EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI WHITE PAPER

on Research, Innovation and Quality Care

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI White Paper

on Research, Innovation and Quality Care

Editors

Ioana Agache
Cezmi A. Akdis
Tomás Chivato
Peter Hellings
Karin Hoffman-Sommergruber
Marek Jutel
Antti Lauerma
Nikos Papadopoulos
Peter Schmid-Grendelmeier
Carsten Schmidt-Weber

Published by the European Academy of Allergy and Clinical Immunology

2018

EAACI EXECUTIVE COMMITTEE

BOARD OF OFFICERS

Ioana Agache, *President*
Peter Hellings, *Secretary General*
Marek Jutel, *Treasurer*
Carsten Schmidt-Weber, *Vice-President Congresses*
Peter Schmid-Grendelmeier, *Vice-President Education & Specialty*
Karin Hoffmann-Sommergruber, *Vice-President Communications & Membership*
Antonella Muraro, *Past President*

SECTION CHAIRPERSONS

Zuzana Diamant, *Asthma*
Knut Brockow, *Dermatology*
Philippe Gevaert, *ENT*
Jürgen Schwarze, *Basic & Clinical Immunology*
Montserrat Alvaro Lozano, *Pediatrics*
Ibon Eguiluz-Gracia, *Junior Members*

INTEREST GROUP REPRESENTATIVES

Oliver Pfaar
Maria Torres

MEMBERS AT LARGE

Antti Lauerma
Isabel Skypala
Stefano Del Giacco
Jose Maria Olaguibel
Liam O'Mahony
Susanne Lau

ADJUNCT MEMBERS

Anthony Frew, *Ethics Committee Chair*
Magdalena Czarnecka-Operacz, *CME Committee Chair*
Musa Khaitov, *Knowledge Exam Chair*
Roy Gerth van Wijk, *Specialty Committe Chair*
Frans Timmermans, *Patients Organisations Committee Chair*
M. Beatrice Bilo, *National Allergy Societies Committee Chair*
Susanne Halken, *Scientific Programme Coordinator*
Darío Antolín-Amérigo, *Newsletter Editor*
Tomás Chivato, *Science Committee Chair*
Edward Knol, *Scientific Media Editor*
Florin-Dan Popescu, *Social Media Editor*
Sylwia Smolinska, *Website Editor*
Peter Walther, *Executive Director*

CONTRIBUTORS

Ioana Agache
Faculty of Medicine, Department of Allergy and Clinical Immunology, Transylvania University of Brasov, Romania

Mubeccel Akdis
Swiss Institute of Allergy and Asthma Research, University of Zürich, Davos, Switzerland

Cezmi A. Akdis
Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich;
Christine Kühne - Center for Allergy Research and Education, Davos, Switzerland

Montserrat Alvaro
Paediatric Allergy and Clinical Immunology Section, Hospital Sant Joan de Deu, Universitat de Barcelona, Barcelona, Spain

Liz Angier
Southampton University, Southampton, UK

Isabella Annesi-Maesano
Sorbonne Université, INSERM, IPLESP, Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Saint-Antoine Medical School, Paris, France

Darío Antolín-Amérigo
Allergy Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

Marina Atanaskovic-Markovic
University Children's Hospital of Belgrade, Faculty of Medicine, University of Belgrade, Serbia

Claus Bachert
Upper Airways Research Laboratory (URL), Ghent University Hospital, Ghent, Belgium

Jean-Pierre Besancenot
Réseau National de Surveillance Aérobiologique (RNSA), Brussieu, France

M. Beatrice Bilò
Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti, Ancona, Italy

Leif Bjermer
Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund, Sweden

Barbara Bohle
Institute of Pathophysiology and Allergy Research, Medical University of Vienna, Vienna, Austria

Matteo Bonini
National Heart and Lung Institute;
Royal Bromton Hospital & Imperial College London, UK

Sergio Bonini
Department of Clinical and Experimental Medicine, University of Campania Luigi Vanvitelli, Naples, Italy

Jean Bousquet
MACVIA-France, European Innovation Partnership on Active and Healthy Ageing Reference Site

Knut Brockow
Department of Dermatology and Allergology, Technical University of Munich, Munich, Germany

Giorgio Walter Canonica
Personalized Medicine Asthma & Allergy Clinic, Humanitas University & Research Hospital, Milano, Italy

Tomas Chivato
School of Medicine CEU San Pablo of Madrid, Madrid, Spain

Mariana Couto
Allergy Unit, Hospital & Instituto CUF Porto, Portugal
Faculty of Medicine, University of Porto

Ignacio Dávila
School of Medicine, Salamanca, Spain;
Allergy Service, University Hospital, Salamanca, Spain;
Institute of Biomedical Research of Salamanca, Spain

Stefano del Giacco
Allergy & Clinical Immunology, Department of Medical Sciences and Public Health, University of Cagliari, Italy

Zuzana Diamant
Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund, Sweden;
Department of Clinical Pharmacy & Pharmacology and Dept of General Practice, UMCG, Groningen, The Netherlands

CONTRIBUTORS

George du Toit
Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, MRC & Asthma Centre in Allergic Mechanisms of Asthma, King's College London, London, UK;
St Thomas NHS Foundation trust, London, UK

Stephen Durham
National Heart and Lung Institute, Imperial College, London, UK

Bernadette Eberlein
Department of Dermatology and Allergy Biederstein, Technische Universität München, Germany

Ibon Eguiluz-Gracia
Allergy Unit and Allergy Research Laboratory, Regional University Hospital of Malaga and Biomedical Research Institute of Malaga (IBIMA), Malaga, Spain

Philippe Eigenmann
University Hospitals of Geneva and Medical School of the University of Geneva, Geneva, Switzerland

María M Escribese
Faculty of Medicine, IMMA Applied Molecular Medicine Institute, CEU San Pablo University, Madrid, Spain

Jean Luc Fauquert
CHU Clermont-Ferrand, Pole pédiatrique, Unité d'allergologie de l'enfant, CHU Estaing, Clermont-Ferrand, France

Wytske Fokkens
Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands

Ru-Xin Foong
Division of Asthma, Allergy and Lung Biology, Department of Paediatric Allergy, King's College London, UK;
Guy's and St. Thomas' NHS Foundation Trust, London, UK

Paweł Gajdanowicz
Department Bioquímica y Biología Molecular, Fac. CC. Químicas, Universidad Complutense de Madrid, Madrid, Spain

Jon Genuneit
Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

Roy Gerth van Wijk
Section of Allergology, department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

Philippe Gevaert
Department of Otorhinolaryngology, Ghent University

Korneliusz Golebski
Department of Experimental Immunology, Academic Medical Center, Amsterdam

Clive Grattan
Norfolk & Norwich University Hospital and St John's Institute of Dermatology, Norfolk, UK

Kate Grimshaw
Clinical and Experimental Sciences and Human Development and Health Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK

Tari Haahtela
Inflammation Centre, Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland

Peter Hellings
Laboratory of Experimental Immunology, University Hospitals Leuven, Belgium

Karin Hoffmann-Sommergruber
Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

Stephanie Hofmaier
Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - University Medicine Berlin, Germany

María Isidoro-García
Molecular Genetics and Pharmacogenetics Unit, University Hospital of Salamanca, Spain;
Director of the Immunoallergy Research Laboratory, University Hospital of Salamanca, Spain;
Coordinator of the Reference Unit of Rare Diseases, DiERCyL, University Hospital of Salamanca, Spain;
Institute of Biomedical Research of Salamanca, IBSAL, Spain;
Adjunt Professor of Molecular Medicine, University of Salamanca, Spain

CONTRIBUTORS

Lars Jacobsen
Allergy Learning and Consulting, Copenhagen, Denmark

Marek Jutel
Wroclaw Medical University, Department of Clinical Immunology, Wrocław, Poland;
ALL-MED Medical Research Institute, Wroclaw, Poland

Ludger Klimek
Center for Rhinology and Allergology, Wiesbaden, Germany.

Edward Knol
Departments of Immunology and Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

Asya Kudryavtseva
Department of children diseases, The I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Susanne Lau
Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany

Antti Lauerma
Inflammation Centre, Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland

Paolo Matricardi
Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - University Medicine Berlin

Cinzia Milito
Department of Molecular Medicine, Sapienza University of Rome, Italy

Charlotte Mørtz
Department of Dermatology and Allergy Centre, Odense Research Center for Anaphylaxis, Odense University Hospital, Odense C, Denmark.

Ralph Mösges
Institute of Medical Statistics, Informatics and Epidemiology, Medical Faculty, University at Cologne, Cologne, Germany

Antonella Muraro
Department of Women and Child Health, Padua General University Hospital, Padua, Italy

Liam O'Mahony
Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

Mikaela Odemyr
European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Brussels, Belgium

Jose M Olaguibel
Servicio de Alergología, Complejo Hospitalario de Navarra, Pamplona, Spain

Markus Ollert
Department of Infection and Immunity, Luxembourg Institute of Health (LIH), Luxembourg

Susanna Palkonen
European Federation of Allergy and Airways Diseases Patients' Associations (EFA), Brussels, Belgium

Oscar Palomares
Dept Bioquímica y Biología Molecular, Fac. CC. Químicas, Universidad Complutense de Madrid, Madrid, Spain

Nikolaos G. Papadopoulos
Division of Infection, Immunity & Respiratory Medicine, University of Manchester, UK

Oliver Pfaar
Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;
Center for Rhinology and Allergology, Wiesbaden, Germany

Isabella Quinti
Department of Molecular Medicine, Sapienza University of Rome, Italy

Santiago Quirce
Dept of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Monika Raulf
Department of Allergology/Immunology, Institute for Prevention and Occupational Medicine of the German, Social Accident Insurance, Institute of the Ruhr-University Bochum, Bochum, Germany

Johannes Ring
Department of Dermatology and Allergy Biederstein, Technische Universität München, München, Germany

CONTRIBUTORS

Peter Schmid-Grendelmeier
University Hospital of Zürich and Allergy Campus Davos, Switzerland

Carsten Schmidt-Weber
Center of Allergy and Environment (ZAUM), Technical University and Helmholtz Center Munich, München, Germany

Jürgen Schwarze
University of Edinburgh, Edinburgh, UK

Mohamed H Shamji
Immunomodulation and Tolerance Group, Allergy and Clinical Immunology, Inflammation Repair & Development, MRC Asthma UK Centre Imperial College London, London, UK

Hans-Uwe Simon
University of Bern, Bern, Switzerland

Isabel Skypala
Royal Brompton Hospital, London, UK;
Imperial College, London, UK

Hermelijn H Smits
Leiden University Medical Center, Leiden, The Netherlands

Michel Thibaudon
Réseau National de Surveillance Aérobiologique (RNSA) , Brussieu, France

Frans Timmermans
Nederlands Anafylaxis Netwerk – European Anaphylaxis Taskforce, Dordrecht, The Netherlands

María José Torres Jaen
Unit of Allergic Diseases, Malaga Regional University Hospital;
Coordinator of the Spanish Allergy Network ARADyAL;
Malaga University ;
Andalusian Centre for Nanomedicine and Biotechnology-BIONAND

Claudia Traidl-Hoffmann
Institute of Environmental Medicine, UNIKA-T, Technical University Munich and Helmholtz Zentrum München - German Research Center for Environmental Health, Augsburg, Germany;
CK CARE – Christine Kühne Center for Allergy Research and Education, Davos, Switzerland

Erkka Valovirta
Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Turku, Finland;
Terveystalo Allergy Clinic, Helsinki, Finland

Paul van Cauwenberge
Ear-, Nose and Throat Dept, Gent University, Gent, Belgium

Cornelis van Drunen
Department of Otorhinolaryngology, Academic Medical Center, Amsterdam

Ronald van Ree
Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands

Susanne JH Vijverberg
Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Jolanta Walusiak-Skorupa
Department of occupational diseases and environmental health, Nofer Institute of Occupational Medicine, Lodz, Poland

Thomas Werfel
Division of Immunodermatology and Allergy Research, Department of Dermatology, Hannover Medical School, Hannover, Germany

Margitta Worm
Allergie-Centrum-Charité, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte, Universitätsmedizin Berlin, Berlin, Germany

Paraskevi Xepapadaki
Allergy Department, 2nd Pediatric Clinic, University of Athens, Greece

CONTENTS

CONTENTS

CONTENTS

FOREWORD

The European Academy of Allergy and Clinical Immunology (EAACI) is the leading scientific and professional organization in the field of allergy and clinical immunology, promoting excellence in patient care, basic and translational research, education and communication of research findings.

EAACI provides an ideal platform for the collaboration and harmonization of the efforts of all stakeholders including patient organizations and health policy makers, involved in translation of basic and clinical research into optimal care for patients with allergy and asthma and other immune-mediated diseases. The research-innovation-quality care nexus is increasingly emphasized and prioritized as a framework to deal with complex socio-environmental problems impacting the increase in the burden of allergic diseases and asthma.

Quality healthcare is key to achieve better quality of life as perceived by an individual. It is the major political issue and in many countries healthcare delivery organizations are part of the national identity. Performance outcome measures are important and the most effective and meaningful measures can only be elaborated through the close collaboration of patients, health care providers, and policy makers.

EAACI believes it is the time for a major revision in every aspect of the healthcare ecosystem, where governments, academia, enterprises and individuals, are actively involved in improving care pathways.

Published by the European Academy of Allergy and Clinical Immunology, the White Paper on Research, Innovation and Quality Care has the following 3 major aims:

1. to present a critical appraisal of allergic diseases and asthma landscape in Europe along with an informed analysis of future trends,
2. to set the quality standards and to provide guidance and training for allergy practice and research;
3. to identify and promote research priorities and better research funding in allergy, asthma and clinical immunology.

Covering risk factors, major diseases, development of healthcare, training and growth of patients' support organisations, the White Paper provides a series of policy recommendations to ensure and improve the future care of allergy, asthma and other immunological diseases. It is meant to provide guidance for daily practice and to define research needs. It will also serve as an advocacy tool for health professionals, policymakers, patients and media.

The White Paper is a collaborative effort of the whole EAACI family i.e. Sections, Interest Groups, Working Groups and patient organisations. Each group prepared a chapter related to their specific expertise. The Editors appreciate the efforts of the section authors in the preparation of this document, which represents the true voice of our Academy and believe that the readers will share their enthusiasm of its' content and value for the allergy, asthma and clinical immunology fields.

EAACI White Paper Editors

Ioana Agache, Cezmi A. Akdis Tomás Chivato, Peter Hellings, Karin Hoffman-Sommergruber, Marek Jutel, Antti Lauerma, Nikos Papadopoulos, Peter Schmid-Grendelmeier, Carsten Schmidt-Weber

A

ADDRESSING THE GAPS IN THE EPIDEMIOLOGY AND RISK FACTORS OF ALLERGIC DISEASES

Jon Genuneit, Ralph Mösges, Markus Ollert

EPIDEMIOLOGY, REGISTRIES, BIG DATA

A 1

DISEASE EPIDEMIOLOGY

GAPS IN KNOWLEDGE

Numerous epidemiological studies on risk and protective factors have produced a large body of evidence that is difficult to grasp for decision makers, stakeholders, and even researchers themselves.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

While well-designed original studies remain at the core of evidence generation, systematic reviews become more and more important to keep track of the evidence, to prevent redundancy, and to provide comprehensive summaries. Comprehensive overviews, conducted by an EAACI Task Force, have documented the growing number of systematic reviews in allergy epidemiology and the research topics they have covered. Research priorities may fall into topics not yet covered or covered less well. Moreover, methodological and reporting quality of a significant portion of the identified systematic reviews was low calling for improvement in future work.

PATIENTS REGISTRIES

GAPS IN KNOWLEDGE

For the more common allergic diseases, like asthma, allergic rhinitis, and atopic eczema, patient registries are faced with problems pertaining to coverage since the patients are treated by many doctors of different specialty and because mild cases may not seek regular health care contact. Although there are several examples of registries, like ANAPHYLAXIE.net, most pertain to the more severe spectrum of selected allergic diseases.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

It is important to overcome the limitation of registries by inclusion of mild cases if feasible. Due to the often limited data that can be acquired in registries, focus should be on a consensus for core items across registries to enable data sharing and pooling for full synergy as exercised by the TREAT Registry Taskforce for atopic eczema.

BIG DATA

GAPS IN KNOWLEDGE

Beyond building on previous evidence and trying to accumulate patient registries, modern technology has enabled ascertainment of big data, that is high-dimensional information on each observational unit generated by using, e.g., "omics"-technologies or time-series of sensor-based measurements.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

While exploitation of "omics"-data of a single type, e.g. in genome-wide association studies has already enabled identification of key determinants of allergic diseases, recent advances in network biology and network analysis open up new avenues to predict key drivers of a given biological process or cellular function.

A roadmap using "omics"-technologies towards personalized therapeutic approaches in allergic diseases includes not only scientific and clinical issues, but also big-data management, legal, and regulatory aspects. Among others, multilayer "omics" analysis along longitudinal cohort studies are desperately required to simultaneously obtain various types of reliable biomarkers.

One of the essential barriers that should be overcome in the near future is to translate patients' subgroup stratification to personalized treatment.

FURTHER READING

1. Genuneit J, Seibold AM, Apfelbacher CJ, Konstantinou GN, Koplin JJ, La Grutta S et al. Overview of systematic reviews in allergy epidemiology. *Allergy* 2017;72:849-856.
2. Genuneit J, Seibold AM, Apfelbacher CJ, Konstantinou GN, Koplin JJ, La Grutta S et al. The state of asthma epidemiology: an overview of systematic reviews and their quality. *Clin Transl Allergy* 2017;7:12.
3. Gerbens LA, Boyce AE, Wall D, Barbarot S, de Booij RJ, Deleuran M et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema registries. *Trials* 2017;18:87.
4. He FQ, Ollert M. Network-Guided Key Gene Discovery for a Given Cellular Process. In: . Advances in Biochemical Engineering/Biotechnology. Springer, Berlin, Heidelberg, 2016.
5. Delhalle S, Bode SFN, Balling R, Ollert M, He FQ. A roadmap towards personalized immunology. *NPJ Syst Biol Appl* 2018;4:9.

María Isidoro-García, Ignacio Dávila

GENETICS AND EPIGENETICS: NEW CHALLENGES IN ALLERGY

A2

GAPS IN KNOWLEDGE

The vertiginous development of high-throughput technologies has led to a new and promising "omics" era for the understanding of complex diseases such as allergic diseases.

Genomics has allowed the identification of genetic associations through GWAs studies. Nevertheless, their contribution to elucidate the etiopathogenesis of allergy has been limited so far.

As complex diseases, environmental factors also influence allergic diseases. Epigenetics is considered a link that integrates both genetic and environmental factors. Methylation, histone modifications and RNAs as regulator mechanism are main epigenetic factors. Specific epigenomic patterns of methylation have been previously reported in allergic patients as well as studies in the histone code and studies focused on RNAs. miRNAs are the most well known in asthma and respiratory diseases, showing different profiles of bronchial expression in patients. Nevertheless, the results are not yet conclusive.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Next Generation Sequencing has emerged with enormous potential, since whole sequencing of the genome will soon be available in clinical laboratories, overcoming the limitation of an a priori selection of genetic variants. New and more powerful collaborative gene-environment interaction studies using Next Generation Sequencing should be developed.

The introduction of nanopores as an imminent technological advance opens enormous expectations in the massive sequencing applied to the analysis of single cell or a population of cells. Thus, the introduction of nanotechnology in the study of allergic diseases should be encouraged.

Mapping the complex interactions to interrogate the histone-code hypothesis will contribute to understand the molecular mechanisms involved in the regulation of expression. In this sense, new locus-specific imaging methods such as chromatin *in vivo* assays will be of great help.

Transcriptomics will provide not only specific patterns of coding transcripts but also differential

expression of non-coding RNAs. It is also necessary to explore other ncRNA in order to support future treatments based on gene therapy. The potential of CRISPER CAS9 technology for functional screening should be explored.

Exosomes held promise as biomarkers and potential therapeutic tools.

Although proteomics or metabolomics are also largely promising, the real breakthrough in this era will be the whole integration in Systems Biology. Integration of phenotypic and genotypic information for a better characterization of patients is demanded. To manage the huge amount of data generated, really powerful bioinformatic approaches will be needed.

Systems Biology will allow the real application of Precision Medicine. Allergy has the advantage of being one of the first specialties that used personalized medicine to tailor allergen immunotherapy.

Pharmacogenomics will also contribute to the application of Personalized Medicine by predicting individual therapy responses based on the patient's genetic background. Pharmacogenetics should include not only pharmacokinetic factors to identify metabolizing mechanisms but also pharmacodynamics. The development of new biological therapies requires the identification of pharmacodynamics targets to predict the patient´s response.

Finally, the recent identification of the interstitium as a new organ with potential for direct sampling as a diagnostic tool, if confirmed, opens an exciting path to be explored in allergy.

In summary, the information obtained by systems biology combined with epigenetic analysis related to environmental factors in a pharmacoepigenomic approach will provide a deeper insight to improve not only our knowledge about allergic diseases, but also the translation from bench to bed, thus progressing to an effective Precision Medicine in the clinical management of the allergic patient.

FURTHER READING

1. Benias PC, Wells RG, Sackey-Aboagye B, Klavan H, Reidy J, Buonocore D et al. Structure and Distribution of an Unrecognized Interstitium in Human Tissues. *Sci Rep* 2018;8:4947.
2. Brook PO, Perry MM, Adcock IM, Durham AL. Epigenome-modifying tools in asthma. *Epigenomics* 2015;7:1017-1032.
3. García-Sánchez A, Isidoro-García M, García-Solaesa V, Sanz C, Hernández-Hernández L, Padrón-Morales J et al. Genome-wide association studies (GWAS) and their importance in asthma. *Allergol Immunopathol (Madr)* 2015;43:601-608.
4. Isidoro-García M, Sánchez-Martín A, García-Sánchez A, Sanz C, García-Berrocal B, Dávila I. Pharmacogenetics and the treatment of asthma. *Pharmacogenomics* 201718:1271-1280.
5. Pascual M, Roa S, García-Sánchez A, Sanz C, Hernandez-Hernandez L, Greally JM et al. Genome-wide expression profiling of B lymphocytes reveals IL4R increase in allergic asthma. *J Allergy Clin Immunol* 2014;134:972-975.
6. Sastre B, Cañas JA, Rodrigo-Muñoz JM, Del Pozo V. Novel Modulators of Asthma and Allergy: Exosomes and MicroRNAs. *Front Immunol* 2017;8:826.
7. Sendín-Hernández MP, Ávila-Zarza C, Sanz C, García-Sánchez A, Marcos-Vadillo E, Muñoz-Bellido FJ et al. Cluster Analysis Identifies 3 Phenotypes within Allergic Asthma. *J Allergy Clin Immunol Pract* 2018;6:955-961.e1.
8. Simeonov DR, Gowen BG, Boontanrart M, Roth TL, Gagnon JD, Mumbach MR et al. Discovery of stimulation-responsive immune enhancers with CRISPR activation. *Nature* 2017;549:111-115.
9. Yang IV, Lozupone CA, Schwartz DA. The environment, epigenome, and asthma. *J Allergy Clin Immunol* 2017;140:14-23.

Tomas Chivato, Cornelis van Drunen, Hans-Uwe Simon,
María M Escribese, Korneliusz Golebski

THE METABOLOME, TRANSCRIPTOME, AND PROTEOME

A3

GAPS IN KNOWLEDGE

Allergic diseases have suffered a steadily increase in developed societies. Roughly affecting more than a quarter of the population, severe allergic pathologies and associated co-morbidities are increasingly common. Therefore, in a near future, the economic impact of allergy might reach a non-maintainable cost. Consequently, it is pivotal to unravel the mechanisms involved in this process to develop new diagnosis, intervention, and prevention strategies. However, one of the main problems found in the quest of these new strategies is the difficulty of having adequately clinically stratified patients that can be used for the development of accurate models.

The approaches that allow us to build a detailed picture of the workings of cellular processes of heath and disease are collectively known as OMICS technologies. Depending on whether the emphasis is on the genetic code of the DNA, the transcribed genes and the proteins derived from these genes, or some of the functional consequences of these proteins, these technologies are aptly named genomics, transcriptomics, proteomics, or metabolomics.

Application of these technologies can have a direct clinical benefit when used to diagnose a particular disease, to predict the natural course of the disease, or to help determine the efficacy of different treatment options. The indirect clinical benefits come from a better and detailed understanding of a disease or some pathophysiological process underlying a disease as this in due course could lead to the development of better diagnostic tools or new treatment options.

Although these technologies can provide a detailed understanding of the biological process in a single cell, in order to fully understand a disease or an underlying pathophysiological process, we would need to understand the interaction between multiple cell types and the interaction between these cells and the external and internal environment.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Technological advances will drive the OMICS world forward allowing higher throughputs, improved detection limits, and better software tools for the analysis and visualization of data. However, the experimental design needs to consider the strengths and weaknesses of the individual OMICS technologies. This is best served by development of appropriate models and extensive integration at multiple levels:

- Establish clear and objective clinical models with well-defined extreme phenotypes that will allow a better understanding of the inflammatory progression along the disease severity.
- Consider experimental models that mimic the interaction between different cell types or between the environment and the immune system.
- Identify the optimal biological sample and the use of each OMIC technique.
- Develop multi-OMIC integration platforms that will significantly improve our knowledge regarding the underlying mechanisms of allergic inflammations.
- Screening of mutations in coding regions or regulatory elements of genes must be combined with an investigation into the functional consequences: changes in transcription/splicing variants and functional activity of the protein.
- When a single cell type is under investigation, consider comparing different related diseases and/or anatomical locations where this cell type could play a role. Always do a direct comparison with the role of this cell type under homeostatic/healthy conditions.

FURTHER READING

1. Villaseñor A, Rosace D, Obeso D, Pérez-Gordo M, Chivato T, Barbas C et al. Allergic asthma: an overview of metabolomic strategies leading to the identification of biomarkers in the field. *Clin Exp Allergy* 2017;47:442-456.
2. Delhalle S, Bode SFN, Balling R, Ollert M, He FQ. A roadmap towards personalized immunology. *NPJ Syst Biol Appl* 2018;4:9.
3. Benson M. Clinical implications of omics and systems medicine: focus on predictive and individualized treatment. *J Intern Med* 2016;279:229-240.
4. Mak AC, White MJ, Eckalbar WL, Szpiech ZA, Oh SS, Pino-Yanes M et al. NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Whole Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma. Am J Respir Crit Care Med *2018* doi: 10.1164/rccm.201712-2529OC. [Epub ahead of print]

Ru-Xin Foong, George du Toit

THE EXPOSOME IN ALLERGY AND ASTHMA: EARLY LIFE EVENTS

A4a

GAPS IN KNOWLEDGE

The link between atopic diseases in childhood is well known and a concept commonly referred to as the 'atopic march'. The trajectory of allergic disease often begins in infancy with eczema and may be followed by the development of food allergies, then rhinoconjunctivitis and later in childhood asthma. There have been studies that suggest that children who develop eczema and allergic sensitization are at significantly greater risk of developing asthma later in childhood. The exact mechanism of how allergic disease develops is yet to be determined. There is emerging evidence that suggests that maternal allergen consumption before and/or during pregnancy may also have an impact on the development of allergic diseases in their children. With the rising prevalence of allergy worldwide, focus has shifted towards early allergen exposure and the possibility of tolerance as a means of preventing the development of allergic diseases.

Early life events have already been a targeted area for researchers when looking at strategies of the prevention of allergic disease which is a change from the historical approach of allergen avoidance. There has been evidence to suggest that breastfeeding reduces the risk of asthma in childhood (5-18 years) and may also reduce the risk of eczema up to 2 years and allergic rhinitis up to 5 years of age. An area of focus has also been in the development of eczema and subsequent food allergy sensitization via barrier disruption in both the skin and gut. There has been success with the application of emollients for the prevention of eczema in infants. The identification of environmental factors such as length of gestation, mode of delivery, type of feeding and early exposure to antibiotics, on the composition of gut microbiome in relation to eczema has also been researched to identify potential targets to help reduce the development of allergic diseases. More recently, a shift from allergen avoidance to tolerance induction through early introduction of allergenic foods has occurred based on several randomised controlled prevention trials which have exposed infants to allergens and demonstrated a protective effect (for peanut, and hens egg) in the development of food allergy.

Research priorities

- For additional randomised controlled trials are required to further assess early exposure to common and multiple food allergens (i.e. peanut, egg, cow's milk, soya, wheat) for the prevention of food allergies via tolerance induction including follow-on studies of these cohorts. Study designs should consider the effect of intervention during all early life time intervals from pre-conception, gestation, birth mode, and early childhood.
- For studies to formally assess the uptake and efficacy of contemporary prevention guidelines in both high risk and unselected children in those countries where they have been applied.
- For additional randomised controlled trials looking at both oral and sublingual immunotherapy as treatment for food allergy (i.e. desensitization strategies) in various age groups. Variability of the treatment regimens and use of those biologicals agents that may improve uptake and persistence of treatment benefit should also be formally assessed in these trials.
- For additional trials focussing on prevention of allergic disease targeting factors influencing the skin and gut barrier (i.e. use of topical emollients, probiotics, environmental influences on gut microbiome) and follow on effects:
  - » More specifically, research of early treatment interventions for prevention of eczema (i.e. use of biologics such as dupilumab) to see if these agents either directly or indirectly reduce other allergic diseases including asthma in children.
- For the development of future strategies to target treatment of children at high risk of developing allergic disease (i.e. early sensitization on allergic testing prior to introduction of foods or severe eczema in early infancy).

Standards and qualities of care

ASTHMA

- International Consensus on (ICON) Paediatric Asthma 2012
- EAACI position statement on asthma exacerbations and severe asthma (2013)

ECZEMA

- EAACI/AAAAI/PRACTALL Consensus Report 2006
- Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I

FOOD ALLERGY

- **EAACI current recommendations for the primary prevention of food allergy 2014:**
  - » There is no special diet required during pregnancy or for the lactating mother for all infants
  - » All infants should be exclusively breastfed for 4-6 months. If breastfeeding is insufficient or not possible, infants at high-risk (of allergy) can be recommended a hypoallergenic formula with a documented preventative effect for the first 4 months
  - » There is no need to avoid introducing complementary foods beyond 4 months and currently the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced irrespective of atopic heredity.
- **Additional Society and Country-specific guidelines have also recently been updated:**
  - » US NIAID Guidelines for prevention of peanut allergy
    - Children with severe eczema, egg allergy or both should have testing (specific IgE and/or skin prick tests) and for introduction from 4-6 months age based on test results
    - Children with mild to moderate eczema should have age-appropriate peanut-containing food introduced around 6 months of age
    - Children with no eczema or food allergy - for introduction of age-appropriate peanut-containing foods into the diet freely with other solid foods.
  - » UK Scientific Advisory Committee on Nutrition/Committee on Toxicity Guidelines on the timing of introduction of allergenic foods into the infant diet
  - » Australasian Society of Clinical Immunology and Allergy (ASCIA) - https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_infant_feeding_and_allergy_prevention.pdf

» Canadian Society of Allergy and Clinical Immunology - http://foodallergycanada.ca/wp-content/uploads/FAQs-for-early-infant-feeding-guidelines.pdf

» Guidance in the context of resource-constrained settings - http://www.jacionline.org/article/S0091-6749(16)31287-8/pdf

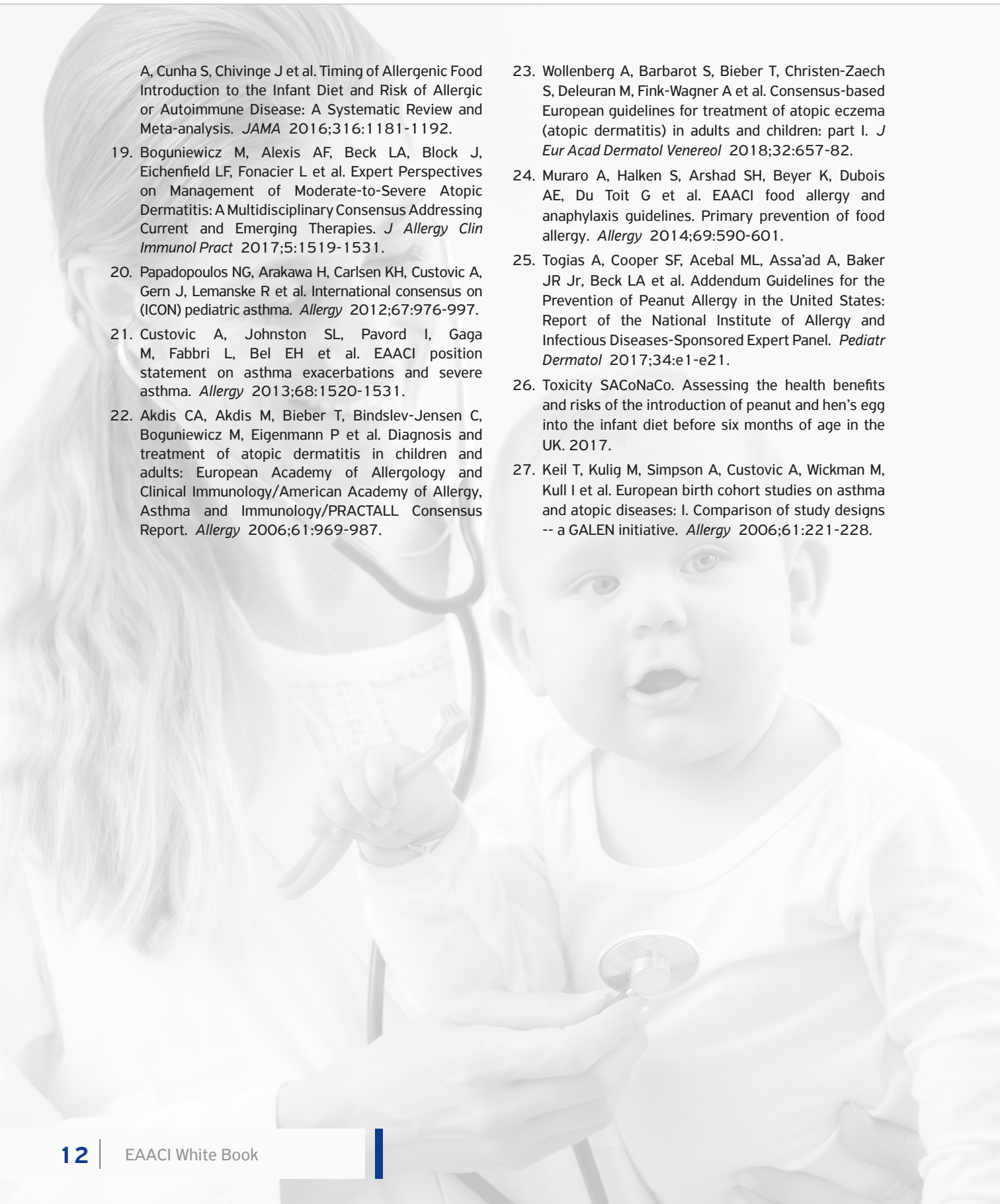
» World Allergy Organization (WAO) Food Allergy - http://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/food-allergy

Innovative approach

Further collaborative work amongst European centres such as the European birth cohort studies on asthma and allergy in the GA2LEN network to collectively research the prevention and treatment of atopic diseases using rigorous study methodologies through early life interventions.

FURTHER READING

1. LEAP (Learning Early About Peanut) and LEAP-On Studies, http://www.nejm.org/doi/full/10.1056/NEJMoa1414850#t=article; http://www.nejm.org/doi/full/10.1056/NEJMoa1514209.
2. EAT (Enquiring About Tolerance) study, http://www.nejm.org/doi/full/10.1056/NEJMoa1514210#t=article.
3. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic and Autoimmune Disease: A systematic review and meta-analysis. Link to full text - https://jamanetwork.com/journals/jama/fullarticle/2553447.
4. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013;6:21.
5. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta paediatrica* 2015;104:38-53.
6. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WYW, Subbarao P et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. *J Allergy Clin Immunol* 2018;141:601-607.e8.
7. Campbell DE, Boyle RJ, Thornton CA, Prescott SL. Mechanisms of allergic disease - environmental and genetic determinants for the development of allergy. *Clin Exp Allergy* 2015;45:844-858.
8. Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC. Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. *JAMA Pediatr* 2014;168:156-162.
9. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA Jr et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol* 2014;133:1373-1382.
10. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014;7:12.
11. Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int* 2018;67:24-31.
12. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014;134:824-830 e6.
13. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;134:818-823.
14. Chan CW, Wong RS, Law PT, Wong CL, Tsui SK, Tang WP et al. Environmental Factors Associated with Altered Gut Microbiota in Children with Eczema: A Systematic Review. *Int J Mol Sci* 2016;17. pii: E1147.
15. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-813.
16. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. *N Engl J Med* 2016;374:1435-1443.
17. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med* 2016;374:1733-1743.
18. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome



A, Cunha S, Chivinge J et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. *JAMA* 2016;316:1181-1192.

19. Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L et al. Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies. *J Allergy Clin Immunol Pract* 2017;5:1519-1531.
20. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R et al. International consensus on (ICON) pediatric asthma. *Allergy* 2012;67:976-997.
21. Custovic A, Johnston SL, Pavord I, Gaga M, Fabbri L, Bel EH et al. EAACI position statement on asthma exacerbations and severe asthma. *Allergy* 2013;68:1520-1531.
22. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy* 2006;61:969-987.
23. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol* 2018;32:657-82.
24. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590-601.
25. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR Jr, Beck LA et al. Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-Sponsored Expert Panel. *Pediatr Dermatol* 2017;34:e1-e21.
26. Toxicity SACoNaCo. Assessing the health benefits and risks of the introduction of peanut and hen's egg into the infant diet before six months of age in the UK. 2017.
27. Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs -- a GALEN initiative. *Allergy* 2006;61:221-228.

Mariana Couto, Asya Kudryavtseva,
Matteo Bonini, Stefano del Giacco

THE EXPOSOME IN ALLERGY AND ASTHMA: DIET, NUTRITION, LIFESTYLE, SOCIAL AND PSYCHOLOGICAL FACTORS, CITY PLANNING AND SOCIAL DETERMINANTS OF HEALTH. THE FUNCTIONAL PHENOTYPE

A4b

GAPS IN KNOWLEDGE

Along with known internal and external factors, such as the atopic predisposition and individual immune system reactions, environmental factors have an impact on the development of allergic disorders. Rapid changes in the modern environment are intertwined with immune health through synergistic biological, psychological, social, and ecological factors. The cumulative measure of environmental influences and associated biological responses throughout life is termed the "exposome." (Figure 1). This includes external factors such as the environment, diet, behavior, social influences and infections, as well as cumulative biological responses to exposures and endogenous processes. The concept of "exposome" includes 3 types of exposures: (1) the general environment, including urban or rural residence, climate, air pollution, education; (2) the specific external environment, including diet, physical activity, tobacco exposure, infection, occupation; (3) the internal body environment (Box 1).

Specific living conditions in childhood, as well as the psychological maturity of mothers, who provide multisensory stimulation vital to the child's psychological development, may influence the risk of allergy onset and progression. Studies have shown the presence of CRF1 receptors on mast cells, structurally similar with CNS receptors. The role of neurogenic inflammation in forming skin, intestinal and airway barriers has been also recognized. Given this close relationship, it has been proposed that the characterization of asthma phenotypes should include functional differences in affective neural circuits, the so-called "neurophenotypes". However, studying neuropeptides role in allergic inflammation is still ongoing.

