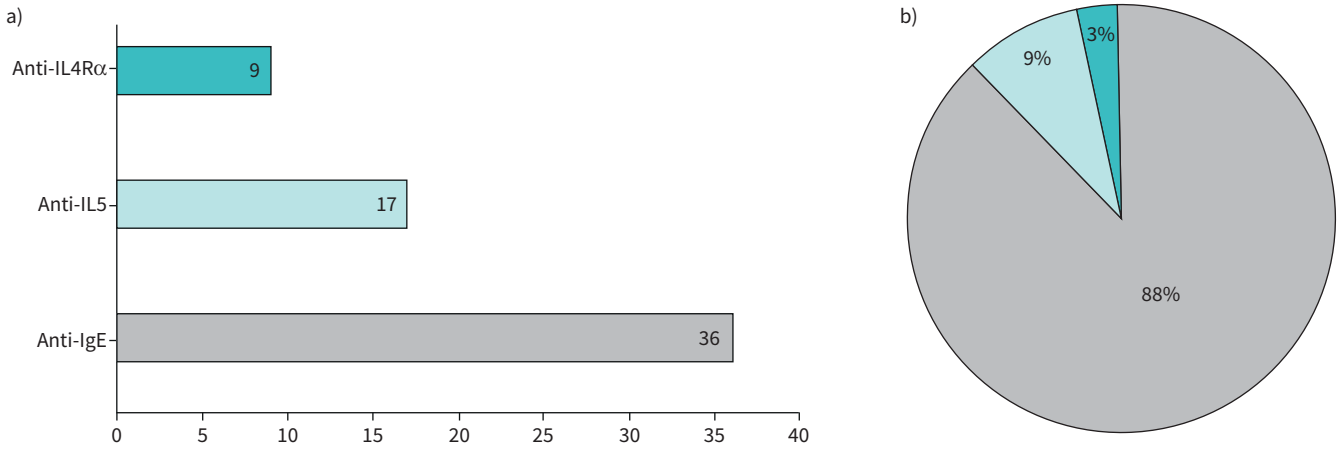

FIGURE 2 a) Number of centres with experience of different biologicals for severe asthma and b) percentage of paediatric asthma patients currently treated with the respective biologicals. All centres have experience of treatment with anti-IgE (omalizumab), except for one centre where approval for treatment is still pending as the drug only became available for children recently. Treatment with anti-interleukin (IL)-5 comprises mepolizumab and reslizumab, and further discrimination due to low numbers did not seem justified. Anti-IL4Rα treatment is dupilumab. IgE: immunoglobulin E.

Discussion

This PERMEABLE survey is a snapshot of real-life severe asthma care in children in Europe. It shows huge differences in the therapy of severe asthma in children across Europe, mainly due to national regulations, structural differences in the health systems and availability of biologicals. Experience of paediatric centres in terms of number of patients treated varies by a factor of 20-fold. While initiation of therapy is generally harmonised and based on GINA and NICE guidelines to harmonise how to assess the success of biological therapy and how to discontinue medication are urgently needed. With multiple biologicals available now in some but far from all European countries, decision-making regarding the choice of biological is inconsistent.

This survey was performed in 25 European countries and Turkey with 37 centres participating. While the survey cannot be representative of all centres in all countries, the included centres were able to give insight

