Handbook of Experimental Pharmacology 268

Claudia Traidl-Hoffmann
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Allergic Diseases – From Basic Mechanisms to Comprehensive Management and Prevention

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Preface

100 million days per year. One can only imagine what could be achieved in that huge amount of time. This is the number of days people with allergies miss at work or in school in Europe within one year, because they do not feel well. Not counting the days when they are physically present, but not quite up to their tasks.

The burden of allergic diseases is high. Not only the symptoms of the diseases itself, such as running and blocked nose, sneezing, itchy skin and others, but also the accompanying impairment in terms of sleeplessness, abandonment of certain activities and food, anxiety of an allergic shock, as well as time-intensive and expensive treatments decrease the quality of life of the patients. Many patients develop mental health issues such as anxiety and depression. Often not only the patients themselves, but also their families suffer under these circumstances.

In 2025, according to estimations, every second inhabitant of the European Union will have to deal with some form of allergy: that makes more than 225 million people. Knowing about the increasing prevalence of allergic diseases, we work for understanding the mechanisms and developing effective prevention and management of allergies. This book aims at providing the current knowledge about allergic diseases to a large number of scientists, practitioners and also the people concerned.

In it, the knowledge and expertise of 65 leading scientists of the field from 8 different countries is brought together to take a close look at all aspects of allergies. What is known about their history, their different forms, the mechanisms of their development, about risk factors, diagnosis, disease management and – above all – about ways to prevent them are all collected in this single volume. It presents the 'state of the art' and also gives an overview of basic science beyond mere textbook knowledge. It maps what is established as well as what is still to be explored, hopefully in the near future, in order to lighten the burden for all the people suffering and prevent further increases in the prevalence of allergies.

This volume covers large ground.

Part I of this book explains the historical and epidemiological background of allergies. In the chapter on the *History of Allergy*, Ring starts with the first descriptions of allergy in antiquity, in the Middle Ages and in Renaissance. The chapter continues with the beginnings of allergology in the early 19th century and finally describes the developments in diagnosis, therapy and in understanding the pathophysiological mechanisms of allergic diseases in the 20th century. Genuneit

and Standl then summarize our knowledge on the *Natural course and risk factors of allergic diseases* in the 21st century from an epidemiological perspective.

Although the mechanisms at work when allergies develop or are triggered are not yet fully known – at least on the molecular level – the chapters of *Part II* describe some of the general mechanisms that have been identified as important. Knol and Gilles take a close look at the four types of hypersensitivity reactions that underlie the overreacting immune systems and bring this distinction that has been developed more than 60 years ago in line with actual findings. Biedermann et al. concentrate on the barrier function of the skin and stress the importance of its integrity which is protected by complex measures such as wound repair or anti-infective immune reactions. New methods, e.g. new sequencing technologies also offer fascinating new insights. Schwierzeck, Hülpüsch and Reiger use these for analyses of various microbiomes. In their article they explain research methods and report findings concerning alterations of the microbiome of the skin, the lung and nasopharynx that correlate with allergic diseases.

Part III then turns towards the various faces of allergic diseases and new forms of medical treatment. Papadopoulos et al. offer an up-to-date view on asthma, presenting up-to-date information on epidemiology, definitions, diagnosis and treatment options. Müller clarifies the peculiarities of allergic conjunctivitis. Traidl et al. give attention to the pathogenesis and pathophysiology of atopic eczema, focusing especially on new therapeutical possibilities offered by targeted treatments, e.g. the IL-4R alpha specific monoclonal antibody dupilumab. Maurer et al. outline the classification, diagnosis and management of urticaria. Pfützner et al. discuss the actual possibilities of Allergen Immunotherapy (AIT) and Wang fathoms the possibilities of precision medicine to treat chronic sinusitis.

Part IV of this book focuses on the treatment of various forms of allergic diseases with different environmental triggers. The first chapter of Part IV focuses on food allergies. Food as one relevant environmental trigger can cause allergic reactions, most commonly in the case of cow´s milk, hen´s eggs, fish, shellfish, peanuts, soybeans, tree nuts or wheat. Bohle and Werfel describe the different mechanisms and types of allergic reactions to food and the possibilities of treatment. The treatment options are exemplified by peanut and apple allergy. Another relevant trigger can be drugs. Mockenhaupt addresses adverse allergic reactions to drugs and focuses on manifestations on the skin. Also, the exposition to allergens at the workplace can lead to a higher risk for allergies in certain occupations. For example, bakers can become allergic against wheat flour proteins or other cereals, which can lead to baker's asthma. In the article by Raulf on *Occupational Respiratory Allergy* the important knowledge on the diagnosis and management of occupational allergies is summarized. In the following chapter, Giminez Arnau and João Luís present an overview on contact dermatitis and emphasize the relevance of patch testing in this context.

Part V now attends to the expressions of allergic diseases on the molecular level. Ferreira examines the role of B cells in the development of allergies as well as in the induction of tolerance with the help of AITs. Ohnmacht und Eyerich offer detailed insight into different kinds of Th- and Treg-cells and the roles they play in the

process of allergic inflammation. Martin and Esser in turn explain progress that has been made in understanding the cellular and pathomechanisms underlying the allergen-induced inflammation processes, findings clearing the way for new ways to treat allergies.

Some factors increase the risk for the development of allergic diseases. Those risk factors are described in *Part VI* of this handbook. There is a genetic component in allergies. Haider et al. summarize the current knowledge on *Genetics of Asthma and Allergic Diseases*. Identifying the specific asthma genes is connected with difficulties, but there are several approaches to disentangle the genetics of asthma and allergy, e.g. based on the definition of allergy subtypes. However, genetics only cannot explain the increase of allergies in the last decades. Environmental factors play an important role in this context. This is why understanding the epigenetic mechanisms, which are explained by Potaczek et al., have the potential to improve treatment and prevention of allergic diseases. Air pollution is one of the environmental factors that are linked to morbidity and mortality. Schikowski describes how air pollution affects our health and what we know about the effect of indoor and outdoor pollution on allergic diseases. The increasing prevalence and incidence of allergic diseases is often referred to lifestyle changes. But not only the behaviour and lifestyle, but also social and environmental structures are changing. Heuson describes how climate change and globalization both increase the exposure to allergens and therefore might increase the risk of allergies. As the exposure to allergens and the prevalence of allergic diseases follow a social gradient, also ethical questions are asked and implications for allergy policies are given.

Part VII now addresses diagnostic possibilities concerning different types of allergies. First, the diagnostic procedure in type-1 allergy is depicted by Treudler and Simon. Mahler and Uter then precisely explain the processes and problems applying and analyzing epicutaneous patch tests, recurring to best practice recommendations developed within current guidelines.

The prevention of allergic diseases is a main public health goal. Therefore, *Part VIII* focuses on the primary (Landgraf-Raulf & von Mutius), secondary and tertiary prevention (Fieten et al.). As there are promising results on the effect of nutritional interventions for the prevention of atopic diseases, Szklany et al. provide an overview on this topic. Last but not least, it is important to educate patients. Patient education can improve the quality of life and decrease symptom severity. Traidl et al. reflect the positive effects of patient education programmes for atopic eczema. Not only patients with atopic eczema, but also patients with other chronic conditions, such as allergic asthma, could benefit from the implementation of education and training programmes.

Allergy research is characterized by enormous success in the recent years. Therapies have improved the lives of many patients. Still allergic diseases do not have the attention and the assessment they deserve. Many patients still trivialize their illness and patient centred care could be improved, also by creating regulations where helpful and necessary. In the course of climate change the numbers of allergic patients will increase. For example, the pollen season on the whole becomes longer, the number of pollen in the air increases, even pollen itself becomes more allergic.

We have to go on to search for solutions to achieve resilience in the face of the changes that will affect our lives. And to search for answers for the many questions that are still to be answered. What exactly turns a person into an allergic person, a certain substance into an allergen? A recent study discusses the possible evolutionary value of the allergic phenotype: being allergic might protect against parasitic infections, accelerate wound healing, protect against venoms or possibly even tumours. Many mechanisms still are not exactly known.

Further research is needed. We need studies that explain the mechanisms of the different types of allergic inflammation to different allergens, the underpinning mechanisms of chronification or the pathomechanisms that lead to the disease, especially ones that translate the results into the complex and sustainable disease management. We need studies that examine hypersensitivity reactions, personal thresholds to allergens and understanding in space and time why a sensitization moves into allergic disease. We need to know which environmental factors or psychosocial factors increase the risk to become allergic and the development of the disease, and we need to distribute this information as best we can. We need to know more about food allergies and intolerances, about allergic diseases of the intestinal tract, more about hypersensitivities against pharmaceuticals, more about allergic rhinoconjunctivitis, about its progression and possible therapies. Our list is not at its end here.

At the end of these introductory thoughts, it remains to say "Thank you" to all who contributed to this large compendium and helped this cornerstone of allergy research to materialize.

We progressed this far, part of the journey still lies ahead.

Augsburg, Germany — Claudia Traidl-Hoffmann
Berlin, Germany — Torsten Zuberbier
Hanover, Germany — Thomas Werfel

Contents

Part I

History and Epidemiology

History of Allergy: Clinical Descriptions, Pathophysiology, and Treatment

Johannes Ring

Contents

Abstract

Allergy has shown a dramatic increase in prevalence in the last decades. However, allergic diseases are probably not new. Asthma and eczema have been described in ancient societies like Egypt, China and in the Greco-Roman culture. In the middle-ages descriptions of hay fever can be found in Persian-Arabian literature (called "rose fever"). Scientific allergology started in the nineteenth century with descriptions of hay fever and experimental studies showing pollen as elicitors. Milestones in the twentieth century comprise the description of anaphylaxis, the creation of the terms "allergy" and "atopy", the Prausnitz-Küstner test

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and finally the discovery of IgE and the development of the Radio-Allergo-Sorbent-Test (RAST) for routine detection of specific IgE antibodies. Progress in cellular immunology led to the description of T-cell subsets Th1 and Th2. Mast cell and basophil research progressed since the first description to histamine release studies. Leukotrienes were detected. Pharmacotherapy started in the early twentieth century with adrenaline (epinephrine) followed by antihistamines and cortisone. Allergen-specific immunotherapy was introduced. Epidemiologic studies pointed to a role of environmental pollutants as allergy enhancing factors and protective influences from farm environment. Through the progress in experimental allergology and immunology targeted therapeutics have been developed for various atopic conditions.

Keywords

Allergy · Biologics · History · Immunoglobulin E · Immunotherapy · Mast cells · Pollen

Allergy has been called the "epidemic of the 21st century", however, allergic diseases are not new – although they have increased in prevalence dramatically in the last 50 years. Let us shortly reflect upon the historical developments of allergic diseases, improvements in understanding of pathomechanisms and discoveries in diagnosis, treatment and prevention.

1 Allergy in Antiquity

Allergic diseases have been described in early medical literature in various cultures like Egypt, China, Indigenous America and in the Greco-Roman culture. Many names found in these scriptures like "asthma", "eczema" or "idiosyncrasy" are still in use today (Samter 1969; Simons 1994; Bergmann and Ring 2014; Schadewaldt 1983).

In Egypt we find descriptions of asthma and asthma therapy in the Papyrus Ebers. It remains open whether the first documented allergic individual really was pharaoh Menes who supposedly died in 2611 BC after a sting of a wasp (Avenberg et al. 1980).

In old China certain plants were used against asthma and runny nose like Ephedra distachya – from which the active substance was isolated in 1878 as ephedrine.

Hay fever itself is not described in the work of Hippocrates, however asthma is mentioned several times and also in the "Corpus Hippocraticum" collected by his pupils. One of the best descriptions was given by Aretaeus from Cappadocia as well as Dioscurides (Bergmann and Ring 2014). The term eczema appeared around 600 AD used by Aetius from Amida alluding to the welling up of a soup in a kettle (ek = out, zeo = live). The first mentioning of food allergy is often quoted as a line in "de natura rerum" by Titus Lucretius Carus

Table 1 Allergic diseases in history (quoted in Bergmann and Ring 2014)

2,641 BC	Pharaoh Menes	Anaphylaxis
460 BC	Hippocrates	Cheese idiosyncrasy
200 BC	Dioscurides	Asthma
70 BC	Lucretius	Food allergy
600	Aetius Amida	Eczema
900	Al Rhazes	Rose fever
1783	Phoebus	Hay fever
1819	Bostock	Autobiography "Hay fever"
1870	Blackley	Pollen, skin test
1872	Quincke	Angioedema
1891	Brocq	Neurodermite
1902	Richet/Portier	Anaphylaxis

"quod alii cibus est
alii fuad acre venenum"

(what is normal food for some can be deadly poison for others) (Table 1).

The best documented probably first atopic individual with a positive family history was emperor Octavianus Augustus who was suffering from symptoms of hay fever.

(catarrhus at spring winds), asthma (tightness of chest) and eczema (multiple itchy skin lesions to be scratched with an instrument) (Fig. 1). Furthermore in the

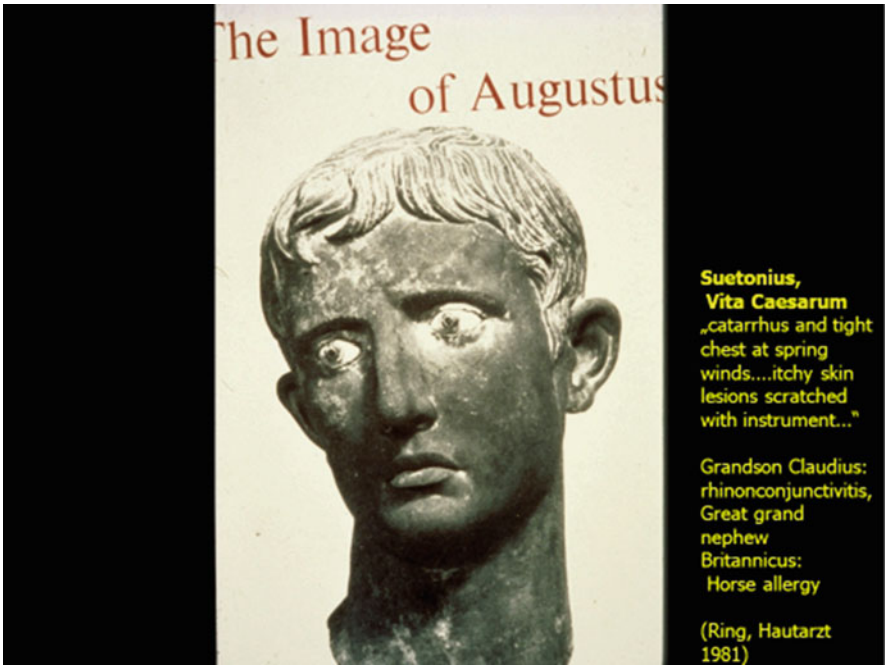

Fig. 1 Emperor Octavianus Augustus (from Ring J, Hautarzt 1985)

Julian Claudian emperor family also Emperor Claudius and Britannicus have been described to be affected by allergic symptoms (Ring 1985).

2 History of Allergy in Middle Ages and Renaissance

The Greco-Roman tradition with the scriptures of Hippocrates and Galen was kept alive in the middle east in the Persian-Arabic medicine from where it returned to Europe in Latin translations via South Italy and Spain. In those scriptures we find early mentioning of "rose fever" – with a similar symptomatology as hay fever by Al Rhazes and Ibn Sina (Avicenna). They also described a disease very similar to urticaria which was called "Essera". Moses Maimonides, personal physician of Sultan Saladin, wrote in depth about asthma and asthma therapy (Avenberg et al. 1980). In the seventeenth and eighteenth centuries more and more descriptions of asthma and seasonal symptoms of the nose can be found (van Helmont 1648).

3 Beginning of Scientific Allergology in the Nineteenth Century

It may be no co-incidence that the first scientific description of the most common allergic disease, namely hay fever, comes from England where industrialisation started. It was given by the physician John Bostock who described his own disease at a meeting of the Royal Society (Bostock 1819). Later in the century Charles Blackley was the first to show that pollen were the causal agent in hay fever, also doing the first skin and conjunctival provocation tests together with pollen measurements in the air (Blackley 1873).

Wyman demonstrated that autumnal catarrh was elicited by ragweed (Wyman 1875). Henry Hide Salter gave the first classic description of asthma in the second half of the nineteenth century (Salter 1864).

First progress was made in elucidating pathophysiology of diseases by the description of different inflammatory cells using new stainings developed by Paul Ehrlich (Ehrlich 1879) especially for eosinophils and mast cells. Charcot and Von Leyden discovered needle-like crystals in the sputum of asthmatics in the last decade of the nineteenth century (Charcot and Robin 1853; Leyden 1872). Curschmann described typical spirales (Curschmann 1882). Atopic eczema was more closely described as "Neurodermite" or "Prurigo diathésique" (Besnier 1892; Wallach et al. 2004). In 1895 the first patch test for contact allergy against mercury was performed by Josef Jadassohn (Jadassohn 1896). Drug reactions were recognised as iodoform exantherma (Neisser 1884).