Furthermore, indoor and outdoor air pollutants have shown to promote the onset of atopic disease. Both traffic-related air pollution and environmental tobacco smoke negatively affect lung development and function. Children and adolescents living in low-income urban communities are at disproportionate risk for severe asthma and present increased cytokines from peripheral blood lymphocytes.

A significant gap exists between the current understanding of disease risk and active measures to alter these exposures affecting health. Increasing evidence supports the important, but not exclusive, role of allergy in severe asthma. Early atopic sensitization is critical in determining the severity of disease later in life. Mechanistic implications of interacting cofactors, such as virus infections, pollution, smoking and work-related exposures, need to be completely uncovered to allow novel therapeutic targets.

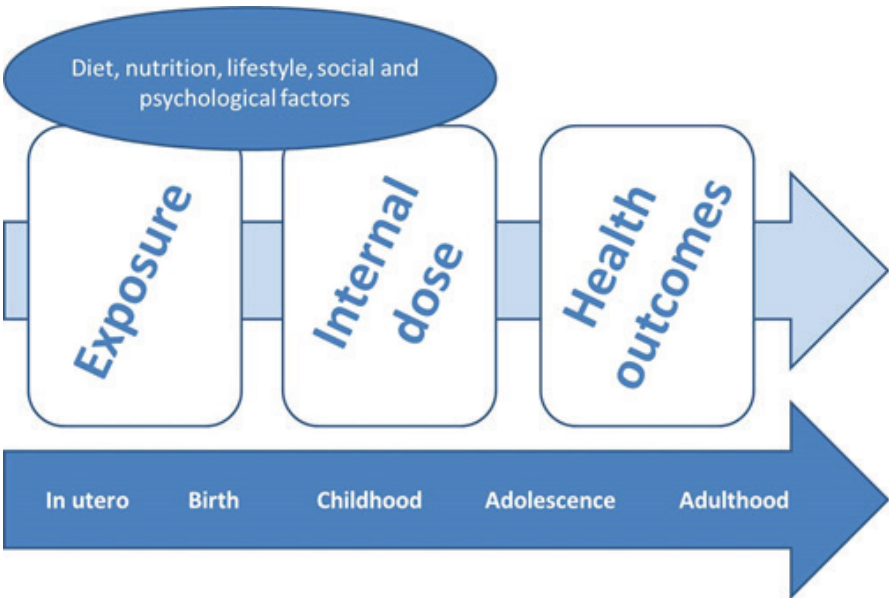


Figure 1. The cumulative environmental influence and associated biological responses throughout life.

Box 1. Different exposures that may affect allergic disease development *

Microbiome	Mode of delivery
	Early life diet
	External environmental biodiversity exposures
	Pre and postnatal antibiotic exposure
Allergens	Dust mites
	Cockroach
	Molds
	Pets
	Mice
Air pollution	Industrial pollution
	Traffic-related air pollution
	Environmental tobacco smoke
	Second-hand smoke
Others	Diet
	Obesity
	Physical activity
	Socioeconomic status
	Psychosocial stressors

**Different exposures that may affect allergic disease development. These exposures have been artificially subdivided in this table for the purpose of better understanding, but actually these and many others interact simultaneously with each other and interfere with allergic disease*

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Exposome-focused projects are needed to examine the complex interplay of environment and genetics to determine the most cost-effective interventions for reducing the risk of allergic disease. A key challenge is to learn the types of exposures, potential interactions, and the exact timings and amounts that impact health.

The minimum air quality standards to prevent detrimental effects on lung development and atopic disease and the timing (i.e. prenatal, first year of life, or cumulative lifetime exposure) when the subjects are most susceptible to air pollution should be identified. Personalized interventions and efficient city planning can be developed to reduce the risks associated with pollution exposure.

Innovative approaches may include: geographic information, system-based pollutant models and personal remote sensing devices and applications for smartphones to monitor and record personal exposures; electronic medical records to access lifelong exposure information and computer search engines to analyze information; innovative methods for chemical measurements using high-resolution mass spectrometry; computer-based models and predictions to combine the cumulative exposures with personal genomics therefore helping to guide healthy choices for diet, exercise, and health behaviors.

Once key exposures and potential interventions are identified, a comprehensive approach among clinicians, patients, health care organizations, insurance providers, government agencies, and urban planners must be undertaken to establish cost-effective primary and secondary prevention strategies to reduce these risks and promote wellness.

FURTHER READING

1. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. *J Allergy Clin Immunol* 2017;140:1-12.
2. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: Early-life events and immune development in a changing world. *J Allergy Clin Immunol* 2017;140:24-40.
3. Holland N. Future of environmental research in the age of epigenomics and exposomics. *Rev Environ Health* 2017;32:45-54.
4. Del Giacco SR, Bakirtas A, Bel E, Custovic A, Diamant Z, Hamelmann E et al. Allergy in severe asthma. Allergy 2017 Feb;72:207-220.
5. Galli SJ. Toward precision medicine and health: Opportunities and challenges in allergic diseases. *J Allergy Clin Immunol* 2016;137:1289-1300.
6. Rappaport SM. Genetic Factors Are Not the Major Causes of Chronic Diseases. *PLoS One* 2016;11:e0154387.
7. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional Brain Imaging of the Interaction between Emotion and inflammation in asthma. *PLoS One* 2012;7:e40921.
8. Letourneau NL, Kozyrskyj AL, Cosic N, Ntanda HN, Anis L, Hart MJ et al. Maternal sensitivity and social support protect against childhood atopic dermatitis. *Allergy Asthma Clin Immunol* 2017;13:26

Michel Thibaudon, Jean-Pierre Besancenot

THE EXPOSOME IN ALLERGY AND ASTHMA: INDOOR AND OUTDOOR ENVIRONMENT

A4c

Allergy is the fourth chronic disease in the world and respiratory allergies rank first among infant chronic diseases (WHO). The environment is a major source of the allergens. Indoor, the allergens are especially house dust mites (*Dermatophagoides pteronyssinus* and *farinæ*), storage mites, pet dander and fungal spores. Outdoor, the main allergens are pollen and fungal spores.

GAPS IN KNOWLEDGE

The different networks set up to monitor the outdoor allergen exposure and to produce information on the allergy risk due to the airborne particles are changing deeply:

- Aerobiological monitoring networks are becoming ever denser, especially for pollen, with more than 500 traps in Europe (figure 1). They follow at present a new European standard (EN TS 16868). The availability of long series enables to study the evolution in the last three decades of the main pollen and fungal spores under the combined influence of climate change (length of pollination, pollen index, transfer of the vegetation to the North and in altitude) and the chemical air pollution (exacerbation of symptoms, modification of the allergen content of biological particles).
- Exposure data can be cross-referenced with clinical data from sentinel physicians' networks or, in the last few years, with symptom load patient's networks. These last ones receive support from the new information technologies and are very important for doctors to better diagnose allergy, and for the patients to better manage their disease.
- Indoor biological particles samplers (impactors, cyclone) are usually help identifying different microorganisms such as bacteria, yeast and moulds. The later are important as allergy sources.

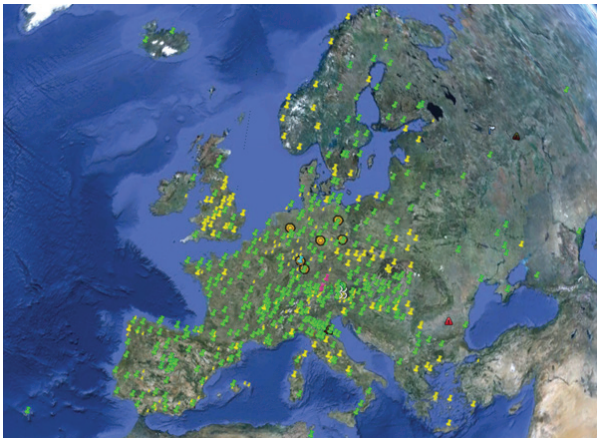


Figure 1. Pollen stations in Europe in 2017 (source EAN).

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

The main evolution started in recent times but still requires many years of development focused on new methods of sampling and analysis of the airborne biological particles.

Aerobiological monitoring networks development must allow real-time analysis to produce daily information on the allergy risk.

The use of modelling, simulation and high-performance computing to forecast pollen (and eventually fungal spores) concentrations has considerably increased, and is expected to increase further. However, the reliability of the information based on these new techniques still needs to be tested by comparison to observations.

At the regulatory level, it is worth noting in recent years an evolution of the legislation on biological particles in some European states such as France. This legislation might be extended to other countries in order to achieve European legislation on airborne pollen and fungal spores. In the same way, we must stress an evolution of the regulation relating to invasive allergenic plants as the different ragweed species.

FURTHER READING

1. Bastl K, Kmenta M, Jäger S, Bergmann KC, Berger U. Development of a symptom load index: enabling temporal and regional pollen season comparisons and pointing out the need for personalized pollen information. *Aerobiologia* 2014;30:269-280.
2. Beggs PJ. Environmental allergens: from asthma to hay fever and beyond. *Curr Clim Change Rep* 2015;1:176-184.
3. Besancenot JP, Thibaudon M. Changement climatique et pollinisation. *Rev Mal Respir* 2012; 29:1238-1253.
4. Galán C, Alcázar P, Oteros J, García-Mozo H, Aira MJ, Belmonte J et al. Airborne pollen trends in the Iberian Peninsula. *Sc Tot Environ* 2016;550: 53-59.
5. Oteros J, Pusch G, Weichenmeier I, Heimann U, Möller R, Röseler S et al. Automatic and online pollen monitoring. *Int Arch Allergy Immunol* 2015;167:158-166.
6. Schiavoni G, D'Amato G, Afferni C. The dangerous liaison between pollens and pollution in respiratory allergy. *Ann Allergy Asthma Immunol* 2017;118: 269-275.
7. Siniscalco C, Caramiello R, Migliavacca M, Busetto L, Mercalli L, Colombo R et al. Models to predict the start of the airborne pollen season. *Int J Biometeorol* 2015;59:837-848.
8. Smith M, Jäger S, Berger U, Sikoparija B, Hallsdottir M, Sauliene I et al. Geographic and temporal variations in pollen exposure across Europe. *Allergy* 2014;69:913-923.
9. Thibaudon M, Caillaud D, Besancenot JP. Méthodes d'étude des pollens atmosphériques et calendriers polliniques. *Rev Mal Respir* 2013;30:463-479.

Santiago Quirce

THE EXPOSOME IN ALLERGY AND ASTHMA: OCCUPATIONAL RISK FACTORS

A4d

GAPS IN KNOWLEDGE

Occupational exposures are significant health hazards and have been associated with several allergic and non-allergic conditions, both as inducers or aggravating factors. Occupational asthma, hypersensitivity pneumonitis and allergic contact dermatitis are the main diseases that can arise from sensitization to workplace agents. Work-related asthma (WRA) is a prevalent lung disease that is associated with undesirable effects on psychological status, quality of life (QoL), workplace activity and socioeconomic status.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

New occupational agents and industrial technologies are continuously being introduced to the work environment and require periodic health surveillance among exposed workers to detect early signs of disease. Better prediction models and algorithms, such as quantitative structure-activity relationship (QSAR) model are needed to predict the chemical asthma hazard.

Primary preventive interventions aimed to reduce exposure levels in the workplace are crucial to reduce the occupational disease burden.

Work-related factors that may lead to uncontrolled symptoms and worsening of prognosis should be properly managed.

Increased susceptibility and vulnerability due to genotypic or gene-environment interactions from workplace exposures should be better defined.

The importance of maternal/paternal occupational exposure to allergens and/or asthmagens in the risk for allergic diseases among offspring deserves a special focus.

Standards and quality criteria

There is a clear need for setting standard occupational exposure limits based on evidence-based methodology coupled with a better standardization and generalization of diagnostic tests, including biomarkers and specific inhalation challenges, for environmentally induced or aggravated diseases.

Western countries have experienced important socio-demographic changes over the last decades, with an older population, an overall higher prevalence of atopy, more women working, and an increase in the number of immigrants. Thus, it is necessary to develop better standards and quality criteria for disease assessment, health promotion and preventive strategies in these populations.

Innovative approach

A theoretical framework for the occupational exposome using a network-based approach for characterizing occupational health problems has been proposed. This model can allow the assessment and characterization of relevant disease-exposure associations in the format of a relational network.

Increased use of social media for exposome data acquisition and for allergic disorders-workplace interactions, and for information dissemination from experts and healthcare providers to workers should be encouraged together with web-based approaches, including e-health and telemedicine, to implement or complement surveillance programs and to disseminate knowledge on work-related exposures.

FURTHER READING

1. Cullinan P, Muñoz X, Suojalehto H, Agius R, Jindal S, Sigsgaard T et al. Occupational lung diseases: from old and novel exposures to effective preventive strategies. *Lancet Respir Med* 2017;5:445-455.
2. De Matteis S, Heederik D, Burdorf A, Colosio C, Cullinan P, Henneberger PK et al. Current and new challenges in occupational lung diseases. *Eur Respir Rev* 2017;26.pii:170080.
3. Quirce S, Antolín-Amérigo D, Domínguez-Ortega J. 'Hidden' occupational allergens such as additives. *Curr Opin Allergy Clin Immunol* 2018;18:67-72.
4. Faisandier L, Bonneterre V, De Gaudemaris R, Bicout DJ. Occupational exposome: a network-based approach for characterizing Occupational Health Problems. *J Biomed Inform* 2011;44:545-552.
5. Escher BI, Hackermüller J, Polte T, Scholz S, Aigner A, Altenburger R et al. From the exposome to mechanistic understanding of chemical-induced adverse effects. *Environ Int* 2017;99:97-106.
6. Quirce S, Campo P, Domínguez-Ortega J, Fernández-Nieto M, Gómez-Torrijos E, Martínez-Arcediano A, et al. New developments in work-related asthma. *Expert Rev Clin Immunol* 2017;13:271-281.
7. Quirce S, Vandenplas O, Campo P, Cruz MJ, de Blay F, Koschel D et al. Occupational hypersensitivity pneumonitis: an EAACI position paper. *Allergy* 2016;71:765-779.
8. Jarvis J, Seed MJ, Stocks SJ, Agius RM. A refined QSAR model for prediction of chemical asthma hazard. *Occup Med (Lond)* 2015;65:659-666.
9. Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F et al; ERS Task Force on Specific Inhalation Challenges with Occupational Agents. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. *Eur Respir J* 2014;43:1573-1587.
10. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.
11. Harber P, Leroy G. Social media use for occupational lung disease. *Curr Opin Allergy Clin Immunol* 2017;17:72-77.

Liam O'Mahony

THE EXPOSOME IN ALLERGY AND ASTHMA – THE MICROBIOME

A4e

GAPS IN KNOWLEDGE

An enormous number of microbes colonize internal and external body surfaces, requiring highly sophisticated mucosal immune cellular and molecular networks to be constantly coordinated.

The composition and diversity of the microbiome varies across body niches, resulting in a series of unique habitats within and between individuals that can change substantially over time. These communities evolve within a host from birth, constantly being modified to maintain a homeostatic balance with the host's immune system. This evolution is influenced by host factors, such as the adaptive and innate immune responses, external factors such as diet, medication and toxin exposure, infection and illness. Importantly, the balance between immune tolerance and inflammation is regulated in part by the crosstalk between immune cells and the microbiome.

Disrupted communication between the microbiome and the host due to altered microbiome composition and/or metabolism is thought to negatively influence immune homeostatic networks. Multiple studies have now shown that changes in the composition of the microbiome associate with many chronic inflammatory diseases including allergies and asthma. However, it is still not clear if changes in the microbiome precede or are the result of the disease.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

Longitudinal studies examining large cohorts for microbiome changes over time during health and those at risk of disease together with mechanistic studies identifying diet-microbiome interactions that influence host immune responses are urgently needed.

Standards and quality criteria

Development of sequencing technologies that can better identify bacterial strains, rather than just species or genera.

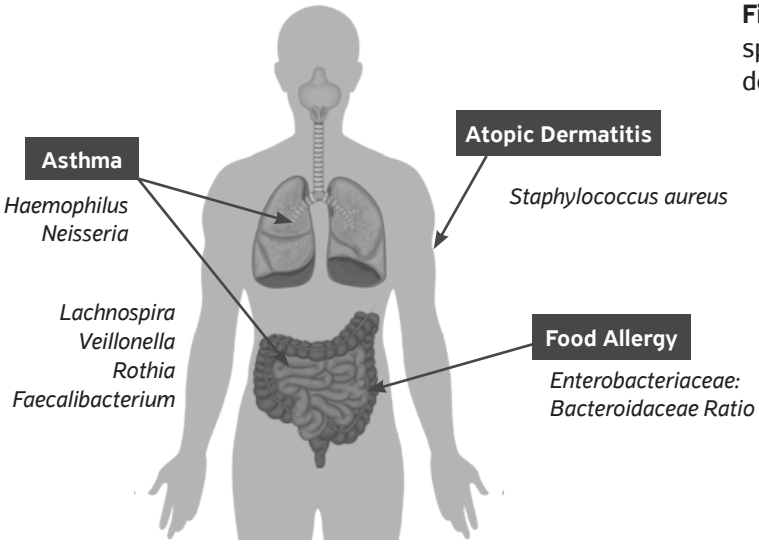


Figure 1. Examples of bacterial species associated with atopic dermatitis, food allergy and asthma.

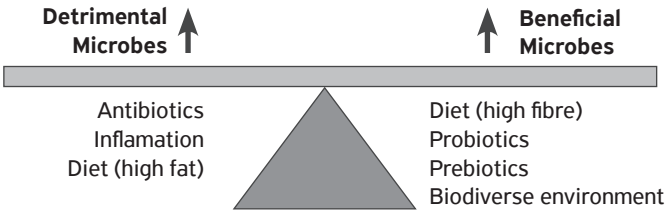


Figure 2. Factors influencing the promotion of detrimental versus beneficial microbes.

Development of bioinformatics tools can combine multiple "omics" data, including microbiome sequencing data, with health outcomes to enable personalized medicine approaches.

Development of culturing methods to grow bacterial strains from multiple body sites (currently less than 10% of human-associated bacteria can be grown *in vitro*) will allow for more precise *in vitro* and *in vivo* assessments.

Innovative approach

Identification of microbiome patterns that associate with medicinal efficacy together with tools for the clinician to integrate microbiome assessments into routine clinical practice (including standardization of assessment method and the algorithms used to determine risk/benefit outcomes) will result in personalized medicine improvements.

FURTHER READING

1. Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L. Microbiome and asthma. *Asthma Res Pract* 2018;4:1.
2. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. *J Allergy Clin Immunol* 2018;141:11-19.
3. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DY, Muraro A et al. The microbiome in allergic disease: Current understanding and future opportunities-2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2017;139:1099-1110.

B

MECHANISMS

Carsten Schmidt-Weber, Mohamed H. Shamji

THE INNATE IMMUNE RESPONSE

B 1

GAPS IN KNOWLEDGE

The remarkable and unchallenged wave of allergies highlight that we still do not have sufficient understanding of environment and of its impact on sensitization or allergy.

Although it is clear that type-2 immunity is critical for allergy, it remains unclear how the innate immune system is engaged by the environment to induce type-2 cytokines in the first place. This knowledge is urgently needed, as it is known that some environmental factors can effectively prevent allergies.

In fact the research community is optimistic that the allergy epidemic can be stopped and eradicated, since children brought up in certain environments are almost fully protected against allergies. In contrast, pollution and other environmental triggers can break allergen tolerance, aggravate allergic responses and require in depth analysis to identify possible health risks before they cause damage.

Allergy research requires a long breath and cannot be accommodated in 1-3 years research grants. In addition research solely geared towards high impact factor publications has not delivered solutions so far.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

The systematic analysis of mechanisms underlying environmental priming and mechanisms of tolerance related to this priming are key aspects that need to be addressed in future. Using very comprehensive analysis methods, it is now possible to assess both: the complex environment and the complex nature of the immune system.

Environmental monitoring (alert systems for pollen and pollutants, identification of risk factors) and research (chemical & biological analytics such as micro- and mycobiome) will shedd new light on the environment-host interactions (models of sensitization, biomarker mining, point of care or even home care-compatible diagnostics and functional food) and on the environment gene interactions (genetics and epigenetics, identification of innate pathways).

The demonstration of induction of type-2 immunity by innate immune cells and amore accurate

description of the innate mechanisms of immune inflammation in allergy (mechanisms of allergic inflammation and resolution) are essential to move the field forward.

Standards and quality criteria

Allergy research requires intensive efforts mainly in-patient context and using primary human cell material, as murine systems have been often misleading. It is noteworthy that murine experiments are still required though, when signalling or anatomically segregated mechanisms are investigated during the development of pre-clinical therapeutics.

Highly networked and interdisciplinary research centers are extremely important for the successful future of allergy research. For examples research facilities with access to allergy and asthma clinics are of major importance.

Efficient patenting of results and support for generation of Spin-off and private partnership models are critical as well. These models should also include a proof of concept center that can conduct critical clinical studies (phase 2a).

Innovative approach

Unlike in other disease areas, it is very well known that the cause of allergic inflammation is an "allergen". We know when it comes and we know that everyone is reacting to it – although some individuals appear asymptomatically whilst others may potentially exhibit severe or even life-threatening reactions. The research on the innate immune system may develop particularly fruitful in allergy, as the immune responses can be effectively tracked.

Advancements in the microbiome assessment further accelerate the understanding of the innate immune system and may highlight certain bacteria as allergy antagonist suitable for functional food or topical applications.

Furthermore, barriers are very important in allergy and are known to tightly interact with dendritic cells as well as innate lymphocytes.

This complex unit of microbiome, epithelial cells, dendritic cells and innate lymphocytes will generate further innovations and access to allergy prevention.

FURTHER READING

1. Kubo M. Innate and adaptive type 2 immunity in lung allergic inflammation. Immunol Rev 2017;278:162-172.
2. Huang Q, Seillet C, Belz GT. Shaping Innate Lymphoid Cell Diversity. *Front Immunol* 2017;8:1569.
3. Huang FL, Liao EC, Yu SJ. House dust mite allergy: Its innate immune response and immunotherapy. *Immunobiology* 2018;223:300-302.
4. Kortekaas Krohn I, Shikhagaie MM, Golebski K, Bernink JH, Breynaert C, Creyns B et al. Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications. *Allergy* 2018;73:837-850.
5. Cosmi L, Liotta F, Maggi L, Annunziato F. Role of Type 2 Innate Lymphoid Cells in Allergic Diseases. *Curr Allergy Asthma Rep* 2017;17:66.
6. Zissler UM, Chaker AM, Effner R, Ulrich M, Guerth F, Piontek G, et al. Interleukin-4 and interferon-γ orchestrate an epithelial polarization in the airways. *Mucosal Immunol* 2016;9:917-926.
7. Landgraf-Rauf K, Boeck A, Siemens D, Klucker E, Vogelsang V, Schmidt S et al. IRF-1 SNPs influence the risk for childhood allergic asthma: A critical role for pro-inflammatory immune regulation. *Pediatr Allergy Immunol* 2018;29:34-41.

Stephen Durham, Mubeccel Akdis

THE ADAPTIVE IMMUNE RESPONSE

B2

GAPS IN KNOWLEDGE

CD4 naive T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and follicular helper T cells, as well as different subsets of regulatory T (Treg) cells. Allergen-specific effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13 and contribute to IgE switch in B cells, tissue migration of T cells and eosinophils, mucus production, regulation of epithelial barrier integrity and eosinophilia.

Peripheral T cell tolerance is characterized by the generation of allergen-specific Treg cells that are able to produce anti-inflammatory cytokines such as IL-10 and TGF-β. Treg cells have the potential to inhibit Th2-type responses and suppress other effector T cells through multiple mechanisms engaging cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1) and histamine receptor 2 (H2R). Non-inflammatory IgG4 antibodies protect from allergic reactions, capturing the allergen to prevent IgE mediated activation of mast cells and basophils.

The allergen-specific B cells are capable of maintaining a memory B cell response as well as differentiating into plasma cells that produce antibodies and therefore are the central cellular component of the humoral immune response. B cell response is maintained differently between healthy and allergic individuals. Healthy individuals show a variation between no allergen-specific B cells, detectable IgG1, IgG4 and IgA B cells and in high dose antigen exposure high amounts of IgG4, relatively low amounts of IgG1 and detectable IgA and IgE responses. In contrast, allergic individuals have high amounts of IgE, together with low or high amounts of IgG1, IgG4 and IgA responses. IgE expressing B cells can be detected in affected tissues such as the bronchi in asthma, nose and sinus tissues. IgG4 production induced upon AIT is confined to IL-10-producing B regulatory cells that play an essential role in peripheral tolerance by suppressing effector T cells, inhibiting pro-inflammatory cytokines and promoting differentiation of Treg cells.

The discovery of T-cell–B-cell cooperation enhanced our understanding of activation of the immune responses and immune regulation. It is one of the most significant examples for a cooperation between two cells in our body. The interaction of the two cells takes place with the formation of an immune synapse and many surface molecules and secreted cytokines to this synapse area. B cells recognize antigens, via B cell receptors and present to T cells through MHC-class 1 molecules. A series of costimulatory ligands and receptors interact, such as CD28, CTLA-4, OX40, CD40L, ICOS on the T cell side and CD80, CD86, OX40L, CD40, ICOSL on the B cell side. In allergic individuals, if this interaction takes place between Th2 memory T cells and naïve B cells, it leads to IgE class-switch

and memory. Regulatory B (Breg) cells, which are able to secrete IL-10, regulate the development, proliferation, and maintenance of CD4+ T effector and memory T cells as well as regulatory T cells. On the other hand, regulatory T cells act on B cells to regulate antibody isotypes, which may contribute to the suppression of inflammatory diseases by the induction of IgG4 and by the suppression of IgE.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Application of such knowledge for specific AIT

According to recent studies of mechanisms of AIT (Figure 1), allergen-specific T cell and B cell interaction aims to dampen Th2-driven allergic inflammation in the affected tissues and induce clinical tolerance (persistence of benefit after discontinuation of immunotherapy), which is in parallel to immunologic tolerance. Generation of allergen-specific Treg and Breg cells and suppression of allergen-specific Th2 cells takes place in the first stage. There is also evidence of later allergen-driven immune deviation in favor of Th1 responses. This immune tolerance environment and Treg and Breg cells directly and indirectly decrease numbers of eosinophils and mast cells and release of their mediators in the affected tissues. T cell B cell interaction leads to IgG4 production with the involvement of IL-10, Treg cells and Breg cells.

Specific preventive strategies for allergy

The development of ideal vaccines with fewer injections and the curative effect are beneficial for specific allergy treatments. Recent vaccines have been developed in the patterns of modified allergens, T cell epitope peptide-based vaccines, recombinant allergen derivative-based vaccines, adjuvant-coupled molecule-based vaccines, nanoparticle-based vaccines, and combined treatment with immunomodifiers. These novel vaccines aim to promote the safety, specificity, and high effectiveness through *in vitro*, *in vivo*, and human clinical trials. Such important discoveries for specific allergen treatments will reveal positive impact with the potential to improve the quality of life of allergic subjects.

FURTHER READING

1. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: Receptors, functions, and roles in diseases. *J Allergy Clin Immunol* 2016;138:984-1010.
2. Varricchi G, Harker J, Borriello F, Marone G, Durham SR, Shamji MH. T follicular helper (Tfh) cells in normal immune responses and in allergic disorders. *Allergy* 2016;71:1086-1094.
3. Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Crameri R et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med* 2004;199:1567-1575.
4. Meiler F, Zumkehr J, Klunker S, Rückert B, Akdis CA, Akdis M. In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure. *J Exp Med* 2008;205:2887-2898.
5. Akdis M. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol* 2006; 18:738-744.
6. James, LK, Till, SJ Potential Mechanisms for IgG4 Inhibition of Immediate Hypersensitivity Reactions. *Curr Allergy Asthma Rep* 2016;16:23.
7. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol* 2013;131:1204-1212.
8. Lund, FE, Randall, TD. Effector and regulatory B cells: modulators of CD4+ T cell immunity. *Nat Rev*

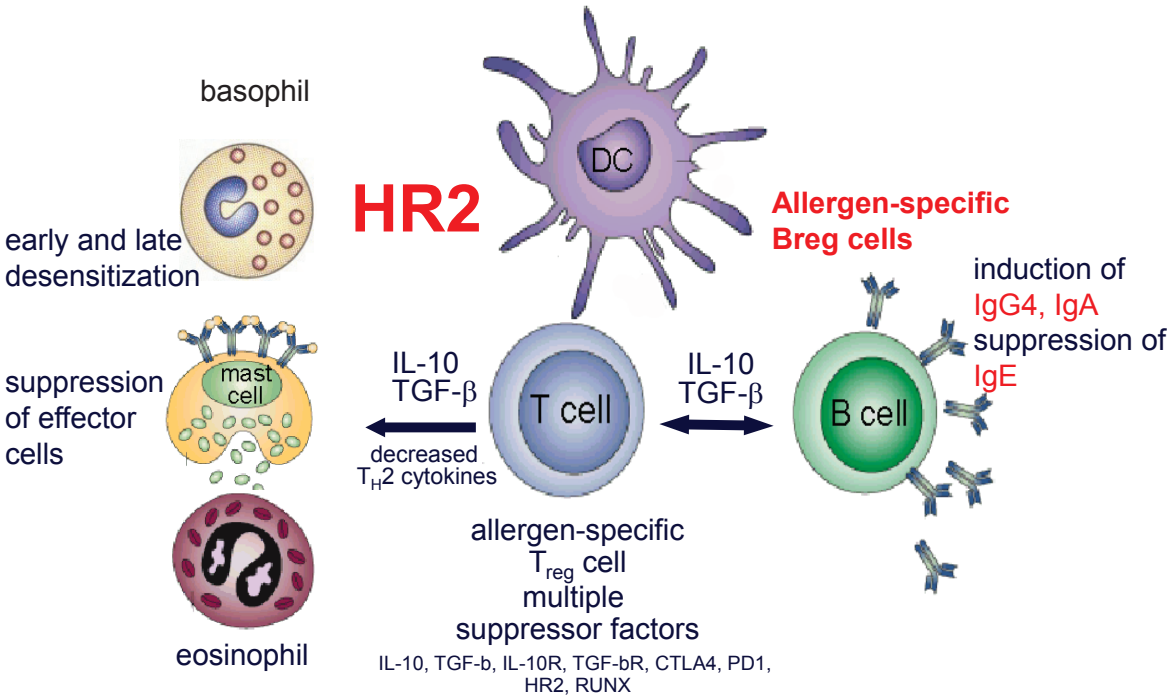


Figure 1. Mechanisms of allergen Immunotherapy. Allergen-specific T reg cells suppress Th2 responses and directly and indirectly suppress mast cells, basophils and eosinophils. Suppression of allergen-specific IgE and inducement of IgG4 by T cells and induction of allergen-specific Breg cells leads to the suppression of effector T cells and dendritic cells.

Immunol 2010;10:236-247.

9. Larsen JN, Broge L, Jacobi H. Allergy immunotherapy: the future of allergy treatment. *Drug Discov Today* 2016;21:26-37.
10. Meiler F, Klunker S, Zimmermann M, Akdis, CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008;63:1455-1463.
11. Fujita H, Soyka, MB, Akdis, M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *Clin Transl Allergy* 2012;2:2.
12. Renand A, Shamji MH, Harris KM, Qin T, Wambre E, Scadding GW et al. Synchronous immune alterations mirror clinical response during allergen immunotherapy. *J Allergy Clin Immunol* 2018;141:1750-1760.e1.
13. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organ J* 2015;8:17.
14. Akdis CA, Akdis M. Advances in allergen immunotherapy: aiming for complete tolerance to allergens. *Sci Transl Med* 2015;7:280ps6.
15. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol* 2017;140:1485-1498.
16. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J. et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy* 2017;72:1156-1173.

Claudia Traidl-Hoffmann, Claus Bachert

THE RESIDENT CELLS/BARRIERS

B3

GAPS IN KNOWLEDGE

The epithelia of skin, lung and the gastrointestinal tract (GI) constitute the outmost barrier system of the organism. They mainly ensure protection from external assaults like pathogens, xenobiotics or UV irradiation. In addition, the epithelia prevents the loss of water and solutes. Lately, our view about the "epithelia" changed from inert mechanical barriers to active organs that sense and react to danger signals. In well-orchestrated manner, the different epithelia mount perfectly adapted defense measures in response to assaults. Today, we know four functional levels of each epithelium barrier that are carefully composed: the microbiome barrier, the chemical barrier, the physical barrier, and the immune barrier.

These barriers do not act separately, but influence each other in an interactive network. Barrier disruption, in general, contributes to pathogenic conditions. More specifically, each alterations of a barrier component can cause pathogenic conditions such as bacterial, viral, or fungal infections, sterile inflammation, allergic sensitization, or tumor development.

The microbial barrier is the outmost layer of the epithelial barrier. Its structure varies very specifically according to the individuum and the linked organ (skin, GI, lung). The microbiome is a complex ecosystem, where an equilibrium of commensals prevents uncontrolled pathogenic bacteria growth and instructs cutaneous immunity. Several studies addressed how commensal bacteria within certain microbial communities control potentially pathogenic bacteria. The result in is an innate immune alertness orchestrated by commensals and the skin's immune system.

The chemical barrier comprises factors that contribute to the epithelia´s acidic surface pH. Together with compounds such as fillagrin they make up the natural moisturizing factor (NMF). Above the latter, the chemical barrier regulates the skin's moisture and acid mantle to inhibit the exponential growth of bacterial pathogens. Consequently, a healthy microbiome barrier relies almost completely on the steady maintenance of the chemical barrier.

The physical barrier has been recognised as the epithelial barrier, which prevents exogenous substances from penetrating into the skin and also for water evaporation out of the body. It is formed by keratinocytes and epithelial cells which preserve the skin's and airway's structure through tight junctions (TJ) from physical injury. The physical barrier is of great interest for drug delivery, because here the first interaction with drug delivery systems takes part and play the major role in skin absorption. Moreabout, the keratinocytes and epithelial cells carry out a number of immune functions, e. g. the secretion of cytokines and antimicrobial peptides as well as antigen presentation. Proteins of the TJ undergo regulations upon contact to microbes both during homeostatic colonization and infection. These interactions with the microbiome and the immune barrier highlight the central role of constituents derived from keratinocytes and epithelial cells for the functioning

of the skin and mucosal barrier. The interactions also demonstrate how sensing and appropriate reaction to alterations in the local microenvironment contribute to the barriers´ proper composition.

The immune barrier, finally, consists of innate and adaptive immune cells which are either already resident or become recruited to the epithelia. Their task is to literally sense danger signals, to protect against pathogens through information in the cytokine network, and eventually to mount memory responses. As we have seen before, the pathways of the immune barrier is partly located in the physical barrier. Its sense mechanism however work up to the chemical barrier and interacts with the microbial barrier.

Thus the four barriers become interrelated in such a structural way that together they resemble an organ on their own.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Barriers play a central role in protection and thus also key in disease prevention.

The best possible understanding about the functions and characteristics of the four different barrier parts is a prerequisite for the development of strategies in order to uphold barrier integrity and, especially in case of disease, to support the recovery of disturbed barriers.

Interventions on the epithelial barrier level are highly promising as targets for therapy and especially prevention of allergic diseases.

FURTHER READING

1. Iwase T, Uehara Y, Shinji H, Tajima A, Seo H, Takada K et al. Staphylococcus epidermidis Esp inhibits Staphylococcus aureus biofilm formation and nasal colonization. *Nature* 2010;465:346-349.
2. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, et al. Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. *Sci Transl Med* 2017;9.pii:eaah4680.
3. Wanke I, Steffen H, Christ C, Krismer B, Götz F, Peschel A et al. Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. *J Invest Dermatol* 2011;131: 382-90.
4. Blume C, Foerster S, Gilles S, Becker WM, Ring J, Behrendt H et al. Human epithelial cells of the respiratory tract and the skin differentially internalize grass pollen allergens. *J Invest Dermatol* 2009; 129:1935-1944.
5. Blume C, Swindle EJ, Dennison P, Jayasekera NP, Dudley S, Monk P et al. Barrier responses of human bronchial epithelial cells to grass pollen exposure. Eur Respir J, 2013. 42: p. 87-97.
6. Yuki, T., et al., Activation of TLR2 enhances tight junction barrier in epidermal keratinocytes. *J Immunol* 2011;187:3230-3237.
7. Bäsler K, Galliano MF, Bergmann S, Rohde H, Wladykowski E, Vidal-Y-Sy S et al. Biphasic influence of Staphylococcus aureus on human epidermal tight junctions. *Ann N Y Acad Sci* 2017;1405:53-70.
8. Altunbulakli C, Costa R, Lan F, Zhang N, Akdis M, Bachert C et al. Staphylococcus aureus enhances the tight junction barrier integrity in healthy nasal tissue, but not in nasal polyps. *J Allergy Clin Immunol* 2018;pii:S0091-6749(18)30312-9.
9. Van Crombruggen K, Vogl T, Pérez-Novo C, Holtappels G, Bachert C. Differential release and deposition of S100A8/A9 proteins in inflamed upper airway tissue. *Eur Respir J* 2016;47:264-274.
10. Eyerich S, Wagener J, Wenzel V, Scarponi C, Pennino D, Albanesi C et al. IL-22 and TNF-alpha represent a key cytokine combination for epidermal integrity during infection with Candida albicans. *Eur J Immunol* 2011;41:1894-1901.
11. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016;138:336-349.
12. Bieber T, Akdis C, Lauener R, Traidl-Hoffmann C, Schmid-Grendelmeier P, Schäppi G et al. Global Allergy Forum and 3rd Davos Declaration 2015: Atopic dermatitis/ Eczema: challenges and opportunities toward precision medicine. *Allergy* 2016;71: 588-592.

Hermelijn H Smits, Jürgen Schwarze

THE ROLE OF INFECTIONS IN THE DEVELOPMENT AND ETIOLOGY OF ALLERGIC DISEASE

B4

GAPS IN KNOWLEDGE

Allergic patients suffer from exaggerated immune responses to essentially harmless antigens and their capacity for immune tolerance to allergens, which occurs in healthy individuals, is hampered.

There is a growing awareness that a 'natural' and rich exposure to environmental micro-organisms in early life - when the immune system is particularly malleable - may be essential for the development of the regulatory arm of the immune system and boost immune tolerance to allergens, avoiding early sensitization. Such microbes do not only occur in the environment but also inhabit each of us, collectively forming the microbiome. A diverse and balanced composition of the microbiome, including the presence of helminths, is linked to the development of a mature and balanced immune system which maintains immune tolerance and supports tissue integrity.

In contrast, both an imbalanced microbiome and severe respiratory viral infections in young children form strong risk factors for recurrent wheeze and asthma. Importantly, infections with both viruses and certain pathogenic bacteria also lead to exacerbations of established asthma. In both cases, this is thought to be mediated by excessive local inflammation in the lungs - facilitating loss of tolerance and allergen sensitization-, immune-neuronal interactions, tissue destruction and incorrect repair.