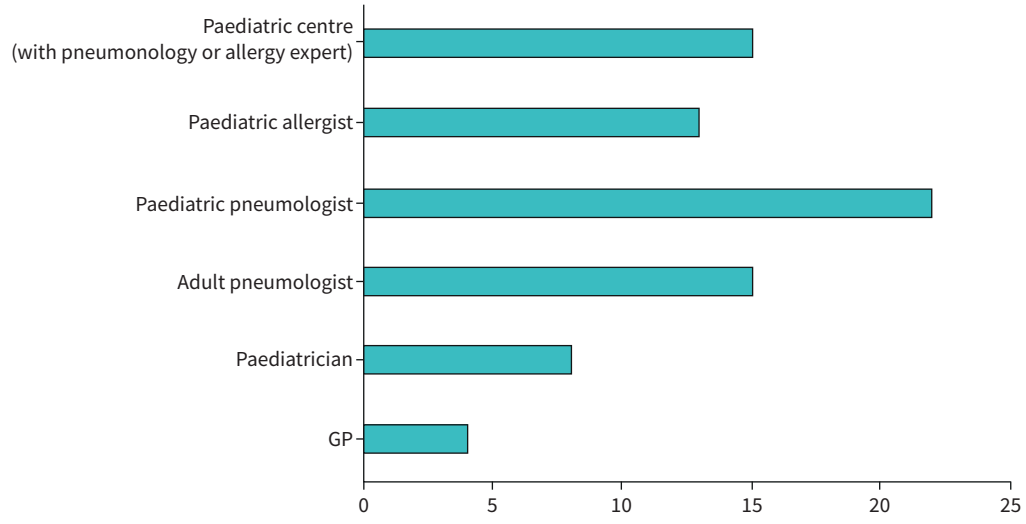

FIGURE 3 Medical disciplines allowed to initiate biological therapy for severe asthma in children across Europe. Cumulative numbers are given (multiple answers were possible per country). Paediatric centres are hospitals specialised in treatment of children where paediatric experts for severe asthma are available (paediatric allergist or pneumologist where subspecialisation is available). GP: general practitioner.