4 Milestones in the Twentieth Century

The progress in experimental allergology started with a famous observation by Charles Richet and Paul Portier who wanted to immunise dogs against physalis venoms. They had started experiments on the yacht of the prince of Monaco (Fig. 2) to be continued in Paris. After repeated injections of the toxin the dog "Neptune" – who was supposed to be protected due to the vaccination – died under dramatic circumstances (Portier and Richet 1902). Richet in observing this phenomenon wanted to call it "Lack of protection" in contrary to "protection" ("phylaxie"). The correct word would have been "aphylaxis", however Richet's temperament preferred the more rhythmic term "anaphylaxis" which soon conquered the world; Richet received the Nobel Prize in 1913, but still did not understand the pathophysiology of the phenomenon believing it to be a lack of protection against a venom rather than a hyperreactivity.

In 1906 the term allergy was born in the Munich Medical Weekly (July 24, 1906) (Fig. 3) by the Viennese paediatrician Clemens von Pirquet who wanted to describe more precisely different phenomena observed during immune reactions proposing a word for the "altered state" which the organism finds out in acquaintance with any organic living or lifeless poison. "For this general concept of altered responsivity I suggest the term allergy" (von Pirquet 1906). Pirquet had become aware of untoward

Fig. 2 Postal stamp in memory of the first description of anaphylaxis by researchers Richet and Portier doing experiments on the yacht of the prince of Monaco (from Ring 2010)


MÜNCHENER
MEDIZINISCHE WOCHENSCHRIFT.
ORGAN FÜR A TISCHE ÄRZTE.
No. 29. 24. Juli 1906.
53 Jahrgang.
Originalien
Allergie.
Von C. v. Pirquet.

Fig. 3 Photograph of the article "allergy" from 1906 with the portrait of the author Clemens von Pirquet on the cover of the Muenchener Medizinische Wochenschrift 1986 for the 80th anniversary

reactions induced by immunity in his studies with diphtheria antitoxin and the occurrence of serum sickness together with Bela Schick.

Maurice Arthus studied experimentally induced skin reactions by repeated injections of non-toxic materials into the skin of rabbits (Arthus 1909), later called "Arthus phenomenon" and classified as Type III by Coombs and Gell (Coombs and Gell 1963). In experimental work Alexandre Besredka published studies on anaphylactic shock in animals which he tried to prevent by antianaphylactic vaccinations (Besredka and Steinhardt 1907); he believed that the brain was involved in anaphylactic shock.

Contrary to experimental allergy in animals, classical allergic diseases like hay fever would occur in humans without obvious active sensitisation – namely, "spontaneously". Also they tended to occur quite often within families. This phenomenon led the American researchers Arthur Fernandez Coca and Robert Anderson Cooke to define this state of altered reactivity by the term "atopy" (Coca and Cooke 1923).

In 1915 Coca founded the scientific "Journal of Immunology". Cooke, who was allergic himself and almost died from a serious anaphylactic reaction after diphtheria antitoxin, founded an out-patient clinic in New York for treatment of allergic

individuals. He also described "blocking antibodies" helping to find an explanation for the effects of immunotherapy.

The notion of close connection of various diseases of respiratory mucosa and skin and beyond was taken up by Kämmerer with his "allergic diathesis" (Kämmerer 1926 and by Wise and Sulzberger (1933). Karl Hansen regarded hay fever and asthma as similar to anaphylaxis and used the term "shock fragment" (Hansen 1941).

After it had become clear that serum sickness developed after a certain period of application of foreign proteins and after reports of transfer of the hypersensitive state by blood transfusion the search for "anaphylactic bodies" in the blood began. The seminal experiment was done in Breslau (Wroclaw) by Karl Prausnitz who injected himself serum of his fish-allergic assistant Heinz Küstner. On the next day he injected a fish extract near the injection site of Küstner's serum which led to an immediate swelling and redness (Prausnitz and Küstner 1921); thus, the transferability of allergy through serum was proven and the method used for decades was called Prausnitz-Küstner-Test.

The idea was taken up for animal experiments by Zoltan Ovary introducing "passive cutaneous anaphylaxis" (PCA) in animals – usually guinea pigs in order to better measure the wheal and flare reaction after the allergen application together with the serum followed by a dye (Evans blue) (Ovary 1999).

Human skin tests were started as scratch by Charles Blackley, then intensified with the intradermal method by Clemens von Pirquet, and standardised scratch test by Oscar Menderson Schloss. The most commonly used "Prick Test" was first used by Pirquet with a "drill" puncture to scarify the skin under a drop of tuberculin. The Prick test which is used today was developed by Helmtraud Ebruster at the Department of Dermatology in Vienna (Ebruster 1959). Major progress using different devices and standardised needles was provided by Morrow Brown in England (Brown et al. 1981; Brown 1992).

Provocation Tests were already done by Charles Blackley but later on by Alfred Wolff-Eisner as "ophthalmo test" (Wolff-Eisner 1906, 1907) and by Noon and Freeman. Later provocation tests became the routine by William Duke (Duke 1925) and Erich Urbach (Urbach 1933).

In 1925 the brothers Simon and Charles Leopold developed an inhalation technique for allergens for experimental settings (Leopold and Leopold 1925). In 1956 Gronemeyer and Fuchs published on the "Inhalation-Pneumometrie-Test" recommending it as routine method for allergy diagnosis in asthma (Fuchs et al. 1956).

In the understanding of allergy pathophysiology two major breakthroughs occurred in the second half of the twentieth century, namely by the detection of immunoglobulin E as well as the discovery of new vasoactive mediators of inflammation.

5 Discovery of Immunoglobulin E

Since Prausnitz and Küstner had shown the transferability of immediate hypersensitivity by serum there was an intensive search to elucidate the nature of these so-called reagins. With modern biochemical methods (e.g. electrophoresis and antibody detection tests) one expected to find the reactivity among the gammaglobulin fraction. Two groups independently from each other pursued the search, namely the group around Kimishige and Teruko Ishizaka in Denver purifying small amounts of what they called "gamma E-globulin" from sera of hay fever patients (Ishizaka et al. 1966).

In Uppsala SGO Johansson together with Hans Bennich studied a myeloma protein from a patient with multiple myeloma with so far unknown characteristics; they called it "IgND" after the initials of the patient (Johansson 1967). They found that 60% of patients with allergic asthma had IgND; they also were able to develop a radio-immuno-assay for IgND antibodies against common allergens like pollen or house dust mite giving the basis for the Radio-Allergo-Sorbent Test (RAST) used for decades to measure specific IgE antibodies. Via an activity of the World Health Organization (WHO) the groups came together and shared reagents so that in 1968 a new immunoglobulin class "IgE" was officially declared in Lausanne (Bennich et al. 1968).

6 T-Cell Immunology

Only in the 50es of the twentieth century it became apparent that lymphocytes were not only able to become neoplastic in lymphocytic leukaemia but have a central function in providing immune responses. The progress in immunology is closely connected to the discovery of more and more new subpopulations of lymphocytes starting with.

T and B cells at the beginning; T stands for thymus and B for Bursa fabrici in birds.

B cells will transform to plasma cells and produce and secrete antibodies. T cells are in the centre of the immunological reactivity and produce a variety of different cytokines characteristic for the respective subpopulations. The first subpopulations detected were T helper and T suppressor cells; among helper cells Th1 and Th2 cells were then differentiated at the end of the 80s. The subpopulations could only be distinguished by the cytokines secreted and not by morphological markers. Th1 cells produce interferon gamma and interleukin 2 thus activating macrophages. In contrast Th2 cells produce interleukin 4, interleukin 5 and interleukin 13 (Mosmann and Coffman 1989) enhancing IgE production in atopic conditions. It became clear that Th2 was the predominant allergy enhancing immune response while Th1 responses were prevalent in organ-specific autoimmune disorders or chronic inflammatory diseases.

In the following decades a multitude of cytokines and T cells subpopulations has been described with characteristic functions relevant for physiology and

pathophysiology (Romagnani 1991). More important and of special interest was the search for the so-called suppressor cells (Tada et al. 1991) which were supposed to mediate immunological tolerance but could not be characterised molecularly so that they almost were forgotten. Yet they survived and were "redetected" in the 90s by Sakaguchi in Kyoto naming them "regulatory T cells" characterised by expression of interleukin 2 receptor (CD 25) (Sakaguchi et al. 1995).

While these regulatory T cells have a beneficial effect in allergic or autoimmune diseases, they are able to prevent normal immunosurveillance in malignant neoplasia. One of the major progresses in modern cancer therapy is the development of a monoclonal antibody against the CTLA 4 marker of regulatory T cells leading to prolonged survival in patients with metastatic malignant melanoma.

One of the mechanisms of allergen-specific immunotherapy (ASIT) is the induction of regulatory T cells thus re-establishing normal homeostasis between different T-cell subpopulations (Norman and Lichtenstein 1978; Ring and Gutermuth 2011).

7 Mast Cells, Basophils and Histamine

Since the discovery and first description of mast cells by Paul Ehrlich in 1877 (the name was given because of the stuffed granules looking like "gemästet", German for "stuffed") it took some decades until they were recognised as carriers and producers of histamine (Riley and West 1952) together with basophil leukocytes in the blood. Also the discovery of several mast cell populations in the periphery or in the bone marrow was a major step forward. Histamine as main mediator of mast cells was recognised as the substance closely mimicking or mediating the effects of anaphylaxis (Dale and Laidlaw 1910). In 1964 Lichtenstein and Osler showed that specific allergen was able to stimulate histamine release from human leukocytes, namely basophils (Lichtenstein and Osler 1964).

After the discovery of IgE and IgE receptor it became clear that mast cells and basophils were carrying a highly specific IgE receptor. Only in 1971 IgE-sensitised mast cells were demonstrated to release histamine after allergen challenge in peritoneal mast cells. Activated mast cells were shown to release a variety of protein and cytokines as well as low molecular weight vasoactive mediators such as histamine, leukotrienes defined as principle of the long known "slow reactive substance of anaphylaxis" (Samuelsson 1983) or platelet activating factor (PAF). Mast cells can be activated not only by allergen but also chemically, e.g., with substance 40/80 and variety of other stimuli and pathways (Austen and Brocklehurst 1960). For the clinical variants of conditions looking like anaphylaxis but without evidence for immunological sensitisation Paul Kallos used the term "pseudo-allergic reactions") (Bergmann and Ring 2014) (Table 2).

Table 2 Milestones in understanding allergic phenomena and diseases (quoted in Bergmann and Ring 2014)

Skin and provocation tests, pollen as elicitors	Blackley	1873
Mast cell	Ehrlich	1877
Patch test	Jadassohn	1895
Anaphylaxis	Richet, Portier	1902
Local anaphylaxis	Arthus	1905
Serum sickness	vPirquet, Schick	1905
Allergy	vPirquet	1906
Hay fever similar to anaphylaxis	Wolff-Eisner	1906
Antiserum against pollen ("Pollantin")	Dunbar	1910
Histamine effects similar to anaphylaxis	Dale, Laidlaw	1910
Prophylactic inoculation	Noon, Freeman	1911
Serum transfer of humoral hypersensitivity	Prausnitz, Küstner	1921
Atopy	Coca, Cooke	1923
Ephedrine (from ma Huang)	Shen, Schmidt	1924
Triple response to histamine	Lewis	1927
Climate chamber without dust	Storm van Leeuwen	1928
Allergic diathesis	Kämmerer	1928
Antihistamine (Phenergan)	Bovet, Staub	1937
Blocking antibodies	Loveless	1940
Shock fragment	Hansen	1941
Cortisone	Kendall, Hench	1949
Passive cutaneous anaphylaxis (PCA)	Ovary	1952
Histamine in mast cell granules	Riley, West	1953
1. Placebo-controlled trial ASIT	Frankland	1954
Bronchial provocation in routine	Fuchs, Gronemeyer	1956
Immune complexes	Dixon	1958
Penicillin-allergy (Hapten bivalent)	DeWeck, Levine	1960
Farmer's lung	Pepys	1961
Type I – IV pathogenic immune reactions	Coombs, Gell	1963
Histamine release from basophils	Lichtenstein, Osler	1964
Immunoglobulin E	Ishizaka	1966
	Johansson	1967
House dust mites	Vorhoorst, Spieksma	1967
Cromoglycate	Altounyan	1967
Contact allergy (mouse)	Macher, Chase	1969
Lymphocyte transformation in allergy	Halpern	1977
Pseudo-allergic reaction	Kallos	1978
Leukotrienes (as SRS-A)	Samuelsson	1979
IgE receptor	Metzger	1984
Th1-Th2-concept	Mossman	1987
Interleukin 4	Coffman	1988
Allergotoxicoloy	Behrendt	1987
Recombinant allergens	Tovey, Kraft	1989

(continued)

Table 2 (continued)

Leukotriene antagonists	Piper	1987
Calcineurin inhibitors topical	Stütz, Meingassner	1995
Anti-IgE	Heusser	1996
Filaggrin mutation in atopic eczema	McLean, Irvine	2007

8 Eosinophils

Since the discovery of eosinophils they have been connected not only with allergic diseases but also with an element of protection. For decades there was a debate whether eosinophils are "good" or "bad", "friends" or "foes" (Simon and Simon 2007).

There is no doubt that eosinophils exert proinflammatory effects in various allergic disorders; there is a new appearance of gastrointestinal eosinophil pathology with regard to diseases like eosinophil esophagitis or eosinophil gastroenteritis which seem to be increasing in prevalence. On the other hand, eosinophils also have beneficial effects in defence reactions and play a role in tissue remodelling. Due to the development of monoclonal antibodies against interleukin 5, the major eosinophil promoting cytokine, there is new hope for a variety of diseases with clear beneficial effects in eosinophil asthma, hypereosinophilic syndrome and other conditions with enhanced eosinophil activation (Renz et al. 2021).

9 Histamine and Antihistamines

In 1907 Windaus and Vogt identified histamine chemically, in 1910 Ackermann isolated histamine as metabolite from bacterial histamine fermentation (Windaus and Vogt 1907).

Henry Dale then did the seminal experiments showing the pharmacological effects mimicking symptoms of anaphylaxis (Dale and Laidlaw 1910). In 1937 Daniel Bovet developed the first antihistamine (Bovet and Staub 1937). In 1942 the first substance dimethylethylene diamine (brand name Antergan) was on the market (Halpern 1942). Histamine acts via several receptors H1, H2, H3, H4, H1 being the most important in allergy. H2 is mostly responsible for histamine effects in the stomach or gastrointestinal tract but also in small vessels in the skin. The discovery of histamine H2 receptors was rewarded with a Nobel Prize to James Black (Black et al. 1972) and H2 antagonists have been proven helpful in decreasing acid secretion and preventing peptic ulcers.

H3 receptors are found in the brain and play a role in vigilance. H4 receptor is expressed on immune cells and may be involved in itch sensation. For allergic disorders H1 antagonists are central. While the first generation (mepyramine, dimetindene, clemastine, etc.) had marked sedative side effects, this was improved for the second generation of antihistamines starting with terfenadine and loratadine

and especially for the "third generation", namely metabolites like fexofenadine, levocetirizine, and desloratadine.

10 Epidemiology of Allergy

Allergic diseases have increased in prevalence in the twentieth century, leading to prevalence rates of around 20% of persons affected with an atopic disease (asthma, hay fever, eczema) in the population. This increase occurred first in the so-called Western countries in the Northern hemisphere, but in the new millennium it became a global phenomenon observed in all continents. The most marked increase in allergy prevalence occurred in the Northern hemisphere in the decades 1960 to 1990 together with significant changes in life style like reduction of rural environments together with increased traffic exhaust exposure and urbanisation (Behrendt et al. 1999). Climate change with increasing pollination periods may contribute to the increased allergy prevalence. The reasons for this increase are explained namely by 2 hypotheses:

1. Decrease of early life immune stimulation through reduced rate of infections and improved hygiene ("hygiene hypothesis") (Strachan 1989) and.
2. Increase of environmental pollutants in the atmosphere – especially of fine particles ("Pollution hypothesis") (Behrendt et al. 2014).

Early studies showing associations between pollutant exposure and allergy came from Japan (Miyamoto and Takafuji 1991) and from comparison of former East and West German school children (Krämer et al. 1999).

In alpine farmers in Austria, Switzerland and Bavaria it was found that farmers' children were suffering less frequently from allergy than non-farmers' children in the same area (Gassner 1985; Von Mutius et al. 2000). Similar findings came from studies in specifically selected, mostly religious, conservative communities with very traditional life style (e.g. anthroposophical families in Stockholm or Amish in the USA) (Fagerstedt et al. 2015; Ober et al. 2017).

Although the exact pathophysiological mechanisms involved are not completely established, it is generally accepted that civilisation in the sense of "Western life-style" is associated with development and exacerbation of allergic diseases (Behrendt et al. 2014; Behrendt and Ring 2021).