Despite extensive data from epidemiologic studies and experimental models, good intervention studies that focus on the concept of early microbial immune priming in the prevention of allergic disease are scarce. The few studies that have tried this, only showed mild or no effects. These disappointing results may, in part, be explained by the failure to establish key elements of the interventions, e.g. changes in microbiome or immune activation. This clearly indicates that we still lack essential insight into these protective mechanisms and how they develop in healthy individuals. This intercalates with our insufficient understanding of the mechanism underlying early inflammatory events in the airway mucosa during respiratory viral or bacterial infections and their long-term effects. Likewise, infection associated events that precede and lead to asthma exacerbations are still insufficiently understood.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

To be able to address the open questions on the role of infections in allergic diseases and asthma (Box 1) we need relevant mechanistic studies to better understand the responses to microbial exposure/infection, in particular in early life, and how to intervene. To allow looking 'backwards', prospective longitudinal cohorts are required combining integrated systems biology and immunology. Resulting data will not only allow more precise phenotyping, but may also provide prognostic factors for allergy and asthma development. Furthermore, controlled human infections combined with systems biology will provide a wealth of mechanistic data and insight into very early infection processes that precede asthma exacerbations and into strategies to reduce their augmenting effects on inflammation.

Overall, a better understanding is necessary of early events in microbial exposure/infection, both those crucial for the development of immune tolerance to allergens and those resulting in augmented inflammatory responses. Such mechanistic insights should pave the way for new intervention strategies based on microbial immune priming and/or biologicals targeting either the infection itself or the induction of strong inflammatory responses linked to disease exacerbation.

Box 1. Priority research questions to underpin the role of infections in allergic diseases and asthma

1	• Can more diverse microbial signals in early life boost regulatory tolerance reactions and prevent allergies and asthma? • If so, what are the most potent signals and how can we improve their translation into successful intervention approaches?
2	• Can we predict which neonates and young infants are at risk of allergies and asthma, before they show disease symptoms? • If so, can we predict which microbial approach would be most effective in preventing these conditions in those children?
3	• What are the early inflammatory events in the lungs of young children in response to respiratory pathogenic bacterial and viral infections? • Why are there such large variations in the inflammatory and clinical responses between children, ranging from mild disease to hospitalization and even admission to the intensive care unit? • What are the long-term immune consequences of early life respiratory infections and how do these contribute to the development of asthma and allergies?
4	• What signals or events lead to a dysbiosis in the (respiratory) microbiome allowing pathogenic bacteria to colonize and infect some children, but not others? • Can we interfere in these events and prevent or restore the dysbiosis? • Can 'protective' microbial signals prevent or reduce the clinical symptoms following respiratory bacterial or viral infections in children?
5	• What are the early immune and inflammatory events after respiratory viral/bacterial infection that contribute to episodes of wheeze and asthma exacerbations?

FURTHER READING

1. Smits HH, van der Vlugt LE, von Mutius E, Hiemstra PS. Childhood allergies and asthma: New insights on environmental exposures and local immunity at the lung barrier. *Curr Opin Immunol* 2016;42:41-47.
2. Smits HH, Hiemstra PS, Prazeres da Costa C, Ege M, Edwards M, Garn H, et al. Microbes and asthma: Opportunities for intervention. *J Allergy Clin Immunol* 2016;137:690-697.
3. Edwards MR, Walton RP, Jackson DJ, Feleszko W, Skevaki C, Jartti T, et al. EAACI Anti-infectives in Asthma and Asthma Exacerbations Task Force. The potential of anti-infectives and immunomodulators as therapies for asthma and asthma exacerbations. *Allergy* 2018;73:50-63.
4. Mackenzie KJ, Anderton SM, Schwarze J. Viral respiratory tract infections and asthma in early life: cause and effect? *Clin Exp Allergy* 2014;44:9-19.
5. Schwartz C, Hams E, Fallon PG. Helminth Modulation of Lung Inflammation. *Trends Parasitol* 2018;pii: S1471-4922(17)30312-4.
6. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017;140:895-906.

Karin Hoffmann-Sommergruber, Edward Knol,
Bernadette Eberlein, Ronald van Ree

ALLERGENS AND ADJUVANTS

B5

GAPS IN KNOWLEDGE

Allergens and intrinsic adjuvanticity

Although our knowledge on individual has increased significantly the question still remains: "What makes an allergen an allergen?".

A single answer fitting all allergens is not to be expected, yet our current understanding on the interaction of allergens and the innate and adaptive immune system has expanded. Allergens have to overcome the epithelial- or epidermal barrier, before interacting with APCs. A number of allergens can actively disrupt this barrier by affecting the tight junctions, thus enhancing the permeability. This has been shown for cysteine protease from house dust mite (Der p 1) for bronchial epithelial, as well as for the major kiwifruit allergen, Actinidin (Act d 1) affecting the intestinal barrier integrity via occluding-degradation. In addition, ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation (Figure 1).

DCs are equipped with receptors such as TLRs and CTLRs, sensing danger signals. For example, the house dust mite allergen Der p 13, a fatty acid binding protein, activates TLR2 mediated innate immune responses, whereas Der p 2 displays functional mimicry with MD-2, binds to TLR4 which induces a robust Th2 driven inflammation response.

Some allergens carry pollen- or microbial-derived lipids and activate via DCs the Th1, Th2 and Th17 mediated allergic inflammation. Co-administration of allergens and lipids can also bind to CD1 receptors and activate T cells accordingly, to mount an inflammatory response. Last but not least, CTLRs are binding allergenic glycoproteins and trigger the respective pathways. For example glycosylated peanut allergen, Ara h 1, is a ligand of DC-SIGN thus acting as a Th2 adjuvant.

Upon allergen uptake DCs subject them to lysosomal degradation, a tightly regulated process. However, it seems that even closely related allergens display different resistance to DC processing as it has been shown for Bet v 1-isoforms. Whether the prolonged stability in lysosomal compartments predicts higher sensitizing capacity of the allergens remains to be verified.

There is growing evidence that upregulation of the innate immune system is involved in an allergic response, via different adjuvant activities. However, how to apply these modified adjuvants for tolerance induction and treatment options and how relevant specific adjuvants are for different routes (oral versus inhalant versus skin administration) remains as one of the future challenges.

Allergen specific immunotherapy and adjuvants

Allergen specific immunotherapy is designed to generate an immune modulation, aiming to prevent and relieve allergic symptoms. In this context, potent adjuvants are required to improve AIT usually via activating CD40, CD80 and CD86 and TLR ligands. This can be achieved by chitin derivatives and nanoparticles. Application of these adjuvants stimulates a range of immune responses such as tolerance induction via Tregs, Bregs, IgG4 or lytic immunity via Th17 and IgG.

For allergy vaccines, first generation (aluminium based) adjuvants are under discussion due to their safety profile. Therefore, second generation adjuvants are needed to improve the safety and efficacy profile including shorter treatment options. For example a recent proof of concept study used grass pollen allergoids coupled to non-oxidized mannan to induce regulatory T cells via PDL1 activation.

Although novel adjuvants, nano-approaches, modified allergens including hypoallergenic and hyperimmunogenic molecules have been developed, studies are lacking to prove their applicability and improved efficacy for personalized immunotherapy.

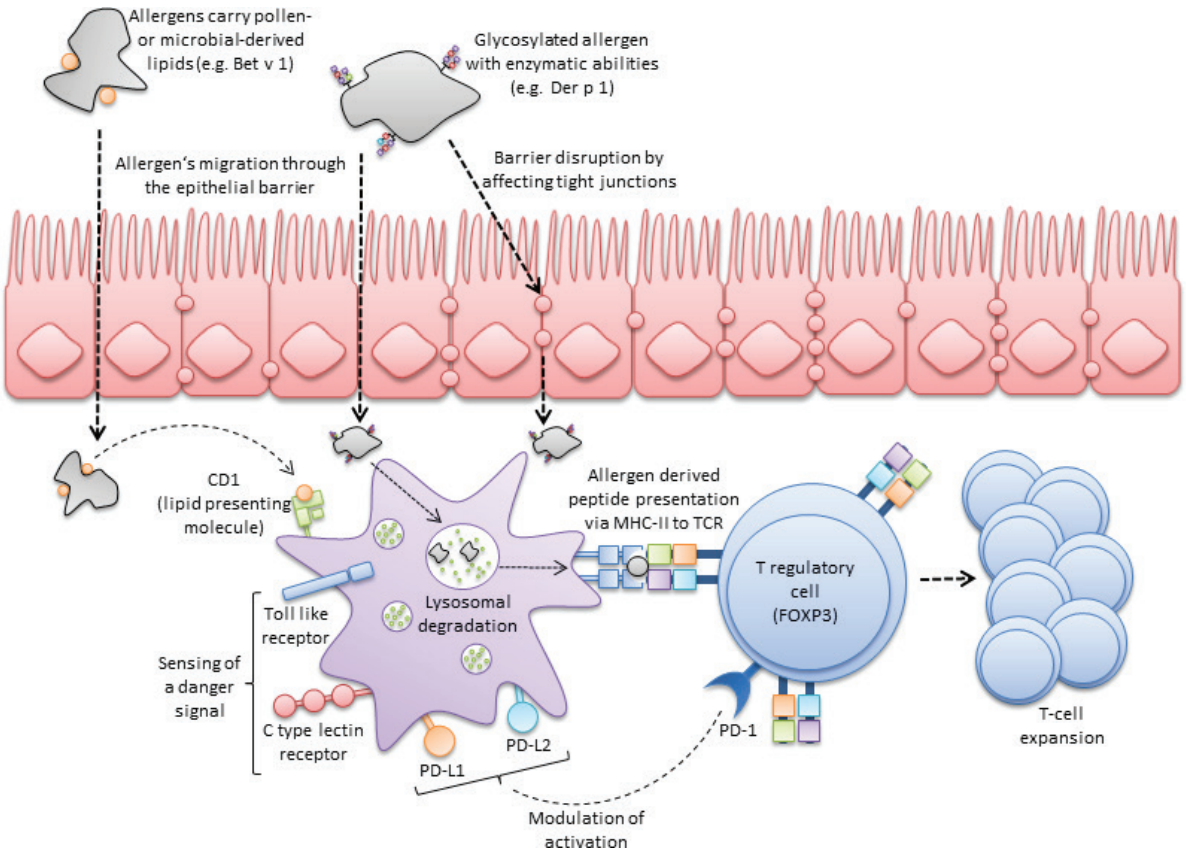


Figure 1. Allergens and their adjuvant activities upregulate the immune responses via different mechanisms.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Better understanding of innate immune reactions facilitating allergic sensitization together with elucidating the role of immunomodulating compounds in allergen sources on the allergic response are necessary to move the field forward.

For achieving more efficient and reliable AIT vaccines the repertoire of potential adjuvants needs to be assessed. In addition, the optimal allergen-adjuvant composition needs to be defined to fine tune the desired long-term tolerogenic immune response in the allergic patient. Application of second generation adjuvants together with validated well-designed proof of concept studies has the potential to improve allergen immunotherapy.

List of abbreviations

APC	antigen presenting cell
CTLR	C-type lectin receptor
DC	dendritic cell
DC-SIGN	dendritic cell-specific ICAM-grabbing nonintegrin
PDL1	programmed death ligand 1
TCR	T cell receptor
TLR	toll like receptor

FURTHER READING

1. Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ. Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. *J Clin Invest* 1999;104:123-133.
2. Cavic M, Grozdanovic MM, Bajic A, Jankovic R, Andjus PR, Gavrovic-Jankulovic M. The effect of kiwifruit (Actinidia deliciosa) cysteine protease actinidin on the occludin tight junction network in T84 intestinal epithelial cells. *Food Chem Toxicol* 2014;72:61-68.
3. Boldogh I, Bacsi A, Choudhury BK, Dharajiya N, Alam R, Hazra TK. ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. *J Clin Invest* 2005;115:2169-2179.
4. Trompette A, Divanovic S, Visintin A, Blanchard C, Hegde RS, Madan R et al. Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein. *Nature* 2009;457:585-588.
5. Satitsuksanoa P, Kennedy M, Gilis D, Le Mignon M, Suratannon N, Soh WT et al. The minor house dust mite allergen Der p 13 is a fatty acid-binding protein and an activator of a TLR2-mediated innate immune response. *Allergy* 2016;71:1425-1434.
6. Shreffler WG, Castro RR, Kucuk ZY, Charlop-Powers Z, Grishina G, Yoo S et al. The major glycoprotein allergen from Arachis hypogaea, Ara h 1, is a ligand of dendritic cell-specific ICAM-grabbing nonintegrin and acts as a Th2 adjuvant in vitro. *J Immunol* 2006;177:3677-3685.
7. Freier R, Dall E, Brandstetter H. Protease recognition sites in Bet v 1a are cryptic, explaining its slow processing relevant to its allergenicity. *Sci Rep* 2015;5:12707.
8. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M et al. Perspectives in allergen immunotherapy: 2017 and beyond. *Allergy* 2018;73 Suppl 104:5-23.
9. Sirvent S, Soria I, Cirauqui C, Cases B, Manzano AI, Diez-Rivero CM et al. Novel vaccines targeting dendritic cells by coupling allergoids to nonoxidized mannan enhance allergen uptake and induce functional regulatory T cells through programmed death ligand 1. *J Allergy Clin Immunol* 2016;138:558-567.e11.

Ioana Agache, Cezmi A. Akdis

ENDOTYPES OF ALLERGIC DISEASES AND ASTHMA

B6

Our understanding of the pathophysiologic processes of allergic diseases showed a significant progress due to major basic and translational scientific discoveries. Accordingly, the view of the pathophysiology of allergic diseases has been upgreaded from a simple approach, with a focus on symptoms and organ functions, towards the recognition of a complex network of immunologic and biochemistry pathways. Disease subtypes related to type of inflammation and complex immune-regulatory networks have been described that open the way for precision diagnosis and targeted-treatments. The four key words endotype, phenotype, theratype and biomarker are nowadays being the main topics of research on the way of building blocks of precision medicine and precision health.

An **endotype** is a subtype of a disease condition, which is defined by a distinct pathophysiological mechanism, whereas a disease **phenotype** defines any observable characteristic of a disease without any implication of a mechanism. Another key word linked to disease endotyping is **biomarker** that is measured and evaluated to examine any biological or pathogenic processes, including response to a therapeutic intervention. In this context the word **theratype** has been introduced that defines a subset of patients that perfectly respond to a certain treatment. These four keywords will be discussed more and more in the future with the upcoming efforts to revolutionize patient care in the direction of **precision medicine** and **precision health**.

GAPS IN KNOWLEDGE

Why do we need disease endotypes and "Precision Medicine" in allergic diseases?

The specialty of allergy and clinical immunology has more than 100 years of experience in precision medicine with allergen immunotherapy that is formulated according to the allergy status of the individual patient.

Apparently, PM is of broad relevance for many reasons for the management of asthma, allergic rhinitis, atopic dermatitis and food allergy in the context of better selection of treatment responders, risk prediction, and design of disease-modifying strategies. 1) There is huge individual variation in all aspects of patient care due to endotypes and phenotypes of these diseases. 2) Causes of allergy development in single individuals, as well as reasons for recent increase in worldwide prevalence are unknown. 3) The natural history, including mecha-

nisms of spontaneous resolution, are unknown, not predictable and show individual variation. 4) There is marginal understanding of interactions between microbes, immune system and allergic disorders with a significant individual variation. 5) There are no established biomarkers for prediction of clinical outcomes, early intervention and possible cure. 6) Novel biologicals for the treatment of allergic disorders are emerging, but need relevant biomarkers and a PM approach for patient selection and follow up the outcomes.

Endotypes concept and daily practice

The concept of disease endotypes has been introduced first in asthma and the attention of the community has been taken with a Practicals of Allergy (PRACTALL) document published by the European Academy of Allergy Clinical Immunology and American Academy of Allergy, Asthma & Immunoloy. Due to focus of precision medicine the concept of endotypes has been well appreciated by other medical disciplines. To emphasize the importance of Precision Medicine (PM) in allergic diseases, it will be good to quote a pioneer in precision medicine, **Sir John Bell**, Professor of Medicine at Oxford University, and Chairman of the Office for the Strategic Coordination of Health Research: "The best example of PM in my opinion does not come from cancer, it comes from asthma. For this condition, we have gone more than 20 years without a new drug, because the disease was not defined very well." (http://www.pharmafile.com/news/). In accordance with this, a wide consensus between academia, governmental regulators, and industry for further development and application of PM in management of allergic diseases and asthma is of utmost importance.

Since the PRACTALL document, there has been some achievements related to disease endotypes and precision medicine in allergic diseases. A general consensus has been obtained in phenotype and endotype concept developed in asthma, chronic rhinosinusitis, allergic rhinitis and atopic dermatitis. Endotypes have been proposed and missing areas have been identified. Several biomarkers have been proposed, biomarker discovery programs have been initiated. Some algorithms have been developed. Theratype concept has been introduced. Precision health concept has been introduced and is under further development for the prevention of children by using allergen immunotherapy.

Assigning unique mechanisms and biomarkers for each endotype is crucial for the validity of the endotype. So far only few (if any) valid endotypes have been identified in allergic disease, all with therapeutic implications. To further elaborate on the definition of an endotype, one must recognize that one major pathogenic pathway such as type 2 immune response is highly complex, including several determinants with nonlinear dynamic interactions (Figure 1) and heterogeneous, since not all determinants are present in all patients or, in a given patient, at all time points. It is now important to understand extensive network and interaction of the cells and cytokines in an imune response and embrace the concept of a "**complex endotype**" consisting of several subendotypes as opposed to an endotype that encompasses a single molecular mechanism. A complex type 2 immune response comprises the whole type 2 immune response involving Th2 cells, type 2 B cells, group 2 innate lymphoid cells, a small fraction of IL-4 - secreting NK cells, IL-4 - secreting NK-T cells, basophils, eosinophils and mast cells and their major cytokines (Figure 2). From a complex network of cytokines, IL-4, IL-5, IL-9, IL-13 and IL-31 are mainly secreted from the immune system cels and IL-25, IL-33 and TSLP from tissue cells, particularly epithelial cells. Both the innate and the acquired immune response contribute to type 2 immune response endotypes. At present, biomarkers are not sufficiently specific to select the endotype specifically responding to a targeted treatment. For example, blood eosinophils predict response to anti-IL-4/IL-13, anti-IL-5, and anti-IgE antibodies, as well as CRTH2 antagonists and the clinician will face a challenge of how best to treat severe asthma patients with high blood eosinophils.

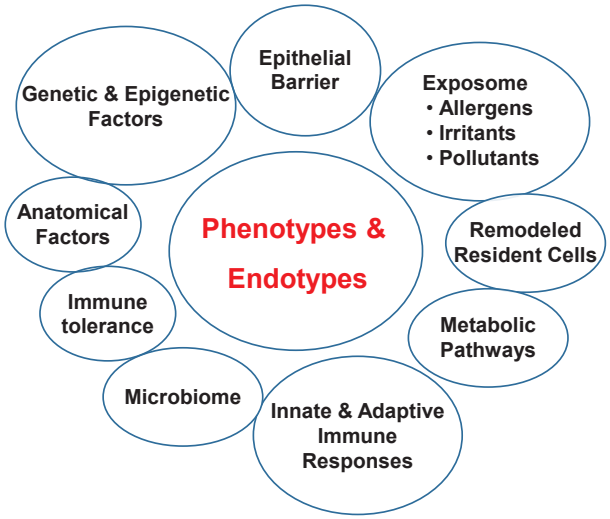


Figure 1. Factors that affect a disease endotype in allergic diseases. For precision medicine in allergic disease, more mechanistic approaches are needed, based on an integrated understanding of the individual patient's biological mechanisms, including the interplay between the immune response and the exposome, infections and microbiome, genetics, epigenetics, psychosocial factors, nutrition, anatomical factors and metabolic pathways.

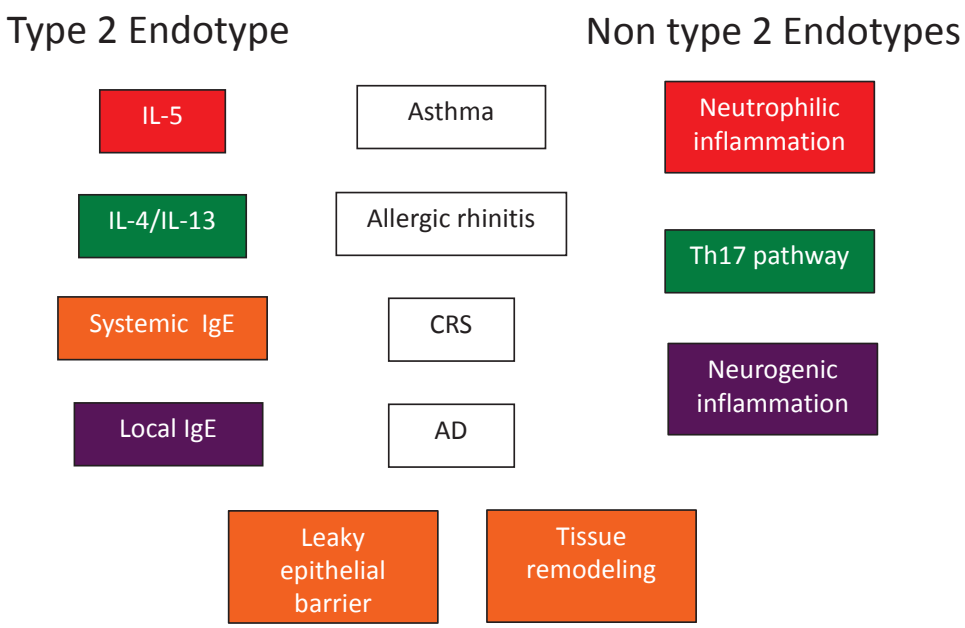


Figure 2. The complex type 2 immune response driven endotype consists of several individual pathways in a complex interaction between inflammatory and tissue cells. The IL-5 pathway is a therapeutic target in asthma validated for severe asthma and was targeted in a proof of concept study in CRS with NP. The IL-4/IL-13 pathway seems similarly important for asthma, CRS with NP and AD. Targeted intervention with dupilumab significantly reduced symptom burden and licenced in AD. Targeting systemic IgE is a well validated intervention in allergic asthma and new anti-IgE monoclonal antibodies are under clinical development. Anti-IgE treatment seemed less rewarding in AD. Local IgE production is a key pathogenic event driving the inflammation process both in AR and CRS.

Growing evidence supports a role for a dysregulated innate immune response promoting neutrophilic inflammation in asthma, rhinitis and CRS for non-type 2 endotypes. The IL-17 pathway has been related to disease severity in asthma, CRS and AD. The neurogenic inflammation pathway appears of particular importance in rhinitis and AD. Tissue remodeling and barrier defects are major players modulating both the type 2 and the non type-2 immune response in asthma, rhinitis, CRS and AD.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

There is no doubt that extensive research on precision medicine combined with basic and translational research will enable individualized and precision approaches not only in allergies and asthma but also in all disciplines of medicine.

Profiling the disease following the concept of complex endotypes and subendotypes linked to validated and qualified biomarkers resulting from the unbiased approach facilitated by the big data driven models will offer novel insights into the disease pathgenesis.

Integrating health information technology with systems medicine and with a patient centered environment is essential for coordination and alignment in translating the research data into functional clinical decision algorithms.

A revised endotypic taxonomy of asthma can stimulate targeted research and interventions to identify biomarkers predicting the implication of distinct endotypes in disease pathogenesis.

Policy makers feel threatened by analytical outputs, and find reasons to reject them, unless they develop high levels of trust in their pedigree and provenance, thus healthcare systems need to adapt based on cost-effective delivering value grounds.

FURTHER READING

1. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-360.
2. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy* 2012;67:835-846.
3. Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2013;131:1479-1490.
4. Papadopoulos NG, Bernstein JA, Demoly P, Dykewicz M, Fokkens W, Hellings PW et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy* 2015;70:474-494.
5. Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU et al. Precision medicine in allergic disease-food allergy, drug allergy, and anaphylaxis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006-1021.
6. Muraro A, Lemanske RF, Hellings PW, Akdis CA, Bieber T, Casale TB et al. Precision medicine in allergic diseases - Airway Diseases and Atopic Dermatitis. PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2016;137:1347-1358.
7. Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. *Allergol Int* 2016;65:243-252.
8. Agache I, Sugita K, Morita H, Akdis M, Akdis CA. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. *Curr Allergy Asthma Rep* 2015;15:29.
9. Akdis CA, Ballas ZK. Precision medicine and precision health: Building blocks to foster a revolutionary health care model. *J Allergy Clin Immunol* 2016;137:1359-1361.
10. Agache I, Strasser DS, Klenk A, Agache C, Farine H, Ciobanu C et al. Serum IL-5 and IL-13 consistently serve as the best predictors for the blood eosinophilia phenotype in adult asthmatics. *Allergy* 2016;71:1192-1202.
11. Galli S. Toward precision medicine and health: Promises Opportunities and challenges in allergic diseases. *J Allergy Clin Immunol* 2016;137:1289-1300.
12. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018;141:529-538.e13.

C

MAJOR ALLERGIC DISEASES

Paul van Cauwenberge, Ludger Klimek

ALLERGIC RHINITIS

C 1

GAPS IN KNOWLEDGE

Allergic rhinitis (AR) is worldwide the most common immune disease and one of the most common chronic diseases - with a still increasing prevalence. Almost one in three European citizens is affected by AR. Allergic rhinitis is still largely underestimated, underdiagnosed and undercured. The socio- economic consequences of AR and its comorbidities are considerable for healthcare systems all around the globe.

AR is an immunologically mediated inflammation of the nasal mucosa caused by allergen contact often characterized by itching, sneezing, secretion and nasal obstruction and clinically subdivided according to the duration of symptoms as being intermittent or persistent. Severity of symptoms and impact on social activities and quality of life is used for grading. The disease can affect social life, school performance, and labor productivity of patients besides the burden of inherent symptoms. AR is accompanied by comorbidities such as conjunctivitis, asthma, food allergies, atopic eczema/atopic dermatitis, sinusitis, and others. AR can also be restricted to the nasal mucosa (Local allergic rhinitis: LAR). Special aspects in children may include the significant increase of AR in school age and the so-called “allergic march” during childhood.

Treatment of AR aims at eliminating both, symptoms and inflammatory reactions of the mucous membranes. Medical treatment is based on – but not limited to – antihistamines and nasal steroids.

Allergen-specific immunotherapy (AIT) is the only causal therapy for AR besides allergen avoidance and there is increasing evidence that AIT should be used as early as possible in the course of the illness to avoid progression of the disease and new sensitisations, but too little is known on longitudinal disease development and treatment effects.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

Longitudinal studies with and without treatments are required in childhood and adults to better understand the natural disease progression and opportunities of medical interventions.

As the most important treatment option for AR allergen-specific immunotherapy should be improved by developing hypoallergenic and more efficacious vaccines, different application routes or addition of adjuvants.

AR is an immunological disease of the upper airway mucosa but is routinely diagnosed using dermal and laboratory blood tests. Tests addressing the nasal mucosa are required especially with regard to its immunological and barrier function.

The differentiation between AR and nonallergic rhinitis needs more reliable and accurate tests.

Local allergic rhinitis needs accurate definition and diagnostic procedures.

Innovative approaches

Component-resolved diagnosis can boost accuracy of the diagnosis and optimise the therapeutic outcome.

Humanized anti-IgE antibodies were shown to have additive effects if combined with AIT.

Such innovative approaches may be useful in special patient populations implementing the stratification strategies coined by the term “stratified medicine” or “precision medicine”. The major endotype of AR is determined by an immunological deviation toward a type 2 immune response and studies on biomarkers may identify patient subpopulations who might benefit from a targeted approach with biologicals. Novel monoclonal antibodies interfering with type 2 cytokines (IL-4, IL-5, IL-13) have been used in AR.

The principle of precision or stratified medicine should be applied to AR both for diagnosis and therapy, however the potential role of anti-IgE and Th2 cytokine-directed antibodies in AR needs further investigation.

FURTHER READING

1. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147-334.
2. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017;140:950-958.
3. Akdis CA, Hellings PW, Agache I. Global Atlas of Allergic Rhinitis and Chronic RhinoSinusitis. European Academy of Allergy and Clinical Immunology 2015.
4. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I et al. Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis - A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. *Allergy* 2017; 72:1297-1305.
5. Morjaria JB, Caruso M, Emma R, Russo C, Polosa R. Treatment of Allergic Rhinitis as a Strategy for Preventing Asthma. *Curr Allergy Asthma Rep* 2018;18:23.
6. Augé J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy* 2018 [Epub ahead of print].
7. Steelant B, Seys SF, Van Gerven L, Van Woensel M, Farré R, Wawrzyniak P et al. Histamine and T helper cytokine-driven epithelial barrier dysfunction in allergic rhinitis. J Allergy Clin Immunol 2018;141:951

Wytske Fokkens, Philippe Gevaert

CHRONIC RHINOSINUSITIS

C2

GAPS IN KNOWLEDGE

Chronic rhinosinusitis (CRS), a disease defined as chronic inflammation of the nose and paranasal sinuses, has a considerable impact on morbidity and quality of life. In Europe, the overall prevalence of CRS is 10.9%, however there is considerable geographical variation, ranging from 6.9% to 27.1%. Smoking, air pollution and the presence of allergy were identified as risk factors for CRS. The EPOS criteria were developed for CRS diagnosis (table 1).

Phenotypically, CRS can be divided in CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). The criterion separating these entities is the presence of nasal polyps that can be found with nasal endoscopy. Whereas in CRSsNP headache is the most prominent symptom, in CRSwNP anosmia and nasal obstruction are predominant. Moreover, especially the patients with CRSwNP often have difficult to control disease combined with severe, often late-onset asthma.

The clinical dichotomization of CRSwNP versus CRSsNP was initially reflected at the molecular level, with a predominance of TH1 cells in patients with CRSsNP and TH2 cells and eosinophils in patients with CRSwNP, however, subsequent studies reported a wider spectrum of immunologic profiles leading to different endotypes (Figure 1).

For now, the mainstay of the treatment of CRSsNP is saline rinsing and chronic use of topical corticosteroids when necessary combined with sinus surgery, usually achieving significant long-term efficacy and/or potentially long-term antibiotics, although the evidence for the latter is limited.

Box 1. EP3OS criteria for diagnosis of chronic rhinosinusitis

Presence of two or more of the following symptoms:

- Nasal blockage, obstruction or congestion
- Nasal discharge (either anterior or posterior nasal drip)
- Facial pain or pressure
- Reduction or loss of smell

One of which should be blockage or discharge
Symptoms should be present during > 12 weeks without complete resolution

AND EITHER:

Endoscopic signs of

- Polyps, and /or
- Mucopurulent discharge, primarily from middle meatus, and/ or
- Oedema or obstruction primarily in middle meatus

CT changes: mucosal changes within the ostiomeatal complex and / or sinuses

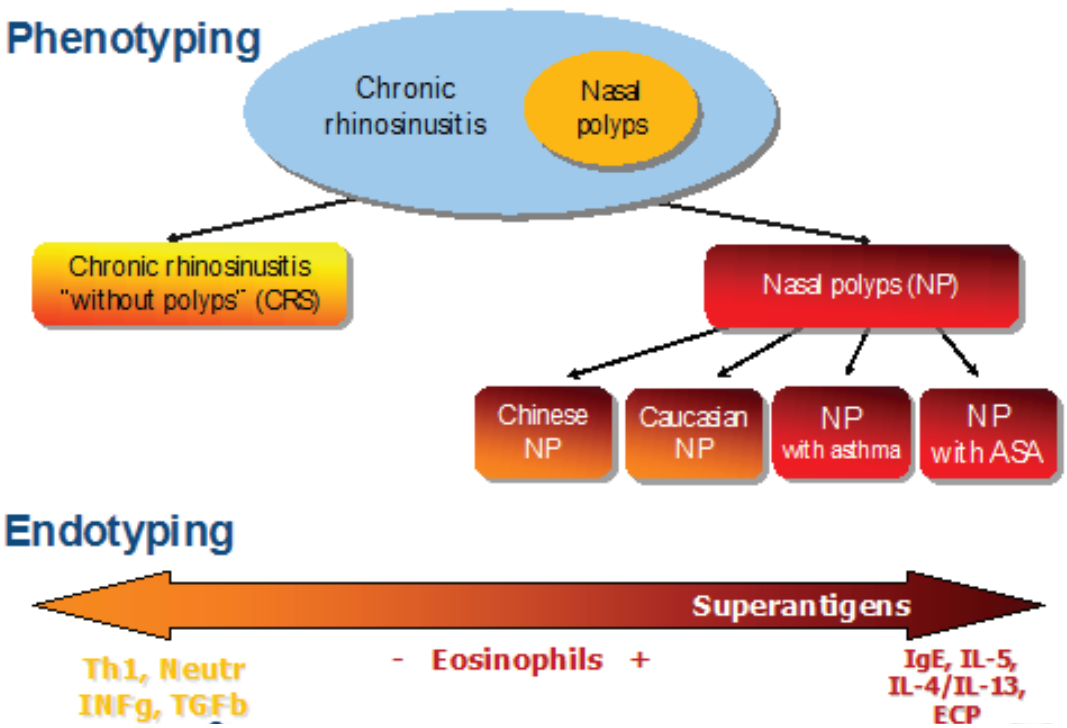


Figure 1. Phenotypes and endtypes in chronic rhinosinusitis with and without nasal polyps.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Endotype classification based on thorough investigation of the pathophysiological mechanisms contributing to the disease will provide more insight in the inter-individual variability of clinical presentation and treatment response in patients with identical phenotypes. In addition, endotyping might in future guide the decision-making process of targeted treatments.

In CRSwNP new treatments based on specific endotypes such as anti-IL-5, anti-IgE, anti-IL4R/13R treatment are at the horizon. These new treatments are partially already available for patients with severe asthma.

The role of the epithelial barrier dysfunction and microbiome and potential pathways for their restoration should be further explored.

FURTHER READING

1. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: Receptors, functions, and roles in diseases. *J Allergy Clin Immunol* 2016;138:984-1010.
2. Varricchi G, Harker J, Borriello F, Marone G, Durham SR, Shamji MH. T follicular helper (Tfh) cells in normal immune responses and in allergic disorders. *Allergy* 2016;71:1086-1094.
3. Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Crameri R et al. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med* 2004;199:1567-1575.
4. Meiler F, Zumkehr J, Klunker S, Rückert B, Akdis CA, Akdis M. In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure. *J Exp Med* 2008;205:2887-2898.
5. Akdis, M. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol* 2006;18:738-744.
6. James LK, Till SJ. Potential Mechanisms for IgG4 Inhibition of Immediate Hypersensitivity Reactions. *Curr Allergy Asthma Rep* 2016;16:23.
7. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Söllner S, Akdis DG et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol* 2013;131:1204-1212.
8. Lund FE, Randall TD. Effector and regulatory B cells: modulators of CD4+ T cell immunity. *Nat Rev Immunol* 2010;10:236-247.
9. Larsen JN, Broge L, Jacobi H. Allergy immunotherapy: the future of allergy treatment. *Drug Discov Today* 2016;21:26-37.
10. Meiler F, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008;63:1455-1463.
11. Fujita H, Soyka MB, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *Clin Transl Allergy* 2012;2:2.
12. Renand A, Shamji MH, Harris KM, Qin T, Wambre E, Scadding GW et al. Synchronous immune alterations mirror clinical response during allergen immunotherapy. *J Allergy Clin Immunol* 2018;141:1750-1760.e1.
13. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organ J* 2015;8:17.
14. Akdis CA, Akdis M. Advances in allergen immunotherapy: aiming for complete tolerance to allergens. *Sci Transl Med* 2015;7:280ps6.
15. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol* 2017;140:1485-1498.
16. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy* 2017;72:1156-1173.

Jean Luc Fauquert

ALLERGIC CONJUNCTIVITIS

C3

GAPS IN KNOWLEDGE

Allergic conjunctivitis (AC) gathers clinical entities that are underdiagnosed: some are very frequent and benign (seasonal and perennial allergic conjunctivitis (SAC, PAC) whereas others are rarer but severe because they are involving the cornea (Vernal keratoconjunctivitis and atopic keratoconjunctivitis (VKC, AKC) or other tissues of the ocular surface (Blepharoconjunctivitis and lid eczema) (Table 1).

Many stakeholders may be involved in AC. General practitioners and pharmacists may intervene in the initial therapeutic management. Ophthalmologists intervene most frequently to cope with complications, allergists in its investigation. ENTs and dermatologist may also frequently be requested since allergic conjunctivitis is very often associated with allergic rhinitis or atopic dermatitis.

The burden of AC is considered high. Benign forms affect more that 20% of the general population. Severe forms are often responsible for various complications, which can impair the visual function. Moreover, dry eye is frequently encountered as a result of long term evolution of AC. Control of the environment is a major point of the therapeutic management of AC.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Epidemiology of AC

Research priorities

- The scope of AC management should be precisely defined. In daily practice this pathology is managed by many stakeholders in variable ways in the different countries of Europe
- The position of AC in the allergic march is unclear. The age of onset and frequency of AC should be evaluated in comparison with other allergic diseases like allergic rhinitis, asthma, and atopic dermatitis. The triggering role of the ocular surface for initiating the allergic reaction cascade is under investigation.

Standards and quality criteria. Epidemiologic AC evaluation should cover a large number of European countries

Table 1.

	SAC	PAC	VKC	AKC	CBC
Incidence	++++	++	+	+/-	-
Immunologic mechanism	IgE	IgE	IgE/non-IgE	IgE/non-IgE	Non IgE
Clinical context	Allergic rhinitis	±allergic rhinitis	Atopy	Atopic dermatitis	± Lid eczema
Conjunctiva	Papillae	Papillae	Giant papillae	Giant papillae	0
Lids	0	0	0	Eczema	Eczema
Cornea	0	± SPK	SPK, Trantas dots, Ulcers, plaque	SPK, ± fibrosis, Chronic ulcers, neovascularisation	0
Priorities for research	Epidemiology; Healthcare costs	Epidemiology; Role of environment; QoL	Mechanisms; QoL; Healthcare costs	Mechanisms; QoL; Healthcare costs	QoL

Innovative approach: as AC is responsible for easy recognizable signs, studies based on online questionnaires once validated should be available.

Pathophysiology, diagnosis and treatment of AC

should be addressed particularly for VKC and AKC. They both account for experimental models of local allergy.

Research priorities

- Ocular surface is obviously an antigen presenting location. Its involvement to induce an allergic reaction located on the ocular surface or expressed in other tissues is a major research theme for the years to come
- Mechanisms of allergy should be addressed specifically for the ocular surface
- Relationship with the dry eye syndrome is to be investigated as AC and the dry eye share many symptoms, with particular respect to local environment.
- Techniques for local sampling need improvement and standardization since non-specific hyper reactivity can be induced by any stimulation of the ocular surface.
- Investigation of the value of specific IgE testing on tears is a primary and urgent concern because ocular allergy can be expressed only locally without any systemic marker.
- The role of allergy and environment factors associated to ocular surface diseases is a research priority. In this regard, the exact position of the Conjunctival Provocation Test (CPT) should be assessed in clinics and research.
- Evidencing the relationship between exposure to allergens or irritants is challenging in occupational medicine
- Therapeutic strategies for benign and severe forms of AC should be addressed in a collaborative way in precision medicine. Flowcharts are required

Standards and quality criteria

- The establishment of laboratories involved in ocular surface investigation and collaboration between ophthalmology and basic allergy research is needed.
- Quality criteria for CPT were published in Allergy 2017. FDA uses CPT to assess the efficacy of local drugs.