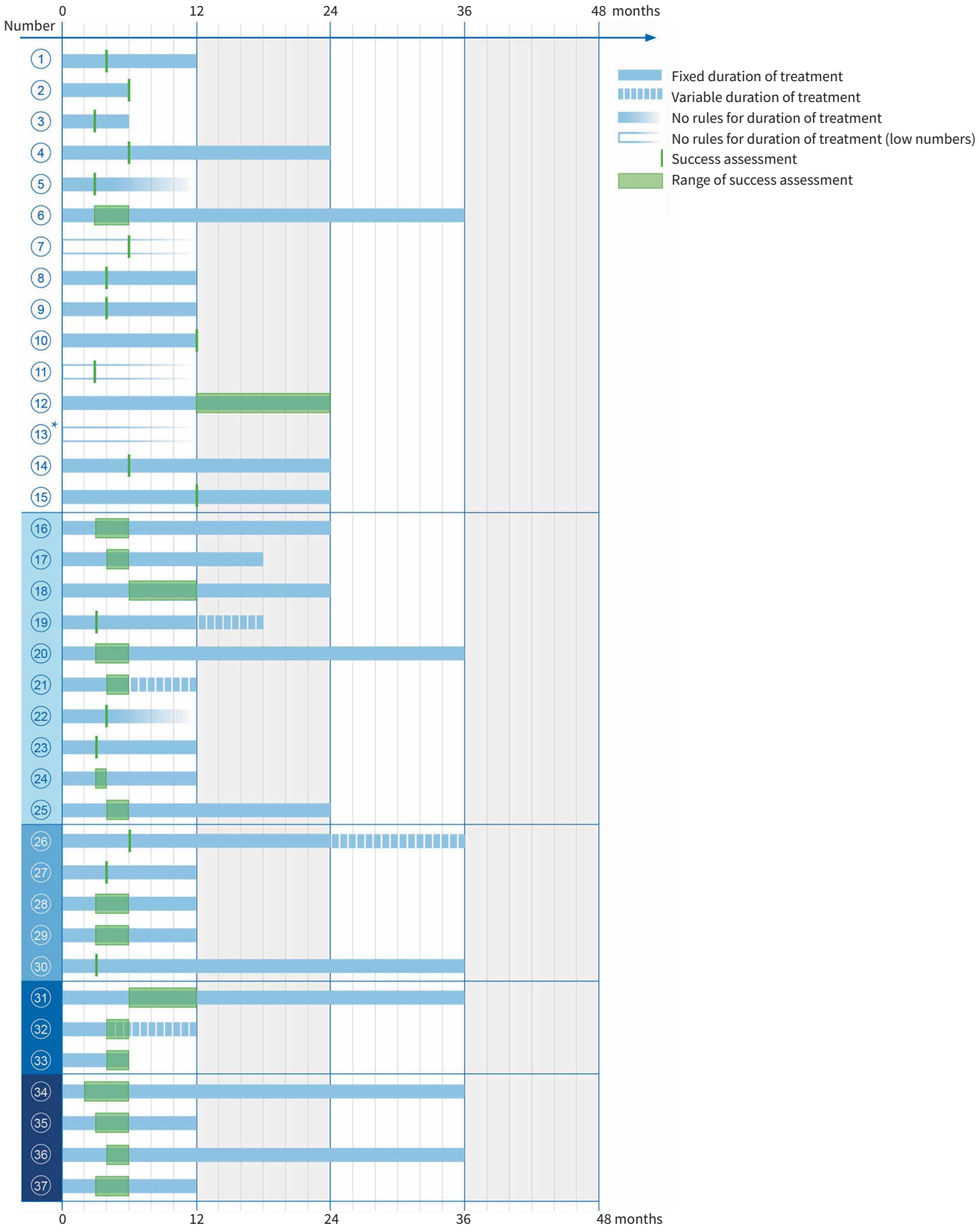

FIGURE 4 Time point for evaluation of therapy success with biologicals and minimal duration of therapy before discontinuation trial is initiated by centre, sorted by centre size. Centres are grouped according to experience in treatment and colour coded as in figure 1. Time point or time frame for assessment of therapy success is depicted in green; the blue bars indicate minimal duration of therapy before a trial for discontinuation is made in the respective centres. *: for centre 13, approval for first patient on biological is still pending.

TABLE 1 Parameters used by centres to evaluate success of treatment with biologicals and strategies as well as outcomes for discontinuation of therapy

	All centres	Centre size[#]		
		0–10	11–50	51 to >100
Parameters to assess therapy success				
ACT	77.8 (28/36)	73.3 (11/15)	80 (12/15)	71.4 (5/7)
Exacerbation frequency	94.4 (34/36)	86.7 (13/15)	100 (15/15)	85.7 (6/7)
Use of rescue medication	80.6 (29/36)	60.0 (9/15)	86.7 (13/15)	100 (7/7)
Lung function	77.8 (28/36)	66.7 (10/15)	73.3 (11/15)	100 (7/7)
Blood eosinophil count	22.2 (8/36)	33.3 (5/15)	13.3 (2/15)	14.3 (1/7)
Nitric oxide	33.3 (12/36)	20 (3/15)	33.3 (5/15)	57.1 (4/7)
IgE level	2.8 (1/36)	0 (0/15)	6.7 (1/15)	0 (0/7)
Discontinuation strategy and success rate				
Stretch intervals	39.4 (13/33)	25 (3/12)	46.7 (7/15)	42.9 (3/7)
Stop and watch	63.6 (21/33)	66.7 (8/12)	53.3 (8/15)	71.4 (5/7)
Other (*e.g.* individual approach)	15.2 (5/33)	16.7 (2/12)	13.3 (2/15)	14.3 (1/7)
Success rate of discontinuation %	50±34.5	35±38.6	50±36.7	62.5±22.1

Categorical data are presented as % (n out of N) or median±SD. ACT: asthma control test; IgE: immunoglobulin E. [#]: to achieve sufficient numbers for comparisons, centres were grouped into three categories for this analysis according to overall treatment experience (number of children ever treated with biologicals).

into general policies and the overall situation in the respective countries. Unfortunately, no comprehensive registry of centres treating children with biologicals exists, neither within countries nor on the European level. During the interviews, it became clear that all centres irrespective of size are strongly interested in collaboration and exchange, which needs to be fostered actively. Simply establishing national registries of physicians treating children with biologicals under a common European roof would be a first step towards developing such a barrier-free exchange between centres.

It became obvious in the survey that a major barrier to setting up such a structure is the fact that many countries lack a clear organisation of services and designated centres where children with severe asthma are assessed for eligibility and treated with biologicals, despite such recommendations by GINA [3]. However, the growing pipeline of biologicals and the small number of children with severe asthma highlight the need for well-organised care in dedicated paediatric severe asthma centres. Given the very small number of children enrolled in Phase 3 studies of novel biologicals [7, 8], the collection of real-world data and collaborative studies are essential for benchmarking and addressing unmet needs in practice such as the selection of different biologicals and decision-making about discontinuation of therapy.