11 Pharmacotherapy

Pharmacotherapy of allergic diseases starts with catecholamines especially ephedrine already used in old China. The breakthrough occurred with the introduction of adrenaline (epinephrine). Adrenaline was discovered in the adrenals in 1893; first therapeutic experiences were gained with adrenal extracts. The purification of the active principle "Epinephrine", "Suprarenin" or "Adrenaline" was done between

Table 3 Allergy treatment recommendations in textbooks before 1950

• Abstinence (avoidance)
• Peptones
• Vaccines (bacterial, tuberculin, etc.)
• Desensitisation
• Non-specific desensitisation (histamine, histaminase, etc.)
• Sympathikomimetics (ephedrine, amphetamine, adrenaline, etc.)
• Parasympathicolytics (belladonna, atropine, hyoscyamus, stramonium-powder, etc.)
• Opiates (opium, codeine, cocaine, etc.)
• Antihistamines
• Expectorants (iodide, etc.)
• Hormones (insulin, pituitary and adrenal extracts)
• Gold salts
• Vitamins and calcium
• Hypnotics (urethane, ether, tribromoethanol)
• X-ray treatment (thorax, spleen)
• Surgery (cervical sympathectomy, ganglion, etc.)
• Miscellanea (aspirin, whisky, etc.)

1901 and 1905, in 1906 the chemical structure was identified by Josef Friedmann (Friedmann 1906).

By the demonstration of several specific adrenergic receptors it became clear that for allergy and asthma especially the Beta 2 adrenergic receptor is important with the respective agonists as treatment principles. Adrenaline itself still has a central role in the pharmacotherapy of anaphylaxis (Ring et al. 2018).

The tremendous progress in allergy therapy is apparent, when we look at the treatment options for allergic diseases found in the textbooks before 1950 (Table 3).

12 Allergens

It took a long time – after the discovery of pollen as elicitors of hay fever by Blackley in 1873 (s above) and the detection of house dust mites as active principle in house dust (Voorhorst et al. 1964) – until the molecular nature of allergens was elucidated in codfish (Elsayed and Aas 1970) and house dust mite (Tovey et al. 1989) and birch pollen (Breiteneder et al. 1992; Kraft and Sehon 1993).

In the field of drug allergy, from where the first patch test for contact allergy originated (Jadassohn 1896), the major breakthrough came by understanding molecular mechanisms of bivalent bridging of IgE on the surface of mast cells and basophils in the example of penicillin allergy (DeWeck 2008).

13 Allergen-Specific Immunotherapy (ASIT)

Early attempts to influence allergic diseases by a kind of vaccination date back into the nineteenth century. In the first decade of the twentieth century several reports had been published using distinct procedures and connected the names Wolf-Eissner, Dunbar and others (Ring and Gutermuth 2011).

The breakthrough came with the study of Leonard Noon and John Freeman observing clear-cut improvement of hay fever symptoms in patients after "prophylactic inoculation" (Noon 1911).

The first clinically controlled trial for allergen-specific immunotherapy was done by Frankland and Augustine in 1953 (Frankland and Augustine 1954). From then on progress in immunotherapy occurred through better purification and standardisation of allergen extracts, introduction of adjuvants and modification of allergens. Today there is no doubt that allergen-specific immunotherapy has been proven effective in a variety for allergic diseases and against a variety of allergens (Norman and Lichtenstein 1978). However, there are still many allergic diseases and many allergen elicitors where there is no ASIT routinely available; this holds especially true for allergic diseases of the skin and food allergy.

In spite of tremendous progress in the field of allergology and immunology as well as in the clinical specialties of pneumology, dermatology and otolaryngology there are still many problems in everyday life for the millions of people suffering from allergic diseases. With the development of biologics, e.g. targeted molecules to specifically block relevant cytokines or factors in the signal transduction cascade of the allergic inflammation, there is a silver streak of hope on the horizon that the life of allergic patients may be profoundly improved in the near future.

References

Arthus N-M (1909) La séro-anaphylaxie du lapin. Arch Int Physiol 7:471

Austen KF, Brocklehurst WE (1960) Inhibition of the anaphylactic release of histamine from chopped Guinea pig lung by chymotrypsin substrates and inhibitors. Nature 186:866–868

Avenberg KM, Harper DS, Larsson BL (1980) Footnotes on allergy. Pharmacia, Uppsala

Behrendt H, Ring J (2021) Allergy – a disease of civilization. In: Oexle K, Molls M, Wilderer P (eds) Violent earth – violated earth. TUM-IAS

Behrendt H, Ewers HJ, Hüttl RF, Jaenicke M, Plassmann E, Rehbinder E, Sukopp H (1999) Allergien und Umwelteinflüsse. In: Umwelt und Gesundheit – Risiken richtig einschätzen. Sondergutachten des Rates der Sachverständigen für Umweltfragen (SRU). Metzler Poeschel, Stuttgart

Behrendt H, Alessandrini F, Buters J, Krämer U, Koren H, Ring J (2014) Environmental pollution and allergy: historical aspects. In: Bergmann K-C, Ring J (eds) History of allergy. Chemical immunology and allergy, vol 100. Karger, Basel, pp 268–277

Bennich HH, Ishizaka K, Johansson SGO, Rowe DS, Stanworth DR, Terry WD (1968) Immunoglobuline E: a new class of human immunoglobulin. Bull World Health Organ 38:151–152

Bergmann KC, Ring J (eds) (2014) History of allergy. Karger, Basel

Besnier E (1892) Premiére note et observations préliminaires pour servir d'introduction á l'étude des prurigos diathésiques (dermatites multiformes prurigineuses chroniques exacerbantes et paroxystiques, du type du prurigo de Hebra). Ann Derm Syphil 3:634–648
Besredka A, Steinhardt E (1907) Du mechanisme de l'antianaphylaxie vis-a-vis du serum de cheval. Ann Inst Pasteur 21:118
Black JW, Duncan WA, Durant CJ, Ganellin CR, Parsons EM (1972) Definition and antagonism of histamine H2-receptors. Nature 236:385–390
Blackley C (1873) Experimental researches on the causes and nature of Catarrhus Aestivus (hay fever or hay asthma). Balière, Tindal and Cox, London (facsimile: Abington, Oxford Historical Books, 1988, pp 155–156)
Bostock J (1819) Case of a periodical affection of the eyes and chest. Med Chir Trans 10:161
Bovet D, Staub AM (1937) Action protectrice des ethers phenoliques au cours de l'intoxication histaminique. CR Soc Biol (Paris) 124:547–549
Breiteneder H, Ferreira F, Reikerstorfer A et al (1992) Complementary DNA cloning and expression in Escherichia coli of Aln g 1, the major allergen in pollen of alder (Alnur glutinosa). J Allergy Clin Immunol 90:909–917
Brown HM (1992) The relationship of aerobiological data to seasonal allergic symptoms: a review of 27 years experience. Immunol Allergy Pract 14:3318–3329
Brown HM, Su S, Thantrey N (1981) Prick testing for allergend standardized by using a precision needle. Clin Allergy 11:95
Charcot JM, Robin CP (1853) Observation de leucocythemie. C R Soc G Mem Soc Biol 5:44
Coca AF, Cooke RA (1923) On the classification of the phenomena of hypersensitiveness. J Immunol 8:163–182
Coombs RRA, Gell PGH (1963) Classification of allergic reactions underlying disease. In: Gell PGH, Coombs RRA (eds) Clinical aspects of immunology. Davies, Philadelphia, p 317
Curschmann H (1882) Über Bronchiolitis exsudativa und ihr Verhältnis zum Asthma nervosum. Dtsch Arch Klin Med 32:1
Dale HH, Laidlaw P (1910) The physiological action of β-iminazolylethylamine. J Physiol 41:318–344
DeWeck A (2008) Memories, failures and dreams. Huber, Bern
Duke WW (1925) Allergy, asthma, hay fever, urticaria and other manifestation of reaction. Mosby, St Louis
Ebruster H (1959) Der Pricktest, eine neuere Cutanprobe zur Diagnose allergischer Erkrankungen. Wien klin Wschr 71:551–554
Ehrlich P (1879) Beiträge zur Kenntnis der granulierten Bindegewebszellen und der eosinophilen Leukocythen. Arch Anat Physiol (Leipzig) 3:166
Elsayed SK, Aas K (1970) Characterization of a major allergen (cod). Chemical composition and immunological properties. Int Arch Allergy Appl Immunol 38:536–548
Fagerstedt S, Hesla HM, Ekhager E, Rosenlund H, Mie A, Benson L, Scheynius A, Alm J (2015) Anthroposophic lifestyle is associated with a lower incidence of food allergen sensitization in early childhood. J Allergy Clin Immunol 137(4):1253–1256.e3
Frankland AW, Augustine R (1954) Prophylaxis of summer hay fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. Lancet 1:1055–1057
Friedmann E (1906) Die Konstitution des Adrenalins. Beitr Z Chem Physiol Pathol 8:95–120
Fuchs E, Gronemeyer W, Iwanoff I (1956) Der inhalative Antigen-Pneumometrie-Test zur Ermittlung des aktuellen Allergens bei berufsbedingtem Asthma bronchiale. Dtsch Med Wochenschr 81:339
Gassner M (1985) Häufigkeit allergologischer Erkrankungen bei Schulkindern einer Landbevölkerung im Hinblick auf die Berufsberatung. Zbl Haut Geschlkr 150:649
Halpern BN (1942) Les antihistaminiques de synthèse. Essais de chimiothérapie des états allergiques. Arch Int Pharmacodyn Ther 681:339–408
Hansen K (1941) Asthma als Schockfragment. Wien Klin Wochenschr 54:175

Ishizaka K, Ishizaka T, Hornbrook MM (1966) Physicochemical properties of reaginic antibody. 5. Correlation of reaginic activity with gamma-E-globulin antibody. J Immunol 97:840–853
Jadassohn J (1896) Zur Kenntnis der medikamentösen Dermatosen. Verh Dtsch Derm Ges 5:103
Johansson SGO (1967) Raised levels of a new immunoglobulin class (IgND) in asthma. Lancet 2:951–953
Kraft D, Sehon A (eds) (1993) Molecular biology and immunology of allergens. CRC press, Boca Raton
Kaemmerer H. (1926) Allergische Diathese und allergische Erkrankungen. Munich, Bergmann
Krämer U, Behrendt H, Dolgner R, Ranft U, Ring J, Willer H, Schlipköter HN (1999) Airway diseases and allergies in East and West German children during the first 5 years after reunification: time trends and the impact of Sulphur dioxide and total suspended particles. Int J Epidemiol 28:865–873
Leopold SS, Leopold CS (1925) Bronchial asthma and allied allergic disorders. J Am Med Assoc 84:731
Leyden EV (1872) Zur Kenntnis des Bronchialasthmas. Arch Pathol Anat 54:324
Lichtenstein LM, Osler AG (1964) Studies on the mechanisms of hypersensitivity phenomena. 9. Histamine release from leukocytes by ragweed pollen allergen. J Exp Med 120:507–530
Miyamoto T, Takafuji S (1991) Environment and allergy. In: Ring J, Przybilla B (eds) New trends in allergy III. Springer, Berlin, pp 459–468
Mosmann TR, Coffman RL (1989) Heterogeneity of cytokine secretion patterns and functions of helper T cells. Adv Immunol 119:382–392
Neisser A (1884) Über Jodoform-Exantheme. Dtsch Med Wochenschr 10:467–468
Noon L (1911) Prophylactic inoculation against hay fever. Lancet i:1572–1573
Norman PS, Lichtenstein LM (1978) The clinical and immunologic specificity of immunotherapy. J Allergy Clin Immunol 61:370–377
Ober C, Sperling AI, von Mutius E, Vercelli D (2017) Immune development and environment: lessons from Amish and Hutterite children. Curr Opin Immunol 48:51–60
Ovary Z (1999) Souvenirs: around the world in ninety years. India Ink Press, New York
Portier P, Richet C (1902) De l'action anaphylactique dé certains vénins. CR Soc Biol 54:170–172/ Trav Labor Physiol 1902; 5:506
Prausnitz K, Küstner H (1921) Studien über die Überempfindlichkeit. Zentralbl Bakteriol 86:160–169
Renz H, Bachert C, Berek C, Hamelmann E, Levi-schaffer F, Raap U, Simon HU, Ploetz S, Taube C, Valent P, Voehringer D, Werfel T, Zhang N, Ring J (2021) Physiology and pathgology of eosinophils: recent developments. Scand J Immunol 93:e13032
Riley JG, West GB (1952) Histamine in tissue mast cells. J Physiol 117:72–73
Ring J (1985) Erstbeschreibung einer "atopischen Familienanamnese" im Julisch-Claudischen Kaiserhaus: Augustus, Claudius, Britannicus. Hautarzt 36:470–474
Ring J (ed) (2010) Anaphylaxis. Karger, Basel
Ring J, Gutermuth J (2011) 100 years of hyposensitization: history of allergen-specific immunotherapy (ASIT). Allergy 66:713–724
Ring J, Klimek L, Worm M (2018) Adrenalin in der Akutbehandlung der Anaphylaxie. Dtsch Aerztebl Int 115:528–534
Romagnani S (1991) Human Th1 and Th2 subsets: doubt no more. Immunol Today 12:256–257
Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 155:1151–1164
Salter HH (1864) On asthma: its pathology and treatment. Blanchard, Philadelphia
Samter M (1969) Excerpts from classics in allergy. Ross Laboratories, Columbus
Samuelsson B (1983) Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. Science 220:568–575
Schadewaldt H (1983) Geschichte der Allergie. 4 volumes, Munich, Dustri 1983–84

Simon D, Simon HU (2007) Eosinophilic disorders. J Allergy Clin Immunol 119:1291–1300
Simons FER (ed) (1994) Ancestors of allergy. Global Medical Communications, New York
Strachan DP (1989) Hay fever, hygiene and household size. BMJ 299:1259–1260
Tada T, Hu FY, Kishimoto H, Furutani-Seiki M, Asano Y (1991) Molecular events in the T cell-mediated suppression of the immune response. Ann N Y Acad Sci 636:20–39
Tovey ER, Johanson MC, Roche AL, Cobon GS, Baldo BA (1989) Cloning and sequencing of a cDNA expressing a recombinant house dust mite protein that binds human IgE and corresponds to an important low molecular weight allergen. J Exp Med 170:1457–1462
Urbach E (1933) Methodik des Allergennachweises. Münch Med Wochenschr 80:134
van Helmont JB (1648) Asthma et Tussis. In: van Helmont JB (ed) Ortus medicinae. Dtsch.: Aufgang der Arzney-Kunst, Sulzbach, Amsterdam, p 366
Von Mutius E, Braun-Fahrländer C, Schierl R, Riedler J, Ehlermann S, Maisch S, Waser M, Nowak D (2000) Exposure to endotoxin or other bacterial components might protect against the development of allergy. Clin Exp Allergy 30:1230–1234
Von Pirquet C (1906) Allergie. Münch Med Wochenschr 53:1457–1458
Voorhorst R, Spieksma-Boezeman MI, Spieksma FT (1964) Is a mite (Dermatophagoides spp.) the producer of the house-dust mite allergen? Allerg Asthma (Leipz) 10:329–334
Wallach D, Taieb A, Tilles G (2004) Histoire de la dermatite atopique. Masson, Paris
Windaus A, Vogt W (1907) Synthese des Imidazol-Äthylamins. Ber Dtsch Chem Ges 40:3691–3695
Wise F, Sulzberger MG (1933) Year book of dermatology and Syphilology. Chic Year B Med 1933:38–39
Wolff-Eisner A (1906) Das Heufieber, sein Wesen und seine Behandlung. J.F. Lehmann, München, pp 130–131
Wolff-Eisner A (1907) Die kutane und konjunktivale Tuberkulinreaktion, ihre Bedeutung für Diagnostik und Prognose der Tuberkulose. Z Tuberk 12:21–25
Wyman M (1875) Autumnal catarrh. Boston Med Surg J 93:209–212

Epidemiology of Allergy: Natural Course and Risk Factors of Allergic Diseases

Jon Genuneit and Marie Standl

Contents

Abstract

The prevalences of allergic diseases, asthma, atopic dermatitis, allergic rhinitis and lately food allergy have been increasing over the last decades. It has been suggested that the prevalence of allergic diseases has reached a plateau in high income countries, while it is still on the rise in low and middle income countries. Generally, allergic diseases more often set on in childhood than in adulthood and affected children contribute more to the rise in allergic disease prevalence than affected adults. Epidemiological evidence suggests that not all atopic dermatitis and asthma cases are attributable to atopic sensitization. Indeed, mainly genetic association studies have prompted the unravelling of barrier dysfunction as a mainstay in the patho-mechanisms leading to atopic dermatitis and to asthma with atopic sensitization secondary to this dysfunction. Epidemiological research on risk and protective factors for allergic disease, acting against the background of genetic susceptibility, has produced an enormous body of evidence. Prominent observations are the 'sibling effect' and the 'farm effect' which gave rise to the

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'hygiene hypothesis' and later the 'biodiversity hypothesis'. Future epidemiological research is required to evaluate and refine these hypotheses in light of the paradigm shift from atopic sensitization to barrier dysfunction with ever increasing options for environmental characterization, currently, e.g., 'omics'--techniques in microbiology and metabolism, and with ever increasing options for phenotyping of allergic techniques, including, e.g., high-resolution time series of symptoms using, e.g., sensing technologies.