Innovative approach

- The ocular surface is easily accessible to investigation. Its role in allergy is of major importance in terms of investigation (local allergy) and treatment (local immunotherapy).
- The precision medicine approach in managing ocular surface diseases based on evidencing allergy involvement in eye diseases could be rewarding

Quality of life and healthcare costs

Previous reports evidenced that quality of life is particularly impaired in patients affected by AC. Moreover, AC remains the most responsible for quality of live impairment in patients with allergy affecting other organs.

Research priorities

- Clinical care pathways to manage AC are a major priority concern. Wrong orientation of the patient is frequent and indication of drugs often missed. Optimizations of the patient's pathways could result in reducing healthcare expenses.
- Quality of life scores should be validated across European countries
- Healthcare costs should be assessed across different countries in Europe.

Standards and quality criteria and innovative approach

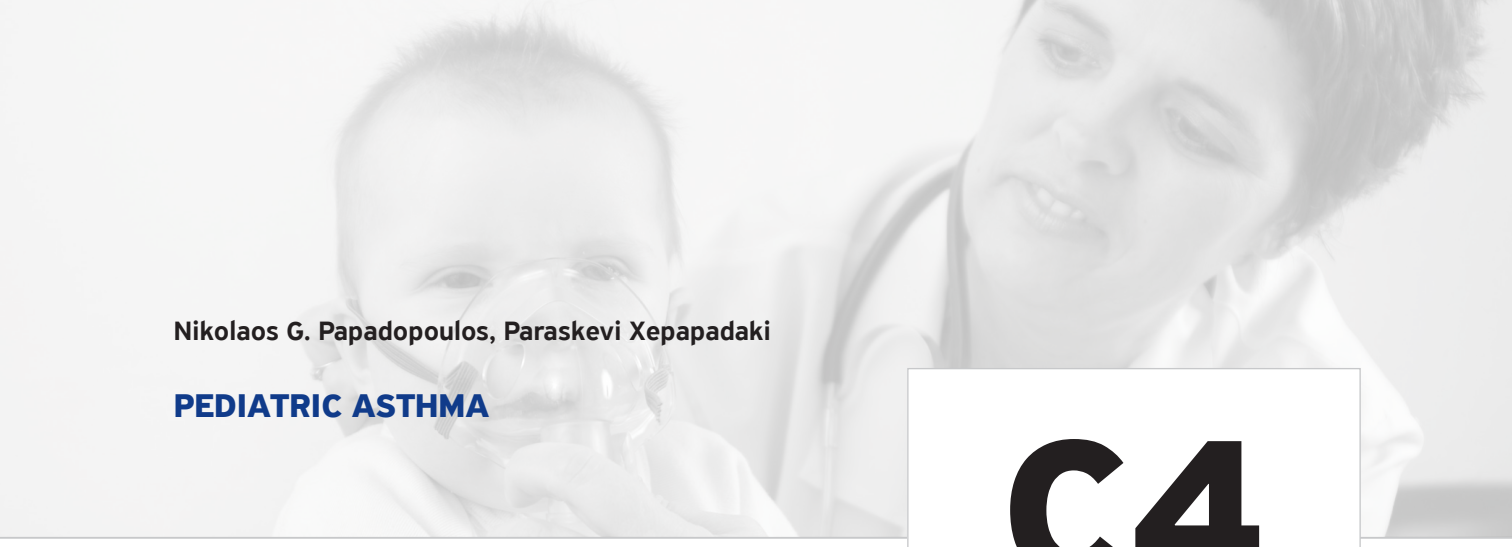
- Use of day-to-day reporting devices for recording and rating ocular symptoms.

List of abbreviations

SAC	Seasonal allergic conjunctivitis
PAC	Perennial allergic conjunctivitis
VKC	Vernal keratoconjunctivitis
AKC	Atopic keratoconjunctivitis
CBC	Contact blepharoconjunctivitis
QoL	Quality of Life
SPK	Superficial punctuate keratitis

FURTHER READING

1. Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012;67:1327-1337.
2. Leonardi A, Piliego F, Castegnaro A, Lazzarini D, La Gloria Valerio A, Mattana P et al. Allergic conjunctivitis: a cross-sectional study. *Clin Exp Allergy* 2015;45:1118-1125.
3. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI position paper. *Allergy* 2014;69:854-867.
4. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, Calder V, Silva D, Kvenshagen BK. Conjunctival allergen provocation test: guidelines for daily practice. *Allergy* 2017;72:43-54.
5. Baye A, Batellier L, Doan S, Bury T, Vitte J. Multiplex assay of specific IgE antibodies in tear fluids by means of microarray technology. *J Fr Ophtalmol* 2016;39:e183-185.
6. Leonardi A, Doan S, Fauquert JL, Bozkurt B, Allegri P, Marmouz F et al. Diagnostic tools in ocular allergy. Allergy 2017;72:1485-1498.
7. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy* 2011;41:1263-1272.
8. Fauquert JL. [Childhood allergic conjunctivitis: the allergist's point of view]. *J Fr Ophtalmol* 2007;30:292-299.



Nikolaos G. Papadopoulos, Paraskevi Xepapadaki

PEDIATRIC ASTHMA

C4

GAPS IN KNOWLEDGE

Most often, asthma starts early in life. From a different perspective, an increasing proportion of children experience recurrent symptoms of airway obstruction. While asthma symptoms are generally more prevalent in the 'western' world, the condition is clearly expanding worldwide, reaching numbers and proportions of pandemic size. The disease burden is high both for the patients and their families, whose quality of life is affected, but also for healthcare systems. While there is ongoing debate on the limits of the 'disease' (or syndrome or symptom, etc.), the number of studies focusing in children is far less than those in adults, and in many cases, showing moderate therapeutic benefit. This can be attributed to developmental differences, such as the size of the airways or the immaturity of the innate and adaptive immune responses, but also to differing pharmacodynamics and less robust outcomes. Efforts for prevention have only provided minimal results, such as in relation to avoidance of tobacco smoke or pollution, and no pharmacological treatment currently appears to be able to reduce or reverse the natural history of the disease. It is also unfortunate that 'asthma' is usually addressed as an isolated lower airway condition, despite overwhelming evidence that most patients experience multiple problems from the nose, skin etc. Another relatively recent trend is the focus on severe asthma, based on the increased cost and unmet need in that part of the disease spectrum. Finally, long-term side effects from medication, especially steroids, are an increasing concern, without nevertheless ignoring the fact that inhaled steroids have been a major landmark in asthma treatment. Recently, several voices have been raised supporting the need for radically new approaches towards asthma. This should certainly apply to pediatric asthma.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Asthma and/or asthma-like disease should be acknowledged from infancy.

A never-ending debate on when asthma starts and how we should call conditions with asthma-like symptoms early in life, have only led to exclusions and agnosticism. Considering that everybody agrees that 'asthma' (whatever it means) is pleomorphic, there is little reason to apply arbitrary cut-off points, such as the age of 5 years, rather than concentrating on the identification of risk fac-

tors associated with persistence or remission of recurrent symptoms of airway obstruction early in life, and their effective management.

Definitions should be agreed, based on the whole spectrum of needs (patients, healthcare systems, research).

Unfortunately, even specialists often forget that definitions are arbitrary and 'asthma' (or any other condition) is exactly and only what the community decides it to be. Therefore, any discussion on what asthma 'is', should be able to demonstrate the possible consequences of a given definition on patients, either directly or indirectly through research, regulation, and the healthcare system, as well as on society in general. Wide definitions (e.g. 'everything that wheezes…') are sensitive, but require additional work for defining subgroups with different management needs and prognosis. On the contrary, narrow definitions (e.g. '12% FEV1 reversibility') are specific and facilitate overall management but leave out and often neglect a large number of patients that do not fulfil the required criteria. In either case, complete solutions are required and this is an unmet need. At a time when concepts like 'precision medicine' and 'treatable traits' are gaining momentum, it makes sense to retain 'old' terms such as asthma in their wider sense, while directing efforts to identify and provide new nomenclature for specific, treatable, syndromes.

Host-environmental interactions, should be scrutinised under a developmental focus.

It is clear that 'pediatric asthma', despite contrasted to 'adult asthma' as a unique phenotype, is much more than one condition. Developmental milestones, as biological functions beyond chronological age, should be incorporated in all research efforts, especially in systems approaches that for the first time promise the description of complexity in a manageable manner. Ongoing efforts of multi-omics analyses need to be aimed towards clinically meaningful conclusions, mainly through robust validation.

Asthma treatments should reach young children much faster.

Despite the ever-growing number of biologicals approaching or already marketed for asthma, plans for pediatric trials always trail behind by quite some time. From the patient and public health perspective there is a major unmet need to reduce this time gap considerably. "Pediatric Investigation Plans", required by the European Medicines Agency, for marketing authorisation of new medicinal products, is a step towards the right direction, but more is needed.

Prevention is the key priority, with potentially enormous impact.

Prevention, that can only take place during childhood (or even during pregnancy), is clearly the ultimate target for asthma and allergic diseases. Nevertheless, due to the complexity of the disease, high regulatory demands and lack of funding, only few studies have looked into primary prevention. Recent results on secondary prevention such as the GAP trial are very promising, while the ongoing PARK study is another example of the direction that research should be taking in the next decade.

FURTHER READING

1. Global Initiative for Asthma (GINA) report. Global strategy for asthma management and prevention In. Available at: http://www.ginaasthma.org; 2017 update.
2. Papadopoulos NG, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R et al. International consensus on (ICON) pediatric asthma. Allergy 2012;67:976-997.
3. Papadopoulos NG, Androutsopoulou A, Akdis C, Dahlen SE, Djukanovic R, Edwards J et al. Asthma research in Europe: a transformative agenda for innovation and competitiveness. *Eur Respir J* 2017;49.pii: 1602294.
4. Papadopoulos NG, Agache I, Bavbek S, Bilo BM, Braido F, Cardona V et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.
5. Asthma Commission. Discussion with two authors of a new Lancet Commission about the need for a new approach to prevent, manage, and cure asthma. The Lancet September 11, 2017.
6. Georgountzou A, Papadopoulos NG. Postnatal Innate Immune Development: From Birth to Adulthood. *Front Immunol* 2017;8:957.
7. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018; 141:529-538 e513.
8. ClinicalTrials.gov. Preventing Asthma in High Risk Kids (PARK). Preventing Asthma in High Risk Kids (PARK). Last update February 2018.

Zuzana Diamant, Susanne JH Vijverberg, Leif Bjermer

ADULT ASTHMA

C5

GAPS IN KNOWLEDGE

Adult asthma can be grouped into 1) long-standing asthma (with symptoms that started in childhood), 2) late-onset or adult-onset asthma and 3) childhood asthma that relapses during adulthood. Adult-onset asthma has been associated with more severe disease and a poorer response to asthma treatment compared to childhood-onset asthma. Clinical predictors of persistence of adult-onset asthma are: older age, worse asthma control, need of higher doses of inhaled corticosteroids, more severe airway hyperresponsiveness, nasal polyps, and higher levels of blood neutrophils and sputum eosinophils.

In the past decade, non-invasive sampling methods combined with high-tech omics technologies helped to confirm the heterogeneity of adult asthma. Applying unbiased clustering analyses on system biology-acquired data is increasingly enabling to link distinct clinical phenotypes to inflammatory and molecular pathways and to identify biomarkers. It has now been established that especially severe adult asthma consists of several different clinical and inflammatory phenotypes and endotypes, characterized by distinct biochemical pathways.

There is an urgent need to characterize underlying pathophysiology and pathways of distinct subphenotypes of asthma with adult onset. Presently, type-2 (T2) asthma has been quite well characterized, including clinically applicable biomarkers i.e., serum IgE, blood eosinophils, sputum eosinophils and FeNO, which has resulted in the development and (near) registration of several T2-targeted treatment modalities including mepolizumab (anti-IL-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5), dupilumab (anti-IL-4/-13), and several CRTH2 antagonists (DP2-antagonist); while the first anti-alarmins, such as tezepelumab (anti-TSLP), are entering clinical development stages. Non-T2 or T2 low asthma still represents an unmet need, whose underlying mechanisms are not fully clarified, hence lacking adequate biomarkers and targeted treatment options. Other unmet needs include more precise biomarkers and cut-offs, composite biomarkers and documentation on their stability/behavior over time. In parallel, a consensus on treatment algorithms (which targeted therapy for which patient) is urgently needed, as well as longitudinal follow-up of response to novel biologicals in real life settings. In addition, there is a need for specific treatment guidelines for elderly asthmatics. Currently available guidelines do not take into account elderly asthmatics as recommendations are usually based on clinical trials in which elderly asthmatic patients (>60 years) are often not included.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

In view of overlapping clinical and pathophysiological features and inflammatory pathways across chronic airway diseases, such as asthma, COPD and ACO (asthma-COPD overlap) along with the urge to provide the right patient with the right therapeutic options, precision medicine guided by treatable traits is being advocated instead of a 'one size fits all' approach according to individual disease labels. Treatable traits consist of pulmonary, extra-pulmonary and behavioral or lifestyle-induced disease components that can be measured and targeted and which may be overlapping across the spectrum of chronic airway diseases (e.g., eosinophilic airway inflammation, airflow limitation, obesity, smoking). The recognition of asthma and COPD as systemic disorders will also highlight pathophysiological links, including modulating relationships between the immune system and the respiratory and gut microbioma.

Presently, biologics are indicated for more severe patients uncontrolled on standard maintenance therapy. However, with new techniques, biologics will become cheaper and hence, more accessible to patients with milder disease. This will change the focus from immediate risk reduction to disease modification aimed to reduce long term health care costs. Moreover, less expensive biologics will also facilitate the use of biomarker-guided combinations aimed to completely control the underlying inflammation. In line with recent developments, combinations of multi-omics technologies, including the combination of genomics, inflammomics and breathomics technologies, with clinical characteristics, are foreseen to be increasingly applied in the management of chronic airway diseases guiding diagnosis, management, therapies and monitoring (including point-of-care testing).

Furthermore, electronic Health (eHealth) and mobile Health (mHealth) will continue to revolutionize the self-management of asthma, as well provide valuable data input for research in the field of chronic airway diseases.

Future (research) strategies for adult asthma should be aimed at education, prevention and alignment with cost-effectiveness in a multidisciplinary setting.

FURTHER READING

1. Dunn RM, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult asthma. *Allergy* 2018; 73:284-294.
2. Westerhof GA, Coumou H, de Nijs SB, Weersink EJ, Bel EH. Clinical predictors of remission and persistence of adult-onset asthma. *J Allergy Clin Immunol* 2018;141:104-109.e3.
3. Hekking PP, Loza MJ, Pavlidis S, de Meulder B, Lefaudeux D, Baribaud F et al. Pathway discovery using transcriptomic profiles in adult-onset severe asthma. *J Allergy Clin Immunol* 2018;141:1280-1290.
4. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G et al. After asthma: redefining airways diseases. *Lancet* 2018;391:350-400.

Knut Brockow, Charlotte Mørtz,
Peter Schmid-Grendelmeier, Thomas Werfel

DERMATOLOGICAL ALLERGIES

C6

Dermatological diseases or manifestations associated with allergies are in particular, but not exclusively, atopic dermatitis, contact dermatitis including occupational contact dermatitis, urticaria, mastocytosis and cutaneous drug hypersensitivity reactions.

ATOPIC DERMATITIS

GAPS IN KNOWLEDGE

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases with a prevalence in the general population of 15-20% in childhood and around 10% in adulthood. The disease starts mostly in infants and leads to debilitating pruritus, sleeplessness and a severe reduction of quality of life in the families.

Although it is well known that a genetic background (e.g. mutations leading to an impaired skin barrier) and allergies associated with increased IgE production contribute to this chronic disease, there are still fundamental deficits in research and management of AD.

Epidemiological data is insufficient, especially in adults with AD. The pathophysiology of an impaired skin barrier function and the consequences of genomics and proteomics in AD remains unclear. It is unknown what leads to the severe itching characteristic for AD and its regulation by psychosomatic factors such as stress. It is not completely known how specific IgE antibodies lead to an eczema and why a non-allergic (“intrinsic”) variant of AD exists. The clinical role of microbial colonization in the course of disease is also still not fully understood. Recently, it has been postulated that sensitization through the skin in patients with AD and impaired barrier function would be crucial for the development of food allergy and the atopic march from cutaneous to respiratory allergic diseases. Approaches on how to counteract this mechanism through improvement of the skin barrier are sparse.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- Better correlation of well-described phenotypes in AD with genotypes, upregulated proteins and biomarkers
- How to prevent AD in children at high risk and secondary prevention
- Develop new treatment approaches addressing the skin barrier destruction as well as immunological target structures relevant in AD.

Standards and quality of care

- Training patients with AD to live with and manage their disease through educational programs

Innovative approaches

- Innovative approaches are needed in the field of microbial colonisation affecting AD severity and how to counteract the barrier impairment leading to sensitizations.

CONTACT DERMATITIS

GAPS IN KNOWLEDGE

Contact dermatitis is a non-infectious inflammation of the skin driven by direct contact with noxious or allergic substances. Contact dermatitis is particularly common on the hands and is often associated with occupational exposure in adults.

Contact dermatitis is a field under constant development because the environment changes over time due to introduction of new chemicals in consumer and industrial products and phasing-out of other chemicals. There is no reliable laboratory test to diagnose the disease or predict the potency of a substance to induce contact dermatitis.

Allergic contact dermatitis (ACD) in children appears to increase, and contact sensitization may already begin in infancy. The prevalence of contact sensitization (15-20%) is much higher than in the prevalence of manifest ACD (5-10%). The diagnosis of ACD is based on exposure history, dermatitis pattern and patch testing. ACD may be difficult to separate from atopic dermatitis in childhood and the diseases may even occur together. Patch testing is relevant as a screening tool in the management of children with atopic dermatitis as they may have unacknowledged contact allergies contributing to or maintaining their skin symptoms. Irritative contact dermatitis has to be differentiated from ACD.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- Understanding the mechanism of allergic and irritative contact dermatitis as well as the development of new diagnostics and predictive *in vitro* test.
- Constant identification of novel relevant contact allergens
- Development of better *in vitro* diagnostic tools

Standards and quality of care

- In order to reduce the number of patients with contact sensitization or contact allergy, the potential of substances to induce contact allergy should be better monitored, and substances at risk should be banned from the market.
- Focus should also be on exposure already in childhood
- In occupations with high risks for contact dermatitis, more preventive measures should be implemented.
- Better monitoring of occupational eczemas, interventional studies to address the efficacy of preventive measures and better monitoring of the allergenic potential of substances should be employed.
- A declaration of potential allergens should be improved.
- Rehabilitation measures for secondary prevention should include educational programs.

Innovative approach

- The relation between atopic dermatitis and allergic contact dermatitis has to be approached including the role of the barrier impairment

URTICARIA

GAPS IN KNOWLEDGE

It has been reported that about 1 in 5 persons in industrialized countries will develop urticaria. The disease is characterized by intensely itching wheals or deeper swellings. The most common trigger factors on a global level appear to be microbial infections, which elicit non-specific inflammatory reactions leading to cutaneous mast cell degranulation. Urticaria may also induced by physical elicitors, may rarely also be caused by IgE-mediated allergy or may arise spontaneous without known cause. It is unclear why in some patients with chronic urticaria analgetics such as acetylsalicylic acid may lead to an exacerbation of urticaria. Some patients show reactivity against their own serum and/or autoantibody production against the IgE receptor or against IgE. Whereas in many patients the disease stops after few days, it becomes chronic and ongoing in others without any known prognostic factors.

Some diseases with distinct pathophysiological causes such as urticarial vasculitis and autoinflammatory syndromes may present with clinical features of urticaria.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- Understanding the mechanism of non-allergic inducible and spontaneous urticaria in order to better target the disease
- Factors affecting the course of chronic spontaneous urticaria and affecting the success of treatment should be investigated.
- At the moment, only few medications are approved for the treatment of urticaria. The development of more and better therapies is needed.
- The study of physical factors inducing urticaria should lead to a better understanding of the pathways involved in mast cell activation in susceptible patients.

Standards and quality of care

- Paper documentation of urticaria severity
- Diagnosis of urticarial syndromes
- Diagnosis of inducible urticaria by standardized tests
- Determination of trigger factors based on information from the history
- Adherence to guideline recommendations

Innovative approach

- Subforms of identified chronic spontaneous urticaria should be described based on severity, course, mechanism and response to therapy.
- The association between mental stress and mental disorders may be studied to look for new treatment approaches.

MASTOCYTOSIS

GAPS IN KNOWLEDGE

Mastocytosis is a disease with an increased number of mast cells and based on a non-genomic activating mutation in *c-kit*. It is detected mainly because of skin lesions (maculopapulous mastocytosis, urticaria pigmentosa) or because of severe anaphylaxis following hymenoptera stings. It remains unsolved why there is a higher reactivity of mast cells to hymenoptera stings in patients with mastocytosis as compared to other allergic patients. As the point mutation in *c-kit* is present in about all adult patients with systemic mastocytosis, a reason for a different severity (indolent vs. aggressive form of mastocytosis) is unknown; also it remains unclear why patients with mastocytosis predominantly react against hymenoptera venom, but not so much against drugs and foods. It is unknown why about 2/3 of children loose this disease till adulthood, in some cases despite presence of a mutation, whereas it is persistent in adults.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- Encompass the search for a hyperreactive mast cell phenotype in mastocytosis or other pathways leading to hyperreactivity.
- Investigate which patient with mastocytosis is at risk for developing severe anaphylaxis.
- Clarify what factor determines the severity and aggressiveness of disease in addition to the *c-kit* mutation.
- Development of new drugs without severe unwanted side effects

Standards of care

- Mastocytosis is underdiagnosed and has to be recognised in patients with anaphylaxis and those with few skin lesions.
- In adults with mastocytosis, a bone marrow biopsy should be taken.
- Osteoporosis has to be looked for (and treated) in all adults with mastocytosis.
- An adrenaline autoinjector has to be prescribed and explained to all patients with mastocytosis at risk for anaphylaxis.
- Patients with hymenoptera venom allergy and mastocytosis require immunotherapy.

Innovative approach

- Alternatives to lifelong hymenoptera immunotherapy should be explored.

FURTHER READING

1. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol* 2018;32:657-682.
2. Muraro A, Lemanske RF Jr, Hellings PW, Akdis CA, Bieber T, Casale TB et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2016; 137:1347-1358.
3. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387:1109-1122.
4. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *J Invest Dermatol* 2017;137:18-25.
5. de Waard-van der Spek FB, Andersen KE, Darsow U, Mortz CG, Orton D, Worm M et al. Allergic contact dermatitis in children: which factors are relevant? *Pediatr Allergy Immunol* 2013;24:321-9.
6. de Waard-van der Spek FB, Darsow U, Mortz CG, Orton D, Worm M, Muraro A et al. EAACI position paper for practical patch testing in allergic contact dermatitis in children. *Pediatr Allergy Immunol* 2015;26:598-606.
7. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis* 2015;73:195-221.
8. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. *Allergy* [Epub ahead of print].
9. Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer MJ. Chronic inducible urticaria: a systematic review of treatment options. *J Allergy Clin Immunol* 2018;141:1726-1734.
10. Ginsberg S, Rosner I, Rozenbaum M, Slobodin G, Zilber K, Boulman N, et al. Autoinflammatory associated vasculitis. *Semin Arthritis Rheum* 2016;46:367-371.
11. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy* 2014;69:1267-1274.
12. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-232.
13. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37: 435-453.
14. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O et al. Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future. *Cancer Res* 2017;77:1261-1270.

Margitta Worm, Barbara Bohle, Antonella Muraro

FOOD ALLERGY

C7

GAPS IN KNOWLEDGE

Food allergy can result in considerable morbidity, impact negatively on quality of life, and prove costly in terms of medical care.

It is mostly IgE-mediated and a chronic disease affecting up to 4% of the European population. The symptoms range from skin symptoms but can sometimes become life threatening. Other food induced allergic disorders are mixed IgE- and cell-mediated disorders like atopic eczema and eosinophilic gastrointestinal manifestations like eosinophilic esophagitis. Cell-mediated food-induced allergic disorders affect primarily infants and include dietary protein induced proctitis and proctocolitis and food protein induced enterocolitis syndrome.

There is a real paucity of 'real-time' data on the frequency, disease burden and outcomes of adult food allergy in Europe, which hampers efforts for healthcare service planning and policy deliberations. Pool prevalence data of food allergy in Europe show a higher prevalence for self-reported food allergy in comparison to sensitization alone and sensitization combined with symptoms. Based on food challenge data and dependent on the food allergen the point prevalence ranges between 1 and 3,7%. The diagnosis of food allergy depends on the patient's clinical history, the determination of the sensitization measured by specific IgE and/or a skin prick test followed by an elimination diet and oral food challenges (Figure 1).

Oral food challenges (OFC) are usually required to confirm the diagnosis of food allergy, to monitor food allergy or to prove oral tolerance to a given food. There are guidelines including the one from EAACI that describes procedures for OFC in detail. OFC can be performed in an open or double-blinded manner. The double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard diagnostic test for the diagnosis of food allergy. In order to avoid severe reactions patients receive the food in titrated doses often with half logarithmic dose increments at set intervals. For many foods such as cow's milk, hen's egg, peanut or tree nuts, these doses range from 3 mg to 3 g of food protein. Food challenges are usually stopped if objective clinical reactions are observed or if the highest challenge dose is consumed without clinical symptoms. For patients with non-IgE-mediated reactions challenges tailored on the individual modalities of reactions should be designed.

IgE antibodies specific for individual food allergens are measured using promising novel diagnostic approaches such as molecular or component resolved diagnosis (CRD), with a potential to improve the specificity of testing and the specificity for the selected food. This can be performed either

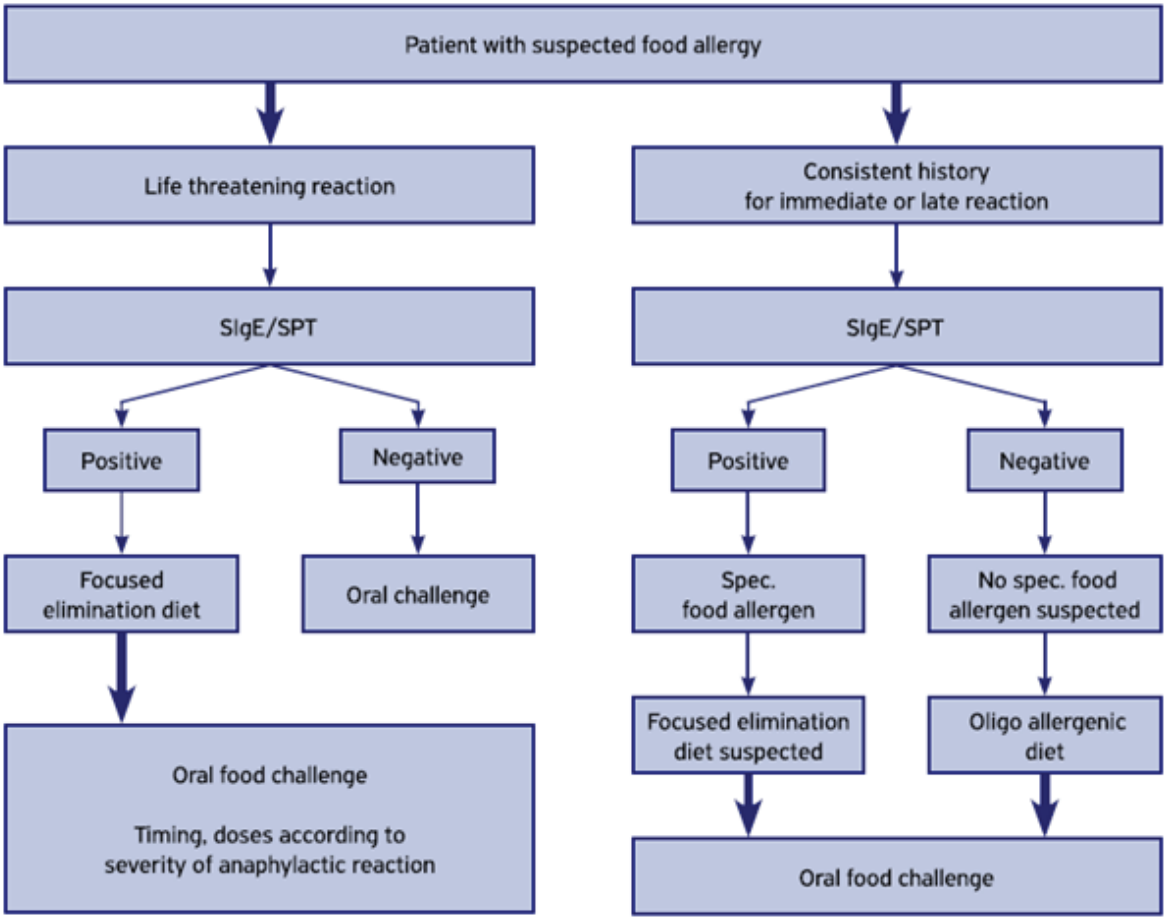


Figure 1. Algorithm of the diagnosis of food allergy, Muraro et al., Allergy, 2014.

in a single test format or in a microarray. The diagnostic accuracy, risk assessment and cost effectiveness of CRD for food allergy requires further research in large scale clinical trials considering not only affected subjects but also sensitized and non-sensitized individuals.

A number of expensive diagnostic alternative approaches are sometimes promoted to physicians and often used by complementary and alternative medicine practices in case of suspected food allergy. Examples are bio-resonance, kinesiology, iridology, hair analysis, cytotoxic test and IgG and IgG4 determination. These tests are not yet validated and cannot be recommended for diagnosing food allergy.

The clinical management of food allergy includes short-term interventions to manage acute reactions and long-term strategies to minimize the risk of further reactions. The latter aim is primarily achieved through dietary modification, education and behavior approaches to avoid allergens in pharmacological and non-pharmacological management strategies for further reactions. Dietary avoidance is the key intervention in the management of food allergy resulting in complete or almost complete with resolution of symptoms. Little research has been published about dietary eliminations due to the difficulty to perform randomized controlled trials in subjects for ethical issues. Individual tolerance levels to the allergenic food may

differ and change over time especially in children and may affect the stringency of avoidance advice. Education is the key-player of an effective long-term elimination diet. Patients, their families, close relatives and caregivers should be aware of risk situations and should be instructed in reading labels and how to avoid the relevant food allergens both in- and outside the home. For the treatment of food allergy, specific immunotherapy with food allergens using the subcutaneous, oral, or sublingual route has been assessed. Although the published data so far have suggested a benefit of specific immunotherapy for food allergy, it is currently recommended to be performed only in highly specialized centers with expert staff and adequate equipment and in accordance with clinical protocols approved by local ethics committees. The need for further exploration of immunotherapy with food allergens is high. As some adverse effects have been reported , the need for further exploration of immunotherapy with food allergens is high.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Individuals suffering from IgE-mediated food allergy usually have to practise life-long food allergen avoidance. There is a general duty of care on the food industry and obligations in European Union legislation to reduce and manage the presence of allergens alongside other food hazards. Major concerns have been raised by patients, carers and patient groups about the use of precautionary 'may contain' labelling to address the issue of unintended presence of allergens; these therefore need to be reconsidered.

New and improved allergen detection methods should be evaluated for their application in food production. There is an urgent requirement for effective communication between healthcare professionals, patient organizations, food industry representatives and regulators to develop a better approach to protecting consumers with food allergies.

General recommendations

- Access to allergy consultation for a better diagnosis and management of food allergy (doctors, dietitians)
- Reimbursement policy
- Research on cofactors increasing symptom severity or the risk of sensitisation
- Education (patients, doctors, dietitians, industry)
- Risk assessment

Specific recommendations (table 1)

Table 1. Specific recommendations.

	Research priorities	Standards and quality criteria	Innovative approach
History	standardised quesionnaires	validated	interactive online-systems
Diagnosis	prick-test material specific IgE testing cellular tests eliminination diet oral challenge test	licensed extracts validated validated systems validated systems validated protocols harmonisation of protocols	recombinant proteins and peptides ex vivo cell testing large cohort studies clinical studies
Therapy	specific immunotherapy	standardised licensed protocols	different routes layer cohort studies
Avoidance	allergen labelling	safety thresholds	QR-codes

FURTHER READING

1. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69:1008-1025.
2. Muraro A, Hoffmann-Sommergruber K, Holzhauser T, Poulsen LK, Gowland MH, Akdis CA et al., EAACI Food Allergy and Anaphylaxis Guidelines. Protecting consumers with food allergies: understanding food consumption, meeting regulations and identifying unmet needs. Allergy 2014;69:1464-1472.
3. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026-1045.
4. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A et al., Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol* 2015;136:258-61. Erratum in: *J Allergy Clin Immunol* 2015;136:1710.
5. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol* 2016;27 Suppl 23:1-250.
6. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol* 2017;28:728-745.
7. Pajno GB, Fernandez-Rivas M2, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018;73:799-815.

Marina Atanaskovic-Markovic, María José Torres Jaen

DRUG ALLERGY

C8

GAPS IN KNOWLEDGE

Hypersensitivity drug reactions (HDR) are type B adverse reactions mediated by immunological and non-immunological mechanisms, and despite being a relatively low prevalence phenomenon, are also on the rise, affecting more than 7% of the general population. HDR can be life threatening, may require or prolong hospitalization and lead to changes in subsequent therapy. DHR can prevent patients from receiving first line treatment, meaning they will receive more toxic and expensive drugs. In the case of antibiotics, this can lead to the induction of microbial resistance. Particularly problematic are those cases where there is no adequate substitution for the first-choice drug where desensitization can be an approach.

In children drug allergy is clearly over diagnosed. Viral infections can lead to skin eruptions and mimic drug hypersensitivity reactions, if a drug is taken at the same time. Most of children are labeled as "drug allergic" based only on history.

Drugs are small molecules that act as haptens and bind to a carrier protein, leading to the formation of adducts, and it is these adducts that induce immunological responses. Betalactam antibiotics have the capacity to spontaneously bind to endogenous proteins while quinolones and antiinflammatory non-steroidal drugs usually need to undergo a biotransformation process to acquire protein binding capacity. The lack of knowledge of the candidate target proteins and the adducts formation is one of the main limitation for developing simple and useful *in vitro* tests to diagnose HDR. Therefore, diagnosis is based on *in vivo* approaches such as skin testing and drug provocation tests (Figure 1), methods that are not risk-free for the patients and are both time consuming and expensive for the healthcare system. This is especially problematic for severe reactions where skin tests and provocation tests are contraindicated and the diagnosis is based solely on the clinical history, often leading to inadequate treatment. In that sense, there is an urgent need to develop and validate new *in vitro* tests to diagnose allergic reactions to drugs and make them available to clinicians in order to improve patient care.

There are many variants under the umbrella of HDR, and patients with similar clinical characteristics (phenotypes) can present very different disease evolution and response to treatments. However, current clinical guidelines often ignore disease heterogeneity and causal pathways, leading to contradictory recommendations. It is therefore absolutely necessary to further classify HDR endotypes taking into consideration not only clinical symptoms but also variations in biological, immunological, and pharmacogenomic characteristics.

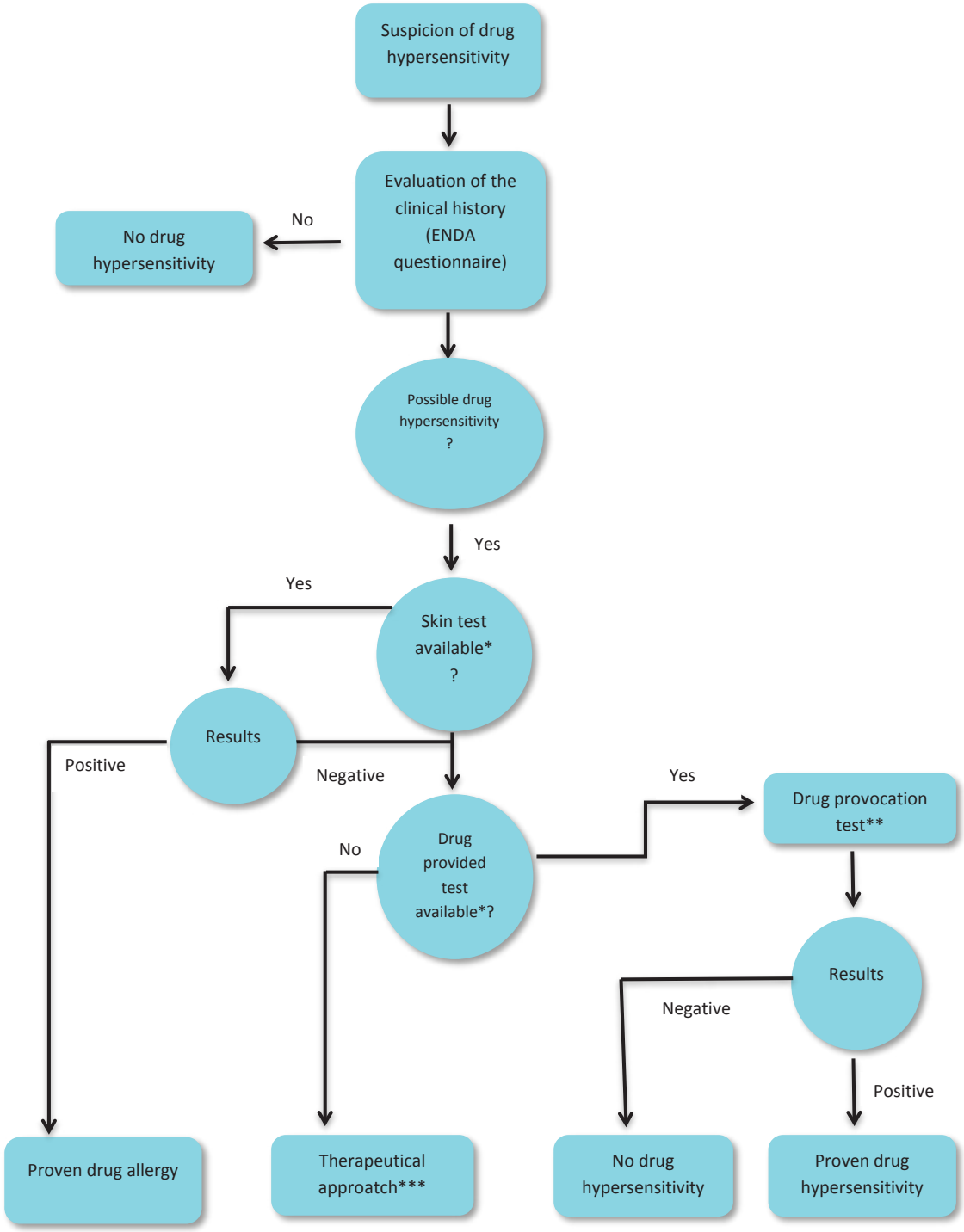


Figure 1. The diagnostic algorithm for drug allergy. * Currently available biological tests to diagnose drug allergy lack sensitivity. **In the absence of contraindications. *** If no alternative is available (e.g. neuromuscular blocking agents, chemotherapeuticaldrugs),readministration of the drug is allowed under surveillance, considering premedication and/or desenzitation.