We acknowledge that treatment of severe asthma in children with biologicals across Europe cannot be compared easily and data will be difficult to harmonise. In some European countries, paediatric pneumonology/allergy are not even recognised specialties, and adult pneumonology/allergy specialists make decisions about treatment of children with biologicals on their behalf. This leads to awkward situations where paediatricians and their patients need to "stand trial" in front of a committee of experts in adult medicine. In other countries (such as Germany) any doctor can prescribe biologicals to children. Thus, there is an unmet need for the paediatric assemblies of ERS and EAACI to implement political pressure at the European level for minimal structural standards in all countries for these therapies in children and to acknowledge the necessity for a paediatric lead in the assessment and management of children with severe asthma requiring biologicals.

We identified three major areas for which action is needed. First, an evidence-driven decision tree is required to guide the choice between different biologicals. Although this exists for adolescents and adults, it is based mostly on adult data, and there is little to guide the choice of biologicals in younger children [8]. To date, there have been no published head-to-head studies, although the results of ongoing trials are awaited. Pharmacogenetic/epigenetics may indicate genes and/or epigenetic modifications associated with treatment response in asthma [9, 10].

Secondly, in order to make use of real-world comparative data, a set of parameters and markers to benchmark therapy success and define response is needed. The clinical parameters used by centres are still very broad, clinically oriented and nonspecific (table 1). While a need for harmonisation exists, patient and

family centred outcomes must also be considered. Artificial intelligence using pattern recognition and fuzzy logic approaches have been applied successfully for such decision-making, *e.g.* in diabetes [11, 12], and it may also help to guide the way in severe asthma.

Thirdly, we identified the need to investigate how and when to end treatment with biologicals, especially in children. Studies to address the issue appropriately in the context of a European network of centres such as established through the survey may be used to develop a set of rules to define the right time and parameters (including appropriate biomarkers) for such decisions.

In summary, substantial differences exist currently in the management of childhood severe asthma across Europe. The need for studies on biomarkers supporting the selection of biologicals, on criteria to assess therapy response to biologicals and on how to end biological therapy in stable patients became evident in this survey. Foremost, an urgent need was identified by clinicians for more collaboration in the field and harmonisation of healthcare structures to foster adequate access to biologicals for children with severe asthma in Europe.

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References

1 Lang A, Carlsen KH, Haaland G, *et al.* Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. *Allergy* 2008; 63: 1054–1060.
2 Nordlund B, Melén E, Schultz ES, *et al.* Prevalence of severe childhood asthma according to the WHO. *Respir Med* 2014; 108: 1234–1237.
3 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. www.ginasthma.org Date last accessed: 20 July 2020. Date last updated: 26 April 2021.
4 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.
5 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.
6 Golebski K, Kabesch M, Melén E, *et al.* PERMEABLE consortium. Childhood asthma in the new omics era: challenges and perspectives. *Curr Opin Allergy Clin Immunol* 2020; 20: 155–161.
7 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.
8 Gupta A, Pouliquen I, Austin D, *et al.* Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. *Pediatr Pulmonol* 2019; 54: 1957–1967.
9 Kabesch M, Tost J. Recent findings in the genetics and epigenetics of asthma and allergy. *Semin Immunopathol* 2020; 42: 43–60.
10 Perez-Garcia J, Espuela-Ortiz A, Lorenzo-Diaz F, *et al.* Pharmacogenetics of pediatric asthma: current perspectives. *Pharmgenomics Pers Med* 2020; 13: 89–103.
11 Dovc K, Piona C, Yeşiltepe Mutlu G, *et al.* Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapy in type 1 diabetes: a double-blind randomized crossover trial. *Diabetes Care* 2020; 43: 29–36.
12 Nimri R, Ochs AR, Pinsker JE, *et al.* Decision support systems and closed loop. *Diabetes Technol Ther* 2019; 21: S42–S56.