Keywords

Comorbidities · Epidemiology · Natural history · Risk and protective factors · Time trends

The prevalences of allergic diseases, asthma, atopic dermatitis (also called atopic eczema), allergic rhinitis and lately food allergy have been increasing over the last decades (Campbell and Mehr 2015; Platts-Mills 2015; Prescott and Allen 2011). It has been suggested that the prevalence of allergic diseases has reached a plateau in high income countries, while it is still on the rise in low and middle income countries (Asher et al. 2006; Lundbäck et al. 2016). Generally, allergic diseases more often set on in childhood than in adulthood and affected children contribute more to the rise in allergic disease prevalence than affected adults.

Allergic rhinitis and asthma are the most common allergic diseases estimated to affect 400 million and 360 million people worldwide, respectively (Greiner et al. 2011; GBD 2015 Chronic Respiratory Disease Collaborators 2017). Allergic rhinitis often occurs in childhood and adolescence with prevalences varying by country, ranging from 10–30% in adults and up to 40% in children (Pawankar et al. 2013). The prevalence of asthma is likely lower, around 4% of adults self-report a doctor's diagnosis and around 10% of children suffer from asthma symptoms (Pearce et al. 2007; Papi et al. 2018). Notably, among children with asthma symptoms, asthma is more severe in low and middle income countries compared to high income countries (Lai et al. 2009). Atopic dermatitis is estimated to affect 10–20% of the population, with about 60% of cases occurring in the first year of life (Weidinger and Novak 2016). It is assumed that there is a high remission rate until late childhood, but recent research indicates that remission rates are lower than previously anticipated (Margolis et al. 2014; Weidinger and Novak 2016).

The estimation of allergic disease prevalence is difficult, because perception of symptoms, diagnostic labelling, and management of these diseases might vary between countries. Moreover, there's no consensus on how to define or operationalize, for instance, asthma in epidemiological studies (Van Wonderen et al. 2009). The International Study on Asthma and Allergies in Childhood (ISAAC) is a worldwide study investigating the prevalence and severity of allergic diseases in children using standardized methodology (Asher et al. 1995), thereby allowing global comparisons. It was established in 1991 and has become the largest worldwide collaborative research project ever undertaken, involving more than

100 countries and nearly two million children. The ISAAC website (http://isaac.auckland.ac.nz) provides ample information including details on all phases of ISAAC and a database of over 500 ISAAC publications. In adults, the European Community Respiratory Health Survey (ECRHS) involved surveys of asthma and allergic rhinitis prevalence in adults aged 20–44 years in 48 centres in 22 European countries (Burney et al. 1994). The ECRHS website (http://www.ecrhs.org) is a good primer for information on the ECRHS investigations and also provides a list of over 200 ECRHS publications.

The prevalences of atopic eczema, asthma, and allergic rhinitis reported in epidemiological studies change sequentially with age across childhood, which has been coined "atopic march" (Hill and Spergel 2018). One hypothesis is that these changes are a consequence of a cascade of symptoms within individual patients, starting with eczema, progressing to asthma, and then to rhinitis. This has been challenged by studies showing that only 3% of the total study population and only about 12% of all children affected by atopic dermatitis experience this cascade of symptoms (Belgrave et al. 2014). Another matter of ongoing debate is the importance of concurrent atopic sensitization and its importance in disease development and progression. ISAAC Phase Two data has documented international variation in the association of allergic markers (specific and total Immunoglobulin E, IgE, and skin prick tests, SPT, with symptoms of allergic diseases (Weinmayr et al. 2010)). Already two decades ago, epidemiological evidence suggested that the population based proportion of asthma cases that are attributable to atopic sensitization is usually less than one half (Pearce et al. 1999). Similarly, epidemiological studies question the causal role of atopic sensitization in atopic dermatitis and show marked variation of the association between the two across studies (Williams and Flohr 2006). Indeed, mainly genetic association studies have prompted the unravelling of barrier dysfunction as a mainstay in the patho-mechanisms leading to atopic dermatitis and to asthma with atopic sensitization secondary to this dysfunction (Williams and Flohr 2006; Weidinger and Novak 2016; Martinez and Vercelli 2013).

Epidemiological research on risk and protective factors for allergic disease, acting against the background of genetic susceptibility, has produced an enormous body of evidence. A multitude of narrative expert reviews such as those cited in this section of this book provide good level of insight. Another approach has been the (systematic) overview of systematic reviews in allergy epidemiology (Genuneit et al. 2017a; Genuneit et al. 2017b). Figure 1 shows the wealth of systematic reviews in allergy epidemiology and which topics have been investigated alongside which diseases. Of note, some diseases like urticaria and anaphylaxis have received much less attention than other allergic diseases. Moreover, some topics have been predominantly investigated in relation to some allergic diseases only, e.g. virtually all systematic reviews on air pollution deal with asthma but only a small portion of them with allergic rhinitis, another respiratory allergic disease. Conversely, dietary and microbial factors have been addressed with several allergic diseases in a much more balanced way.

Looking at the results of this overview for systematic reviews on asthma epidemiology, specifically, Fig. 2 depicts the broad range of factors that have been

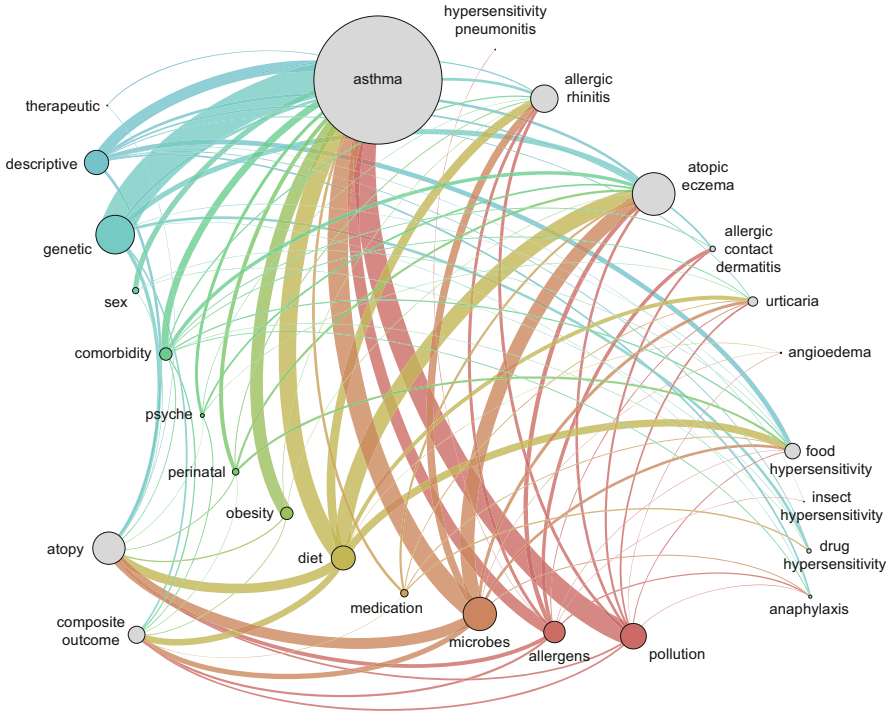

Fig. 1 Interrelations between indexed allergic diseases and topics form a systematic overview of systematic reviews in allergy epidemiology (Genuneit et al. 2017a). Bubble diameter is proportional to the number of systematic reviews with the respective index term. Line thickness is proportional to the number of systematic reviews dealing with the connected index terms. Colours are arbitrary: disease terms are shaded in grey, topics are shaded from blue/green to red, and lines are coloured corresponding to the topics

suspected or implicated in asthma development. The figure is seemingly dominated by systematic reviews on genetic factors which may be easier to conduct than those on other factors. Clearly, studies of migration from countries with low asthma prevalence to countries with high asthma prevalence prove the importance of environmental factors because prevalence is lower in immigrants than in natives of the host country and rises to a similar proportion with increasing length of residence (Cabieses et al. 2014). Moreover, the onset of the 'epidemic' of allergic diseases in western societies and their rising prevalence during urbanization suggest that non-genetic factors associated with such lifestyle may play a causal role in allergic disease development. Prominent epidemiological observations are the 'sibling effect' (Strachan 1989) and the 'farm effect' (von Mutius and Vercelli 2010) which gave rise to the 'hygiene hypothesis' (Strachan 2000) and later the 'biodiversity hypothesis' (Haahtela 2019). Future epidemiological research is required to evaluate and refine these hypotheses in light of the paradigm shift from atopic sensitization to barrier dysfunction with ever increasing options for environmental

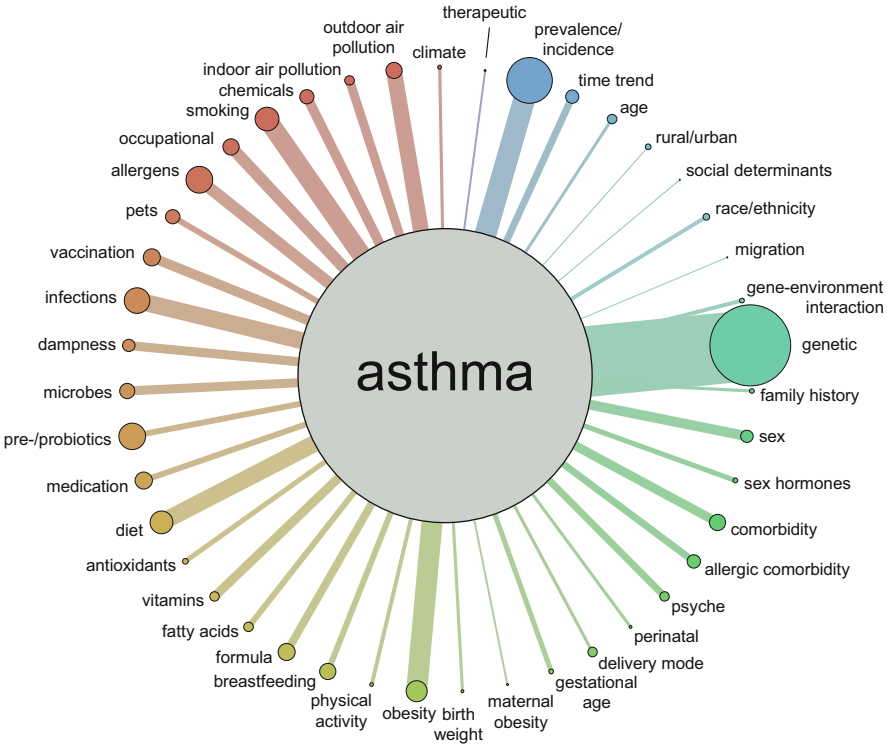

Fig. 2 Topics indexed along with asthma. Bubble diameter is proportional to the number of systematic reviews with the respective index term (based on all 421 systematic reviews on allergy epidemiology represented in Fig. 1, including non-asthma systematic reviews). Line thickness is proportional to the number of systematic reviews dealing with the connected index terms. Colours are arbitrary, covering the spectrum from blue to red in clockwise order

characterization, currently, e.g., 'omics'-techniques in microbiology and metabolism, and with ever increasing options for phenotyping of allergic techniques, including, e.g., high-resolution time series of symptoms using, e.g., sensing technologies.

References

Asher MI, Keil U, Anderson HR et al (1995) International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 8:483–491. https://doi.org/10.1183/09031936.95.08030483

Asher MI, Montefort S, Björkstén B et al (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 368:733–743. https://doi.org/10.1016/S0140-6736(06)69283-0

Belgrave DCM, Granell R, Simpson A, Guiver J, Bishop C, et al. (2014) Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med 11(10): e1001748. https://doi.org/10.1371/journal.pmed.1001748

Burney PG, Luczynska C, Chinn S, Jarvis D (1994) The European Community Respiratory Health Survey. Eur Respir J 7:954–960

Cabieses B, Uphoff E, Pinart M et al (2014) A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. PLoS One 9:e105347. https://doi.org/10.1371/journal.pone.0105347

Campbell DE, Mehr S (2015) Fifty years of allergy: 1965-2015. J Paediatr Child Health 51:91–93. https://doi.org/10.1111/jpc.12806

GBD 2015 Chronic Respiratory Disease Collaborators (2017) Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet Respir Med 5:691–706. https://doi.org/10.1016/S2213-2600(17)30293-X

Genuneit J, Seibold AM, Apfelbacher CJ et al (2017a) Overview of systematic reviews in allergy epidemiology. Allergy 72:849–856. https://doi.org/10.1111/all.13123

Genuneit J, Seibold AM, Apfelbacher CJ et al (2017b) The state of asthma epidemiology: an overview of systematic reviews and their quality. Clin Transl Allergy 7:12. https://doi.org/10.1186/s13601-017-0146-y

Greiner AN, Hellings PW, Rotiroti G, Scadding GK (2011) Allergic rhinitis. Lancet 378:2112–2122. https://doi.org/10.1016/S0140-6736(11)60130-X

Haahtela T (2019) A biodiversity hypothesis. Allergy 74:1445–1456. https://doi.org/10.1111/all.13763

Hill DA, Spergel JM (2018) The atopic march: critical evidence and clinical relevance. Ann Allergy Asthma Immunol 120:131–137. https://doi.org/10.1016/j.anai.2017.10.037

Lai CKW, Beasley R, Crane J et al (2009) Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 64:476–483. https://doi.org/10.1136/thx.2008.106609

Lundbäck B, Backman H, Lötvall J, Rönmark E (2016) Is asthma prevalence still increasing? Expert Rev Respir Med 10:39–51. https://doi.org/10.1586/17476348.2016.1114417

Martinez FD, Vercelli D (2013) Asthma. Lancet 382:1360–1372. https://doi.org/10.1016/S0140-6736(13)61536-6

Margolis JS, Abuabara K, Bilker W, Hoff stad O, Margolis DJ (2014) Persistence of mild to moderate atopic dermatitis. JAMA Dermatol 150:593–600

Papi A, Brightling C, Pedersen SE, Reddel HK (2018) Asthma. Lancet 391:783–800. https://doi.org/10.1016/S0140-6736(17)33311-1

Pawankar R, Canonica GW, Holgate ST et al (2013) The WAO White Book on Allergy (Update 2013). WAO, UK

Pearce N, Pekkanen J, Beasley R (1999) How much asthma is really attributable to atopy? Thorax 54:268

Pearce N, Aït-Khaled N, Beasley R et al (2007) Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 62:758–766. https://doi.org/10.1136/thx.2006.070169

Platts-Mills TAE (2015) The allergy epidemics: 1870-2010. J Allergy Clin Immunol 136:3–13. https://doi.org/10.1016/j.jaci.2015.03.048

Prescott S, Allen KJ (2011) Food allergy: riding the second wave of the allergy epidemic. Pediatr Allergy Immunol 22:155–160. https://doi.org/10.1111/j.1399-3038.2011.01145.x

Strachan DP (1989) Hay fever, hygiene, and household size. Br Med J 299:1259

Strachan DP (2000) Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 55(Suppl 1):S2–S10

Van Wonderen KE, Van Der Mark LB, Mohrs J et al (2009) Different definitions in childhood asthma: how dependable is the dependent variable? Eur Respir J 36:48–56. https://doi.org/10.1183/09031936.00154409

von Mutius E, Vercelli D (2010) Farm living: effects on childhood asthma and allergy. Nat Rev Immunol 10:861–868. https://doi.org/10.1038/nri2871

Weidinger S, Novak N (2016) Atopic dermatitis. Lancet 387:1109–1122. https://doi.org/10.1016/S0140-6736(15)00149-X

Weinmayr G, Genuneit J, Nagel G et al (2010) International variations in associations of allergic markers and diseases in children: ISAAC phase two. Allergy 65:766–775. https://doi.org/10.1111/j.1398-9995.2009.02283.x

Williams H, Flohr C (2006) How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 118:209–213. https://doi.org/10.1016/j.jaci.2006.04.043

Part II

General Mechanisms

Allergy: Type I, II, III, and IV

Edward F. Knol and Stefanie Gilles

Contents

Abstract

Hypersensitivity reactions are overreactions of the immune system clinically seen as allergic and autoimmune diseases. Gell and Coombs originally described four different types of hypersensitivity reactions almost 60 years ago, and their description still applies in large parts. However, some modifications and extensions have been included in original definition. Especially in allergic diseases, it became clear that often, multiple types of hypersensitivity reaction can occur simultaneously. This improved insight is not only important for a better understanding of hypersensitivity disorders, but is especially of importance for improved diagnostics and directing therapeutic interventions.

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Keywords

Allergy · Gell and Coombs · Hypersensitivity

1 Introduction

In many inflammatory diseases an overreacting immune system is the underlying pathomechanism. Both cellular and humoral players interact in different manners to cause tissue damage. Most (but not all) of these reactions are directed against harmless or self-antigens and are referred to as hypersensitivity reactions. It was in 1963 that Philip Gell and Robert Coombs (Gell and Coombs 1963) developed a classification of four different types of hypersensitivity reactions. Although many immunological processes, including MHC-restriction, role of cytokines, and even IgE (Bennich et al. 1968), have been discovered in the almost 60 years thereafter, this simple classification is still used. The four types of hypersensitivity reactions do not only describe the immunological pathomechanism for allergy, including drug allergies, but also for many autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, myasthenia gravis, and response to infectious agents, such as poststreptococcal glomerulonephritis. Both for diagnostics and for therapeutic interventions, it is important to recognize the relevant type of hypersensitivity reaction in a specific disease. In this chapter the immune players, and their interactions, in the type I-IV hypersensitivity reactions will be described. In addition, the limitations and challenges of the Gell and Coombs's classification in allergic disease will be discussed, taken our recent insights into account. Finally, we will take a closer look into hypersensitivity reactions involved in chronic atopic diseases and viral infections.