The precise diagnosis will allow for stratified treatments and a better characterization of subjects in genetic and epidemiologic studies and clinical trials. Therefore, it is necessary to identify risk factors and biomarkers associated with allergic diseases, especially those related to severity. New diagnostic *in vitro* and *in vivo* tests are required to assess the presence and severity of drug allergy. Currently, research efforts focus on improving diagnostic tests and on developing tools that provide better prognostic performance.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- In vitro diagnostic methods
- Classification and stratification of drug allergy based on the endotype/biomarkers driven approach
- Effective de-labelling of patients

Standards and quality criteria

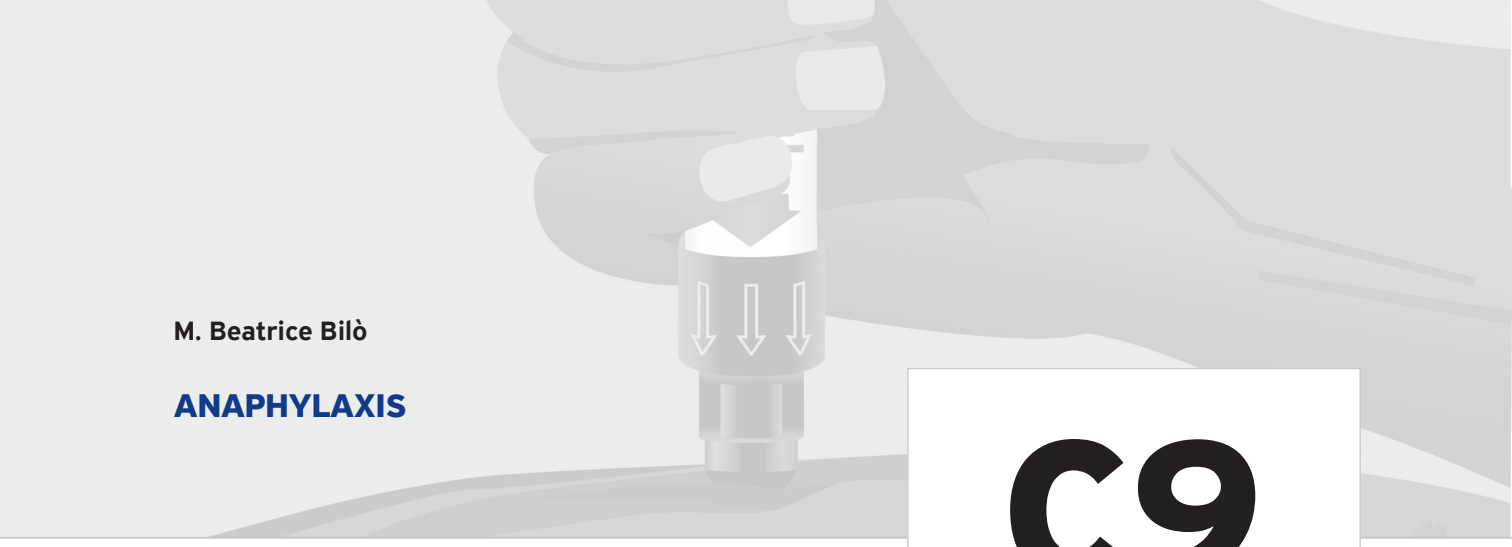
- Performance and interpretation of skin tests, drug provocation tests and *in vitro* tests.
- Quality standard for *in vitro* testing

Innovative approach

- Nanotechnology has been applied to improve *in vitro* diagnosis
- Cellular tests such as basophil activation tests are promising as *in vitro* diagnostic tools

FURTHER READING

1. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA et al. International Consensus on drug allergy. *Allergy* 2014;69:420-437.
2. Atanaskovic-Markovic M, Caubet JC. Management of drug hypersensitivity in the pediatric population. *Expert Rev Clin Pharmacol* 2016:1-9.
3. Ariza A, Collado D, Vida Y, Montañez MI, Pérez-Inestrosa E, Blanca M et al. Study of protein haptenation by amoxicillin through the use of a biotinylated antibiotic. *PLoS One* 2014;9:e90891.
4. Ariza A, García-Martín E, Salas M, Montañez MI, Mayorga C, Blanca-Lopez N et al. Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. *Sci Rep* 2016;6:23845.
5. Garzon D, Ariza A, Regazzoni L, Clerici R, Altomare A, Sirtori FR et al. Mass spectrometric strategies for the identification and characterization of human serum albumin covalently adducted by amoxicillin: ex vivo studies. *Chem Res Toxicol* 2014;27:1566-1574.
6. Ariza A, Garzon D, Abánades DR, de los Ríos V, Vistoli G, Torres MJ et al. Protein haptenation by amoxicillin: high resolution mass spectrometry analysis and identification of target proteins in serum. *J Proteomics* 2012;77:504-520.
7. Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU et al. Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006-1021.



M. Beatrice Bilò

ANAPHYLAXIS

C9

GAPS IN KNOWLEDGE

Anaphylaxis is the most severe allergic reaction, it involves multiple organ systems, can be caused by a number of triggers and conditions, and be deadly.

Despite rapid advances in allergy and immunology with identification of new allergens, biomarkers and cofactors, as well as the availability of new diagnostic tools, there are still many gaps in evidence and knowledge.

There is still much to be done to identify genetic and epigenetic markers and cofactors for determining risk of anaphylaxis to specific allergens, performing an individual risk assessment, and preventing future episodes by developing personalized risk reduction strategies.

Gaps in knowledge on anaphylaxis management have been observed at different levels, patients, community as well as physicians. Many physicians mismanage the diagnosis of anaphylaxis, evaluation of the severity of the allergic reaction, and the use of adrenaline. A gap between best practice recommendations and Emergency Department (ED) care for anaphylaxis has also been reported. These findings highlight the need for a simpler definition of anaphylaxis especially for non-allergists to improve the diagnosis and consequently the appropriate treatment with adrenaline.

Further identified gaps in the management of anaphylaxis include infrequent or delayed use of adrenaline autoinjector (AAI) by the patients for acute allergic reactions, as well as inadequate AAI training and prescription rates for patients at risk.

A recent review of a number of English language anaphylaxis management plans underlines a wide variety of content, with no plans having 100% of the recommended material. Therefore, more appropriate training for patients, families and caregivers of patients is necessary.

Finally, very few interventions aim to increase adherence to existing anaphylaxis guidelines and best practice through integrated knowledge translation strategies.

Box 1. Anaphylaxis: research priorities

Population studies to unravel candidate genes and the role of the microbiome in the pathogenesis of anaphylaxis.
Cross-sectional studies to evaluate diagnostic accuracy of any mediator (beyond tryptase) for a range of potential allergens.
Large prospective cohort studies of patients at risk of anaphylaxis in real-life settings to provide a clearer understanding of the magnitude of risk factors for future occurrence of anaphylaxis, allowing to personalize avoidance advice and auto-injector prescription.
Research into the etiology, frequency, timing, severity and predictors of biphasic reactions in people who have received emergency treatment for anaphylaxis and the resulting effect of these on morbidity and mortality.
Further pharmacokinetic studies to determine the optimal dose and dosing interval, especially for adult patients experiencing anaphylaxis.
Further work on other routes of adrenaline administration as adjuvants to intramuscular adrenaline.
Randomized controlled studies to assess the effectiveness of systemic glucocorticosteroids in preventing late manifestations of anaphylaxis and whether the addition of antihistamines improves the respiratory and/or cardiovascular features of anaphylaxis.
Prospective studies, including well phenotyped participants and clear criteria for anaphylaxis, to identify who should have an adrenaline auto-injector and how many should they have access to.
Randomized controlled trial to determine whether differing periods of observation following emergency treatment for anaphylaxis have a detrimental effect on morbidity and mortality and to gather information about resource use.
Randomized controlled studies to provide evidence on the effectiveness of anaphylaxis management plans, in improving outcome in different subgroup of patients (e.g., age, allergy type, different reaction's severity, different risk levels).
Studies on the efficacy of training of patients and direct caregivers/parents of children and other groups such as teachers, day care workers, nurses, and physicians.
Studies on the effect of specialist services on health-related quality of life of people who have experienced suspected anaphylaxis.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

Box 1 shows some research priorities in the field.

Standards and quality criteria

The quality of acute and long-term anaphylaxis management is variable influencing the poor outcomes experienced by many patients. Clinical practice guidelines have the potential to improve outcomes, but they often prove challenging to implement in routine clinical care. Quality standards and indicators are potentially important tools designed to help clinicians and healthcare organiza-

tions assess the quality of care compared to evidence-based recommendations. However, data on routinely use at scale in relation to anaphylaxis is scarce.

A recent systematic review of the literature identified some indicators that were summarized against the most recent international anaphylaxis guidelines and critically evaluated using the four stage quality indicator process recommended by the Agency for Healthcare Research and Quality (AHRQ). Even though they cover many aspects of the acute and long-term management of anaphylaxis, the majority of indicators were developed through expert consensus, and only a few of these have undergone the four stages of development recommended by AHRQ. Further work is therefore needed before these indicators can be recommended for routine use in clinical practice.

Innovative approach

Assistive mobile healthcare technologies have demonstrated potential to support the management of chronic conditions such as diabetes and cardiovascular disease, but there has been a lack of application to the management of anaphylaxis. Since the strengths of mobile technology include a wide acceptance and easy use, there is a need to build and validate appropriate apps and sensing systems.

Besides intensified physician training programs, an improvement of the electronic medical records in the ED with alarm system reminding the need to prescribe AAI and referral to an allergy specialist may contribute to further improve the long-term management of anaphylaxis.

The use of the electronic medical record data in the pharmacies can be also useful in identifying patients at risk of anaphylaxis in need of AAI for self-administration.

Finally, potential easy-to-carry non-invasive alternative adrenaline form for the treatment of anaphylaxis in community settings may overcome the issues of dosages, fear of needle, bulky shape and large size, and multiple devices to be placed in various locations.

FURTHER READING

1. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026-1045.
2. Simons E, Ardusso L, Beatrice Bilò M, El-Gamal Y, Ledford D, Ring J et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2010;4:13-37.
3. Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. *Allergy* 2010;65:435-444.
4. Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017;140:321-333.
5. Papadopoulos N, Agache I, Bavbek S, Bilo B, Braido F, Cardona V et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;2:21.
6. Waserman S, Avilla E, Ben-Shoshan M, Rosenfield L, Adcock AB, Greenhawt M. Epinephrine Autoinjectors: New Data, New Problems. *J Allergy Clin Immunol Pract* 2017;5:1180-1191.
7. Dhami S, Sheikh A, Muraro A, Roberts G, Halken S, Fernandez Rivas M et al. Quality indicators for the acute and long-term management of anaphylaxis: a systematic review. *Clin Transl Allergy* 2017;7:15.
8. National Institute for Health and Clinical Excellence (NICE). Anaphylaxis clinical audit tool implementing NICE guidelines. 2011. https://www.nice. org.uk/guidance/cg134/resources.
9. Mercer RD, Jones CJ, Smith HE. Reviewing the Content and Design of Anaphylaxis Management Plans Published in English. *J Allergy Clin Immunol Pract* 2017;5:1288-1294.

Monika Raulf, Jolanta Walusiak-Skorupa

OCCUPATIONAL ALLERGY AND ASTHMA

C10

GAPS IN KNOWLEDGE

Currently, occupational asthma (OA) is the most frequent occupational respiratory disease, constituting about 15-20% of the overall adults asthma. Changes both at the workplaces and in the European workforce pose new challenges that require appropriate strategy and evidence-based recommendations.

Transformations in industrial and technological structure in European countries result in launching new emerging exposures that are potential respiratory hazards. Many of them e.g. nanoparticles are neither well recognised in terms of their respiratory effects nor identified as asthmogens. Recent reports on new causes of occupational allergy should implicate in health-based risk assessment when new constituents are introduced into the workplace.

Although a decline in the incidence of OA is being observed, it is not clear if the problem is not underestimated or reflects fear of workers of lowering quality of life or loss of income after occupational disease is recognised. Interestingly, in some kinds of exposure i.e. in cleaners, high frequency of asthma symptoms has been reported. Their aethiopathogenesis is not well recognised, however irritant-mediated mechanisms have been postulating rising new diagnostic and prophylactic challenges. Gender-specific differences may cause different impact in work-related asthma and should be considered for working conditions and work-related diseases.

Several studies indicate that occupational induced allergy and asthma generally arise in the first few months on the job, while pre-existing symptoms tend to worsen, but evidence-based advice for young subjects with a history of an atopic disease starting exposure are missing so far. The main focus is therefore on secondary prevention.

Major effort has been put into prevention of work-related asthma (WRA), however research of intervention activities are necessary to evaluate their effectiveness and to develop evidence-based recommendations. Our knowledge also remains limited whether reduction of exposure may be an alternative to cessation of it. On the other hand, as OA may persist after removal from the exposure, ceasing contact with the asthmogen in sensitised workers before they develop symptoms may be also an alternative approach. An appropriate patient's management is necessary especially to avoid loss of income.

Risk factors of occupational allergy still are under debate (Figure 1). Setting occupational exposure limits for sensitisers seems to be a challenge. It would diminish problem significantly, as the relation dose-response has been documented for many allergens, although some very sensitive subjects can still develop hypersensitivity. It also leads us to a question of individual susceptibility that is many-di-

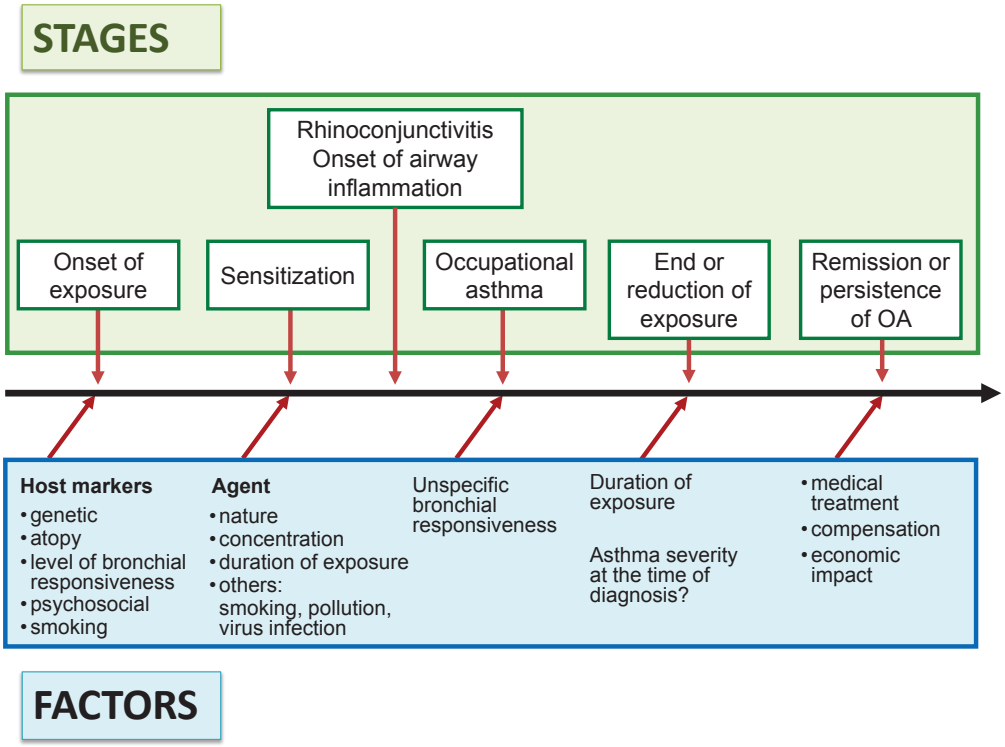


Figure 1. Stages and potential factors influencing the onset and prognosis of occupational asthma (modified according to Gautrin D, Malo JL in Occupational Asthma. Edited by Sigsgaard T, Heederik D; 2010; Springer Basel).

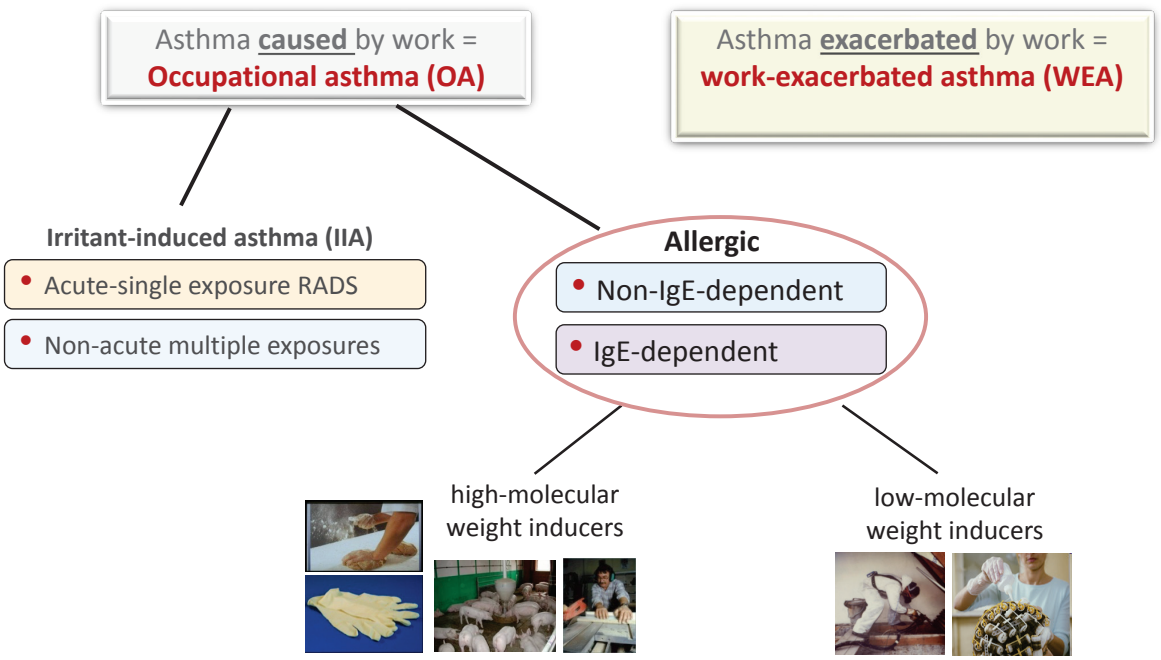


Figure 2. Work-related asthma (WRA) phenotypes (modified according to Moscato et al. EAACI consensus statement for investigation of work-related asthma in non-specialized centres Allergy 2012; 67: 491–50

mensional. Currently, also transgenerational effects are postulated like maternal or father's exposure.

Furthermore, full characteristics of different OA phenotypes needs to be improved (figure 2). Emergence of new biomarkers for asthma and allergy susceptibility, and even differential response to treatment or to allergen avoidance is also impacting occupational airways diseases, thus these new tools are being developed towards the precision or personalized medicine in that field.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- International trends in the prevalence and incidence of occupational allergic respiratory diseases including the influence of gender, race and ethnicity which should not be overlooked in occupational health research
- New insights on the pathogenesis of OA with special attention in characterizing different phenotypes (e.g. allergic versus irritative phenotype and the entity induced by organic dust exposure), defining OA endotypes and identification of biomarkers that assess and differentiate e.g. between irritant versus allergen-based asthma response;
- Cluster analysis of different asthma phenotypes in large cohort with well-defined patients with OA;
- New emerging exposures as a result of recent technological developments – early identification of respiratory hazards and continuous respiratory health surveillance;
- Evaluation of intervention efficacy and development of evidence-based recommendations for prevention;
- Occupational exposure limits for sensitizers and development of methods for measuring airborne allergens even in low levels;
- Communication and dissemination of risk management tools based on hazard-related information

Standards and quality criteria

- Standardized methods for nasal and bronchial provocation tests with occupational agents with assessment of airway inflammation.

Innovative approach

- Identify the multiple mechanisms, allergic and non-allergic, that cause OA and develop molecular screening approaches to differentiate among these mechanisms.
- Develop validated predictive assays specific to respiratory sensitization.
- Developing and implementation of new diagnostic tools and algorithms based on non-invasive methods and biomarkers and/or allergen component-resolved diagnostic (CRD) used in precision or personalized medicine into the occupational respiratory allergy field;
- In the absence of hazard-specific dose-response information, a benchmarking based approach can be used to assess the need for tighter exposure control.

FURTHER READING

1. De Matteis S, Heederik D, Burdorf A, Colosio C, Cullinan P, Henneberger PK et al. Current and new challenges in occupational lung diseases. *Eur Respir Rev* 2017;26. pii: 170080.
2. Cullinan P, Muñoz X, Suojalehto H. Occupational lung diseases: from old and novel exposures to effective preventive strategies. *Lancet Respir Med* 2017;5: 445-455.
3. Vincent MJ, Bernstein JA, Basketter D, LaKind JS, Dotson GS, Maier A. Chemical-induced asthma and the role of clinical, toxicological, exposure and epidemiological research in regulatory and hazard characterization approaches. *Regul Toxicol Pharmacol* 2017;90:126-132.

Isabella Quinti, Cinzia Milito

IMMUNE DEFICIENCIES

C11

GAPS IN KNOWLEDGE

Primary immunodeficiency diseases (PID) are rare diseases. A recent study estimated that 6 million people may be living with a PID worldwide, of which only 27,000– 60,000 having been definitely diagnosed. The International Union of Immunologic Societies (IUIS) Expert Committee for PID classifies PID on the basis of the major immunological defects underlying single disease entities involving the innate or the adaptive immune response (Box 1). There are many PID with signs and/or symptoms of allergies (Box 2).

The field of PID is rapidly expanding with more than 300 genetically defined disorders that have been clinically described and molecularly analyzed. The molecular dissection of these entities has led to the discovery of new immunologic pathways and to novel and effective disease-specific therapies. The IUIS classification includes a number of diseases in which infections are not the major clinical features (e.g. auto-inflammatory disorders or hereditary angioedema), highlighting the strong relationship existing between immunodeficiency, autoimmunity and auto-inflammation. The monogenetic PID disorders continue to reveal molecular mechanisms underpinning our understanding of tolerance and immunity. Targeted therapeutic strategies are in development.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

- The study of the interaction between the microbiota, barrier, and mucosal immune system likely represents a modifiable factor contributing to the clinical manifestations associated with immune dysregulation.
- International collaborative efforts to standardize reporting, such as the USIDNET and ESID-registry and collaborative projects within European Societies such as EAACI and ESID are important to further characterize the true phenotypes of the expanding range of conditions and long-term outcomes of the new emerging therapeutic options. Together this will help raise awareness and improve treatment for not only monogenic PID, and may inform molecularly

Box 1. Primary Immune Deficiencies Classification

Severe Combined Immune Deficiencies	• Interleukin-2Rγ-chain deficiency (XL) • JAK3 deficiency (AR) • 7Rα deficiency (AR) • Coronin-1Adeficiency (AR) • RAG1, RAG2 deficiency (AR) • Artemis deficiency (AR) • DNA ligase IVdeficiency (AR) • Adenylate kinase 2 deficiency (AR)	• ADA deficiency (AR) • Purine nucleosidephosphorylase deficiency(AR) • ZAP-70 tyrosinekinase deficiency(AR) • MHC class I deficiency (AR) • MCH class II deficiency (AR) • ITK deficiency (AR) • Omenn Syndrome (AR; XL in IL2RG deficiency)
Predominant antibody deficiencies	• X-linked Agammaglobulinemia (XL) • Autosomal recessive Agammaglobulinemia due to μ heavy chain, λ5, Igα, Igβ, BLNK deficiency (AR) • Hypogammaglobulinemia due to defective B cell development	• Hypogammaglobulinemia due to defective B cell activation as a result of T-cell deficiencies • Hypogammaglobulinemia due to heterozygous GOF mutation in PIK3CD • Hypogammaglobulinemia due to heterozygous mutations in IKAROS (AD)
Syndromes of immune dysregulation and autoimmunity	• Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) (XL) • IPEX-like: • CD25 (IL-2Rα) deficiency (AR) • STAT5B deficiency (AR) • STAT1 GOF mutation • STAT3 GOF mutation (AD) • CTLA-4haploinsufficiency (AD) • LRBA deficiency (AR) • Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy (APECED) (AR)	• Autoimmune lymphoproliferative syndrome (ALPS), due to defective apoptosis • Immune dysregulation with colitis (IL10 deficiency (AR), IL-10Rα and IL-10Rβdeficiency (AR) • HLH without hypopigmentation (Perforindeficiency (AR), Munc 13-4/UNC13Ddeficiency(AR), Syntaxin 11deficiency (AR), Munc 18-2/STXBP2deficiency (AR or AD), SH2D1A deficiency (XLP1) (XL), XIAP deficiency (XLP2) (XL) • HLH with hypopigmentation (Chediak-Higashi Syndrome(AR), Griscelli Syndrome Type 2 (AR), Hermansky-Pudlak Syndrome Type 2 (AR)
Combined immunodeficiencies with associated syndromic features	• Wiskott-Aldrich Syndrome (WAS), X-linked thrombocytopenia (XLT), X-linked congenital neutropenia (XLN) • DNA-repair defects with increased radiosensitivity • Thymic defects: DiGeorge Syndrome (22q11.2 deletionsyndrome) (AD); CHARGE syndrome (AD);	• Immune osseous dysplasia • Hyper IgE syndromes (HIES): AD-HIES or Job Syndrome; AD-STAT3 deficiency (AD-dominant negative); AR-HIES; DOCK8 deficiency (AR); Comel–Netherton Syndrome (AR) • Dyskeratosiscongenita (DKC) • Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)
Defects of the innate immune system	• Defects of phagocyte number or function: » Severe congenital neutropenias (SCN) » Defects of leukocyte adhesion (LAD) » Defects of the respiratory burst—Chronic granulomatous disease (CGD) • Defects in innate immunity resulting in susceptibility to selected microorganisms:	» Mendelian susceptibility to mycobacterial disease (MSMD) » Susceptibility to Human Papillomavirus (HPV) » Susceptibility to herpes simplex encephalitis (HSE) » Susceptibility to invasive fungal infections/mucocutaneous candidiasis
Auto-inflammatory fever syndromes	• Familial Mediterranean Fever (AR) (AD) • Cryopyrinopathies due to cryopyrin deficiency (AD) • TNF receptor-associated periodic syndrome (TRAPS) due to TNFR deficiency (AD)	• Pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome (PAPA) (AD) • Deficiency of IL-1R antagonist (DIRA)(AR) • Coatomer protein complex, subunit alpha(COPA) defect (AD)
Complement deficiencies	• C1 inhibitor deficiency (AD)	

Box 2. PID with signs and/or symptoms of allergies

AD-HIES; JobSyndrome; AD-STAT3 deficiency	Recurrent staph and candida infections, "cold" abscesses affecting lymph nodes and lungs (with resulting pneumatoceles), CMC, severe atopy, neonatal eczema, hyperextensible joints, bone fractures, retention of primary teeth, aneurisms are common
AR-HIES; DOCK8 deficiency (AR)	Cutaneous viral infections, recurrent systemic infections, severe atopy, food allergies, malignancies (skin), combined immune deficiency, may have low TRECs
Comel–Netherton Syndrome (AR)	Bacterial infections, failure to thrive, congenital ichthyosis, bamboo hair, atopic diathesis ,LECTI deficiency, low TRECs have been observed
Omenn syndrome presentations of SCID	Severe infections as in classic SCID, erythroderma ,eosinophilia, lymphadenopathy, hepatosplenomegaly, oligoclonal T cells, TRECs low in most cases
Wiskott-Aldrich Syndrome	Bacterial and viral infections, congenital thrombocytopenia, eczema, autoimmunity, malignancy, congenital neutropenia resulting from GOF mutations in the GTPase binding domain of WAS gene
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	Recurrent bacterial and viral infections including atypical mycobacteria, ectodermal dysplasia, elevated IgM, conical teeth, defect in skin pigmentation, colitis
Immune Dysregulation polyendocrinopathy, enteropathy, X-linked (IPEX)	Autoimmune enteropathy, eczema, early onset type1 diabetes, thyroiditis, cytopenias, lack of Treg cells
Congenital Defects of Innate cells CARD9 deficiency (AR)	Invasive candida infection, deep dermatophytosis; reduced TH17 cell
Familial Mediterranean Fever(AR [AD])	Fever, rash, sterile peritonitis, pleuritis, monoarthritis;vasculitis; amyloidosis
Hyper IgD syndrome due to Mevalonate Kinase (MVK) deficiency (AR)	Fever, rash, abdominal pain, peritonitis, pleuritis,arthritis, vasculitis
TNF receptor-associated periodic syndrome (TRAPS) due to TNFR deficiency (AD)	Fever, rash, peritonitis, pleuritis, arthritis, splenomegalydue to impaired TNF removal, amyloidosis
C1 inhibitor deficiency (AD)	Hereditary angioedema

guided treatments for a much wider range of conditions including allergies.

- Reduce the underdiagnose and misdiagnose by early recognition of warning signs and symptoms and by an early detection of the underlying immune defect
- Reduce the delay of diagnosis by increased awareness on PID among healthcare professionals. In particular, pediatricians, gastroenterologists, allergists and pulmonologists may be the first specialists encountering these patients.
- PID has been suggested as a relevant unrecognized cause of chronic respiratory and intestinal disease. Preventing relevant complications includes early diagnosis of chronic lung diseases, chronic sinusitis, enteropathy, lymphoproliferative diseases, gastrointestinal carcinomas. An early detection and the consequent establishment of appropriate treatment strategies may significantly reduce the occurrence of new infections and of the long-term sequels.
- Ameliorate treatment strategies by promptly using antimicrobial therapies, immunoglobulin replacement, hematopoietic stem cell transplantation, molecularly targeted immunosuppression with monoclonal antibodies and specific immunomodulatory agents, gene therapy and gene editing.
- Improve Quality of Life. The analysis of patients' experience is surprisingly complex, and it is generally connected with the concepts of health-related quality of life (HRQoL), patients' empowerment, and care satisfaction. Disability in PID is due to autoimmune complications, malignancies, recurrent gastrointestinal infections, and chronic lung involvement, with a strong impact on patients' daily functioning. The focus on the patients' experience of illness requires a rigorous scientific approach to determine factors affecting the burden of disease to maximize patient's wellbeing and to minimize the impact of disease.

FURTHER READING

1. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol* 2018;38:96-128.
2. Ochs HD, Petroni D. From clinical observations and molecular dissection to novel therapeutic strategies for primary immunodeficiency disorders. Am J Med Genet A 2018;176:784-803.
3. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W et al. The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. *J Clin Immunol* 2018;38:129-143.
4. Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007. *J Clin Immunol* 2014;34:954-9061.
5. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL et al. Primary immunodeficiency diseases worldwide: more common than generally thought. *J Clin Immunol* 2013;33:1-7.
6. Quinti I, Pulvirenti F. Health-Related Quality of Life and Patients' Empowerment in the Health Care of Primary Immune Deficiencies. *J Clin Immunol* 2017;37:615-616.

D

MANAGEMENT OF ALLERGIC DISEASES

Oscar Palomares, Paweł Gajdanowicz, Marek Jutel

GOLDEN STANDARDS FOR ALLERGY DIAGNOSIS

D 1

GAPS IN KNOWLEDGE

The oldest, and to some extent most straightforward test to diagnose IgE mediated allergic disease is the skin prick test (SPT). It measures local response of mast cells after allergen provocation. Diagnostic panels, according to European guidelines, cover a set of 18 allergen extracts. Besides its relative low cost and low risk for systemic reactions the specificity and sensitivity of SPT are affected by rather high variability related to age, body mass and skin barrier status.

Other diagnostic tests, so called *in vitro* tests, are gaining in popularity nowadays. Such tests measure the concentration of allergen specific IgE antibodies in patient's serum. The growing market enables to select various test types from dozens of manufacturers allowing the detection of virtually all types of allergen-specific IgE (asIgE).

The third arm of allergy diagnosis is composed of *in vivo* allergen challenge methods (nasal, bronchial, conjunctival, food challenge), which are used for diagnostics generally less frequently, being very helpful in more complicated settings (e.g food allergies).

Allergic rhinitis

Medical history with information about presence, severity and duration of nasal symptoms is crucial for AR diagnosis. Symptoms usually follow allergen exposure, but some irritating agents like tobacco smoke and some spices may also induce non-allergic response. Demonstration of sensitisation by asIgE using SPT, *in vitro* tests or challenge tests helps to diagnose AR where there is a clear link between symptoms and natural allergen challenges or when response to treatment is successful.

Asthma

Like for other diseases, medical history is a crucial factor for proper diagnosis. Dyspnoea, wheezing, chest tightness and reversible airflow obstruction are the most important symptoms. Clinically two types of tests are used for diagnosis of asthma, spirometry and bronchial challenge test. By spirometry testing it is possible to detect changes in the airflow and observe asthma-characteristic reversibility of such an obstruction after SABA and/or corticosteroid treatment. Among challenge procedures non-specific AHR responsiveness to histamine, methacholine or other indirect activators such as mannitol are mostly used.

Food allergy

The diagnosis of food allergy integrates medical history, clinical symptoms, detection of asIgE and, when necessary elimination diet and oral challenge with suspected food. Demonstration of IgE sensitization by SPT or *in vitro* testing is crucial for food

allergy diagnosis. Food allergies may trigger more severe side reactions that persists longer than in case of other allergies, thus provocation tests should be performed with caution only in clinical settings well equipped for emergencies events.

Drug allergy

Drug allergy is diagnosed on the basis of medical history when two or more reproducible reactions occur. When possible SPT or *in vitro/ex vivo* tests should confirm sensitization. In other cases, drug challenge can be helpful. Drug provocation tests are considered as a gold standard for diagnosing of allergy to NSAIDS, local anaesthetics, non-beta-lactam antibiotics and other drugs for which safer tests do not exist or are not standardized. Drug challenge tests should always be carried out in clinical settings.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Recent findings indicate that allergic diseases are complex and heterogeneous syndromes encompassing different phenotypes and endotypes characterized by specific pathophysiological mechanisms. In a near future, the diagnosis of specific allergic endotypes will require the use of novel technologies and approaches to identify suitable biomarkers that allow not only diagnosis but also the identification and stratification of allergic patients according to specific disease-related inflammatory, immunological, metabolic and remodelling pathways. Some of these technologies are currently under development and at different stage of implementation in clinical routine.

Remarkably, the identification of the clinically relevant allergens is nowadays possible due to the availability of well-defined purified natural and recombinant allergens. The use of these purified allergens in combination with novel biotechnological platforms, bioinformatics and databases has contributed to the implementation of the *in vitro* allergen-based diagnosis concept of component-resolved diagnosis (CRD), which allow the identification of the causative allergens at the molecular level.

Combination of CRD with proper *in vivo* challenge in stable and validated allergen exposure chambers (ACC) will definitively contribute to improve the current diagnosis protocols for allergic diseases. ACC will enable the identification of allergenic sources triggering subjective symptoms and, at the same time, the identification of objective parameters that confirm them.

Similarly, the optimization and validation of cellular assays such as the basophil activation test (BAT) will be of undoubtable help to improve current allergy diagnosis tools. Currently, efforts in the standardization of BAT as an allergy diagnostic tool is ongoing and significant advances have been achieved in drug and food allergy diagnosis.

Finally, it is very important to keep in mind that biotechnology has experienced spectacular advances over the last decades, and it is expected to grow faster within the upcoming years. Biotechnology together with the explosion of the –omic approaches is contributing to significantly improve the diagnosis of allergic diseases. The implementation of the –omic technologies (genomics, transcriptomics, proteomics, lipidomics, metabolomics, etc) into the field of allergy diagnosis will enable, in the future, the identification of novel potential biomarkers in a hypothesis-free-based manner. These biomarkers will allow, after proper validation in large and independent cohort of patients, to improve the current diagnosis of allergic patients by allowing the stratification according to specific endotypes. At this regard, further research is fully demanded. Novel strategies to identify potential biomarkers in a fully unbiased manner so that true patient stratification according to specific underlying pathophysiological mechanism clinically relevant is required. Similarly, proper approaches to further validate and standardized these potential biomarkers for clinical application is also needed.

FURTHER READING

1. Jutel M, Papadopoulos NG, Gronlund H, Hoffman HJ, Bohle B, Hellings P et al. Recommendations for the allergy management in the primary care. *Allergy* 2014;69:708-718.
2. Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries - actual status. *Allergy* 2013;68:836-843.
3. Agache I, Bilò M, Braunstahl GJ, Delgado L, Demoly P, Eigenmann P et al. In vivo diagnosis of allergic diseases--allergen provocation tests. *Allergy* 2015;70:355-365.
4. Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU et al. Precision medicine in allergic disease-food allergy, drug allergy, and anaphylaxis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006-1021.
5. Bousquet J, Anto JM, Akdis M, Auffray C, Keil T, Momas I et al. Paving the way of systems biology and precision medicine in allergic diseases: the MeDALL success story: Mechanisms of the Development of ALLergy; EU FP7-CP-IP; Project No: 261357; 2010-2015. *Allergy* 2016;71:1513-1525.
6. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol* 2016; 27 Suppl 23:1-250.
7. Bernstein, JA, Correlation between a pollen challenge chamber and a natural allergen exposure study design for eliciting ocular and nasal symptoms: early evidence supporting a paradigm shift in drug investigation? *J Allergy Clin Immunol* 2012;130:128-129.
8. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015;70:1393-405.
9. Palomares O, Crameri R, Rhyner C. The contribution of biotechnology toward progress in diagnosis, management, and treatment of allergic diseases. *Allergy* 2014;69:1588-1601.

Giorgio Walter Canonica

TREATMENT OF ALLERGIC DISEASES

D2a

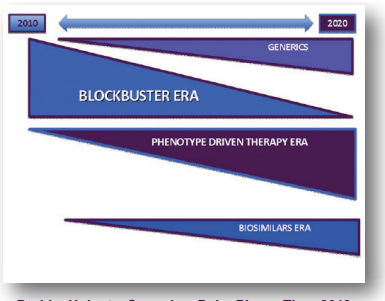
GAPS IN KNOWLEDGE

Few years ago, we envisaged the possible changes of Allergy & Asthma Treatments in a decade. Actually in the last ten years blockbuster drugs practically disappeared, whereas generic treatments acquired a very relevant role in daily therapy of allergic patients; in fact the patent for several molecules expired in the last few years and this event completely modified the scenario of allergy treatment in Europe (Figure 1).

In the meantime, what we defined as phenotype driven therapy has evolved into Precision Medicine, where the target is the Endotype of the patient to be treated, and into Personalized Medicine, including also all the aspects related to the "patient as person". Great insights in this last topic are the concepts of *Humanomics* and *Personomics* highlighting how mandatory is nowadays to properly investigate patient's personality and behaviours. As prove of the growing awareness of this aspects are the consolidated and promoted use of PROs – Patient Related Outcomes. In this context two aspects have to be highlighted: the P4 medicine and the Quality of Life (QoL) evaluation in clinical practice. P4 (Preventive-Predictive-Personalized-Participatory) medicine, described few years ago by L. Hood, has been also accepted and promoted by NIH. In P4, the fourth P- Participatory means an innovative approach to medicine, where the patient's role is not passive anymore, but an active role, which means first a real awareness and knowledge of the disease and of the prescribed treatment. This is the way to reach adherence to treatment, one of the most difficult target in daily practice. P4 Medicine is also promoting the use of technologies for a better management of the diseases. In the allergy field several technologies applied to daily practice (such as MASK) have been developed, both for monitoring the clinical situation and supporting the better strategic treatment for the patient with allergic rhinitis for instance.