2 Immune Players in Type I, II, III, and IV Hypersensitivity Reactions

The Coombs and Gell's classification divides hypersensitivity reactions into four pathophysiological types, namely the immediate (type I), cytotoxic (type II), immune complex-mediated (type III), and delayed hypersensitivity (type IV) reactions. The different pathophysiological mechanisms lead to varying latency periods for the four classes: type I allergic symptoms appear already after a few seconds to minutes; symptoms of type II reactions appear after minutes to hours; signs of type III reactions set in after a few hours; and finally, for type IV reactions, a long latency of 2–3 days is typical. Of note, the sensitization phase preceding all hypersensitivity reactions takes much longer and might have occurred many years before. The sensitization phase will not be discussed here.

Type I hypersensitivity reactions refer to the acute allergic reaction that takes place after an allergen challenge. The most important humoral player is allergen-specific immunoglobulin E (IgE), which is induced in a T helper-2 milieu associated with diseases of the atopy spectrum, such as allergic rhinitis, allergic asthma, food

allergies, atopic dermatitis, and anaphylaxis. Allergen-specific IgE is bound via its Fc-tail to high-affinity Fc receptors (FcεRI) on mast cells in tissue and basophils in blood. Allergen binding to multiple IgE molecules on mast cells and basophils, so-called IgE crosslinking, will activate these cells and result in degranulation and immediate release of several pre-formed inflammatory mediators, including histamine, leukotrienes, and prostaglandins (Kay 2001). This leads to itch and edema at the site of allergen exposure, which accounts for the well-known allergic symptoms, i.e. itch (allergic rhinitis, conjunctivitis, atopic dermatitis), sneezing and runny nose (allergic rhinitis), redness of eyes (allergic conjunctivitis), abdominal pain and diarrhea (food allergy), wheeze and difficulty breathing (asthma), or sudden loss in blood pressure (anaphylaxis). In addition, mast cells and basophils will release inflammatory cytokines and chemokines. These can be prestored, such as TNF-α, or newly sensitized, such as IL-4, IL-13 and RANTES/CCL-5 (Varricchi et al. 2018). The cytokines and chemokines regulate the so-called delayed allergic response after mast cell and basophil activation that starts about 8 h after the initial early response and is also more prolonged. In this late phase response, a marked cellular infiltrate is found at the site of mast cell degranulation, including T cells, eosinophils, basophils, and macrophages as the most prominent cells. These are not part of the type I hypersensitivity response and we will come to them later.

The *type II, cytotoxic, hypersensitivity* reaction is mainly driven by IgG as well as IgM antibodies, which bind to specific structures on the body's own cells. The most common pathomechanism in type II hypersensitivity reactions is the opsonization of the antigen-bearing cell with antibodies, followed by phagocytosis or destruction. This can be via two mechanisms: either via antibody-dependent cellular cytotoxicity (ADCC) involving mostly neutrophils, macrophages, and NK cells or via classical (antibody-mediated) complement activation. Some examples of type II hypersensitivity driven diseases are autoimmune hemolytic anemia with erythrocyte membrane proteins as target antigens, autoimmune thrombocytopenic purpura with platelet membrane proteins as target antigens, or pemphigus vulgaris with proteins of epidermal intercellular junctions as target antigens.

Not all type II hypersensitivity reactions necessarily result in direct cell death. In some instances, binding of an autoreactive antibody to a cellular receptor can also change its function, either by activating or by blocking it. In this case, the resulting pathophysiology is triggered by the altered receptor function. An example for such a type II hypersensitivity reaction is myasthenia gravis, where the acetylcholine receptor is targeted by autoantibodies, which inhibits binding of acetylcholine to the receptor, resulting in muscle weakness. Another example is Graves' disease, in which autoantibody binding to the thyroid-stimulating hormone (TSH) receptor leads to chronic receptor stimulation and hyperthyroidism. Because the receptor binding antibodies are different from the antibodies mediating cell death, these reactions are now also classified as type V hypersensitivity reactions (Basu and Banik 2018).

Type III hypersensitivity reactions are, like type II reactions, mediated by IgG or IgM antibodies. In contrast to type II, however, the antibodies are now part of larger order antigen-antibody complexes, the so-called *immune complexes*. Immune

complexes are a normal system to remove antigens from the circulation. However, in the situation of access antigen, too many and relatively large immune complexes can form micro-precipitates on the endothelium of small vessels, e.g. in microvasculature of the skin and kidneys. These precipitates ultimately cause tissue damage and vessel obstruction via local complement activation, initiation of the clotting cascade, and attraction of inflammatory cells, i.e. neutrophils, macrophages, and platelets. In systemic lupus erythematosus (SLE), immune complexes are directed against self-DNA and nucleoproteins released after cell death, leading to nephritis, arthritis, and vasculitis. Poststreptococcal glomerulonephritis is caused by streptococcal cell wall antigens and often occurs after the primary infection has been cleared. Pneumonitis can be caused by antigens forming local immune complex precipitates from pigeons and hay dust or mold spores causing pigeon-breeder's lung or farmer's lung, respectively.

Type IV, delayed type, hypersensitivity (DTH) reactions are unique in that antibodies do not play a primary role, although often elevated antibody levels, secondary to disease development, can be detected. Central in DTH responses are T lymphocytes that kill antigen-displaying cells or secrete cytokines, mainly TNF-α, IFN-γ, and IL-17. Type IV hypersensitivity reactions are part of the pathophysiology of many classical autoimmune diseases in which self-reactive T cells recognize auto-antigens, e.g. myelin basic protein in multiple sclerosis or glutamate decarboxylase and islet-specific glucose-6-phosphatase catalytic subunit-related protein in type 1 diabetes. Even in many well-known autoimmune diseases the relevant T cell antigen is not clearly known yet, as for example in rheumatoid arthritis, where autoreactive T cells might target collagen or citrullinated self-proteins.

Some well-known examples of DTH reactions typically referred to as "delayed-type allergic responses" or "allergic contact dermatitis" involve the skin. The antigens that are recognized in allergic contact dermatitis are typically small molecules, such as nickel ions, acrylates, or topical antibiotics, which form haptens, i.e. covalent complexes of the molecules with cellular proteins that make up the antigenic surface. After about 48 h an induration with redness and swelling at the site of challenge is seen. Histopathologically, at 48–72 h, a perivascular mononuclear infiltrate in the dermis is found consisting of macrophages and $CD4^+$ T cells. If a DTH reaction is very severe or becomes chronic, a granulomatous inflammation can develop locally. To test for allergic contact dermatitis, an epicutaneous test ("patch test") is performed, in which the suspected allergen is applied within a carrier (e.g., Vaseline) to the skin by means of a "Finn Chamber" which is then covered by a patch. After 48 and 72 h, the doctor reads the result. Local erythema, swelling, and edematous papules, indicative for contact dermatitis, are mainly the result of infiltrating antigen presenting cells (APCs), phagocytes, and T cells as well as localized apoptosis of hapten-displaying cells.

Apart from the skin, also the airways are occasionally the target of DTH reactions, as in some forms of occupational asthma, e.g. to epoxy chemicals. DTH reactions of the airways are usually secondary to DTH reactions of the skin, and sensitization to contact allergens is thought to occur mainly via the skin. Therefore, patch tests can usually help to diagnose DTH reactions even if they affect the lung. Ultimately, a

bronchial challenge has to be performed in addition to confirm that the contact allergen is indeed the asthma trigger.

3 Limitations and Challenges of the Gell and Coombs's Classifications

When looking in detail into players of the immune system and mechanisms involved in different diseases it becomes clear that many diseases do not strictly follow one specific type of hypersensitivity reaction but combinations of different types, mostly in different phases of the disease. This is also the case in many allergic diseases, as exemplified below.

In drug allergy many different types of hypersensitivity reactions can occur (Coombs and Gell 1968; Descotes and Choquet-Kastylevsky 2001) . Most common are the type I reactions, driven by drug-specific IgE antibodies, and type IV reactions, driven by drug-specific T cells. These can even occur simultaneously in the same patient (DiFonzo et al. 1999). Even for an individual drug the response per patient can be composed of each of the four types of hypersensitivity reactions. Penicillin reactions can develop in immediate hypersensitivity due to pre-formed IgE antibodies, following a typical type I reaction pattern, in hemolytic anemia due to type II reactions and in serum sickness-like reactions due to immune complexes as in type III hypersensitivity. In addition, a late onset skin rash due to a DTH reaction can be the result of type IV hypersensitivity to penicillin. Other antibiotics may also trigger different types of hypersensitivity reactions (Vervloet et al. 1999).

4 Challenges in Allergic Inflammatory Reactions

In allergic diseases it has become clear that, especially in the more chronic phases of disease, the typical type I hypersensitivity mechanisms do not really apply. Important indications for this came from intervention studies. In development of cat allergen peptide immunotherapy is became clear that the late phase allergic reactions after peptide injections were independent of IgE and were major-histocompatibility complex (MHC) restricted. This indicates that APCs and T cells were sufficient to induce the allergic inflammatory reactions (Haselden et al. 1999). By attempts to treat allergic diseases with an anti-IgE antibody (omalizumab) it became clear that even long-term depletion of IgE has only limited effects; in allergic asthma, only about one third of patients responded to the IgE blockade with life-transforming effects, such as being able to withdraw from corticosteroids. One third had clinically less beneficial outcomes, and another third experienced no response to anti-IgE treatment at all (Holgate 2012). In atopic dermatitis the blockade of IgE by omalizumab has not extensively been examined. It seems that, overall, there is even less clinical benefit of IgE depletion in atopic dermatitis, although one cannot rule out that this might be due to the pharmacological limitation of omalizumab to block high IgE serum levels (Wang et al. 2016). The limited effects of omalizumab

in treating allergic asthma and atopic dermatitis are indicative of the complex immune dysregulation other than IgE as the primary pathogenic mechanism.

Other intervention studies have shown that blockade of the Th2 cytokines IL-4 and/or IL-13 might have more pronounced effects. This is demonstrated by blocking IL-4 and IL-13 binding to the shared IL-4-receptor-α chain by dupilumab in atopic dermatitis. Effects are significant, they are not related to IgE levels and occur well before IgE levels have been reduced in serum (Beck et al. 2014). Further results indicate that the main pathomechanism at play in chronic atopic dermatitis is most probably mediated by cytokines derived from infiltrating Th cells of diverse subsets and are largely independent of IgE-mediated responses.

Even classical DTH reactions have been observed in atopic dermatitis patients with IgE sensitizations after applying patch tests with the relevant allergen to the skin (Mitchell et al. 1982). The results of these experimental challenge studies stress the role of skin resident APCs and T cells. In a somewhat challenging statement one might hypothesize therefore that in chronic allergic inflammatory reactions, IgE is only an indicator of the Th2 activity.

Does this mean that in allergy the role of IgE is very limited? This is certainly not the case. IgE-allergen interactions are still crucial in the acute allergic reaction, as can be seen, e.g., in food allergic reactions or anaphylaxis. In addition, there is an important extra role of IgE, which, apart from its Fc-mediated binding to mast cells and basophils, is related to binding via its Fc-part to Fcε-receptors on antigen presenting cells (van Neerven et al. 2006). In atopic dermatitis patients it was demonstrated that IgE was not only bound to dermal mast cells but also to epidermal Langerhans cells (Bruijnzeel-Koomen et al. 1986). The function of allergen-specific IgE on antigen presenting cells is to facilitating allergen uptake, processing and presentation to T cells. Binding of IgE to FcεRs makes the antigen presenting cell approximately 100-fold more sensitive to pick up minute amounts of allergens and present this to T cells (Mudde et al. 1990). Overall, there is evidence that, at least in atopic dermatitis, immune players from both type I (IgE) and type IV hypersensitivity (antigen presenting cells and T cells) are involved in the pathogenesis (Leung 2000). Thus, while it is clear that in chronic allergic diseases, such as atopic dermatitis, the MHC class II-restricted presentation of allergen-derived peptides to T cells by APCs is crucial, there is still a difference to "classical" DTH reactions. Here, the reactive T cells are cytotoxic and/or Th1 cells, producing mainly IFN-γ, whereas in chronic atopic diseases, the T cells are mainly Th2 and will release IL-4, IL-5, and IL-13 (Kay 2001). To include this reaction type in the Gell and Coombs's classifications, Pichler introduced therefore an additional hypersensitivity reaction, namely Type IVb, which is related to eosinophilic inflammation and a Th2 response, characterized by IL-4, IL-5, and IL-13 (Pichler et al. 2010).

5 Hypersensitivity Reactions to Viruses

In the light of the present coronavirus pandemic, there is another emerging aspect of the concept of hypersensitivity, namely hypersensitivity to viruses. Hypersensitivity to a pathogenic microbe appears anachronistic at first glance, since the very function of the immune system is to defend the host against microbial infections.

However, several pathogenic viruses are known to trigger hypersensitivity reactions directed against the virus itself. The best-known phenomenon of hypersensitivity against viruses is antibody-dependent enhancement (ADE) (Lee et al. 2020). ADE is dependent on virus-specific antibodies, usually of IgG isotype, which classifies it as a type II hypersensitivity reaction (or type III, if larger immune complexes are involved). It is mediated via IgG-FcγRIIa interactions, and the IgG antibodies involved are often non-neutralizing types. Apart from mediating enhanced phagocytosis of IgG-opsonized virus particles, engagement of FcRs can trigger the activation of downstream effector functions, such as ADCC or excess cytokine secretion, which in turn causes immune pathology. ADE has been demonstrated for Ebola virus (Takada et al. 2001) and HIV infection (Robinson Jr et al. 1988), but it is also observed with many other viruses, whether macrophage-tropic or not, including respiratory viruses such as RSV (van Erp et al. 2019) and Influenza virus (Ochiai et al. 1992). Finally, the "cytokine storm" associated with severe COVID-19 could be indicative of ADE via enhanced immune activation. Higher antibody titers against SARS-CoV-2 appear to be associated with more severe COVID-19 (Zhao et al. 2020), whereas strong T cell responses are found across all, asymptomatic, symptomatic, and severe cases (Mathew et al. 2020; Sekine et al. 2020). However, whether ADE is indeed associated with SARS-CoV-2 infection is still subject to research, and more dedicated in vivo studies are needed (Fig. 1).

6 Conclusion

Hypersensitivity reactions are responsible for various immune pathologies, i.e. autoimmunity and allergy. However, they can also be the unwanted by-product of protective anti-microbial immune responses, which is why they also have to be considered when confronted with immediate or long-term clinical complications after viral and bacterial infections.

The classification of hypersensitivity reactions by Gell and Coombs has been of great importance in our understanding the interactions of different immune players with external- and auto-antigens. However, since this original classification our knowledge of the inflammatory diseases involving hypersensitivity reactions has increased tremendously, mainly due to experiences gained from treatments with biologicals that selectively inhibit individual immune players. This has increased our understanding of the limitations and challenges of the Gell and Coombs classification. The current modified Gell and Coombs classification of hypersensitivity reactions is of help not only in diagnostics, but also in selecting treatment options.

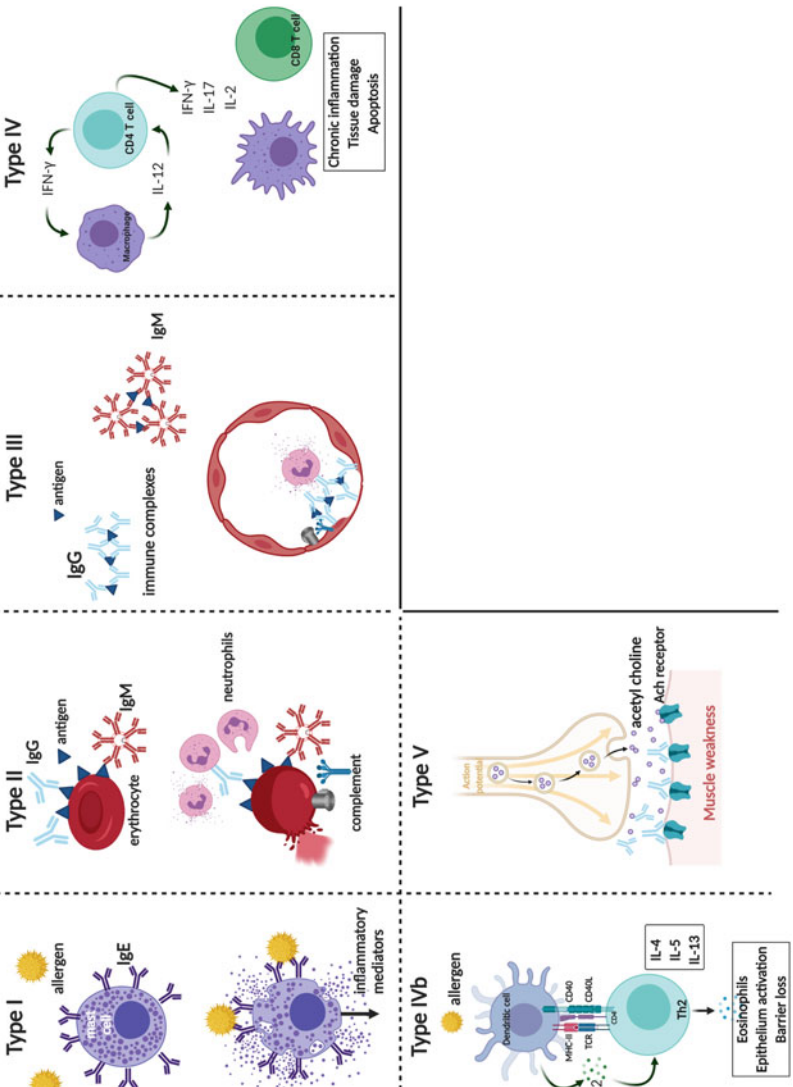

Fig. 1 Modified Gell and Coombs classification. Antigens can induce many different hypersensitivity reactions. Type I hypersensitivity reactions are IgE-mediated. Cross-linking of high-affinity IgE receptors (FcεRI) by IgE-antigen complexes on mast cells and basophils leads to degranulation and release

of mediators, which cause a variety of symptoms. Type II reactions are IgG- or IgM-mediated, and cause cell destruction due to interaction with Fcγ receptor–bearing neutrophils, NK cells or macrophages. Type II reactions also include the activation or inhibition of cellular receptors by specific autoantibodies and are then often referred to as Type V reactions. Type III reactions are also IgG or IgM mediated. Immune complexes cannot be cleared and precipitate in the microvasculature. This leads to complement deposition and activation in small vessels and recruitment of neutrophils and their activation via IgG-FcγR interaction, resulting in the so-called "frustrated phagocytosis" and release of tissue damaging products. In addition, local complement activation also results in tissue damage. Type IV reactions correspond to Th1 reactions with high IFNɣ secretion and involve monocyte/macrophage activation. CD8 cell involvement often occurs. Type IVb reactions correspond to chronic allergic inflammation with Th2 responses with high IL-4/IL-5/IL-13 and eosinophilic inflammation; they are often associated with an IgE-mediated type I reaction. More information can be found in Abbas et al. (2018), Kumar et al. (2018), MacPherson and Austyn (2012), Pichler et al. (2010) Created with BioRender.com

References

Abbas AK, Lichtman AH, Pillai S (2018) Hypersensitivity disorders. In: Abbas AK, Lichtman AH, Pillai S (eds) Cellular and molecular immunology, 9th edn. Elsevier, Philadelphia, pp 437–457

Basu S, Banik BK (2018) Hypersensitivity: an overview. Immunol Curr Res 2(1):105

Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR (2014) Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 371(2):130–139

Bennich HH, Ishizaka K, Johansson SG, Rowe DS, Stanworth DR, Terry WD (1968) Immunoglobulin E: a new class of human immunoglobulin. Immunology 15(3):323–324

Bruijnzeel-Koomen CAFM, van Wichen DF, Toonstra J, Berrens L, Bruijnzeel PL (1986) The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. Arch Dermatol Res 278(3):199–205

Coombs RRA, Gell PGH (1968) Classification of allergic reactions responsible for drug hypersensitivity reactions. In: Coombs RRA, Gells PGH (eds) Clinical aspects of immunology, 2nd edn. Davis, Philadelphia, pp 575–596

Descotes J, Choquet-Kastylevsky G (2001) Gell and Coombs's classification: is it still valid? Toxicology 158(1-2):43–49

DiFonzo M, Romano A, Quarantino D, Papa G, Viola M (1999) Type-I allergy to cephaloridine and type IV allergy to ampicillin in the same subject: a case report. Allergy 54(S. 52):199

Gell PGH, Coombs RRA (1963) The classification of allergic reactions underlying disease. In: Coombs RRA, Gells PGH (eds) Clinical aspects of immunology. Blackwell, Oxford

Haselden BM, Kay AB, Larché M (1999) Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. J Exp Med 89 (12):1885–1894

Holgate ST (2012) Trials and tribulations in identifying new biologic treatments for asthma. Trends Immunol 33(5):238–246

Kay AB (2001) Allergy and allergic diseases. First of two parts. N Engl J Med 344(1):30–37

Kumar V, Abbas AK, Aster JC (2018) Diseases of the immune system. In: Kumar V, Abbas AK, Aster JC (eds) Robbins basic pathology, 10th edn. Elsevier, Philadelphia, pp 121–188. https://www-clinicalkey-com.proxy.library.uu.nl/#!/browse/book/3-s2.0-C20140017194. Accessed 3 Jun 2020

Lee WS, Wheatley AK, Kent SJ, DeKosky BJ (2020) Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol 5(10):1185–1191

Leung DY (2000) Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 105(5):860–876

MacPherson GG, Austyn JM (2012) Immunity, disease and therapy. In: MacPherson GG, Austyn JM (eds) Exploring immunology. Concepts and evidence, 1st edn. Wiley-Blackwell, Augsburg, pp 259–312

Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-Cervantes L, Pampena MB, D'Andrea K, Manne S, Chen Z, Huang YJ, Reilly JP, Weisman AR, Ittner CAG, Kuthuru O, Dougherty J, Nzingha K, Han N, Kim J, Pattekar A, Goodwin EC, Anderson EM, Weirick ME, Gouma S, Arevalo CP, Bolton MJ, Chen F, Lacey SF, Ramage H, Cherry S, Hensley SE, Apostolidis SA, Huang AC, Vella LA, UPenn COVID Processing Unit, Betts MR, Meyer NJ, Wherry EJ (2020) Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 369(6508):eabc8511

Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TA (1982) Basophils in allergen-induced patch test sites in atopic dermatitis. Lancet 1(8264):127–130

Mudde GC, Van Reijsen FC, Boland GJ, de Gast GC, Bruijnzeel PL, Bruijnzeel-Koomen CA (1990) Allergen presentation by epidermal Langerhans' cells from patients with atopic dermatitis is mediated by IgE. Immunology 69(3):335–341

Ochiai H, Kurokawa M, Matsui S, Yamamoto T, Kuroki Y, Kishimoto C, Shiraki K (1992) Infection enhancement of influenza A NWS virus in primary murine macrophages by anti-hemagglutinin monoclonal antibody. J Med Virol 36:217–221

Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D (2010) Drug hypersensitivity reactions: pathomechanism and clinical symptoms. Med Clin North Am 94(4):645–664

Robinson WE Jr, Montefiori DC, Mitchell WM (1988) Antibody-dependent enhancement of human immunodeficiency virus type 1 infection. Lancet 1:790–794

Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, Llewellyn-Lacey S, Kamal H, Bogdanovic G, Muschiol S, Wullimann DJ, Kammann T, Emgård J, Parrot T, Folkesson E, Karolinska COVID-19 Study Group, Rooyackers O, Eriksson LI, Henter JI, Sönnerborg A, Allander T, Albert J, Nielsen M, Klingström J, Gredmark-Russ S, Björkström NK, Sandberg JK, Price DA, Ljunggren HG, Aleman S, Buggert M (2020) Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 183 (1):158–168.e14

Takada A, Watanabe S, Okazaki K, Kida H, Kawaoka Y (2001) Infectivity-enhancing antibodies to Ebola virus glycoprotein. J Virol 75:2324–2330

van Erp EA, Feyaerts D, Duijst M, Mulder HL, Wicht O, Luytjes W, Ferwerda G, van Kasteren PB (2019) Respiratory syncytial virus infects primary neonatal and adult natural killer cells and affects their antiviral effector function. J Infect Dis 219(5):723–733

van Neerven RJ, Knol EF, Ejrnaes A, Würtzen PA (2006) IgE-mediated allergen presentation and blocking antibodies: regulation of T-cell activation in allergy. Int Arch Allergy Immunol 141 (2):119–129

Varricchi G, Raap U, Rivellese F, Marone G, Gibbs BF (2018) Human mast cells and basophils-how are they similar how are they different? Immunol Rev 282(1):8–34

Vervloet D, Pradal M, Castelain M (1999) Antibiotics, antiviral, antifungal drugs. In: Vervloet D, Pradal M, Castelain M (eds) Drug allergy. Pharmacia & Upjohn, pp 53–104

Wang H, Li Y, Huang Y (2016) Efficacy of Omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. J Allergy Clin Immunol 138(6):1719–1722

Zhao J et al (2020) Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa344

Cutaneous Barriers and Skin Immunity

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Contents

Abstract

The skin barrier provides us with several lines of protection from outside hazards. Its most outward layers, the stratum corneum and the epidermis seal our body with an acidic, dry, and rather cool surface, hostile to microbes. Yet, there are also fine-tuned interactions between the mostly commensal microbiota on top of the

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skin surface, with underlying epidermal cells as well as the immune system, to preserve a healthy steady state and to initiate repair processes when necessary. We take a concise look at the recent insights on the inner workings of this complex barrier.

Keywords

Immunity · Microbiome · Skin barrier · Staphylococcus

1 Introduction

The skin is one of the largest organs of our body and constitutes the first defense line against environmental aggressors. Perhaps the most important function of the skin is to form a barrier, which protects human and animal beings from chemical, physical, and microbial havoc. Compromised integrity of this barrier, e.g. by trauma or infection, leads to often severe pathologies, which are counteracted by complex measures like wound repair or anti-infective immune reactions.

2 Factors Shaping Epithelial Barriers

2.1 Building Up the Frontline: Stratum Corneum Proteins, Lipids, and pH

The barrier function of the skin largely depends on the uppermost epidermal layer, the stratum corneum. During cornification, keratinocytes from lower skin layers are transformed into anucleated flattened corneocytes which are embedded in a highly organized lipid matrix. They get surrounded by an insoluble protein structure, the *cornified envelope* (CE), which serves as a scaffold for the attachment of lipids (Candi et al. 2005). Besides proteins like involucrin or loricrin, filaggrin (FLG) is particularly important for CE formation. During cornification, proFLG is dephosphorylated and proteolyzed into small FLG monomers. These bind to keratin intermediate filaments and cause their aggregation into tight bundles promoting the collapse of the cell into a flattened shape (Candi et al. 2005; Sandilands et al. 2009). Corneocyte caspase-14 degrades FLG to free amino acids, a natural moisturizing factor crucial for maintaining epidermal hydration (Kezic et al. 2009; Hoste et al. 2011). Epidermal *lipids* are essential for skin barrier function as they embed the corneocytes in the stratum corneum. The sebaceous glands create the skin's water-lipid mantle that limits transcutaneous water and electrolyte loss (Feingold 2009). Ceramides, cholesterol, and free fatty acids are equally abundant epidermal lipids (Pappas 2009). The stratum corneum is acidified to *pH* 4 to 6, e.g. by generation of free fatty acids by secretory phospholipase A2 or active proton transport to the extracellular compartment (Panther and Jacob 2015), inhibiting growth of pathogenic microbes such as *Staphylococcus aureus* and *Candida albicans* (Feingold 2009) (Fig. 1a). Atopic eczema (AE) is among the most frequent chronic

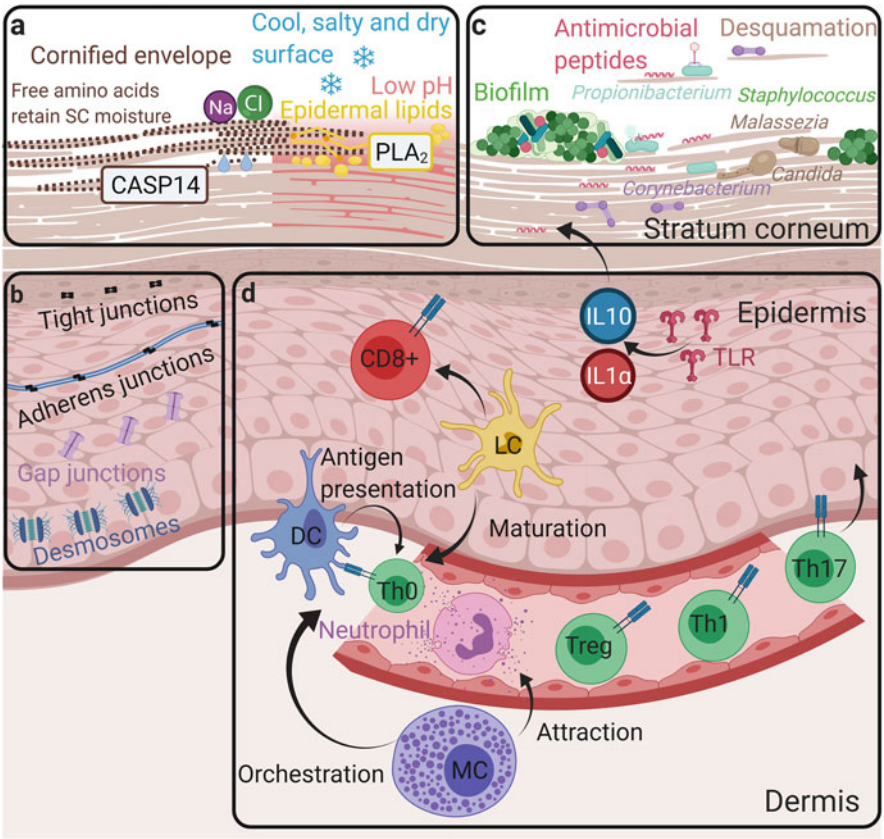

Fig. 1 The skin barrier. (**a**) The stratum corneum barrier. The cornified envelope (CE) serves as a scaffold for the attachment of lipids, which are partially hydrolyzed by secretory phospholipase A2 (PLA_2) to free fatty acids that contribute to the low skin pH. Caspase (CASP) 14 degrades CE filaggrin to free amino acids that retain moisture. The overall cool, salty, dry, and low pH skin surface is a hostile habitat for microbial life. (**b**) The nucleated epidermis barrier. Different types of junction proteins and desmosomes seal the intercellular space between epidermal cells while also enabling the exchange of selected molecules. (**c**) The skin microbiome. Bacteria, their phages, and yeasts populate the skin surface. Formation of biofilms protects them from antimicrobial immunity. Skin microbes are continuously shed of by desquamation. (**d**) Skin Immunity. Microbes are sensed by toll like receptors (TLR), leading to antimicrobial peptide secretion and immune cell recruitment. Langerhans cells (LC) maturate naïve T helper (TH) cells, aided by dendritic cell (DC) antigen presentation and mast cells (MC): orchestrating the immune response. Created with BioRender.com

inflammatory skin diseases, affecting 10–20% of children and 2–5% of adults in industrialized countries (Yamazaki et al. 2017). It is clearly associated with dysregulation of FLG, ceramides, and skin acidity (Jungersted et al. 2008).

2.2 Equally Important: Barrier Proteins of the Nucleated Epidermis

Tight junctions (TJs) are close contacts between the plasma membranes of neighboring epithelial and endothelial cells. They mainly regulate the paracellular permeability (Gruber et al. 2015). TJs form complex structures of interacting transmembrane proteins including claudins (Cldn), occludin (Ocln), as well as cytoplasmic plaque proteins like zona occludens proteins. The transmembrane proteins allow passive selective diffusion of ions and small hydrophilic molecules along concentration gradients. Cldn proteins are indispensable for the formation of intramembrane strands and determine tissue-specific permeability properties. They consist of two extracellular loops which determine the junctional ion selectivity (Cummins 2011). In pre-clinical animal studies, the knockout of Cldn-1/5/7/18 is associated with tissue dysfunction, e.g. water imbalance, inflammation, or cancer. The knockout of Cldns such as Cldn-2, −15, or −19 leads to metabolic disorders (Tsukita et al. 2019). An impaired skin barrier function has also been found in the context of altered *adherens junction* formation and desmosomes. *Gap junctions* (GJs) form conduits between adjacent cells and allow the passage of ions and small molecules, enabling direct intercellular communication. They are composed of connexin protein subunits that homo- or heterodimerize on the plasma membrane to form connexons (Proksch et al. 2008). Their importance in barrier function is highlighted by patients with missense mutations that cause Vohwinkel syndrome (connexin 26) or the Clouston syndrome (connexin 30) (Richard 2005) (Fig. 1b). *Keratins* are major structural proteins in keratinocytes. Lending structural stability and flexibility to keratinocytes they maintain the integrity of the skin (Proksch et al. 2008; Chamcheu et al. 2011).