On the other hand technologies applied to inhalation therapy have been promoted: new devices with a better inhalation performance, with simplified procedures and new apparels able to monitor, coupled to the inhalator device, adherence to treatment of each single patient. In order to promote a better evaluation of PROs, new tools to measure and monitor QoL in daily practice have been developed too: for the upper and lower airways RAPP and specifically for urticaria CUPP, whose further evolution as App for mobile phones will support even more allergic patients to monitor properly their outcomes.

Actually in the last couple of decades guidelines, such as ARIA, GINA, EAACI/GA²LEN/EDF/WAO Guideline for Urticaria etc., provided an excellent grasp for management and treatments of our pa-



Braido, Holgate, Canonica. Pulm.Pharm.Ther. 2012

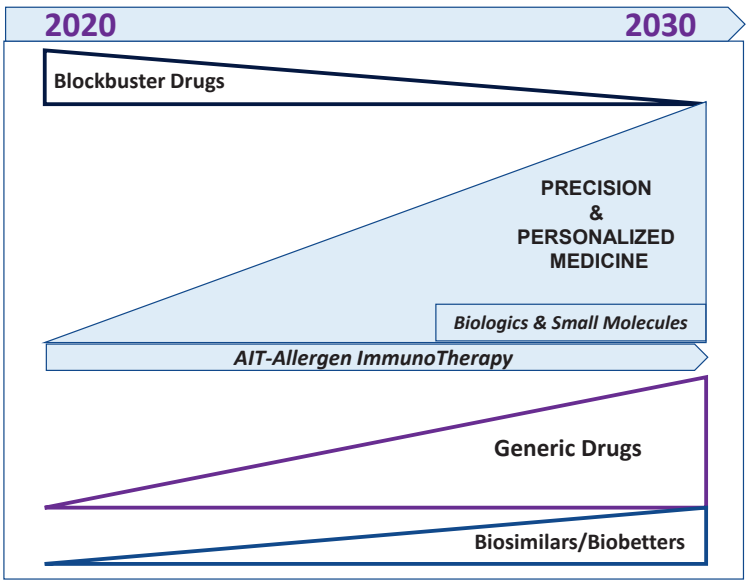


Figure 1. Current and Future scenarios in Allergy & Asthma treatment. The evolution in Allergy and Asthma treatment in two decades: in the upper part is reported the profound change we expected in the last decade. The scenario actually changed accordingly. A further change is predictable in the next ten years, where Precision & Personalized Medicine will play a growing role.

tients with a scientific approach firstly with Evidence Based Medicine and then by the GRADE methodology. Unfortunately guidelines are not followed properly by physicians, in allergy as in other disciplines: this evidences should prompt Scientific Societies and Patients Association, possibly all the stakeholders, to promote better education and implementation.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

The Real Life Studies

The rationale is coming form the evidence such as the example of Omalizumab: only 5% of the asthma patients currently treated in clinical practice with Anti-IgE monoclonal antibodies could have been enrolled in the Phase II-III registration trials and in addition, in clinical practice again, the percentage of responders is less then 70%. These facts are prompting to use other paradigm of investigation such as pragmatic or observational trials, whose results will allow a better definition of the population eligible for a certain treatment and a better sustainability of reimbursement for the costly therapies.

Precision and Personalized Medicine for Definition/Identification of Responders to biologics and AIT

The research, by means of any omic science, should be concentrated on discovey of biomarkers able to predict the response to expensive treatments, such as biologics, small molecules and also AIT, which we reported to be a prototype of Precision Medicine.

An additional natural aim of the current research is to identify new targets of treatments, disease mechanisms and to test new “bullets” to block those same mechanisms. All this requires a great research effort by the companies and academy, since their collaborations will provide new effective and safe treatments.

FURTHER READING

1. Braido F, Holgate S, Canonica GW. From 'blockbusters' to 'biosimilars': an opportunity for patients, medical specialists and healthcare providers. *Pulm Pharmacol Ther* 2012;25:483-486.
2. Canonica GW, Ferrando M, Baiardini I, Puggioni F, Racca F, Passalacqua G et al. Asthma: personalized and precision medicine. *Curr Opin Allergy Clin Immunol* 2018;18:51-58.
3. FitzGerald JM, Poureslami I. The need for humanomics in the era of genomicsmand the challenge of chronic disease management. *Chest* 2014;146:10-12.
4. Ziegelstein RC. Personomics. *JAMA Intern Med* 2015;175:888-889.
5. Braido F, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A et al. Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: a GA(2)LEN taskforce position paper. *Allergy* 2010;65:959-968.
6. Baiardini I, Braido F, Bindslev-Jensen C, Bousquet PJ, Brzoza Z, Canonica GW et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in patients with urticaria: a GA(2)LEN taskforce position paper. *Allergy* 2011;66:840-844.
7. Auffray C, Charron D, Hood L. Predictive, preventive, personalized and participatory medicine: back to the future. *Genome Med* 2010;2:57.
8. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. Allergy 2015;70:1372-1392.
9. Canonica GW, Arp J, Keegstra JR, Chrystyn H. Spiromax, a New Dry Powder Inhaler: Dose Consistency under Simulated Real-World Conditions. *J Aerosol Med Pulm Drug Deliv* 2015;28:309-319.
10. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J* 2009;18:243-249.
11. Braido F, Paa F, Ponti L, Canonica GW. A new tool for inhalers' use and adherence monitoring: the Amiko® validation trial. *Int J Eng Res Sci* 2016;2:156-166.
12. Braido F, Baiardini I, Stagi E, Scichilone N, Rossi O, Lombardi C et al. RhinAsthma patient perspective: a short daily asthma and rhinitis QoL assessment. *Allergy* 2012;67:1443-1450.
13. Baiardini I, Braido F, Molinengo G, Caminati M, Costantino M, Cristaudo A. Chronic Urticaria Patient Perspective (CUPP): The First Validated Tool for Assessing Quality of Life in Clinical Practice. *J Allergy Clin Immunol Pract* 2018;6:208-218.
14. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. Allergy 2015;70:1372-1392.
15. Global Initiative for Asthma (GINA) - 2017 GINA Report, Global Strategy for Asthma Management and Prevention. http://ginasthma.org/2017-ginareport-global-strategy-for-asthma-management-and-prevention/ (accessed July 2017).
16. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. *Allergy* 2018; [Epub ahead of print].
17. Baiardini I, Braido F, Bonini M, Compalati E, Canonica GW. Why do doctors and patients not follow guidelines? *Curr Opin Allergy Clin Immunol* 2009;9:228-233.
18. Yao D-K, Wang L-X, Curran S, Ball P. Adherence to treatment guidelines in the pharamacological management of chronic heart failure in an Australian polulation. *J Geriatr Cardiol* 2011;8:88-92.
19. Caminati M, Senna G, Chieco Bianchi F, Marchi MR, Vianello A, Micheletto C et al. Omalizumab management beyond clinical trials: the added value of a network model. *Pulm Pharmacol Ther* 2014;29:74-79.
20. Braunstahl GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med* 2013;107:1141-1151.
21. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med* 2013;1:e29-30.
22. Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M et al. Allergen Immunotherapy (AIT): a prototype of Precision Medicine. *World Allergy Organ J* 2015;8:31.

Montserrat Alvaro

PEDIATRIC ALLERGY AND CLINICAL IMMUNOLOGY. UNMET NEEDS IN TREATMENT

D2b

GAPS IN KNOWLEDGE

The burden of allergic diseases in children has been significantly increasing during the last years. Different ways of life (life style in big and industrialised cities as opposed to little towns or even farms, age of food introduction, new treatments, etc) have probably influenced the development of new diseases, while some others like allergy, have increased in incidence. On the other hand, there have been significant advances in the understanding of the pathophysiological pathways in allergy and specifically in tolerance induction, as well as the development of new therapeutic options which need paediatric trials. For this purpose, new modes of trials in the paediatric population should be identified and implemented.

Prevention trials in food allergy (food allergy) have opened the way to new concepts in the introduction of foods, in atopic and non-atopic children, in order to prevent the FA epidemic. Many questions have aroused such as the specificity of these interventions. More studies are needed to achieve the correct and more effective strategy in FA prevention.

Once it has affected the child, FA can have significant effects on morbidity and quality of life even in their families. The risk of anaphylaxis in IgE-mediated FA is high. Until very recently a single approach was available for the treatment of FA: avoidance of the offending food. From our point of view, this approach only represents a lack of treatment and it also leaves the child unprotected from hidden or small amounts of the offending food. There is therefore interest in novel strategies for its treatment with the recently developed immunotherapy for FA. Recently the European Academy of Allergy and Clinical Immunology (EAACI) has published Guidelines on the use of this novel approach.

Atopic dermatitis is a complex skin disease frequently associated with other diseases of the atopic march. Special attention must be paid to its prevention and to the restoration of the skin barrier which will help in the avoidance of the passing of allergens through the impaired skin.

In respiratory allergy, asthma is a major public health problem affecting over 300 million people worldwide. Allergic sensitization is a strong risk factor for asthma inception and severity in children. Current asthma therapies control symptoms and inflammation, but the underlying immune response can only be modified by allergen specific immunotherapy (AIT). EAACI has published a systematic review in which an important body of evidence has shown that the administration of AIT in patients with allergic asthma can result in reductions in symptom and medication scores. Research should follow in this field, especially in children, as

their immunological state is more easily modulated. Nevertheless the current regulatory guidelines have triggered discussion of critical ethical aspects in paediatric trial designs.

Allergic rhino-conjunctivitis is also a very common chronic condition that can result in considerable morbidity and impairment of quality of life. Symptoms can, in many cases, be controlled with avoidance measures and pharmacological therapies (oral, intranasal and ophthalmic H1-antihistamines, intranasal corticosteroids and antileukotrienes). Again AIT is an additional potential treatment option, particularly for those with more troublesome disease. EAACI has also published a systematic review, in which it is concluded that AIT is effective in achieving clinically important short-term improvements in symptom, medication, and combined symptom and medication scores. Unmet research need in rhinitis in children are studies focusing on potential for AIT to alter the natural history of allergy and the progression of rhinitis to asthma.

In chronic urticaria (CU), the new accepted guidelines focus in children only with a few sentences. The treatment has not changed from the previous guideline. More epidemiological data should be found and published.

Drug allergy is also a big area of research and new techniques in the diagnosis and the practice of desensitization should be developed.

The correct diagnosis of allergy is also an important field of research and innovation in paediatric allergy. New advances in methods such as component resolved diagnosis and basophil activation test will help in more accurate diagnosis and treatments.

In clinical immunology, the advances in genetics during the last years has allowed a better and early diagnosis of primary immunodeficiencies (PIDs) in children. The correct identification and classification of these diseases must go on for the wellbeing of the children who suffer from PID. Prenatal diagnosis and newborn screening programs for a number of T and B lymphocyte deficiencies will facilitate early diagnosis and therapeutic interventions. Genetic counselling should be an important component of the care of patients with PIDs as well as their families.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

The key areas for investment in paediatric allergy and clinical immunology research are:

- Prevention in allergic diseases.
- The best way to reach tolerance for the management of FA
- Better diagnostic tools for the allergic child and for primary immune deficiencies.
- Newborn screening programs for PIDs.
- New drug development and trials specifically designed for the pediatric population
- Innovation and technology for better clinical care, public health and research tools.

FURTHER READING

1. Tsilochristou O, Maggina P, Zolkipli Z, Sanchez Garcia S, Uysal P, Alvaro Lozano M et al. Current state and future of pediatric allergology in Europe: A road map. *Pediatr Allergy Immunol* 2018;29:9-17.
2. Pfaar O, Alvaro M, Cardona V, Hamelmann E, Mösges R, Kleine-Tebbe J. Clinical trials in allergen immunotherapy: current concepts and future needs. *Allergy* 2018;[Epub ahead of print].
3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-813.
4. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med* 2016; 374:1733-1743.
5. Alvaro M, Muraro A. Oral immunotherapy in food allergy: present and future. *An Pediatr (Barc)* 2015;82:213-215.
6. Pajno G, Fernández Rivas M, Arasi S, Roberts G, Akdis C, Alvaro-Lozano M et al. EAACI Guidelines on Allergen Immunotherapy: IgE-mediated Food Allergy. *Allergy* 2018;73:799-815.
7. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016;138:336-349.
8. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. *Allergy* 2017;72:1825-1848.
9. Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015;26:431-437.
10. European Medicines Authority (EMA). EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy. Human Medicines Development and Evaluation; 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_ and_procedural_guideline/2009/11/WC500015814.pdf.
11. Rose K, Kopp MV. Pediatric investigation plans for specific immunotherapy: questionable contributions to childhood health. *Pediatr Allergy Immunol* 2015;26:695-701.
12. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. International study of asthma and allergies in childhood (ISAAC) phase three: a global synthesis. *Allergol Immunopathol (Madr)* 2013;41:73-85.
13. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65:1525-1530.
14. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. *Allergy* 2017;72:1597-1631.
15. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013;68:1102-1116.
16. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. *Allergy* 2018;[Epub ahead of print]

Oliver Pfaar

ALLERGEN IMMUNOTHERAPY (AIT) IN ALLERGIC DISEASES

D2c

GAPS IN KNOWLEDGE

Allergen Immunotherapy (AIT) has been clinically used for more than 100 years now for the treatment of allergic diseases such as allergic rhinoconjunctivitis or allergic asthma. In contrast to other therapeutic modalities, this treatment is the only disease-modifying option available as it changes the errant underlying immunological mechanisms of these diseases. As such, this treatment improves in general the quality of live and productivity of allergic patients which has been clearly demonstrated in a multitude of clinical trials which have been analysed in recent metaanalyses and systematic reviews of the EAACI. Based on this evidence, several international guidelines following highest methodological standards have been recently published in the field of AIT . However, there remain important gaps in AIT that have to be urgently addressed in the future by clinicians, methodologist, regulatory authorities and other stakeholders

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Improving the grade of evidence on clinical efficacy of AIT

Though many evidence exists on both subcutaneous (SCIT) and sublingual (SLIT) in general, a product specific evaluation of different AIT products on the market is recommended by multiple scientific societies as there is no generic class effect in AIT . Hence, more clinical trials following guidance from both regulatory agencies and current methodological standards as requested from academia is warranted.

Enhancing patient education and information: AIT as treatment with disease-modifying capacity

Though clinical trials in AIT have been performed since more than 100 years and much evidence has been found on its clinical efficacy, there is still a shortage of allergic patients receiving this treatment. Therefore, both physicians and patients should be better informed about the merits of this therapy. Also there is a suboptimal adherence to this treatment which should also be optimized by better patient education and thorough information.

Optimizing the design and reporting of results in future AIT trials

There is a high heterogeneity of clinical endpoints (both primary and secondary) used in (pivotal-) trial on AIT in the past. With the aim for a better standardization (and comparison between different trials of different products in AIT), the EAACI has published a Position Paper on clinical endpoints in AIT. The requested standards should be strictly followed in designing clinical trials in the future and also the reporting of the results should be in line with international standards such as CONSORT.

Consolidating regulatory prerequisites: focus on children and adolescents

Though there is a clear guidance from the European Manufacturing Agency (EMA) about methodological standards for trials and requirements for AIT product registration in Europe, the according Pediatric Investigational Plan (PIP) as published by the Pediatric Committee of the EMA is still under much debate regarding its feasibility and ethical considerations. Therefore, there is an important need that all stakeholders involved in the development and registration of products in AIT for pediatric and adolescent allergic patients are involved in further discussions and findings of solutions

Further Developing of new approaches in AIT: alternative vaccines and routes of administration

Though AIT is in clinical routine use, modifications and improvement of the agents such as combination therapy with adjuvants or biologicals, the use of recombinant vaccines or peptides in AIT as well as new routes of application and other therapeutic approaches should be consistently followed .

FURTHER READING

1. Noon L, Cantar B. Prophylactic Inoculation against Hay Fever. *Lancet* 1911:1572-1573.
2. Durham SR, Leung DY. One hundred years of allergen immunotherapy: time to ring the changes. *J Allergy Clin Immunol* 2011;127:3-7.
3. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol* 2016;137:358-368.
4. Antonella Muraro, Graham Roberts (ed.). 2017. Immunotherapy Guidelines Part 1: Systematic Reviews. Zurich: European Academy of Allergy and Clinical Immunology. ISBN 978-3-9524815-0-9.
5. Muraro A, Roberts G, Halken S, Agache A, Angier L, Fernandez-Rivas M, et al. EAACI Guidelines on Allergen Immunotherapy: Executive Statement. *Allergy* 2018;73:739-743.
6. Halken S, Larenas-Linnemann D, Roberts G, Calderon MA, Angier E, Pfaar O et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol* 2017;28:728-745.
7. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy* 2018;73:765-798.
8. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int* 2014;23: 282-319.
9. European Medicines Agency. Commitee for medicinal products for human use (CHMP): Guideline on the Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases (CHMP/EWP/18504/2006). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf; 2008. 2008.
10. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. European

Academy of A, Clinical I, Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;69:854-867.
11. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Patient engagement and patient support programs in allergy immunotherapy: a call to action for improving long-term adherence. *Allergy Asthma Clin Immunol* 2016;12:34.
12. Pfaar O, Kleine-Tebbe J, Hormann K, Klimek L. Allergen-specific immunotherapy: which outcome measures are useful in monitoring clinical trials? *Immunol Allergy Clin North Am* 2011;31:289-309.
13. Bousquet PJ, Calderon MA, Demoly P, Larenas D, Passalacqua G, Bachert C et al. The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: A Global Allergy and Asthma European Network (GA(2)LEN) article. *J Allergy Clin Immunol* 2011;127:49-56, 56.e1-11.
14. Calderon MA, Gerth van Wijk R, Eichler I, Matricardi PM, Varga EM, Kopp MV, et al. Perspectives on allergen-specific immunotherapy in childhood: an EAACI position statement. *Pediatr Allergy Immunol* 2012;23:300-306.
15. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M et al. Perspectives in allergen immunotherapy: 2017 and beyond. *Allergy* 2018;73 Suppl 104:5-23.
16. Calderon MA, Demoly P, Gerth van Wijk R, Bousquet J, Sheikh A, Frew A, et al. EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. *Clin Transl Allergy* 2012;2:20.

Susanne Lau, Erkka Valovirta, Lars Jacobsen

PREVENTION OF ALLERGY AND ATOPIC DISEASES

D3

Clinical studies have confirmed that allergy is a systemic disease. Allergy is an immunological condition expressed by a local symptomatic response following allergen exposure. Prevention of allergy, atopic eczema/atopic dermatitis and asthma implicate to either modulate potentially harmful immune deviation or to avoid potentially harmful exposures to either allergens or other factors that may favour the development of an atopic inflammation.

We know populations for example in the farming community or the Amish people in the US where asthma and allergies are less prevalent. Although, potentially beneficial and preventive factors like drinking raw milk or traditional farming practices influencing innate and adaptive immunity (have been identified, no standardized preventive strategy has been developed for the non-farming population at risk for atopy.

The definition of primary, secondary and tertiary prevention of allergic diseases has been published in the WHO 2003 report (WHO). For primary prevention of allergy and atopic diseases like atopic dermatitis in infancy, more general recommendations have been proposed by many societies, for example breast feeding during the first 4-6 months, avoidance of tobacco smoke exposure, no postponement of solid food if no specific allergy has been proven. In contrast, for secondary and tertiary prevention as treatment options, both, exposure to a specific allergen if only sensitization but not allergy is present in the case of peanut sensitization but also avoidance (in the case of house dust mite sensitization in an atopic child at risk for asthma) have been suggested.

GAPS IN KNOWLEDGE

Allergen specific immunotherapy (AIT) is interfering with the basic pathophysiological mechanisms and modulates the allergic immune response (Jacobsen 2012, Jutel 2016).

AIT is considered to be a potentially disease-modifying intervention in IgE-mediated allergic disease, with the potential for preventive as well as therapeutic effects. For example, we know that children with allergic rhinitis (AR) have a 3-fold increase risk of developing allergic asthma. Studies assessing the long-term effectiveness of AIT in children with allergic rhinoconjunctivitis (ARC) indicate that AIT might reduce the risk of developing asthma.

Therefore, AIT implies the potential for changes in the long-term prognosis of respiratory allergy. AIT should be recognized not only as first-line therapeutic treatment for allergic rhinoconjunctivitis and asthma but also as a secondary preventive treatment for respiratory allergic diseases. If individuals have been exposed and sensitized to an allergen, secondary prevention is defined as measures preventing IgE related allergy symptom from appearing. Finally, tertiary prevention is defined as prevention/reduction of allergy symptoms and prevention of exacerbations of disease an in patients with asthma and/or allergic diseases. These definitions can be discussed and different levels of secondary prevention defined. Preventing asthma development in children with rhinoconjunctivitis can also be considered secondary prevention as well as the potential prevention of further sensitivities and sensitizations in patients who are already sensitized to one allergen. Recently, the results of the EAACI task force "Allergen Immunotherapy" have been published, offering guidelines for treatment and prevention.

The preventive effect of AIT can be argued in terms of the immunological changes that follows the treatment. AIT do influence immunological mechanisms leading into suppression of the seasonal increase in eosinophilia, reduction of the late-phase reactivity and a shift from a Th2- to Th1-like response is initiated and maintained. T regulatory cells, down regulating the Th2 response plays a central role in the immunological basis for effective AIT.

The key for prevention by AIT, is a two to three year course of subcutaneous or sublingual AIT and can be recommended for children and adolescents with moderate to severe allergic rhinitis (AR) triggered by grass/birch pollen allergy in order to prevent asthma development for up to two years post-AIT. Trial data further supports a preventive effect on asthma symptoms and medication for up to 10 years after initiation of therapy.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Standard and quality criteria

Only AIT extracts should be prescribed which have been shown to be effective in clinically controlled trials. A class effect can be assumed if detailed information on allergen contents and potency is available.

Research priorities

We need more evidence concerning AIT for prevention in individuals with AR triggered by house dust mites or other allergens and for the prevention of allergic sensitization. Evidence for the preventive potential of AIT as disease modifying treatment exists but there is an urgent need for more high-quality clinical trials (see EAACI AIT Guidelines). In future, harmonized study protocols are needed with a common definition for reasonable endpoints and comorbidity, age and severity of airway disease should be taken into account. This is especially necessary for AIT studies on allergic asthma.

FOOD ALLERGY

GAPS IN KNOWLEDGE

Food allergy, especially to peanuts and tree nuts is increasing. Infants and children with atopic eczema are at special risk, predominantly if a filaggrin mutation is present.

In the randomized controlled LEAP study including high risk children with AE and hen`s egg sensitization, feeding of peanut protein early in infancy until age 5 years was exceptionally preventive, reducing the incidence of peanut allergy by 70%

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

As recommendation, the feeeding of peanut protein in children at risk with either eczema and hen`egg allergy and/or sensitization to peanut without clinical relevance was included in official feeding recommendations. Whether these recommendations should be applied for the general population and countries with a low prevalence of peanut allergy remanis to be discussed.

ATOPIC DERMATITIS

GAPS IN KNOWLEDGE

Atopic eczema is charcterized by a skin barrier dysfunction and an increased transepidermal water loss. Approximately 20% of eczema patients show genetic mutation in structural proteins like filaggrin, often accompanied by a Th2-deviated immune response.

Severity of atopic eczema correlates with the risk of food allergy and sensitization to foods. First studies in a smaller group of patients showed promising results in terms of prevention of eczema using early emollient therapy.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

As this approach of primary prevention of infantile eczema can be easily implemented in the daily care of an infant, larger trials should be performed in order to study the potentially beneficial effect of emollients enhancing skin barrier function.

GAPS IN KNOWLEDGE

Infants with atopic eczema were found to have a different gut micribiom compared to unaffected individuals. Different trials with different strains of probiotic bacteria have achieved heterogeneous results, some findings are promising, however, until now, not the ideal product for prevention has been identified, furthermore clear ideas regarding dose and length of treatment are missing.

The mode of delivery seems to be an influencing variable for the development of the microbiome in early infancy and thus for the immune system and the onset of asthma and allergy. Birth via cesarian section increases the risk for hen`s egg allergy during the first years of life.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Innovative approach

An interventional trial investigates the transfer of maternal vaginal micorobiome on the the new born, if cesarian section was necessary. Results are to expected and may alter recommendations for primary prevention of allergy and asthma.

FURTHER READING

1. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksünger Ö, Kalb B et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol* 2017; 139:1591-1599.e2.
2. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558-62.
3. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;127:661-667.
4. Dhami S, Nurmatov U, Halken S, Calderón MA, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergic disease: protocol for a systematic review. *Pediatr Allergy Immunol* 2016;27:236-241.
5. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016;22:250-253.
6. Dotterud CK, Storrø O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol.* 2010;163:616-623.
7. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-813.
8. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S et al. Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen. *Clin Exp Allergy* 1997;27:1007-1015.
9. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C et al; GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;364:701-709.
10. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A et al. Consensus

communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *Allergy* 2015;70:1193-1195.

11. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol* 2017;28:728-745.
12. Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997;99:254-260.
13. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2015;134: 824-830.
14. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U. Perennial sensitisation early in life and chronic asthma in children. *Lancet* 2006;368: 763-770.
15. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;62:943-948.
16. Jacobsen L, Wahn U, Bilo MB. Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: the effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy. *Clin Transl Allergy* 2012;2:8.
17. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol* 2016; 137:358-368.
18. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015; 136:556-568.
19. Kelleher M, Dunn-Galvin A, Hourihane JO, Murray D2, Campbell LE, McLean WH, et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2015; 135:930-935.
20. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017;28:18-29.
21. Larsen JN, Broge L, Jacobi H. Allergy immunotherapy: the future of allergy treatment. *Drug Discov Today* 2016;21:26-37.
22. Marenholz I, Nickel R, Rüschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;118:866-871.
23. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109:251-256.
24. Mosges R, Palomares O, Pfaar O, Smolinska S, Sokolowska M, Asaria M et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006;61:855-859.
25. Ozdemir C, Kucuksezer UC, Akdis M, Akdis CA. Specific immunotherapy and turning off the T cell: how does it work? *Ann Allergy Asthma Immunol* 2011;107:381-392.
26. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 2007;119:881-891.
27. Penders J, Gerhold K, Stobberingh EE, Thijs C, Zimmermann K, Lau S et al. Establishment of the intestinal microbiota and its role in infantile eczema: results from a randomized placebo-controlled trial. *J Allergy Clin Immunol* 2013;132;601-607.
28. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKh, Fiocchi A et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013;6:18.
29. Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. *J Allergy Clin Immunol* 1988;82:470-480.
30. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014; 134:818-823.
31. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med* 2016;375:411-421.
32. Turner PJ, Campbell DE, Boyle RJ, Levin ME.

Primary Prevention of Food Allergy: Translating Evidence from Clinical Trials to Population-Based Recommendations *J Allergy Clin Immunol Pract* 2018;6:367-375.

33. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sørensen HF et al. GAP investigators. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018;141:529-538.e13.
34. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011;128:948-955.
35. Wachholz PA, Nouri-Aria KT, Wilson DR, Walker SM, Verhoef A, Till SJ et al. Grass pollen immunotherapy for hayfever is associated with increases in local nasal but not peripheral Th1:Th2 cytokine ratios. *Immunology* 2002;105:56-62.
36. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
37. Walker SM, Varney VA, Gaga M, Jacobson MR, Durham SR. Grass pollen immunotherapy: efficacy and safety during a 4-year follow-up study. *Allergy* 1995;50:405-413.
38. Wilson DR, Nouri-Aria KT, Walker SM, Pajno GB, O'Brien F, Jacobson MR et al. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. *J Allergy Clin Immunol* 2001;107:971-976.
39. WORLD HEALTH ORGANIZATION. Prevention of Allergy and Allergic Asthma. WHO Rep [Internet]. 2002 Jan; Available from: http://www.who.int/respiratory/publications/WHO_NMH_MNC_CRA_03.2.pdf

E

INTEGRATED CARE FOR ALLERGIC DISEASES

Marek Jutel, Johannes Ring

REVISED NOMENCLATURE FOR ALLERGIC DISEASES

E 1

GAPS IN KNOWLEDGE

Recent years brought significant progress in understanding of pathophysiologic processes. Growing bunch of molecular data on humans, particularly those associated with individual patients allowed discovery of yet unknown opportunities to use this set of data to improve health outcomes. Molecular development together with advances in information technologies as well electronic medical records provide excellent opportunity to create a new system of disease nomenclature (disease taxonomy). This nomenclature would describe diseases on the basis of their intrinsic biology in addition to traditional "signs & symptoms", leading to better understanding of allergic disease mechanisms, pathogenesis and treatments. The revised nomenclature nomenclature should also allow easy incorporation of newly appearing data to existing knowledge.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Innovative approach

Over the last two decades allergists have been involved more and more in the management i.e. diagnosis, treatment and prevention of conditions which are not truly "allergic" according to the current terminology. They are designated with different diagnoses and names using a variety of terms like "idiosyncrasy", "pseudo-allergy", "allergy-like reactions", "intolerance" and many more. At the moment the umbrella term for all these conditions including allergy is "hypersensitivity" which can be further subdivided into allergy, intolerance, idiosyncrasy etc.

Fig 1 describes proposed the innovative approach for allergic diseases nomenclature.

Hypersensitivity can be defined as: "Occurrence of objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal individuals".

Immune-allergy = „immunologically mediated allergy"

The term „immune–allergy" or „immunological allergy" will cover all conditions which have been called „allergic" until now and can be further subdivided at libitum into IgE-mediated, cytotoxic, immune complex, type IV a, b, c, d etc. With this definition one could also include as a subgroup of "immunological allergy" some "eosinophilic" diseases that are on the rise and at the moment can-

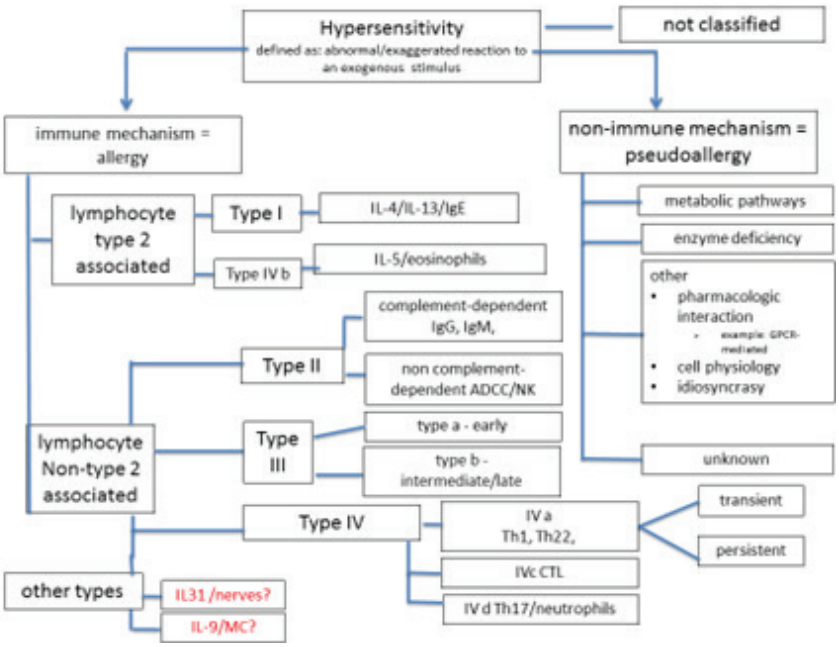


Figure 1.

not be called "allergic" although there is evidence for hypersensitivity to exogenous stimuli.

Non-immune allergy = " Occurrence of signs and symptoms of allergy without detectable immunological sensitization.

"Non-immune (not immunologically mediated) allergies can be further subdivided into "intolerance" phenomena due to metabolic effects (e.g. lactose intolerance) or disturbed transport mechanisms (e.g. fructose malabsorption) as well as the often not well understood so-called "idiosyncratic" or "pseudo-allergic reactions".

Anaphylaxis = "an acute generalized potentially life threatening reaction with variable symptoms comprising more than two organs". Nothing would have to change for this term. The current definition and classification into an immunological versus non-immune anaphylaxis serves as an example how successful a change in nomenclature can be.

However our specialty, is called "Allergology". Therefore logically we prefer "Allergy" as the wider "embracing" term. Thus Hypersensitivity could be replaced by allergy. A new definition of "Allergy" reaching beyond the immunologically mediated hypersensitivity reactions, by providing both a wider umbrella for our specialty and a more appealing classification Owill strengthen our reputation in medicine. It will attract more patients and facilitate our conversations with people suffering from various hypersensitivity conditions.

Advantages of the proposed new nomenclature

The new terminology would make our discipline stronger and broader. It allows to include much more clinical conditions as well as define and name them very specifically and logically according to the mechanisms involved; this could finally lead to development of new diagnostic procedures and molecularly targeted therapies as well more effective prevention strategies.

FURTHER READING

1. Pirquet C von: Allergie. *Münch Med Wochenschr* 1906;30:1457-1458.
2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organisation (WAO). *J Allergy Clin Immunol* 2004;113:832-836.
3. Bergmann KC, Ring J (eds): History of Allergy. Karger, Basel 2014

Roy Gerth van Wijk, Ibon Eguiluz-Gracia,
Jose M Olaguibel

EDUCATION AND TRAINING IN ALLERGY AND CLINICAL IMMUNOLOGY: SPECIALIST AND POSTGRADUATE

E2

GAPS IN KNOWLEDGE

Allergic diseases are characterised by a high prevalence and a substantial burden of disease. Therefore, there is a need for access to primary care physicians and specialists who can adequately diagnose and treat patients with allergic disorders.

However, there are clear gaps in education and training of healthcare professionals. Gaps in postgraduate training is illustrated by a recent study among primary care physician reporting major deficits in knowledge and skills in the provision of allergy care such as lack of knowledge of immunotherapy.

Allergy care provided by specialists is being characterised by heterogeneity: in some countries full specialists and in other subspecialists practice in allergy. European training requirements (ETR) for the full specialty are available, however this ETR from 2003 needs to be updated. Although there are criteria for the training in the specialty, UEMS surveys underline the wide variety in duration of training programs. Also striking differences can be seen in training pathways of physicians seeing allergic children. As there are no generally accepted requirements for subspecialists, recently an EAACI position paper has been published aiming to propose the minimal requirements for training and certification of subspecialists. At an international level education can be improved by the conventional instruments of allergy schools, masterclasses and other meetings, however for a better outreach other tools should be developed as e-learning (platforms), e-based gaming etc.

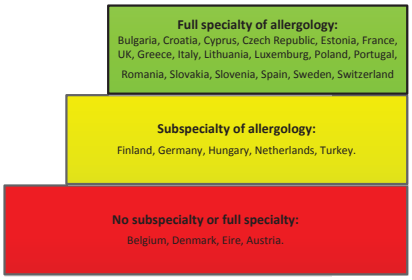
The diversity of the status of the Allergy specialty (Figure 1) in the different European countries causes a parallel heterogeneity in the training programs of physicians taking care of patients with allergic diseases and asthma.

In countries with a full specialty residents/fellows in Allergology should have an educational period of 4-5 years including specific training. Sometimes, the number of available training centres is insufficient. Moreover, the educational curricula - not always including specific training in paediatric allergy or in clinical immunology beyond allergic diseases – may differ substantially.

In countries with subspecialties board-certified otorhinolaryngologists, pulmonologists, dermatologists, paediatricians or internists can follow a two-year training period. The educational programs display a high degree of variability depending on the original medical specialization and focusing on the allergic conditions related to the original medical background.

Finally, the situation in countries without a formal (sub)specialty, may range from no recognition at all (Belgium) to the existence of the official category of “physician with special competence” (Norway). In these countries training in allergic diseases largely relies on the personal initiative of interested physicians.

Figure 1. Different allergy services across Europe.



RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Need for harmonisation and standardisation of training requirements for specialists and subspecialists in allergy and clinical immunology.

To improve harmonization of the training in Allergology, it is crucial to establish a full specialty in all European countries, and to define precisely its competences, including those in relation to paediatric allergy and clinical immunology. Well-regulated subspecialties may form an intermediate step to the specialty. This general recognition will facilitate the creation of an adequate network of allergy training centres. Only upon these premises, it will be possible to achieve a true harmonization of the training programs in Allergology allowing the mutual recognition and exchange of specialists within Europe.

Need for e-learning tools to outreach to the enlarge the target population of doctors seeing allergic patients.

General practitioners (GP) are gatekeepers to healthcare systems in most European countries. Their education in Allergology can help establishing cost-efficient strategies for the management of allergic patients. In this regard, the novel e-learning tools and platforms have the potential to improve both the management of allergic patients in primary care, and the referral strategy of individuals to specialized Allergy Units. Furthermore, they might guarantee the maintenance of proper standard care, provided by GP's to the allergic patient. In addition, e-learning tools and platforms are increasingly important in undergraduate education. Also, the UEMS (Union Européenne de médicines spécialists) accredits e-learning programs for postgraduate education of medical specialists.

FURTHER READING

1. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;64:123-148.
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758-764.
3. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007;62:91-96.
4. Ryan D, Gerth van Wijk R, Angier E, Kristiansen M, Zaman H, Sheikh A et al. Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy. *Allergy* 2018;73:827-836.
5. Gayraud J, Giannakopoulos D. UEMS Allergology: UEMS; 2014 [updated 2014. Available from: https://uemsallergology.eu/specialty-in-europe/our-way-of-working.
6. Tsilochristou O, Maggina P, Zolkipli Z, Sanchez Garcia S, Uysal P, Alvaro Lozano M et al. Current state and future of pediatric allergology in Europe: A road map. *Pediatr Allergy Immunol* 2018;29:9-17.
7. Gerth van Wijk R, Eguiluz-Gracia I, Gayraud J, Gutermuth J, Hamelmann E, Heffler E et al. The roadmap for allergology in Europe: The subspecialty of allergology as "stop-over" on the way to a full specialty. An EAACI position statement. *Allergy* 2018;73:540-548.
8. de Monchy JG, Demoly P, Akdis CA, Cardona V, Papadopoulos NG, Schmid-Grendelmeier P et al. Allergology in Europe, the blueprint. *Allergy* 2013;68:1211-1218.

Isabel Skypala, Kate Grimshaw, Liz Angier

ALLIED HEALTH/ PRIMARY CARE/PHARMACISTS

E3

GAPS IN KNOWLEDGE

An allergy can present in many ways to different services, so it is essential to that allied health professionals (AHP) and those working in Primary Care or in a Pharmacy are equipped to support patients with allergic disease. Evidence shows that nurses, dietitians, psychologists, respiratory therapists and pharmacists are already involved in the diagnosis and management of asthma, atopic dermatitis, food allergy and allergic rhinitis. However data suggests some AHPs feel they only have moderate proficiency in allergy management and need to increase their knowledge. Education programmes work well, but these need to be competency driven and based on evidence.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- The need to focus research on population health models and risk stratification of patients with allergic disease, linked to cost and quality measures. The results of this work should inform the health economics of community care versus specialist care for allergy sufferers, whilst considering the safety of such care and the patient experience.
- Workforce planning and remodeling, is also needed to ensure capacity and capability within the allied health and primary care community to deliver integrated allergy services. This may require inter-professional education at undergraduate and post-graduate level to provide learning requirements.
- Research into the development of communication and IT infrastructures across both primary and secondary care will be important to integrate gold standard allergy care across all healthcare settings, as will the use of quality pathways, algorithms for testing and step management in the community.

Standards and quality criteria

Training of primary care practitioners to develop leadership in integrated care, ensure the safety of allergy community care and optimize the patient experience is essential. Developing AHPs, GPs

and primary care practitioners to deliver integrated care will also require cultural and behavioural changes, and essentially, facilitation by secondary care allergy and asthma specialists.

Competencies recognise the importance of attaining and demonstrating both practical skills and a theoretical grounding in the subject. They additionally provide a standardised framework of consistent quality criteria for the effective and safe allergy patient care against which practitioners can demonstrate proficiency both to themselves and also to other health care professionals within the multi-disciplinary team. Competency driven practice fits into the modern delivery of health care which considers the team member's competency to deliver the required care and not the 'role' or hierarchy of that person within the health system. Competencies for AHPs working in allergy have been developed by the European Academy of Allergy & Clinical Immunology (in press), but these need to be developed further by considering other providers, including GPs and Pharmacists who may be providing allergy care in an isolated setting.

Innovative approach

Good examples of innovative approaches to the development of GPs and Allied Health professions working in allergy include the upskilling of UK GPs in allergy diagnosis and management through the 'Itchy sneezy wheezy' project. Also there is community training ongoing in Finland to provide GP-led allergen immunotherapy services. In some European countries, nurses and/or dietitians have been trained to diagnose, manage and treat patients with asthma and allergic conditions. In the UK, dietitians are providing direct management advice to parents of children with cow's milk allergy, facilitated by an Allergy charity.

FURTHER READING

1. Borgmeyer A, Gyr PM, Jamerson PA, Henry LD. Evaluation of the role of the pediatric nurse practitioner in an inpatient asthma program. *J Pediatr Health Care* 2008;22:273-281.
2. Nicol NH, Ersser SJ. The role of the nurse educator in managing atopic dermatitis. *Immunol Allergy Clin North Am* 2010;30:369-383.
3. Berni Canani R, Leone L, D'Auria E, Riva E, Nocerino R, Ruotolo S et al. The effects of dietary counseling on children with food allergy: a prospective, multicenter intervention study. *J Acad Nutr Diet* 2014;114:1432-1439.
4. Venter C, Laitinen K, Vlieg-Boerstra BJ. Nutritional aspects in diagnosis and management of food hypersensitivity-the dietitians role. Special issue Food hypersensitivity. *J Allergy (Cairo)* 2012;2012:269376.
5. Knibb RC, Semper H. Impact of suspected food allergy on emotional distress and family life of parents prior to allergy diagnosis. *Pediatr Allergy Immunol* 2013;24:798-803.
6. Jarernsiripornkul N, Chaipichit N, Chumworathayi P, Krska J. Management for improving patients' knowledge and understanding about drug allergy. *Pharm Pract (Granada)* 2015;13:513.
7. Shelledy DC, Legrand TS, Gardner DD, Peters JI. A randomized, controlled study to evaluate the role of an in-home asthma disease management program provided by respiratory therapists in improving outcomes and reducing the cost of care. *J Asthma* 2009;46:194-201.
8. Groetch ME, Christie L, Vargas PA, Jones SM, Sicherer SH. Food allergy educational needs of pediatric dietitians: a survey by the Consortium of Food Allergy Research. *J Nutr Educ Behav* 2010;42:259-264.
9. Reeves L, Meyer R, Holloway J, Venter C. The development and implementation of a training package for dietitians on cow's milk protein allergy in infants and children based on UK RCPCH competencies for food allergies - a pilot study. *Clin Transl Allergy* 2015;5:4.
10. Ogrinc G, Headrick LA, Mutha S, Coleman MT, O'Donnell J, Miles PV. A framework for teaching medical students and residents about practice-based learning and improvement, synthesized from a literature review. *Acad Med* 2003;78:748-756.
11. Lewis-Barned N, Davies E. Working in partnership with patients–what does it mean in clinical practice?. *Medicine* 2016;44:611-614.

Mikaela Odemyr, Susanna Palkonen, Frans Timmermans

THE ROLE OF PATIENTS' ORGANISATIONS

E4

Allergy patient organisations were formed because of the need to tackle every-day life issues of patients and caregivers, which are not properly addressed within the traditional healthcare system. This relates to quality of life in allergy, particularly severe or complex forms, and for children. For patients, allergy prevention goes with care and cannot be separated.

Since the beginning, the creation of patient groups was related to the need not to have to fight the system for care and support, but to be placed in the center of care as a patient, through care coordination, co-decision making, follow up, psychological support and connection between health and social care and everyday life challenges.

GAPS IN KNOWLEDGE

While the role of patients in participating in healthcare has been studied, the role or value of (allergy) patient groups has not.

Patient groups have developed from self-help groups, providing peer-support and patient education to couple the healthcare, into advocacy organisations who provide patient centered services, information, support, driving policy and research for care, prevention and patient participation, often in partnership with professionals. They are no longer dependent on doctors but equal partners. Allergy patient groups channel collective patient view and thus have the responsibility to be transparent, accountable, democratic, representative, independent and base on evidence.

The missing piece is that the movement is unequal across Europe. The strength of the organisations does not match population of the country represented, on the contrary. The groups in Nordic countries are big, while in big countries like France or Spain patients' organisations are quite small and in some Eastern European countries they do not exist at a national level. The size of the groups is not however in linear on their effectiveness in delivering value for patients!

Resources do not exist or they are not provided at the same pace as patient involvement is sought for. In particular public, non-commercial funding is lacking.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Mapping allergy patient groups in Europe; services, role, representativeness and challenges could help developing a database and targeted capacity building

For allergy patients the current development of patient centered, integrated or participatory care and research, together with the acknowledgement of the need to involve patients in policy is very important. European level initiatives include the systematic involvement of patients by the European Medicines Agency, the current proposal from the European Commission on coordination on HTA in Europe and Interest Group of Asthma Allergy at the European Parliament.

Involvement of patient organisations as co-planners and evaluators of integrated care initiatives can only benefit the society to deliver cost-effective services and products based on needs that support active patients.

Integrated care has been studied, patient centeredness less, what is patient centeredness in allergy care? This could lead to innovative deployable approach in healthcare

The author(s) have successfully fought the system for right care and environments at home, daycare and school for their children with severe asthma and food allergy so that they can fulfill their dreams as anyone else, and are involved in local, national and European level patient movement and members of the EAACI Patient Organisation Committee.

Integrating allergy care with patients equals good productive life despite allergy.

FURTHER READING

1. Personalized Medicine. Empowered Patients in the 21st Century? Barbara Prainsack. NYO Press. ISBN: 9781479814879.
2. Integrated care models: an overview. WHO Regional Office for Europe. October 2016 http://www.euro.who.int/__data/assets/pdf_file/0005/322475/Integrated-care-models-overview.pdf.
3. The Added Value of Patient Organisations. European Patients Forum. 11/2017 http://www.eu-patient.eu/globalassets/library/publications/epf_added_value_report_final.pdf

Anaphylaxis Canada

Anaphylaxis Canada

Anaphylaxis Ireland

Anaphylaxis Ireland

Anoiksi NGO

ASOCIACIÓN ESPAÑOLA DE ALÉRGICOS A ALIMENTOS Y LÁTEX

AEPNAA

Asociacion espanola de alergicos a alimentos y latex

AFPRAL

Association Francaise pour la Prevention des Allergie (AFPRAL)

ASSOCIATION QUÉBÉCOISE DES ALLERGIES ALIMENTAIRES

Association québécoise des allergies alimentaires

Astma-Allergi Danmark

Astma-Allergi Danmark

Deutscher Allergie- und Asthmabund e.V.

Deutscher Allergie und Asthmabund eV

EFA European Federation of Allergy and Airways Diseases Patients Associations

Patients Association

FOOD ALLERGY ITALIA

Food Allergy Italia

FARE Food Allergy Research & Education

Food Allergy Research & Education

CRECIENDO CON ALERGIAS

Fundacion Creciendo con Alergias Alimenarias

Cezmi Akdis, Jean Bousquet,
Philippe Eigenmann, Clive Grattan

EAACI JOURNALS AND PUBLICATIONS

E5

Writing is the most important means for communicating scientific work. Research and publication complement teaching and training, clinical care, and public health works. EAACI's journals and publications are vital and dynamic elements of the scientific environment, research communication and education of our specialty.

EAACI journals

The Academy's three journals, Allergy, Pediatric Allergy and Immunology and Clinical and Translational Allergy, have a major influence on the practice of allergy and clinical immunology throughout the world. Together, the journals chronicle the latest advances in cellular and molecular biology, genetics, novel epidemiological studies and practice-shaping clinical trials, publish state-of-the-art articles and clinical guidelines.

Allergy journal

Allergy (original title Acta Allergologica) was established in 1948. In its history it was supported by an outstanding Editorial Team (box 1).

The aim of the journal is to cover the scientific output of specialty of allergy, asthma, basic and clinical immunology.

The mission of Allergy is to become the journal for all aspects of the science, practice, education and policy making of Allergy & Clinical and Basic Immunology in overall health care milieu. The vision is to advance, impact and communicate all aspects of the discipline of Allergy/Immunology including educational, basic, translational and clinical research.

Allergy publishes approximately 200 articles per year and its impact factor is 7.3.

Pediatric Allergy and Immunology (PAI)

Pediatric Allergy and Immunology has been established in 1990 by Bengt Björkstén as the first journal addressing allergic and immunologic diseases in childhood (box 2).

The journal became the official journal of the European Society of Pediatric Allergy and Clinical Immunology (ESPACI), and later after the merger of ESPACI with EAACI, the official journal of the EAACI-Section on Pediatrics.

The journal is the main international journal in the field, reaching clinicians and researchers beyond Europe, including all continents. The aim of the journal is to link clinical and translational aspects of pediatric allergy, asthma, immunodeficiency and clinical immunology. Major focuses of the journal include prevention and early life events leading to allergic diseases. PAI publishes 8 issues per year with approximately 80 to 100 original articles. The 2016 impact factor of PAI is 3.775.

Clinical and Translational Allergy (CTA)

Before research funders and governments started to push hard for open access publishing of original research EAACI launched the open access journal "Clinical and Translational Allergy" (CTA) in 2011

Box 1. Allergy Editorial Team

Founding Editor-in-Chief in 1948 was Prof. Ernst B. Salén (Sweden). Prof. Egon Bruun was also Editor-in-Chief during the earlier years.

From 1970 the Editors-in-Chief were:

- *Prof. Gunnar Bendixen, Denmark (1970-1992)*
- *Prof. Gunnar S. Johansson, Sweden (1993-2002)*
- *Prof. Jean Bousquet, France (2003-2009)*
- *Profs. Thomas Bieber & Hans-Uwe Simon, Germany (2010-2017)*
- *Prof. Cezmi Akdis, Switzerland took over the journal from 1st of March 2018.*

Curent Editorial Team of Allergy

Deputy Editor

- *Maria Torres, Spain*

Managing Editor

- *Kyle Megan Howell, Switzerland*

Associate editors

- *Heimo Breiteneder, Austria*
- *Reto Crameri, Switzerland*
- *Zuzana Diamant, Netherlands*
- *Thomas Eiwegger, Canada*
- *Wytske Fokkens, Netherlands*
- *Robyn O'Hehir, Australia*
- *Liam O'Mahony, Switzerland*
- *Oliver Pfaar, Germany*
- *Claudia Traidl-Hoffmann, Germany*
- *De Yun Wang, Singapore*
- *Stephan Weidinger, Germany*
- *Luo Zhang, China*

Editorial board

- *Ioana Agache, Romania*
- *Mübeccel Akdis, Switzerland*
- *Evangelos Andreakos, Greece*
- *Heimo Breiteneder, Austria*
- *Lorenzo Cecchi, Italy*
- *Adam Chaker, Germany*
- *Yoon-Seok Chang, Korea*
- *Gennaro, D'Amato, Italy*
- *Peter Hellings, Belgium*
- *Domingo Barber Hernandez, Spain*
- *Martin Himly, Austria*
- *Karin Hoffmann-Sommergruber, Austria*
- *Alan Irvine, Ireland*
- *Marek Jutel, Poland*
- *Ludger Klimek, Germany*
- *Edward Knol, The Netherlands*
- *Gerard Koppelman, The Netherlands*
- *Susanne Lau, Germany*
- *Marcus Maurer, Germany*
- *Gunnar Nilsson, Sweden*
- *Natalija Novak, Germany*
- *Kimihiro Okubo, Japan*
- *Oscar Palomares, Spain*
- *Hai Qi, China*
- *Claudio Rhyner, Switzerland*
- *Peter Schmid-Grendelmeier, Switzerland*
- *Carsten Schmidt-Weber, Germany*
- *Bulent Sekerel, Turkey*
- *Dagmar Simon, Switzerland*
- *Mohamed Shamjo, United Kingdom*
- *Gunter Sturm, Austria*
- *Peter Valentin Tomazic, Austria*
- *Bernard Thong, Singapore*
- *Sanna Toppila-Salmi, Finland*
- *Thomas Werfel, Germany*
- *Willem van de Veen, Switzerland*
- *Cornelis van Drunen, The Netherlands*
- *Marianne van Hage, Sweden*
- *Menno van Zelm, Australia*
- *Susanne Vijverberg, The Netherlands*
- *Andreas Wollenberg, Germany*
- *Stephan von Gunten, Switzerland*
- *Liu Zheng, China*

Box 2. PAI Editorial Team

Editors-in-Chief :

- *Bengt Björkstén, Sweden (1990-1997)*
- *John Warner, UK (1997-2010)*
- *Ulrich Wahn, Germany (2010-2017)*
- *Philippe Eigenmann, Switzerland took over the journal from 1st of January 2018.*

Current Editorial Board of PAI

Managing editor

- *Doris Kollmann, Germany*

Associate editors

- *Alexandra Santos, UK*
- *Motohiro Ebisawa, Japan*
- *Hugh Sampson, USA*
- *Ömer Kalayci, Turkey*
- *Jennifer Koplin, Australia*
- *Jon Genuneit, Germany*
- *Marina Atanaskovic-Markovic, Serbia*

Editorial board

- *Katie Allen, Australia*
- *Montserrat Alvaro Lozano, Spain*
- *Hugo van Bever, Singapore*
- *Kirsten Beyer, Germany*
- *Wesley Burks, USA*
- *Jean-Christoph Caubet, CH*
- *Adnan Custovic, London, UK*
- *Stefano Del Giacco, Italy*
- *Antoine Deschildre, France*
- *George Du Toit, UK*
- *Jean-Luc Fauquert, France*
- *Olga Fedorova, Russia*
- *Alessandro Fiocchi, Italy,*
- *Luis Garcia-Marcos, Spain*
- *Susanne Halken, Denmark*
- *Eckard Hamelmann, Germany*
- *Gunilla Hedlin, Sweden*
- *Jonathan Hourihane, Ireland*
- *Arne Host, Denmark*
- *Jocelyn Just, France*
- *Gideon Lack, UK*
- *Susanne Lau, Germany*
- *Mike Levin, South Africa*
- *Eric Melen, Sweden*
- *Antonella Muraro, Italy*
- *Antonio Nieto, Spain*
- *Giovanni Pajno, Italy*
- *Nikos Papadopoulos, Greece*
- *Giovanni Passalacqua, Italy*
- *Petr Pohunek, Czech Republic*
- *Paul C. Potter, South Africa*
- *Jeanine Reichenback, Switzerland*
- *Graham Roberts, UK*
- *Caroline Roduit, Switzerland*
- *Nelson Rosario, Brazil*
- *Jurgen Schwarze, United Kingdom*
- *Pakit Vichyanond, Thailand*
- *Gary Wong, Hong Kong*

under the initiative of Jan Lötvall, who was the founding Editor in Chief (box 3).

Open access publishing enables free access to all content ensuring a wide dissemination of articles; the electronic format and expert peer review allows for very rapid publication. Clinical and Translational Allergy is an international journal reaching out far beyond the borders of Europe. Online publication in Clinical and Translational Allergy gives the opportunity to publish large datasets, large numbers of color illustrations and moving pictures, to display data in a form that can be read directly by other software packages so as to allow readers to manipulate the data for themselves, and to create all relevant links (for example, to PubMed, to sequence and other databases, and to other articles). The 2016 impact factor of CTA is 3.239.

EAACI Atlases

To tackle the huge global health problem of allergy and asthma the European Academy of Allergy and Clinical Immunology published the “Global Atlas of Asthma” (2013), “Global Atlas of Allergy” (2014) and “Global Atlas of Allergic Rhinitis and Chronic

Box 3. CTA Editoria Team

Editors-in-Chief :

- *Founding Editor, Jan Lötvall, Sweden*
- *Clive Grattan, since 2013*
- *Jean Bousquet, since 2016*

Current Editorial Board of CTA

Associate editors

- *Ioana Agache, Romania*
- *Claudia Alessandri, Italy*
- *Alberto Alvarez-Perea, Spain*
- *Montserrat Alvaro, Spain*
- *Barbara Bohle, Austria*
- *Onur Boyman, Switzerland*
- *Victoria Cardona, Spain*
- *Magdalena Czarnecka-Operacz, Poland*
- *Gennaro D'Amato, Italy*
- *Stefano R. Del Giacco, Italy*
- *Fatima Ferreira, Austria*
- *Lars Jacobsen, Denmark*
- *Marek Jutel, Poland*
- *George Konstantinou, Greece*
- *Antonella Muraro, Italy*
- *Nikos Papadopoulos, Greece*
- *Lars K Poulsen, Denmark*
- *Dermot Ryan, UK*
- *Sanna Toppila-Salmi, Finland*
- *Maria J Torres, Spain*
- *Carina Venter, UK*

Editorial board

- *Sevim Bavbek, Turkey*
- *Fulvio Braido, Italy*
- *Yoon-Seok Chang, South Korea*
- *Luis Delgado, Portugal*
- *Pascal Demoly, France*
- *Philippe Eigenmann, Switzerland*
- *Penny Fitzharris, New Zealand*
- *Wytske Fokkens, Netherlands*
- *Roy Gerth van Wijk, Netherlands*
- *Kiran Godse, India*
- *Peter Hellings, Belgium*
- *Michihiro Hide, Japan*
- *Edward Knol, Netherlands*
- *Lin-Feng Li, China*
- *Carmen Rondon, Spain*
- *Peter Schmid-Grendelmeier, Switzerland*
- *Stephen A Tilles, USA*
- *Massimo Triggiani, Italy*
- *Ronald van Ree, Netherlands*
- *Thomas Werfel, Germany*

Rhinosinusitis: (2015). Written by international key opinion leaders the Atlases provide a platform for strategic planning for allergic diseases and asthma in a multifaceted way, integrating research, education and global policies. They provide strong evidence which calls attention to the burden of allergic diseases asthma, warrant their recognition as a high priority for national health strategies, to demonstrate the necessity for an increase in research, to evaluate the best ways to prevent and control the disease, to provide guidance on how to overcome barriers and to alert political bodies to ensure a truly global approach. The Atlases have been translated into Spanish, Chinese and Greek.

Monographs and user guides

The EAACI Molecular Allergology Users's Guide introduce the current position of the EAACI on *in vitro* methods of Molecular Allergology, their advantages and limitations and how they can be used in an up-to-date diagnostic work-up of the allergic patients. More than 50 authors from over 15 countries and five continents have drafted the 40 chapters composing the first edition of the Handbook.

Consensus documents

'As part of its mission, EAACI collaborates with the major scientific organisations in the field to develop international consensus documents (ICONS) and documents focusing on practical aspects of allergy aiming to deliver updated and evidence based recommendations for clinicians (the PRACTALL programme in cooperation with the American Academy of Allergy and Clinical Immunology).

Ioana Agache, Sergio Bonini

MAJOR RESEARCH THEMES IN ALLERGY AND ASTHMA

E6

1. There has been a tremendous change in the diagnosis and monitoring in allergic diseases and asthma due to new techniques and research approaches with significant impact on the specialty. Techniques such as molecular diagnosis, more accessible tools for human immunophenotyping, the application of omics and sophisticated imaging are deepening our understanding of allergic diseases and asthma
2. Personalized care based on molecular, immunologic and functional endotyping of the disease and the increased use of 'biological' drugs (antibodies and antagonists) to block or modify disease mechanisms, are increasingly important in treating allergy and asthma
3. Data driven disease endotyping using new statistical tools (Supervised analysis, Latent Class Analysis, Bayesian Network Analysis, Topological Data Analysis, etc.) shift the research approach from the phenotype/cluster approach with investigator-imposed subjective disease clustering (hypothesis driven) to an unbiased, endotype/biomarker driven approach
4. Focus on prevention and environment. When Benjamin Franklin said that an ounce of prevention is worth a pound of cure, he hadn't bargained for the weird weights and measures of today's care and health system. We need to get better at measuring the benefits of prevention and do more of it over the long term. There are no quick fixes. Local context is key – there is rarely a single, one-size-fits-all solution. A long-term view needs to be implemented: the really big prize lies much further upstream, where compelling evidence is emerging of return on investment from public health programmes and work in schools, communities and housing.

Allergy and asthma research encompasses a wide range of diseases and can be classified according to major themes that cover both the origins and consequences of diseases in an evolving scientific environment.

Five major research themes have been identified:

GAPS IN KNOWLEDGE

As a multifactorial diseases allergic diseases and asthma natural history reflects the combined effects of genetic factors, development-specific exposures (in utero, early-life and childhood exposures) and the biological responses to those exposures (allostasis). Although many epidemiological, genetic, environmental, and immune risk factors for allergic diseases and asthma are known, distinguishing which risk factors are causal, their mechanism of action and how interaction between these factors initiates disease remains poorly understood.

Although it is recognized that up to 90% of allergies and asthma results from development-specific exposure with a secondary role of the genetic background significant less research is oriented on describing the developmental exposome.

Current barriers to our understanding include the limitations of research during gestation and the perinatal period, inadequacies of animal models in recapitulating the onset of human disease, differences between human and experimental animal developmental stages and difficulties to document low dose exposure (limited by the sensitivity of the assay), intermittent exposure (limited by the frequency of testing) and transient exposure (the system should be in place at the time of the exposure).

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Standards and quality criteria

- Validated criteria for selecting the best assay(s) to assess biological response for the research question of interest. These criteria should be updated periodically to incorporate emerging tools and technologies
- Guidelines for sample collection, repositories and biobanks standards for use with emerging and anticipated technologies
- Complex unifying models based on language standards for exposures

Innovative approach

The exposomic approach is particularly applicable to the study of environmental causes of allergic diseases and asthma since provides risk profiles instead of single predictors while concomitant access to biological data, exposure data, and health outcomes evaluates the biologic plausibility of the hypothesis. There are several targets in the exposomics research: epigenetics, regulatory mRNAs, microbiome composition, diversity and metabolites, receptors activation or inactivation. Revealing which factors are most critical for defining the state of disease or dysfunction, and the correlation with factors of exposure will provide a means to develop intervention strategies.

Specific domains of the exposomics approach

- Studies that address both the relevance of specific developmental windows and the importance of coincident exposures, including lifestyle factors, diet and the concept of One Health; one of the best models are environmental wide association studies (EWAS)
- Validated methods assessig the developing human infant immune system
- Specific evaluation of gene-environment interaction at different stages of human development (in utero, early life, peripubertal, etc)
- Cross-omics and bioinformatics tools linking exposure data to biochemical and molecular changes in the body – the integrative multidimensional exposomics
- Use the biological response (allostasis) as the footprint of transient exposure
- Integrating data from several cohorts that together mimic all life stages

ALLERGIC DISEASES AND ASTHMA IN THE CONTEXT OF ENVIRONMENTAL HEALTH

GAPS IN KNOWLEDGE

Natural and man build environment like air quality, water and soil, and also all the physical, chemical, biological and social features of our surroundings have a major influence on the control and severity of allergic diseases and asthma. Although the precision medicine revolution has potential to transform environmental measures we still have a long way to go to more effectively identify whom should be targeted. Some environmental interventions like air quality regulation cannot be targeted to any subgroup, genetic, or otherwise. Others, like breastfeeding, vaccination, antismoking campaigns, exercise, or diets, could in principle, but they need to prove practical or cost efficient. The most efficient prevention would be to identify those at high risk to avoidable exposures. But simply evaluating genetic risks is not sufficient since we need to co-factor the interaction with environment.

The importance of nutraceuticals is expanding globally in terms of scientific services, legal aspects, and marketing strategies for health promotion, reduction of disease, and health care costs. However they are marketed without a prescription and their safety and efficacy is yet to be proven, especially if consumed in supra-dietary doses as nutritional supplements

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Standards and quality criteria

- Validated criteria to define the safety and efficacy of functional foods and nutraceuticals for the management of allergic diseases and asthma
- Define step-wise approach for environmental intervention: high-risk groups and population level
- Methodological approach proving causality instead of associations

Innovative approach

- The One Health concept evaluating the interconnections between human, environment and animal health and food and water safety
- An integrated surveillance network for the environment impact on allergies and asthma

DRUG DEVELOPMENT AND BIOMEDICAL ENGINEERING

GAPS IN KNOWLEDGE

New medicines such as advanced therapies (gene therapies, cell and tissue therapies, regenerative medicine), the increasing number of biologicals and biosimilars soon exceeding the number of chemical drugs and the introduction of sophisticated devices and biomedical engineered products, all call for a new approach in drug development, evaluation and monitoring. Paradoxically

however, innovation might not reflect in a better health care. In fact, the high costs for developing new medicines, the low probability for a new product to answer the strict regulatory requirements to obtain market authorization and, finally, the financial constraints of most national health services that cannot afford reimbursement for extremely expensive drugs, represent limiting factors for investments in the pharmaceutical area and patient access to new safe and effective drugs. Therefore, gaps in knowledge in this area are not confined to technological progress or to identifying new molecular targets through a better understanding of mechanisms of diseases, but also refer to new regulatory pathways that may prevent the actual "lost in translation".

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Standards and quality criteria

- Standard and quality criteria for drug development of new advanced therapies and biotechnological products, while requesting the same accuracy and reliability, may differ from those of "old" chemical drugs in terms of study design and evaluation techniques.
- Standard operational procedures and quality criteria should be harmonized among all countries, including those with an emerging pharmaceutical industry such as India and China.
- All world citizens should have access to new safe and effective drugs by developing models that, reducing the risk of investments, eventually reduce the price of new medicines, and by establishing heath policies on the basis of reasonable priorities and social equanimity.

Innovative approach

Innovative regulatory approaches include:

- Early collaboration in drug development of all stakeholders
- Development of validated biomarkers and companion diagnostics that enable the dissection of heterogeneous diseases into well-defined phenotypes and endotypes
- Joint health technology assessment scientific advice
- Adaptive pathways for drug development that allow evaluation and monitoring during the entire life-cycle.

BIG DATA AND INFORMATION TECHNOLOGY

GAPS IN KNOWLEDGE

Healthcare is at present largely based on evidence provided by randomized controlled clinical trials and observational/epidemiological data in selected populations. There is however a massive amount of data available from healthcare records, registries, biobanks whose potential in improving knowledge has not yet been fully explored. The availability of new information technology techniques for collecting, analyzing and relating the "big data" provided by the real world opens new horizons to a new, more comprehensive knowledge.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Standards and quality criteria

- Big data are quite heterogeneous and come from a large variety of sources. Their quality should be carefully checked and new hypothesis deriving from big data should be experimentally tested before neglecting the actual evidence and adopting new diagnostic and therapeutic approaches.
- Availability of big data requests that industry, regulatory bodies, scientists and clinicians accept transparency policies which make available their data to the community through open platforms.
- Big data imply a risk for citizens' and patients' privacy. This should be protected by adequate regulations and accurate anonymization techniques of individual personal data.

Innovative approach

The availability and analysis of big data is expected to open a new era in the computing science, with profound effects also in the area of biology and medicine. In fact, computers will not only be instruments to provide answers by elaborating data on the basis of pre-defined algorithms, but will be able to learn themselves from data analysis (machine learning) and to provide solutions on the basis of original algorithms. Artificial Intelligence will certainly favor a tremendous progress in medical sciences, but will also create a new relationship between humans and machines with relevant implications in ethics and responsibilities of the medical profession.

TRANSLATIONAL RESEARCH AND IMPLEMENTATION SCIENCE

GAPS IN KNOWLEDGE

The present healthcare system is clearly not ready for precision medicine. Access of patients to new drugs based on precise endotyping still poses significant problems on the sustainability of the healthcare system and the related ethical aspects are a raising concern.

A significant shift in the doctor-patient relationship is expected with the well-informed patient advocating for its own care and connected in real time with the healthcare provider that is provided with personalized information from patient portals.

Rapid learning systems can shape vast amounts of "omics" and "real-world" data unbiased by any pre-selection criteria into real-time clinical decision support at the point of care leading to harmonised care based on quality criteria.

There is clearly a huge job to be done in upskilling the healthcare providers, and it's a matter not only of skills but also of attitudes and culture, which are harder to change. Electronic records linked to multiple and qualities assured databases are essential, but there is also a big need for bio-informaticians who can ensure that the data is available, high quality, and well managed.

Innovative solution

- Translational research fosters the multidirectional and multidisciplinary integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science. For example drug development or primary prevention based on molecular endotypes or the developmental exposome can be prospectively validated using evidence-based clinical management to improve care across the severity spectrum. Investigators with expertise in molecular biology and exposomics need to engage in research planning with the informatics, genetics, clinical, health-economics and drug development experts. User-friendly large datasets support this cooperation
- Implementation science focuses on identification of all major contributions to improvement of health care, from individual factors up to policy and public health interventions. There are effective strategies to implement evidence-based practices grouped into six different categories—planning, education, financing, restructuring, quality management, and attention to policy context. This approach can support implementation of the precision medicine approach in a wide range of health care systems.

FURTHER READING

1. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 2005;14:1847-1850.
2. Miller GW, Jones DP. The nature of nurture: refining the definition of the exposome. *Toxicol Sci* 2014;137:1-2.
3. Wild CP. The exposome: from concept to utility. *Int J Epidemiol* 2012;41:24-32.
4. Vriejheid M. The exposome: a new paradigm to study the impact of environment on health. *Thorax* 2014;69:876-878.
5. Bahreinian S, Ball GD, Vander Leek TK, Colman I, McNeil BJ, Becker AB et al. Allostatic load biomarkers and asthma in adolescents. *Am J Respir Crit Care Med* 2013;187:144-152.
6. North ML, Brook JR, Lee EY, Omana V, Daniel NM, Steacy LM et al. The Kingston Allergy Birth Cohort: Exploring parentally reported respiratory outcomes through the lens of the exposome. *Ann Allergy Asthma Immunol* 2017;118:465-473.
7. Dhondalay GK, Rael E, Acharya S, Zhang W, Sampath V, Galli SJ et al. Food allergy and omics. *J Allergy Clin Immunol* 2018;141:20-29.
8. Bonini S, Bonini M. Biosimilars and drug development in immunologic diseases. *J Allergy Clin Immunol* 2017;139:1461-1464.
9. Rasi G, Bonini S. Innovative medicines; new regulatory procedures for the third millennium. *Expert Opin Biol Ther* 2015;15:5-8.
10. Bonini S, Eichler H-G, Wathion N, Rasi G. Transparency and the European Medicines Agency. Sharing of clinical trial data. *N Engl J Med* 2014;371:2552-2555.
11. Butler D. Translational research: crossing the valley of death. *Nature* 2008;453:840-842.
12. Woolf SH. The meaning of translational research and why it matters. *JAMA* 2008;299:211-213.
13. Kabashima K, Biedermann T. A new era for translational atopic dermatitis research and management. *Exp Dermatol* 2018;27:313-317.
14. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychol* 2015; 3:32.
15. Bender BG. A bootstrap approach to implementation science. *Ann Allergy Asthma Immunol* 2016;117:213-216.

Antti Lauerma, Tari Haahtela

COMMUNITY BASED APPROACHES FOR OPTIMAL OUTCOMES AND ACCOUNTABLE POPULATION HEALTH

E7

GAPS IN KNOWLEDGE

Allergy and asthma have become an increasing burden in Europe over past 50 years. Although, the reasons for the increase are debated, there is no reason to wait for action to reduce the burden. The experience from Finnish asthma (1994-2004) and allergy programs (2008-2018) shows that cutting the disability and costs is possible.

At the European level, this information is, however, redundant, if the experience cannot be translated and interpreted for others to build up their own action plans according to local needs.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Innovative approach

When making an action plan you need:

- **An idea**. What is the new information in prevention and management to be implemented? What is not working in the current health care system that should be corrected?
- **An organization that implements education and backs it up**. These programs are marked educational efforts to improve standard of care and information. In Finland, the programs were implemented (1) to health care workers by a professional NGO for respiratory disease (Finnish Lung Health Association, Filha), and (2) to patients and lay public by two patient NGOs (Allergy-, Skin- and Asthma Federation and Organisation for Respiratory Health in Finland).
- **A motivated steering group having experience on running complex projects**. 7-10 persons are ideal, as shown also in business cases where team efforts have been studied. Keep the organization as flat as possible.
- **Clear goals**. One goal is not enough, 10 goals are too much. Define 3-5 goals, so that they can be easily followed and kept in mind. Prefer measurable (quantitative, numerical) goals. If you want to reduce the burden, not just increase awareness! Do not develop or promote so much, just tell what you are going to do (Figure 1).

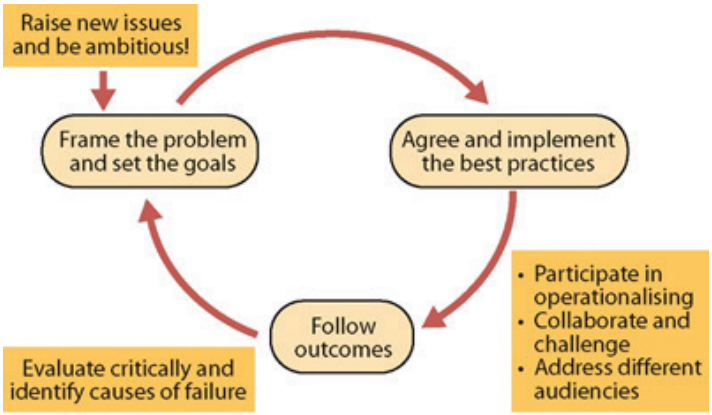


Figure 1. The circle of improvement. (Modified from Mickwitz P. A framework for evaluating environmental policy instruments: context and key concepts. Evaluation 2003).

- **To define specific tasks for each goal, tools to make the job**, as well as outcomes that you measure to keep you on the right track (use available registries and improve them!).
- **Time**. The program will not show immediate success, in 1-2 years you see some effect, in 5 years you achieve a lot. The planning takes easily a year.
- **To focus first on severe forms of disease, and get numerical results** (e.g. reduction in emergency visits). Show that you are saving money or stopping cost increase (you are dependent on decision makers funding and good will).
- **To get a win already in the beginning choose the first achievable steps**. This keeps everyone motivated even in long run.
- **To employ guided self-management, eHealth and mHealth**. Empower the patient. Compliance and adherence are old terms, partnership is the word!
- **Funding**. Try to have some public funding as seed money. If you succeed to get support from you Ministry and Public Health Administration, you are a winner!
- **To communicate**. Consider to employ a professional to build up information strategy and continuity.

Allergy & asthma organizations in Europe can spread out the best practices of prevention and management and show impressive results in a relatively short period of time. These efforts may pave the way also to other public health interventions to stop the "epidemic" of non-communicable diseases.

FURTHER READING

1. Haahtela T, Herse F, Karjalainen J, Klaukka T, Linna M, Leskelä RL et al. The Finnish experience to save asthma costs by improving care in 1987-2013. *J Allergy Clin Immunol* 2017;39:408-414.
2. Haahtela T, Valovirta E, Bousquet J, Mäkelä M; and the Allergy Programme Steering Group. The Finnish Allergy Programme 2008-2018 works. *Eur Respir J* 2017;49 (6).pii: 1700470.
3. Selroos O, Kupczyk M, Kuna P, Łacwik P, Bousquet J, Brennan D et al. National and regional asthma programmes in Europe. *Eur Respir Rev* 2015;24:474-483.
4. Szefler SJ, Holguin F, Wechsler M (eds.). Personalizing Asthma Management for the Clinician. Elsevier, US 2017.
5. Valovirta E, Haahtela T, Saarinen K, et al. Provision of care – implementation of the Finnish allergy programme 2008-2018. In: I. Agache, P. Hellings (eds.) Implementing Precision Medicine in Best Practices of Chronic Airway Diseases. Elsevier 2018, in press.

Paolo Matricardi, Stephanie Hofmaier,
Darío Antolín-Amérigo

INNOVATION IN HEALTH IT

E8

GAPS IN KNOWLEDGE

The use of Health Information Technologies (HIT) by allergic patients and physicians has continued to grow significantly over the last years.

Allergists need to be aware of patient-to-patient differences in triggers, drivers, age of appearance, persistence, degree and type of inflammation, severity of symptoms and response to treatment of their patients. To cope with this complexity, a strategy of "precision medicine" has become crucial. eHealth technology, such as mobile applications ("apps") are being discovered as a promising tool for disease management by monitor symptoms, medication intake, quality of life and even the environment.

Despite all the mentioned advantages and potentials of health information technology (HIT), there is a common lack of regulatory structures (Box 1). In order to ensure the best patient care, authorities should promote not only the further use of eHealth technologies, but also its regulations according to quality criteria.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Innovative approach

Overall, HIT bears promising potential in the following areas (Box 2):

- **Clinical Support and Knowledge Enhancement**

  Through eHealth technologies, the real-time and continuous collection of patient-related data is facilitated enormously. Also in the field of allergology, various patient- and/or doctor-centered systems have been developed. These render support in the diagnostic process, e.g. through Clinical Decision Support Systems (CDSS) or real-time symptom recording matched to pollen counts. Also adherence to prescribed treatments can be improved, especially via mobile applications. While providing support for clinical decisions and a better doctor-patient and doctor-doctor communication, HIT also allows a straightforward real-time collection of data for scientific purposes. However, standards and quality criteria are needed to ensure the reliability of the acquired data.