3 Epithelial Microbiome and Its Interactions

3.1 Healthy Skin Microbiome

The human skin is populated by diverse commensal microbiota, including bacteria, archaea, eukaryotes (fungi, mites), and viruses. Host factors such as age or gender shape the skin ecosystem and thereby microbiota composition (Schommer and Gallo 2013). Distinct skin ecological niches are colonized by different microbial communities. Despite the constant exposure to environmental factors, adult skin microbiota remain relatively stable overtime. Ribotyping (see also II.4.1. Microbiome of Barrier Organs in Allergy - Who runs the world? Germs! Microbiome sequencing and analysis) of bacteria from various clinical niches revealed at least 19 phyla (prominently *Actinobacteria*, *Firmicutes*, *Proteobacteri*a, and *Bacteroidetes*) and around 204 genera, of which *Propionibacteria, Corynebacteria,* and *Staphylococci* were most abundant. The abundance of each genus is strongly influenced by the ecological characteristics of the local niche. *Propionibacteria* and *Staphylococci* predominate on sebaceous sites (e.g., forehead)

while *Corynebacteria* prevailed on moist sites (e.g., armpit), although *Staphylococci* are also represented. The microbiome of dry sites (volar forearm) is most diverse, with a greater prevalence of *β-Proteobacteria* and *Flavobacteriales* (Grice et al. 2009). In contrast, fungi contribute less than 1% of skin microbiome members. *Malassezia* colonizing sebaceous regions (ears, forehead) contribute more than 90% to the fungal skin microbiome (Oh et al. 2014). Low numbers of *Demodex* mites populate healthy skin as well (Balato et al. 2018). Metagenomics studies identified a large viral population of the skin, mainly composed of *Propionibacterium* and *Staphylococcus* specific bacteriophages (Hannigan et al. 2015) (Fig. 1c).

3.2 Host–Microbiome Interactions

The microbial inhabitants of human skin have co-evolved with their host to form relationships that can range from mutualistic over saprophytic to pathogenic. This depends largely on host status and microbiota composition (Christensen and Brüggemann 2014). Most microbes profit from homeostasis, while training cutaneous immunity and otherwise protecting their host from invading pathogens in turn (Schommer and Gallo 2013; Meisel et al. 2018). The skin controls the growth of its residents by physically limiting microbial penetration but also through its constant desquamation leading to their removal. Additionally, low temperature, pH, dryness, and saltiness prevent growth of many microorganisms (Oh et al. 2014).

3.3 The Microbiome in Skin Disorders

Many studies have linked microbiome alterations with skin diseases like AE, psoriasis, or acne. However, it is often still controversial whether skin dysbiosis is a result or cause of such illnesses (Lynch et al. 2016). Therefore, current human microbiome studies aim to gather large datasets to better understand the role of the microbiome and ultimately to develop new therapeutic strategies (Nelson et al. 2010). Microbial dysbiosis may result from genetic predisposition, current infections or antibiotic therapy, resulting in aberrant immune responses that compromise the epithelial barrier integrity and allow penetration of microbial antigens. Prolonged antigen exposure may further dysregulate immune responses, eventually resulting in chronic inflammation (Balato et al. 2018). Reduced microbiome diversity and *S. aureus* colonization are observed in over 90% of AE patients (Grice and Segre 2011). *S. aureus* penetrating the epidermis induces the release of several Th2 cytokines and secretion of serine proteases like kallikreins, degrading filaggrin and desmoglein-1, thus further compromising skin barrier integrity (Williams et al. 2017). Other Staphylococci, e.g., *S. epidermidis* also increase on AE lesions, repressing other genera (Kong et al. 2012). *Psoriasis*, another skin inflammatory disorder is characterized by increased keratinocyte proliferation, cutaneous immune infiltration, angiogenesis, and hyperkeratosis (Schommer and Gallo 2013). In contrast to AE, an increased alpha-diversity is observed on psoriatic lesions, with

increased *Firmicutes* and decreased *Actinobacteria*, especially *Propionibacteria* (Langan et al. 2019) (see also II.4.3. Microbiome of Barrier Organs in Allergy - Who runs the world? Germs! The skin microbiome and allergy).

4 Skin Immunity and Tissue Repair

The immune barrier of the skin orchestrates the defense against invading pathogens and is in constant dialogue with commensal microbiota (Skabytska et al. 2016; Eyerich et al. 2018).

4.1 Innate Immunity

The skin senses microbial signals by different pattern recognition receptors like toll like receptors (TLRs), resulting in distinct patterns of gene expression and activation of various immune responses (Meisel et al. 2018). This way, expression of innate factors such as IL1a, or secretion of *antimicrobial peptides* (AMPs) like cathelicidins and β-defensins by keratinocytes and sebocytes is regulated (Chen et al. 2018). Furthermore, pathogens such as *S. aureus* trigger their subsequent elimination by attracting neutrophils (Yamazaki et al. 2017). Besides, yeast commensals such as *Malassezia* are able to induce a type 17 response orchestrating antifungal immunity and exacerbating skin inflammation (Sparber et al. 2019). A recent study analyzed the impact of microbiota on skin transcriptomes of mice and identified a total of 2,820 differentially expressed genes mainly involved in host innate immunity and epidermal differentiation (Meisel et al. 2018). On the other side, many skin residents have evolved strategies to evade host defenses. *S. epidermidis* biofilm associated polysaccharides protect it from soluble factors and phagocytosis (Christensen and Brüggemann 2014). Resistance to AMPs is also mediated by various proteases or AMP inhibitors.

Epidermal antigens are presented to T cells by *Langerhans cells* (LCs), a skin exclusive antigen presenting cell type. Maturated LC maturate naive Th cells to various Th subtypes depending on the surrounding milieu. They mount effective $CD8^+$ T cells responses to viral infections and also are essential for hypersensitivity reactions that drive expulsion of leishmania as well as contact dermatitis. They are also responsible for mounting allergic reactions to lipid antigens via nonconventional MHC molecule CD1a presentation (Kim et al. 2016). *Dermal dendritic cells* (dDCs) complement the LCs by presenting dermal antigens. They provide immune-surveillance against invading pathogens and are able to secrete amounts of TNF-α but are also assumed to contribute to the genesis of psoriasis (Matejuk 2018). *Mast cells* (MC) are mainly located in the upper dermis. Well known for their detrimental role in Th2 autoimmunity and allergy, they are increasingly appreciated as orchestrators of adequate inflammatory responses (Fig. 1d). Upon infection, they initiate recruitment of neutrophils, DCs, and T cells, but also exert direct antimicrobial action, e.g., by release of MC protease or NETosis (Dudeck et al. 2019).

Recently, anti-tumor activity by LPS-activated MC recruiting T cells via the release of CXCL10 was shown (Kaesler et al. 2019).

4.2 Adaptive Immunity

Much is still to learn about how skin bacteria modulate adaptive immunity. We know that *S. aureus* influences T cell numbers and functionality by directly inducing Th cell paralysis (Kaesler et al. 2016) or by superantigen mediated Treg proliferation (Ou et al. 2004). With simultaneous activation of the IL4 receptor, S. aureus derived TLR2-ligands were shown to induce AE chronification (Kaesler et al. 2014). Other commensals, e.g. *S. epidermidis,* act immunoregulatory as well, by inducing DC IL10 secretion (Volz et al. 2018) or CD17A+ CD8+ T cells strengthening the epithelial barrier (Naik et al. 2015). Recent evidence suggests a narrow neonatal window of opportunity during which commensals can permanently shape skin immunity (Scharschmidt et al. 2015). Yet another way, how the skin microbiota induces immunoregulation is the induction of myeloid derived suppresser cells by TLR2/6-binding lipopeptides, typical DAMPs of Gram$^+$ bacteria (Skabytska et al. 2014). Furthermore DAMPS of commensal bacteria via nonclassical MHCI presentation induce T cells with a immunoregulatory and tissue repair signature (Linehan et al. 2018).

5 Summary

There is still much to learn about the inner workings of our skin. Skin immunity and wound healing are far from completely understood, and a comprehensive investigation of the skin's microbiome has just begun. Nevertheless, our current insight shows a multi-facetted organ, confining us from the environment.

References

Balato A, Cacciapuoti S, Di Caprio R, Marasca C, Masarà A, Raimondo A, Fabbrocini G (2018) Human microbiome: composition and role in inflammatory skin diseases. Arch Immunol Ther Exp (Warsz) 67:1–18

Candi E, Schmidt R, Melino G (2005) The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Biol 6:328–340

Chamcheu JC, Siddiqui IA, Syed DN, Adhami VM, Liovic M, Mukhtar H (2011) Keratin gene mutations in disorders of human skin and its appendages. Arch Biochem Biophys 508:123–137

Chen YE, Fischbach MA, Belkaid Y (2018) Skin microbiota–host interactions. Nature 553:427–436

Christensen GJM, Brüggemann H (2014) Bacterial skin commensals and their role as host guardians. Benefic Microbes 5:201–215

Cummins PM (2011) Occludin: one protein, many forms. Mol Cell Biol 32:242–250

Dudeck A, Köberle M, Goldmann O, Meyer N, Dudeck J, Lemmens S, Rohde M, Roldán NG, Dietze-Schwonberg K, Orinska Z, Medina E, Hendrix S, Metz M, Zenclussen AC, von Stebut E, Biedermann T (2019) Mast cells as protectors of health. J Allergy Clin Immunol 144:S4–S18

Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T (2018) Cutaneous barriers and skin immunity: differentiating a connected network. Trends Immunol 39:315–327

Feingold KR (2009) The outer frontier: the importance of lipid metabolism in the skin. J Lipid Res 50:S417–S422

Grice EA, Segre JA (2011) The skin microbiome. Nat Rev Microbiol 9:244–253

Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, Program NCS, Bouffard GG, Blakesley RW, Murray PR, Green ED, Turner ML, Segre JA (2009) Topographical and temporal diversity of the human skin microbiome. Science 324:1190–1192

Gruber R, Börnchen C, Rose K, Daubmann A, Volksdorf T, Wladykowski E, Vidal-y-Sy S, Peters EM, Danso M, Bouwstra JA, Hennies HC, Moll I, Schmuth M, Brandner JM (2015) Diverse regulation of Claudin-1 and Claudin-4 in atopic dermatitis. Am J Pathol 185:2777–2789

Hannigan GD, Meisel JS, Tyldsley AS, Zheng Q, Hodkinson BP, SanMiguel AJ, Minot S, Bushman FD, Grice EA, Heitman J (2015) The human skin double-stranded DNA virome: topographical and temporal diversity, genetic enrichment, and dynamic associations with the host microbiome. MBio 6

Hoste E, Kemperman P, Devos M, Denecker G, Kezic S, Yau N, Gilbert B, Lippens S, De Groote P, Roelandt R, Van Damme P, Gevaert K, Presland RB, Takahara H, Puppels G, Caspers P, Vandenabeele P, Declercq W (2011) Caspase-14 is required for Filaggrin degradation to natural moisturizing factors in the skin. J Investig Dermatol 131:2233–2241

Jungersted JM, Hellgren LI, Jemec GBE, Agner T (2008) Lipids and skin barrier function – a clinical perspective. Contact Dermatitis 58:255–262

Kaesler S, Volz T, Skabytska Y, Koberle M, Hein U, Chen KM, Guenova E, Wolbing F, Rocken M, Biedermann T (2014) Toll-like receptor 2 ligands promote chronic atopic dermatitis through IL-4-mediated suppression of IL-10. J Allergy Clin Immunol 134:92–99

Kaesler S, Skabytska Y, Chen K-M, Kempf WE, Volz T, Köberle M, Wölbing F, Hein U, Hartung T, Kirschning C, Röcken M, Biedermann T (2016) *Staphylococcus aureus*-derived lipoteichoic acid induces temporary T-cell paralysis independent of Toll-like receptor 2. J Allergy Clin Immunol 138:780–790.e786

Kaesler S, Wölbing F, Kempf WE, Skabytska Y, Köberle M, Volz T, Sinnberg T, Amaral T, Möckel S, Yazdi A, Metzler G, Schaller M, Hartmann K, Weide B, Garbe C, Rammensee H-G, Röcken M, Biedermann T (2019) Targeting tumor-resident mast cells for effective anti-melanoma immune responses. JCI Insight 4(19):e125057

Kezic S, Kammeyer A, Calkoen F, Fluhr JW, Bos JD (2009) Natural moisturizing factor components in the stratum corneum as biomarkers of filaggrin genotype: evaluation of minimally invasive methods. Br J Dermatol 161:1098–1104

Kim JH, Hu Y, Yongqing T, Kim J, Hughes VA, Le Nours J, Marquez EA, Purcell AW, Wan Q, Sugita M, Rossjohn J, Winau F (2016) CD1a on Langerhans cells controls inflammatory skin disease. Nat Immunol 17:1159–1166

Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, Nomicos E, Polley EC, Komarow HD, Program NCS, Murray PR, Turner ML, Segre JA (2012) Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 22:850–859

Langan EA, Künstner A, Miodovnik M, Zillikens D, Thaçi D, Baines JF, Ibrahim SM, Solbach W, Knobloch JK (2019) Combined culture and metagenomic analyses reveal significant shifts in the composition of the cutaneous microbiome in psoriasis. Br J Dermatol 181(6):1254–1264

Linehan JL, Harrison OJ, Han S-J, Byrd AL, Vujkovic-Cvijin I, Villarino AV, Sen SK, Shaik J, Smelkinson M, Tamoutounour S, Collins N, Bouladoux N, Dzutsev A, Rosshart SP, Arbuckle JH, Wang C-R, Kristie TM, Rehermann B, Trinchieri G, Brenchley JM, O'Shea JJ, Belkaid Y (2018) Non-classical immunity controls microbiota impact on skin immunity and tissue repair. Cell 172:784–796.e718

Lynch SV, Phimister EG, Pedersen O (2016) The human intestinal microbiome in health and disease. N Engl J Med 375:2369–2379

Matejuk A (2018) Skin Immunity. Arch Immunol Ther Exp (Warsz) 66:45–54

Meisel JS, Sfyroera G, Bartow-McKenney C, Gimblet C, Bugayev J, Horwinski J, Kim B, Brestoff JR, Tyldsley AS, Zheng Q, Hodkinson BP, Artis D, Grice EA (2018) Commensal microbiota modulate gene expression in the skin. Microbiome 6

Naik S, Bouladoux N, Linehan JL, Han S-J, Harrison OJ, Wilhelm C, Conlan S, Himmelfarb S, Byrd AL, Deming C, Quinones M, Brenchley JM, Kong HH, Tussiwand R, Murphy KM, Merad M, Segre JA, Belkaid Y (2015) Commensal–dendritic-cell interaction specifies a unique protective skin immune signature. Nature 520:104–108

Nelson KE, Weinstock GM, Highlander SK, Worley KC, Creasy HH, Wortman JR, Rusch DB, Mitreva M, Sodergren E, Chinwalla AT, Feldgarden M, Gevers D, Haas BJ, Madupu R, Ward DV, Birren BW, Gibbs RA, Methe B, Petrosino JF, Strausberg RL, Sutton GG, White OR, Wilson RK, Durkin S, Giglio MG, Gujja S, Howarth C, Kodira CD, Kyrpides N, Mehta T, Muzny DM, Pearson M, Pepin K, Pati A, Qin X, Yandava C, Zeng Q, Zhang L, Berlin AM, Chen L, Hepburn TA, Johnson J, McCorrison J, Miller J, Minx P, Nusbaum C, Russ C, Sykes SM, Tomlinson CM, Young S, Warren WC, Badger J, Crabtree J, Markowitz VM, Orvis J, Cree A, Ferriera S, Fulton LL, Fulton RS, Gillis M, Hemphill LD, Joshi V, Kovar C, Torralba M, Wetterstrand KA, Abouellleil A, Wollam AM, Buhay CJ, Ding Y, Dugan S, FitzGerald MG, Holder M, Hostetler J, Clifton SW, Allen-Vercoe E, Earl AM, Farmer CN, Liolios K, Surette MG, Xu Q, Pohl C, Wilczek-Boney K, Zhu D (2010) A catalog of reference genomes from the human microbiome. Science 328:994–999

Oh J, Byrd AL, Deming C, Conlan S, Kong HH, Segre JA (2014) Biogeography and individuality shape function in the human skin metagenome. Nature 514:59–64

Ou L-S, Goleva E, Hall C, Leung DYM (2004) T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. J Allergy Clin Immunol 113:756–763

Panther D, Jacob S (2015) The importance of acidification in atopic eczema: an underexplored avenue for treatment. J Clin Med 4:970–978

Pappas A (2009) Epidermal surface lipids. Dermatoendocrinol 1:72–76

Proksch E, Brandner JM, Jensen JM (2008) The skin: an indispensable barrier. Exp Dermatol 17:1063–1072

Richard G (2005) Connexin disorders of the skin. Clin Dermatol 23:23–32

Sandilands A, Sutherland C, Irvine AD, McLean WHI (2009) Filaggrin in the frontline: role in skin barrier function and disease. J Cell Sci 122:1285–1294

Scharschmidt TC, Vasquez KS, Truong H-A, Gearty SV, Pauli ML, Nosbaum A, Gratz IK, Otto M, Moon JJ, Liese J, Abbas AK, Fischbach MA, Rosenblum MD (2015) A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 43:1011–1021

Schommer NN, Gallo RL (2013) Structure and function of the human skin microbiome. Trends Microbiol 21:660–668

Skabytska Y, Wölbing F, Günther C, Köberle M, Kaesler S, Chen K-M, Guenova E, Demircioglu D, Kempf WE, Volz T, Rammensee H-G, Schaller M, Röcken M, Götz F, Biedermann T (2014) Cutaneous innate immune sensing of toll-like receptor 2-6 ligands suppresses T cell immunity by inducing myeloid-derived suppressor cells. Immunity 41:762–775

Skabytska Y, Kaesler S, Volz T, Biedermann T (2016) How the innate immune system trains immunity: lessons from studying atopic dermatitis and cutaneous bacteria. J Dtsch Dermatol Ges 14:153–156

Sparber F, De Gregorio C, Steckholzer S, Ferreira FM, Dolowschiak T, Ruchti F, Kirchner FR, Mertens S, Prinz I, Joller N, Buch T, Glatz M, Sallusto F, LeibundGut-Landmann S (2019) The skin commensal yeast malassezia triggers a type 17 response that coordinates anti-fungal immunity and exacerbates skin inflammation. Cell Host Microbe 25:389–403.e386

Tsukita S, Tanaka H, Tamura A (2019) The Claudins: from tight junctions to biological systems. Trends Biochem Sci 44:141–152

Volz T, Kaesler S, Draing C, Hartung T, Röcken M, Skabytska Y, Biedermann T (2018) Induction of IL-10-balanced immune profiles following exposure to LTA from *Staphylococcus epidermidis*. Exp Dermatol 27:318–326

Williams MR, Nakatsuji T, Sanford JA, Vrbanac AF, Gallo RL (2017) *Staphylococcus aureus* induces increased serine protease activity in keratinocytes. J Investig Dermatol 137:377–384

Yamazaki Y, Nakamura Y, Núñez G (2017) Role of the microbiota in skin immunity and atopic dermatitis. Allergol Int 66:539–544

Microbiome of Barrier Organs in Allergy: Who Runs the World? Germs!