Box 1. Unmet needs of Health IT

Protection of personal data
Regulatory structures and quality management
Cost and implementation of Health IT
Unbalanced implementation
Challenges in terms of interoperability

Box 2. Opportunities of Health IT

Fast and easy transfer of information
Facilitated collection of clinical and environmental data
Educational potential
Support in the implementation of programmes and policies
Patient empowerment, through enhanced communication
Identification of relevant data
Improved disease management, through continuous flow of information

- **Strategic Programmes and Policies**: Health IT entails not only a perfect approach to disseminate relevant and curated information, but the instant flow of information will also ease the implementation of pathways or preventative measures. While the positive impact of HIT on the timeline of patient care remains controversial, eHealth technologies have shown to go along with health economic advantages and improved disease management. However, as any new technology, Health IT implementation requires a learning period for patients and professionals.
- **Patient Empowerment**: Customizable mobile applications and website information will become a priority, as the information provided for patients should not only be of high quality, but also individualized. The access to a mobile app, which registers treatment intake, symptoms and work productivity, appears to facilitate the assessment of patients with allergic rhinitis. In the same line, another app offers adrenaline injection training achieving significantly better-practiced injections compared to usual written guidelines.
- **Big Data**: Big data refers to the development and processing of data sets, which are so voluminous and complex that traditional software applications are inadequate to deal with them. The real impact of big data on the management of allergic conditions remains elusive, but recent reports predict important savings (between 13 to 17%) when health IT is fully integrated in health care. In order to uncover the cause of allergic diseases it is indispensable to bring genetic, epigenetic, and environmental data sets together.
- **Identifying Relevant Data**: Due to the vast amount of generated data, there is a need to develop software and hardware capable to bear, learn and identify relevant data. In this regard, Cluster analysis offers a novel multidimensional approach for identifying asthma phenotypes that exhibit differences in clinical response to treatment algorithms. There is a need of identifying subtypes of asthma in clinical and general populations, also to understand causal mechanisms of the subtypes and discerning what is relevant to implement prevention and management strategies.

FURTHER READING

1. Hanania NA, Diamant Z. The road to precision medicine in asthma: challenges and opportunities. *Curr Opin Pulm Med* 2018;24:1-3.
2. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410-419.
3. Jameson JL, Longo DL. Precision medicine - personalized, problematic, and promising. *N Engl J Med* 2015;372:2229-2234.
4. Bousquet J, Arnavielhe S, Bedbrook A, Fonseca J, Morais Almeida M, Todo Bom A et al. The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: The MASK study. *Allergy* 2018;73:505-510.
5. Bianchi A, Tsilochristou O, Gabrielli F, Tripodi S, Matricardi PM. The smartphone: A novel diagnostic tool in pollen allergy? *J Investig Allergol Clin Immunol* 2016;26:204-207.
6. Bousquet J, Schünemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. *J Allergy Clin Immunol* 2016;138:367-374.
7. Tripodi S, Comberiati P, Di Rienzo Businco A. A web-based tool for improving adherence to sublingual immunotherapy. *Pediatr Allergy Immunol* 2014;25:611-612.
8. Pizzulli A, Perna S, Florack J, Pizzulli A, Giordani P, Tripodi S et al. The impact of telemonitoring on adherence to nasal corticosteroid treatment in children with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy* 2014;44:1246-1254.
9. Prabhakaran L, Chee WY, Chua KC, Abisheganaden J, Wong WM. The use of text messaging to improve asthma control: a pilot study using the mobile phone short messaging service (SMS). *J Telemed Telecare* 2010;16:286-290.
10. Elliott T, Shih J, Dinakar C, Portnoy J, Fineman S. American College of Allergy, Asthma & Immunology Position Paper on the Use of Telemedicine for Allergists. *Ann Allergy Asthma Immunol* 2017;119:512-517.
11. Hernandez-Munoz LU, Woolley SI, Luyt D, Stiefel G, Kirk K, Makwana N et al. Evaluation of AllergiSense Smartphone Tools for Adrenaline Injection Training. *IEEE J Biomed Health Inform* 2017;21:272-282.
12. Kayyali B, Knott D, Van Kuiken S. The big-data revolution in US health care: Accelerating value and innovation, January 2013. Available from: https://www.mckinsey.com/~/media/mckinsey/industries/healthcare%20systems%20and%20services/our%20insights/the%20big%20data%20revolution%20in%20us%20health%20care/the_big_data_revolution_in_healthcare.ashx Accessed February 18th 2018.
13. Kottyan LC, Weirauch MT, Rothenberg ME. Making it big in allergy. *J Allergy Clin Immunol* 2015;135:43-5.
14. Muraro A, Fokkens WJ, Pietikainen S, Borrelli D, Agache I, Bousquet J, et al. European symposium on precision medicine in allergy and airways diseases: report of the European Union Parliament Symposium (October 14, 2015). *Allergy* 2016;71:583-587.
15. Jones SS, Rudin RS, Perry T, Shekelle PG. Health information technology: An updated systematic review with a focus on meaningful use. *Ann. Intern. Med* 2014;160:48-54.
16. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-224.
17. Belgrave D, Henderson J, Simpson A, Buchan I, Bishop C, Custovic A. Disaggregating asthma: Big investigation versus big data. *J Allergy Clin Immunol* 2017;139:400-407.

Peter Hellings, Ioana Agache

PRECISION MEDICINE AND PRECISION HEALTH IN ALLERGY AND ASTHMA

E9

Precision medicine represents a novel approach in health care, embracing four key principles: personalized care based on molecular, immunologic and functional endotyping of the disease, with participation of the patient in the decision making process of therapeutic actions, and considering predictive and preventive aspects of the treatment. Asthma, allergic rhinitis, chronic rhinosinusitis, food allergy and atopic dermatitis are ideally suited for precision medicine, because they represent an umbrella of different diseases that partially share biological mechanisms underlying disease development and chronicity (endotypes) and present similar visible properties (phenotypes) that require an individualized approach for a better selection of treatment responders, risk prediction and design of disease-modifying strategies.

GAPS IN KNOWLEDGE

Precision medicine is impacting healthcare in several domains, from pharmacogenomics, better selection of treatment responders, risk prediction and design of disease-modifying strategies to ethics and patient-centered care models. It requires the creative and energetic involvement of many stakeholders (biologists, physicians, technology developers, data scientists, patient groups, governments, and more) and the coordination and setting priorities is quite difficult in practice.

Most of the current biomarkers in allergic diseases and asthma predict treatment response and very few forecast disease risk and progression. In addition they are suitable only for research settings. There is a significant overlap between disease phenotypes and biomarkers, with the classic example of blood eosinophils being at the same time a visible property and a surrogate biomarker related to asthma exacerbations and response to steroid or to all type-2 targeted intervention. In addition the same biomarker such as serum IgE or periostin might not show consistent validity.

In describing asthma endotypes one must recognize that the pathogenic pathway is highly complex, including several determinants and heterogeneous, since not all determinants are present in all patients or, in a given patient, at all time points. Assigning unique mechanisms and biomarkers for each endotype is crucial for the validity of the endotype.

Implementing precision medicine in a clinical setting requires seamless integration of data from clinical evaluations and bio-medical investigations with genomics and other endotyping profiling to characterise an individual patient's disease pro-

gression followed by mainstreaming all these data back to the point of care in a format that is ready and easy to use by the clinician.

There is limited evidence that precision medicine care pathways improve clinical outcomes, increases cost effectiveness and affordability leading to a better quality of care. Reconciling concerns about rising costs of molecular diagnosis, accessibility and affordability of the precision medicine approach is central to the debate over implementing precision medicine at a larger scale. Several attempts have been made at political and medical level to highlight the need for future implementation of precision medicine into daily care, without uniform success.

None of the disease endotypes are included in the existing taxonomies of allergic diseases and thus communication between research and clinic still remains confusing.

A final gap in the current practice of endotyping is the diagnosis of mixed endotypes underlying a phenotype in the majority of patients with a particular chronic inflammatory condition. Studies have demonstrated that patients with a mixed endotype respond less well to treatment than those with a pure endotype, having an impact on both prediction of success of treatment as well as participation of the patient in the decision-making process.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

- Longitudinal follow-up of clinical and molecular profiles is essential to confirm the validity of an endotype. The alternative is to embrace the concept of the dynamic complex endotype and to investigate better the mechanisms driving the dynamic changes.
- The unbiased approach of multidimensional endotyping might prove an useful tool generating novel hypothesis
- Defining the hierarchical position of distinct cytokines in allergic diseases pathogenesis with the description of meaningful clinical endotypes is needed to ensure the success of cytokine inhibition and to transform the therapeutic landscape in allergic diseases in a precision based fashion.
- Designing methods for streaming data capture, real-time data aggregation, machine learning, predictive analytics and visualization solutions to integrate wellness or health monitoring data elements with the electronic medical records maintained by health care providers permits better resource utilisation. The development of computational approaches and tools to effectively integrate multidomain data (such as cognitive IT-systems) and real-time databases for molecular profiling data could become a pragmatic solution to several knowledge management problems in the practice and science of precision medicine. “Interventional informatics” approach can substantially improve human health and wellness through the use of data-driven interventions at the point of care of broader population levels.
- To move beyond a select few genes/drugs, the successful adoption of pharmacogenomics into routine clinical care of allergic diseases and asthma should be prioritised
- Before the precision medicine approach is broadly advocated, there is an urgent need to show robust data on its’ value on patient-reported outcomes, on cost-effectiveness and on secondary/tertiary prevention. An agreement between all stakeholders on a flexible framework balancing the use of randomised control trials (the golden standard for evidence at present) against “big data” and observational analysis while including health-economic impact analysis (encompassing cost effectiveness and long-term savings) for regulatory and payer approval are essential steps to move the field forward.

Standards and quality criteria

- Validation and qualification of biomarkers
- Learning how healthcare professionals engage with and use precision-medicine care pathways and what resources are needed to promote high-quality care of patients will serve to orient the dynamic governance that includes all stakeholders and is designed to remain agile and responsive to emerging opportunities and experience.
- Data-driven policies balancing privacy and security concerns with participant and public interests in the sharing of data for research are urgently needed
- Global, multi-discipline partnerships and rethinking healthcare are important prerequisites to move the field forward. Both science and policy priorities need to be defined agreed and implemented. The collaborative medicine approach with open access to research databases worldwide will speed the discovery of new targets

Innovative approach

Implementation of precision medicine in the clinic requires several steps:

- An improved disease taxonomy is a current unmet need because
- Full patient monitoring using novel digital technology and the concept of endotypes and novel biomarkers
- Improved understanding and common usage of disease phenotypes, endotypes and biomarkers preferentially at the point of care
- Biomarker and endotype-linked patient care and usage of precision therapies.
- We need to encourage "valuable" innovation and enterprises willing to assume the risk in developing precision-medicine approaches, while continuously measuring and documenting the benefit.

FURTHER READING

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;372:793-795.
2. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfill the promise of personalised medicine. *Lancet* 2015, 385:2118-2119.
3. Goldman DP, Gupta C, Vasudeva E, Trakas K, Riley R, Lakdawalla, DN et al. The value of diagnostic testing in personalized medicine. *Forum Health Econ Policy* 2013;16:121-133.
4. Arron JR, Townsend MJ, Keir ME, Yaspan BL, Chan AC. Stratified medicine in inflammatory disorders: From theory to practice. *Clin Immunol* 2015;161:11-22.
5. Muraro A, Fokkens WJ, Pietikainen S, Borrelli D, Agache I, Bousquet J et al. European symposium on precision medicine in allergy and airways diseases: report of the European Union parliament symposium (October 14, 2015). *Rhinology* 2015;53:303-307.
6. Wagner JA. Overview of biomarkers and surrogate endpoints in drug development. *Dis Markers* 2002;18:41-46.
7. Agache I, Rogozea L. Endotypes in allergic diseases. *Curr Opin Allergy Clin Immunol* 2018;18:177-183.
8. De Greve G, Hellings PW, Fokkens WJ, Pugin B, Steelant B, Seys SF. Endotype-driven treatment in chronic upper airway diseases. *Clin Transl Allergy* 2017;7:22.
9. Agache I, Rogozea L. Asthma Biomarkers: Do They Bring Precision Medicine Closer to the Clinic? *Allergy Asthma Immunol Res* 2017;9:466-476.
10. Biomarkers Definition Working Group Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Therapeutics. 2001;69:89-95.
11. Agache I, Akdis CA. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. *Allergol Int* 2016;65:243-252.
12. Agache I, Sugita K, Morita H, Akdis M, Akdis CA. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. *Curr Allergy Asthma Rep* 2015;15:29.
13. Agache I, Strasser DS, Pierlot GM, Farine H, Izuhara K, Akdis CA. Monitoring inflammatory heterogeneity with multiple biomarkers for multidimensional endotyping of asthma. *J Allergy Clin Immunol* 2018;141:442-445.
14. Gibson CJ, Dixon BE, Abrams K. Convergent evolution of health information management and

FURTHER READING

health informatics: a perspective on the future of information professionals in health care. *Appl Clin Inform* 2015;6:163-184.

15. Bahk CY, Goshgarian M, Donahue K, Freifeld CC, Menone CM, Pierce CE et al. Increasing Patient Engagement in Pharmacovigilance Through Online Community Outreach and Mobile Reporting Applications: An Analysis of Adverse Event Reporting for the Essure Device in the US. *Pharmaceut Med* 2015;29:331-340.
16. Holeman I, Cookson TP, Pagliari C. Digital technology for health sector governance in low and middle income countries: a scoping review. *J Glob Health* 2016;6:020408.
17. Manyazewal T, Oosthuizen MJ, Matlakala MC. Proposing evidence-based strategies to strengthen implementation of healthcare reform in resource-limited settings: a summative analysis. *BMJ Open* 2016;6:e012582.
18. Greene SM, Tuzzio L, Cherkin D. A framework for making patient-centered care front and center. *Perm J* 2012;16:49-53.
19. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I et al. Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis - A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. *Allergy* 2017;72:1297-1305.
20. Hellings PW, Borrelli D, Pietikainen S, Agache I, Akdis C, Bachert C et al. European Summit on the Prevention and Self-Management of Chronic Respiratory Diseases: report of the European Union Parliament Summit (29 March 2017). *Clin Transl Allergy* 2017;7:49.

Isabella Annesi-Maesano, Jean Bousquet

THE PUBLIC HEALTH AND THE ENVIRONMENTAL HEALTH PERSPECTIVE

E10

GAPS IN KNOWLEDGE

Allergy constitutes one of the most pervasive disorders universally with 30- 40% of the world population now affected by one or more allergic conditions. Allergy is spreading and globally 1 individual out of 2 will be allergic by 2050. This is why both public health and environmental health - the branch of public health that is concerned with all aspects of the natural and built environment that may affect human health in view to promote preventive actions to protect individuals from developing diseases - find important application in the case of allergic diseases.

In the field of allergy, public health and environmental health perspectives should consist in promoting a healthier environment for allergic patients; intensifying primary and secondary prevention; and influence public policies in all sectors so as to address the root causes of environmental and socioeconomic threats to allergic health.

RESEARCH PRIORITIES, QUALITY CRITERIA, INNOVATIVE APPROACH

Research priorities

In order to efficiently prevent allergic diseases, it is urgent at the community level to:

- **ASSESS the needs of the community** by systematically collecting, assembling, and making available information on the allergic status of the community, including statistics on allergic status, community health needs, environmental health and epidemiologic data, and other studies on allergy conditions and problems.
- **INVESTIGATE the occurrence of allergic effects and allergic hazards** by systematically developing more detailed information on the magnitude of the allergy problem, duration, trends, location, population at risk, and how to proceed to prevent or control it.
- **ANALYZE both environmental and socioeconomic determinants of allergic conditions**. Identifying these factors helps in planning intervention efforts for prevention or control of allergic conditions.

Box 1 Key steps for building a healthier environment for allergic patients

Public health and environmental health have contributed and still contribute to understand allergic conditions, promote a healthier environment for allergic patients, intensify prevention and influence public policies so as to address major risk factors for allergic health.

A better knowledge of the impact of the exposome on allergy development is crucial for urging individuals, health professionals and policy makers to take actions to mitigate the effect of environmental changes and to adapt to them.

In the long-term, the use of all available information (including family resemblance of allergies, individual, genetic, and epigenetic factors and omics, and exposures to risk factors for developing or exacerbating disease), as well as features of the environments, should be used to sustain and enhance health and prevent the development of allergic diseases in the frame of precision medicine.

Standards and quality criteria

Projections indicate that allergic problems will increase as air pollution and ambient temperatures rise due to environmental and climate changes, affecting pollen counts, molds, stinging insect numbers that are well-known risk factors for allergic diseases.

Promoting a healthier environment for allergic patients

- Adopt and enforce WHO standards on chemical air pollution or greenhouses gases to lower their emissions and stop climate change respectively.
- In particular, reduce short-lived air pollutants, powerful climate forcers that remain in the atmosphere for a shorter period of time (than longer-lived climate pollutants, such as carbon dioxide (CO2)) (methane, fluorinated gases including hydrofluorocarbons (HFCs), and black carbon) so to reduce greenhouse effects in the short term.
- Establish environmental control measures by the lowering of indoor air pollution, tobacco smoking and allergen and drug exposures.

Intensifying primary and secondary prevention

- Develop national allergy action plans to promote primary and secondary prevention of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, etc.)
- Increase public awareness of allergic diseases and their prevention
- Train health care professionals and medical students on how to inform on primary and secondary prevention of allergic diseases.

Innovative approach

Recent data have shown that a fully comprehension of allergy development may result only from the taking of an exposomic approach into account. The exposome is the totality and the interactions of external environmental exposures (external exposome) to which an individual is exposed in life and their consequences in the body (internal exposome) (Figure 1, box 1).

The specific external exposome involved in allergic diseases includes primarily indoor and outdoor aeroallergens and chemical air pollutants including tobacco smoking. To it, non-specific external exposome has to be added, namely the action of climate change, urbanization and loss of biodiversity that affect sources, emissions and concentrations of main aeroallergens and chemical air pollutants that may influence allergic diseases.

The impact of external exposome on environment- or lifestyle-driven aberrancies in the gut, skin, nasal and lung microbiome composition as well as the interactions with other environmental factors (diet, drugs, consumer products, mobility, etc.) has also to be investigated.

Observations of epigenetics changes that represent a key mediator of allergic diseases and other omics will be relevant to understand the allergic processes leading to the various allergic endotypes and phenotypes.

Although daunting, proof of concept studies are presently being conducted that show the promise of the exposomic investigation and integration of different kinds of data to explain the allergy epidemics. The implementation of tools and methods (sensors, geographic information systems, and *ad hoc* survey instruments) to build the exposome is in progress.

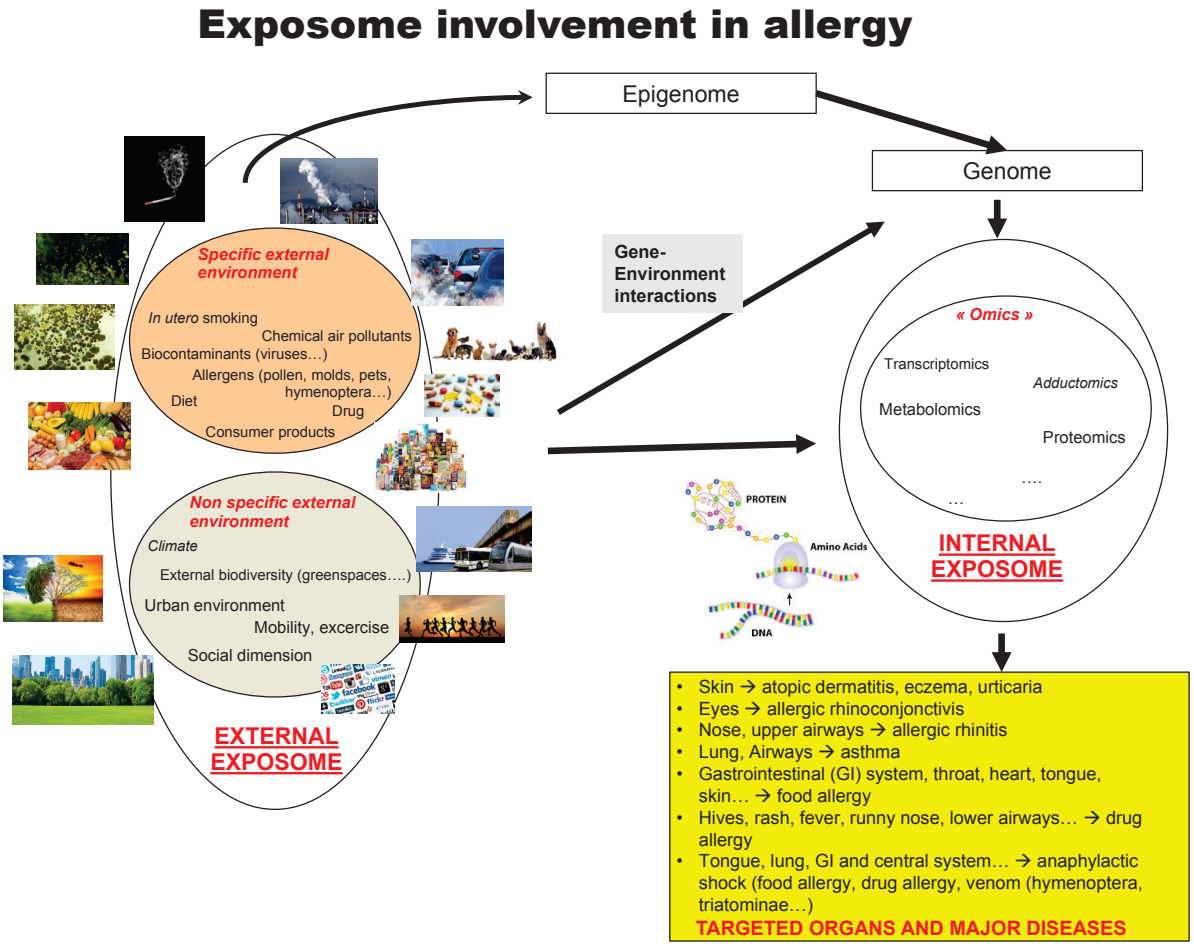


Figure 1.

FURTHER READING

1. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. J Allergy Clin Immunol. 2017;140:1-12.
2. Cecchi L, D'Amato G, Annesi-Maesano I. External exposome and allergic respiratory and skin diseases. J Allergy Clin Immunol. 2018;141:846-857.
3. Loh M, Sarigiannis D, Gotti A, Karakitsios S, Pronk A, Kuijpers E, Annesi-Maesano I, Baiz N, Madureira J, Oliveira Fernandes E, Jerrett M, Cherrie JW. How Sensors Might Help Define the External Exposome. Int J Environ Res Public Health. 2017;14.
4. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: Early-life events and immune development in a changing world. J Allergy Clin Immunol. 2017;140:24-40.
5. Galli SJ. Toward precision medicine and health: Opportunities and challenges in allergic diseases. J Allergy Clin Immunol. 2016;137:1289-300.
6. Tanno LK, Haahtela T, Calderon MA, Cruz A, Demoly P; Joint Allergy Academies. Implementation gaps for asthma prevention and control. Respir Med. 2017;130:13-19.

F

CONCLUSION

EAACI Executive Committee

EAACI WHITE PAPER - RECOMMENDATIONS AND POLICY

ALLERGY, CLINICAL IMMUNOLOGY AND ASTHMA RESEARCH

We witness a tremendous progress in the diagnosis and monitoring of allergic diseases and asthma due to new techniques and research approaches with significant impact on the specialty. Modern techniques such as molecular diagnosis, more accessible tools for human immunophenotyping, the application of omics and sophisticated imaging are responsible for the deep changes towards our better understanding of allergic diseases and asthma.

Research on allergy, clinical immunology and asthma encompasses a wide range of pathologies, which are classified according to major domains that cover their origin, pathogenesis and health economic consequences in the evolving scientific environment.

Five major research themes have been identified:

1. **The developmental exposome.** The 'exposome' term ignites huge discussions amongst all medical disciplines, largely because of its ambitious attempt to assess almost all possible environmental exposures. The exposome during intrauterine life and early childhood reveals which factors are most critical for defining the state of disease or dysfunction, and the correlation with factors of exposure provides means to develop intervention strategies.
2. **Allergic diseases and asthma in the context of population and environmental health.** Natural and man-made environment like air quality, water and soil, and also all the physical, chemical, biological and social features of our surroundings have a major influence on the control and severity of allergic diseases and asthma. In the field of allergy, public health and environmental health perspectives should promote a healthy environment for allergic patients; intensify primary and secondary prevention; and influence public policies in all sectors as well as address the fundamental causes of environmental and socioeconomic threats to patients. The "One Health" concept evaluating the interconnections between human, environment and animal health and food and water safety should be further assessed. Defining a step-wise approach for environmental intervention in high-risk groups at the population level is further warranted.
3. **Drug development and biomedical engineering**. Advanced therapies (gene therapies, cell and tissue therapies, regenerative medicine), the increasing number of biologicals and biosimilars soon exceeding the number of chemical drugs and the introduction of sophisticated devices and biomedical engineered products,

all call for a new approach in drug development, evaluation and monitoring. Standard and quality criteria for drug development of new advanced therapies and biotechnological products, while requesting the same accuracy and reliability, may differ from "old" chemical drugs in terms of study design and evaluation techniques.

4. **Big data and information technology**. The availability of new information technology for collecting, analyzing and relating the "big data" provided by the real world opens new horizons to a new, more comprehensive knowledge. In fact, computers will not only be instruments to provide answers by elaborating data on the basis of pre-defined algorithms, but will be able to learn themselves from data analysis (machine learning) and to provide solutions on the basis of original algorithms. Artificial Intelligence will certainly favour a tremendous progress in medical sciences, but will also create a new relationship between humans and machines with relevant implications in ethics and responsibilities of the medical profession. A significant shift in the doctor-patient relationship is expected with the well-informed patient advocating for its own care and connected in real time with the healthcare provider that is provided with personalized information from patient portals. Availability of big data requests that industry, regulatory bodies, scientists and clinicians accept transparency policies which make their data available to the community through open platforms. Big data imply a risk for citizens' and patients' privacy. This should be protected by adequate regulations and accurate anonymization techniques of individual personal data.
5. **Translational research and implementation science.** Translational research fosters the multidirectional and multidisciplinary integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science. Implementation science focuses on identification of all major contributions to improvement of health care, from individual factors up to policy and public health interventions.

METHODOLOGY FOR EVIDENCE GENERATION – STANDARDS AND QUALITY CRITERIA

Well-designed original studies, guidelines for sample collection, repositories and biobanks standards for use with emerging and anticipated technologies, validated criteria for selecting the best assay(s) to assess biological response for the research question of interest, better disease models, high quality systematic reviews and real-life studies should be facilitated with a high standard methodological approach proving causality instead of associations. Quality of life scores should be validated across European countries and healthcare costs should be assessed across different countries in Europe. Efficient patenting of inventions and support for generation of spin-off and private partnership models are critical as well. These models should also include a proof of concept center that can conduct critical clinical studies (phase 2a). Highly networked and interdisciplinary research centers are extremely important for the successful future of allergy and asthma research.

Relevant mechanistic studies will allow a better understanding of the responses to microbial exposure/infection, in particular in early life will guide proper intervention. Controlled human infections combined with systems biology will provide a wealth of mechanistic data and insight into very early infection processes that precede asthma exacerbations and into strategies to reduce their augmenting effects on inflammation. Identification of microbiome patterns that associate with medicinal efficacy together with tools for the clinician to integrate microbiome assessments into

routine clinical practice (including standardization of assessment method and the algorithms used to determine risk/benefit outcomes) will result in personalized medicine improvements. In describing disease endotypes one must recognize that the pathogenic pathway is highly complex, including several determinants and heterogeneous, since not all determinants are present in all patients at all time points. Assigning unique mechanisms and biomarkers for each endotype is crucial for the validity of the endotype. Defining the hierarchical position of distinct cytokines in the pathogenesis of allergic diseases with the description of meaningful and clinically useful endotypes is needed to ensure the success of cytokine inhibition and to transform the therapeutic landscape in allergic diseases in a precision based fashion. Data driven disease endotyping using new statistical tools (Supervised analysis, Latent Class Analysis, Bayesian Network Analysis, Topological Data Analysis, etc.) shift the research approach from the phenotype/cluster approach with investigator-imposed subjective disease clustering (hypothesis driven) to an unbiased, endotype/biomarker driven approach.

Component-resolved diagnosis (CRD) can boost accuracy of the diagnosis and optimise the therapeutic outcome. Combination of CRD with proper in vivo challenge in validated allergen exposure chambers will definitively contribute to improve the current diagnosis protocols for allergic diseases. Biotechnology together with the explosion of the –omic approaches is contributing to significantly refine the diagnosis of allergic diseases.

To allow looking 'backwards', prospective longitudinal cohorts and Integrating data from several cohorts that together mimic all life stages are required in combination with integrated systems biology and immunology. Multilayer "omics" analysis of longitudinal cohort studies is very much needed to simultaneously obtain various types of reliable biomarkers. Resulting data will not only allow more precise phenotyping, but may also provide prognostic factors for allergy and asthma development. Validated methods assessing the developing human immune system from intrauterine life to all age groups are desired.

Longitudinal studies with and without treatments and specific evaluation of gene-environment interaction at different stages of human development (e.g. in utero, early life, peripubertal, etc) are required in childhood and adults to better understand the natural disease progression and opportunities of medical interventions.

Studies that address both the relevance of specific developmental windows and the importance of coincident exposures, including lifestyle factors, diet and the concept of One Health; one of the best models are environmental wide association studies (EWAS) and the integrative multidimensional exposomics where cross-omics and bioinformatics tools link exposure data to biochemical and molecular changes in the body. The usage of the biological response (allostasis) as the footprint of transient exposure is also required to better understand risk and protective factors for allergy and asthma

INNOVATIVE APPROACH

A roadmap using "omics"-technologies towards personalized therapeutic and prevention approaches in allergic diseases should be developed based on scientific and clinical research including big-data management, legal, and regulatory aspects. To move beyond a selection of few genes/drugs, the successful adoption of pharmacogenomics into routine clinical care of allergic diseases and asthma should be prioritised

The exposomic approach is particularly applicable to the study of environmental causes of allergic diseases and asthma since provides risk profiles instead of single predictors, while concomitant access to biological data, exposure data, and health

outcomes evaluates the biologic plausibility of the hypothesis. Host-environmental interactions should be scrutinised under a developmental focus. Exposome-focused projects are needed to examine the complex interplay of environment and genetics to determine the most cost-effective interventions for reducing the risk of allergic disease. A key challenge is to learn the types of exposures, potential interactions, and the exact timings and amounts that impact health. Personalized/precision interventions and efficient home, school, workplace and even city planning can be developed to reduce the risks associated with exposome, such as pollution. Innovative approaches may include: geographic information, system-based pollutant models and personal remote sensing devices and applications for smartphones to monitor and record personal exposures; electronic medical records to access lifelong exposure information and computer search engines to analyze information; innovative methods for chemical measurements using high-resolution mass spectrometry; computer-based models and predictions to combine the cumulative exposures with personal genomics, therefore helping to guide healthy choices for diet, exercise, and health behaviors. An integrated surveillance network for the environment impact on allergies and asthma is of great benefit. Exposure data can be cross-referenced with clinical data from sentinel physicians' networks or, in the last few years, with symptom load patients' networks. These last concepts receive support from the new information technologies and are very important for doctors to better diagnose allergy, and for the patients to better manage their disease.

The systematic analysis of mechanisms underlying environmental priming and mechanisms of tolerance related to this priming are key aspects that need to be addressed in future. Using very comprehensive analysis methods, it is now possible to assess both: the complex environment and the complex nature of the immune system. Understanding the complex unit of microbiome, epithelial cells, dendritic cells, macrophages and innate lymphoid cells as well as T and B cells of the adaptive immune response will generate further innovations and access to allergy prevention. The best possible understanding about the functions and characteristics of the skin, intestinal and respiratory barriers is a prerequisite for the development of strategies in order to uphold barrier integrity and, especially in case of disease, to support the recovery of disturbed barriers. Research on cofactors increasing symptom severity or the risk of sensitisation is of similar importance.

Prevention is the key priority, with a potentially enormous impact. The effect of intervention during all early lifetime intervals from pre-conception, gestation, birth mode, and early childhood should be evaluated. Primary preventive interventions aimed to reduce exposure levels in the workplace are crucial to reduce the occupational disease burden. Nevertheless, due to the complexity of the disease, high regulatory demands and lack of funding is quite challenging. A long-term view needs to be implemented: the really big prize lies much further upstream, where compelling evidence is emerging of return on investment from public health programmes and work in schools, communities and housing. Although the precision medicine revolution has potential to transform environmental measures and to develop into precision health and precision prevention We still have a long way to go to more effectively identify who should be targeted. Some environmental interventions like air quality regulation cannot be targeted to any subgroup, genetic, or otherwise. Others, like breastfeeding, vaccination, antismoking campaigns, exercise, or diets, could in principle, but they need to prove practical or cost efficient. The most effective prevention would be to identify those at high risk to avoidable exposures. However, simply evaluating genetic risks is not sufficient, since we need to co-factor the interaction with environment. Collaborative work amongst European and international centers to collectively research the prevention of atopic diseases and asthma using rigorous standardised study methodologies is desirable. Once key exposures and potential interventions are identified, a comprehensive approach among clinicians, patients, health care organizations, insurance providers, government agencies, and urban planners must be undertaken to establish cost-effective primary and secondary prevention strategies to reduce these risks and promote wellness. National allergy and asthma action plans promoting primary and secondary prevention of allergic diseases should be coupled with increased public awareness of allergic diseases and their prevention and with training of healthcare professionals and medical

students on how to inform on primary and secondary prevention of allergic diseases

A revised disease taxonomy should be agreed, based on the whole spectrum of needs (patients, healthcare systems, research). Endotype-based classification based on thorough investigation of the pathophysiological mechanisms contributing to the disease will provide more insight in the inter-individual variability of clinical presentation and treatment response in patients with identical phenotypes. This nomenclature would describe diseases on the basis of their intrinsic biology in addition to traditional "signs & symptoms", leading to better understanding of allergic disease mechanisms, pathogenesis and treatments. The revised disease taxonomy should also allow easy incorporation of newly appearing data to existing knowledge. The novel terminology would make our discipline stronger and broader.

Implementing precision medicine in the clinical setting requires seamless integration of data from clinical evaluations and bio-medical investigations with genomics and other endotyping profiling to characterise an individual patient's disease progression followed by mainstreaming all these data back to the point of care in a format that is ready and easy to use by the clinician. Reconciling concerns about rising costs, accessibility and affordability of the precision medicine approach is central to the debate on implementing precision medicine at a larger scale. Designing methods for streaming data capture, real-time data aggregation, machine learning, predictive analytics and visualization solutions to integrate wellness or health monitoring data elements with the electronic medical records maintained by health care providers permits better resource utilisation. The development of computational approaches and tools to effectively integrate multidomain data (such as cognitive IT-systems) and real-time databases for molecular profiling data could become a pragmatic solution to several knowledge management problems in the practice and science of precision medicine. "Interventional informatics" approach can substantially improve human health and wellness through the use of data-driven interventions at the point of care of broader population levels. An agreement between all stakeholders on a flexible framework balancing the use of randomised control trials (the golden standard for evidence at present) against "big data" and observational analysis while including health-economic impact analysis (encompassing cost effectiveness and long-term savings) for regulatory and payer approval are essential steps to move the field forward. Learning how healthcare professionals engage with and use precision-medicine care pathways and what resources are needed to promote high-quality care of patients will serve to orient the dynamic governance that includes all stakeholders and is designed to remain agile and responsive to emerging opportunities and experience. Global, multi-discipline partnerships and rethinking healthcare are important prerequisites to move the field forward. Both science and policy priorities need to be defined agreed and implemented. The collaborative medicine approach with open access to research databases worldwide will speed up the discovery of new targets. We need to encourage "valuable" innovation and enterprises willing to assume the risk in developing precision-medicine approaches, while continuously measuring and documenting the benefit.

Patient empowerment and patient centeredness in allergy and asthma care are essential steps for a sustainable healthcare system based on the precision medicine approach. Reaching the 5 Ps (self-efficacy, self-awareness, confidence, coping skills and health literacy) and the 5 Es (education, expertise, equality, experience, engagement) of patient empowerment is a joint effort of patients' organisations and of healthcare professionals. Mapping allergy patient groups in Europe, their services, role, representativeness and challenges could help developing a database and targeted capacity building

Clinical care pathways to manage allergic diseases are a major priority. Wrong orientation of the patient into non-evidence based care pathways is not uncommon, with effective treatment not being offered to patients. Optimization of the patients' care pathways will undoubtedly result in reducing health care expenses.

Electronic Health (eHealth) and **mobile Health (mHealth)** will continue to revolutionize the self-management of allergic diseases asthma. Through eHealth technologies, the real-time and continuous collection of patient-related data is facilitated enormously. Patient- and/or doctor-centered systems render support in the diagnostic process through Clinical Decision Support Sys-

tems (CDSS) and improve adherence to the management plan. Health information technology (HIT) also allows a straightforward real-time collection of data for scientific purposes.

Harmonisation and standardisation of training requirements for specialists and subspecialists in allergy and clinical immunology is of vital importance. To improve harmonization of the training in Allergology, it is crucial to establish a full specialty in all European countries, and to define precisely its' competences, including those in relation to paediatric allergy and clinical immunology. Well-regulated subspecialties may form an intermediate step to the specialty. This general recognition will facilitate the creation of an adequate network of allergy training centres. Only upon these premises, it will be possible to achieve a true harmonization of the training programs in Allergology allowing the mutual recognition and exchange of specialists within Europe. **Training of other healthcare** practitioners to develop leadership in integrated care in allergic patients, ensure the safety of allergy care and optimize the outcomes. Educating allied health, primary care practitioners and pharmacists to deliver integrated care requires significant cultural and behavioural changes, and essentially, facilitation by secondary care allergy and asthma specialists.

Competencies recognise the importance of attaining and demonstrating both practical skills and a theoretical grounding in the subject. They additionally provide a standardised framework of consistent quality criteria for the effective and safe allergy patient care against which practitioners can demonstrate proficiency both to themselves and also to other health care professionals within the multi-disciplinary team. Competency driven practice fits into the modern delivery of health care, which considers the team member's competency to deliver the required care and not the 'role' or hierarchy of that person within the health system. Competencies for allied health care professionals working in allergy have been developed by the EAACI, but these need to be developed further by considering other providers, including primary care and pharmacists who may be providing allergy care in isolated settings. **E-learning tools** facilitate outreach to a larger target population of healthcare professionals seeing allergic patients.

At the regulatory level, it is worth to note the recent evolution of the legislation in some European states. These regulations might be extended to other countries in order to achieve European legislation on environment control (air quality, smoking, indoor and outdoor pollution, invasive allergenic plants, standard occupational exposure), periodic health surveillance among exposed workers to detect early signs of disease, reporting of new environmental hazards, etc. Allergy and asthma treatments should reach young children much faster, thus a revision of the pediatric investigation plan is urgently needed. Reimbursement policies should ideally be aligned across European states, with allergen immunotherapy recognized as an effective and safe treatment with preventive potential.

Finally, healthcare costs will utilise at least 5% of their Gross Domestic Products of all countries in the world and this will make the biggest locomotive of the economy and highest public demand. The diseases in our scope affecting almost one third of the world population will be one of the highest public health burden. All patients should have easy access to new safe and effective drugs and other treatment options thanks to developing of models, which by reducing the risk of development investments will reduce the price of new medicines, and also help to establish heath policies on the basis of reasonable priorities and social equanimity.

European Academy of Allergy and Clinical Immunology

EAACI Headquarters
Hagenholzstrasse 111
3rd Floor
8050 Zurich
Switzerland
Tel: +41 44 205 55 33
info@eaaci.org