Vera Schwierzeck, Claudia Hülpüsch, and Matthias Reiger

Contents

Abstract

Over the last few decades, allergic diseases have been steadily increasing worldwide, a phenomenon that is not yet completely understood. Recent evidence, however, suggests that alterations in the microbiome may be a contributing factor. The microbiome refers to all microorganisms in a habitat including bacteria, fungi, and viruses. Using modern sequencing technologies, we are now capable of detecting and analyzing the human microbiome in more detail

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than ever before. Epidemiological and experimental studies have indicated that a complex intestinal microbiome supports the development of the immune system during childhood, thus providing protection from allergic diseases, including food allergy. The microbiome becomes an important part of human physiology and forms dynamic relationships with our various barrier systems. For example, bacterial dysbiosis is a hallmark of atopic eczema and correlates with disease progression. Similarly, the lung and nasopharyngeal microbiome is altered in patients with asthma and allergic rhinitis. While these results are interesting, the underlying mechanisms are still unclear and need to be investigated with functional studies. This review gives a short overview of the terminology and methods used in microbiome research before highlighting results concerning the lung, skin, and intestinal microbiome in allergic diseases.

Keywords

Allergy · Microbiome · Sequencing

1 Microbiome Sequencing and Analysis

The interest in microbiome research is blossoming. Bacteria co-inhabit the human body in a 1:1 ratio of human to bacterial cells, most of which live with us as commensals (Khan et al. 2019). However, the effect of the microbiome on human health is immense. As early as 1989, Strachan proposed the hygiene hypothesis stating that household size inversely correlates with atopic diseases, which sparked interest in bacterial community structures (Strachan 1989). Later, Haahtela further evolved this theory into the biodiversity hypothesis, linking a low bacterial biodiversity to diseases like atopic eczema (Haahtela et al. 2013). As up to 20–60% of bacteria colonizing the human body are non-cultivable there is a need for culture-independent approaches in microbiology (Pei et al. 2004). In 2005, time and costs for sequencing were significantly reduced when the first sequencer performing massive parallel sequencing became commercially available, thus openening the field for non-experts performing microbiome research (Shendure et al. 2017).

The term microbiome refers to all genes of microorganisms in one habitat including bacteria, archaea, lower and higher eukaryotes, and viruses. However, when we talk about the microbiome we often refer to only the collection of bacterial genes found in a certain habitat (Marchesi and Ravel 2015). The 16S rRNA gene has a total length of 1,500 base pairs (bp) and consists of highly conserved nucleotide sequences, characterised by 9 hypervariable regions (Chakravorty et al. 2007; Janda and Abbott 2007). Since amplicon read length is limited (restricted until now to an amplicon size of $\leq$300 bp), only parts of the 16S rRNA gene are sequenced (Cruaud et al. 2017). The variable region chosen for 16S rRNA gene sequencing will depend on the sequenced habitat and the colonizing bacteria, since discrimination down to

species level is possible in different variable regions depending on the bacterial family (Walker et al. 2015).

Whereas the gut microbiome has already been investigated for two decades via 16S sequencing, new low biomass environments like skin, lung, and placenta microbiome demand for new gold standards and identification of contaminants (Goffau et al. 2018; Kong et al. 2017). Dry skin, for example, only harbors approximately 10^3 bacterial cells per cm^2 compared to 10^{11} bacterial cell/mL colon content (Bibel and Lovell 1976; Sender et al. 2016). General considerations when performing any microbiome research include study design, sampling and storage, sample processing, primer choice and sequencing.

Beyond the experimental design, however, the bioinformatic processing of genetic information may also be a source of bias (Sinha et al. 2015). Generally, the sequences are clustered into Operational Taxonomic Units (OTUs), according to sequence similarities of 97%. A relatively new approach is the formation of amplicon sequence variants (ASV), which do not set a threshold but rather take single nucleotide differences into account (Callahan et al. 2017). These clusters are subsequently identified and annotated to taxonomy using public available databases. Different databases do not perform equally well, which can be explained by the size, curation, and last update of the database; best results were obtained with Ezbiocloud (Park and Won 2018). Thereafter, quality controls to remove PCR errors such as chimera amplicons and singletons need to be performed.

Finally, the samples can be analyzed. Classically, the alpha-diversity (diversity within a sample), beta-diversity (diversity between samples, determined by a distance Matrix), and the taxonomy are analyzed (Bray and Curtis 1957; Lozupone and Knight 2005). Alpha diversity looks either at the richness (who is there) or the evenness (their distribution). Simpson and Shannon take both into account (Jost 2007; Wagner et al. 2018).

Alternatively, metagenomics can be performed which offers more genetic and functional information by looking at all genomes from a certain habitat (Ranganathan et al. 2019). Ever since 2008, the human microbiome project (HMP) by the US National Institutes of Health (NIH) has been characterizing the microbiome of healthy individuals including nose, mouth, skin, gut, and urogenital tract via 16S NGS, as well as metagenomics. The wide breadth of analysis covers not only healthy individuals, but also those with conditions such as preterm birth, inflammatory bowel diseases, and prediabetes (The Integrative Human Microbiome Project 2019).

Beyond the microbiome, the mycobiome, which refers to the fungal community in a habitat, and the virome, which represents the viral community of RNA and DNA viruses, both have to be considered in the equation of human health. So far, however, both fields are still understudied. The mycobiome is analyzed via either internal transcribed spacer (ITS) regions or RNA (18S, 5.8S and 28S rRNA). Most critical in mycobiome research are reliable databases for the taxonomic classification of the fungi and the primer selection for amplification (Jo et al. 2017). The virome faces challenges like low biomass, inadequate bioinformatic tools for the analysis, and a lack of curated databases. However, it is even more challenging due to a lack of

common markers for viruses and a high heterogeneity (Zou et al. 2016). The human virome could have a direct effect on the host-health, or by altering the microbial composition of the host.

2 The Microbiome in Early Childhood and Allergy

Pioneers of pediatrics, such as Theodor Escherich, have been fascinated with the bacteria that colonize the human intestine in newborns. Theodor Escherich investigated meconium and demonstrated that bacteria will colonize a child's intestine within 3–24 h after birth. In addition, he demonstrated that bacterial colonization is influenced by breast feeding (Escherich 1989). While these early studies explored the bacterial composition using conventional culture methods, many of the key findings remain valid today. Since it has become clear that genetics alone cannot explain the steady increase of childhood allergies in industrialized countries, scientists have directed their attention to the microbiome as an influencing factor for the development of allergic diseases (Huang et al. 2017). Thus, microbiome studies have become part of a modern view on David Strachan's hygiene hypothesis.

The colonization of a child's intestine is comparable to the assembly of a new community of microorganisms. The origin of these microorganisms is the maternal microbiome as well as the environment. For this reason, key factors that influence the intestinal microbiome after birth depend on mode of delivery and diet (Bäckhed et al. 2015). The first bacteria that colonize the neonatal intestine are more facultative anaerobes than obligate anaerobes (Koenig et al. 2011). The genera *Bacteroides, Bifidobacterium,* and *Escherichia* dominate the intestinal microbiome of infants delivered via vaginal birth. These bacteria are acquired during the passage through the birth canal. Conversely, newborns delivered by cesarean section show an intestinal microbiome that includes bacteria species associated with the skin and mucosa, e. g. *Haemophilus* species and staphylococci. Gradually, these differences seem to decrease over the first months of life as the intestinal bacterial communities assemble and stabilize (Chu et al. 2017).

There is increasing evidence that a complex intestinal microbiome is essential for shaping the immune system during infancy and protects from the development of allergic diseases (Gomez de Agüero et al. 2016). Interestingly, germ-free mice show reduced IgA levels but higher IgE levels, as compared to control animals (Cahenzli et al. 2013; Herbst et al. 2011). Additional data suggest that there is a critical time window when bacterial colonization is protective (Cahenzli et al. 2013). While these results are based on animal models, they fit with epidemiological observations (Metzler et al. 2019).

Prophylactic antibiotic administration and no vaginal contact during cesarean delivery impact the composition of the microbiome after birth (Chu et al. 2017). Several studies have investigated the association between mode of delivery and the development of allergic diseases. One study recruited 2,917 children and followed them up to 8 years of age. Here, cesarean section significantly correlated with asthma, especially if both parents were allergic themselves. The risk for

sensitization, however, was only increased if parents were not allergic (Roduit et al. 2009). Despite inconsistent results, an experimental pilot study recently proposed "vaginal seeding" after cesarean delivery (Dominguez-Bello et al. 2016). Detailed analysis during the first week after birth showed that newborns inoculated with their mother's vaginal fluids developed a microbiome that resembled the one of children born via vaginal delivery. However, "vaginal seeding" is still experimental as sufficient data regarding the safety and patient benefit is lacking.

The PASTURE (Protection against Allergy-Study in Rural Environment) birth cohort study prospectively collected data to investigate the association between prenatal and postnatal exposure and the development of allergic diseases. Among the environmental factors investigated was also antibiotic consumption. 1,133 children from rural areas of five European countries (Austria, Finland, France, Germany, and Switzerland) were included and observed for the first 6 years of their life (von Mutius and Schmid 2006). Prenatal exposure to antibiotics was significantly associated with food allergy and atopic eczema (AE) in the first year of life (Metzler et al. 2019). A dose-response relationship between the number of antibiotic courses early in life and AE was also detected, suggesting a time window where antibiotics are a risk factor for developing allergic diseases. Children with three or more courses of antibiotics in their first year of life showed a seven-fold increase in risk to develop AE, up to the age of four.

3 The Skin Microbiome and Allergy

3.1 Key Bacterial Species and Fungi in the Skin Microbiome

Our largest organ, the skin, is not only a physical barrier but is, in fact, home to a complex microbiome which dynamically interacts with both this barrier and the human immune system (Eyerich et al. 2018; Naik et al. 2012). Depending on the skin environment, which varies depending on the body region, the skin harbors different bacteria (Costello et al. 2009). Moist skin areas, e.g. armpits, are mainly colonized by staphylococci and corynebacteria. Propionibacteria are typically found on sebaceous skin regions such as forehead and back. Their best-known representative, *Cutibacterium acnes*, is able to metabolize triglycerides, thus maintaining the skin's acidic pH value. The skin microbiome is influenced by internal factors such as age and gender, but also external factors including personal habits, psychological stress, and environmental factors (UV radiation and humidity) (Harter et al. 2019).

Furthermore, most body surfaces are colonized with fungi, the most common of which are genera *Malassezia*, *Candida*, *Aspergillus,* and *Penicillium*.

3.2 Skin Microbial Analyses: New Findings for AE

Dysbalance in the skin microbiome is a hallmark of AE. Exposure to bacteria not only leads to the maturation of the innate and adaptive immune response, but

commensals like *Staphylococcus epidermidis*, *Staphylococcus hominis,* and *Staphylococcus lugdunensis* are also capable of inducing production of antimicrobial peptides (AMPs) in human keratinocytes. For example, commensals inhibit the growth of *Staphylococcus aureus* via antimicrobial substances or antibiotics themselves, which are regulated by quorum sensing mechanisms (Naik et al. 2012; Williams et al. 2019; Zipperer et al. 2016). Cultivation-based studies have already found that *S. aureus,* in particular, plays a role in AE. A flare in AE is correlated with an overgrowth of *S. aureus,* resulting in a lower skin microbiome diversity and changes in the barrier layers and the immune system (Altunbulakli et al. 2018; Kong et al. 2012). However, it remains unclear whether microbial changes are a cause or consequence of the disease. Modern sequencing-based microbial analysis is limited to the identification of microorganisms on a species level, yet for pathogenicity and functionality (such as that of *S. aureus*), identification to strain level is important. It has been demonstrated that clonal expansion of *S. aureus* strains occurs in AE patients with severe symptoms (Byrd et al. 2017).

Additionally, more *Malassezia* DNA was detected in lesional skin mainly in sebaceous regions such as head and neck, and a connection with disease severity was established. More detailed investigations have shown that different strains occur in healthy people and patients. This indicates that at least one pathogenic strain is involved in the deterioration of AE and skin inflammation (Glatz et al. 2015).

Nowadays, the role of viruses, such as the human papilloma virus (HPV), polyomavirus, bacteriophages, or herpes viruses, is also investigated in AE (Traidl et al. 2018). Bacteriophages are characterized by a high variability and can serve as vectors for the adaptation of their host bacteria (Hannigan et al. 2017).

4 The Lung Microbiome and Allergy

In general, the focus of respiratory microbial research is on the nasopharynx, the uppermost and most accessible section of the respiratory system. The nasopharynx is not only easier to sample, but is also the most likely site of contact between inhaled material and epithelial cells. This constant contact and exchange with the environment influences the composition of the respiratory microbiome, especially in healthy individuals (Dickson et al. 2015). The microbiome of the nasopharynx differs significantly from the lower respiratory tract (below the glottis), but there are nevertheless certain similarities, especially regarding the oral flora (Marsh et al. 2016). However, the different airway sections are more similar than inter-individual variation (Dickson and Huffnagle 2015). For a long time it was thought that the lung was sterile in a healthy state, but today it is known that the lung is only sparsely populated with about 2,000 genomes per cm^2, and that the limitation of a low microbial density is a fundamental prerequisite for maintaining health (Hilty et al. 2010). In healthy people, bacteria of the genera *Prevotella*, *Streptococcus*, *Veillonella*, *Neisseria*, *Haemophilus,* and *Fusobacterium* dominate the lung microbiome, which is subject to constant change. In respiratory diseases such as asthma and allergic rhinitis, reduced diversity and higher proportion of

proteobacteria in the nasopharynx was associated with allergic rhinitis in a study with newborns, whereas *Corynebacterium* spp. were associated with healthy babies (Le Ta et al. 2018). In asthma patients, various studies have observed a dysbiosis in the lung microbiome (Hooks and O'Malley 2017). For example, it was shown that in the sputum of asthma patients the phylum Proteobacteria was increased, and also the diversity of the samples of asthma patients was higher compared to those of healthy study participants (Marri et al. 2013). In addition to the bacterial microbiome of the respiratory tract, viruses and fungi also play a role. The latter may be relevant since fungal spores can make up a high proportion of the air we breathe (Pashley et al. 2012). Fungal spores in the air and a sensitization against certain fungi lead to increased IgE levels in atopic individuals and are associated with allergic asthma. Nevertheless, it is still unclear whether and how dysbiosis of the mycobiota plays a role in allergic asthma (Kozik and Huang 2019).

5 The Intestinal Microbiome and Allergy

The intestinal microbiome is a complex ecosystem containing approximately 2,000 bacterial species. In addition, the human intestine is also colonized with fungi and viruses. However, only recent studies have started to focus on the intestinal mycobiome and virome (Lim et al. 2015; Zuo et al. 2019). Future studies will be necessary to investigate how intestinal viruses and fungi influence our immune system.

Our intestinal immune system faces the challenge to discriminate harmless antigens derived from food or commensals from pathogens. An abnormal immune reaction to food proteins and the failure to establish oral tolerance results in food allergy. Several studies based on mouse models have connected the development of food allergies to the intestinal microbiome. In one of those studies germ-free mice were reconstituted with microbiome samples of healthy infant donors or infants suffering from cow's milk allergy. Then the animals were sensitized and challenged with a milk-derived protein. Germ-free control animals and mice that had received the microbiome of milk-allergic infants developed a significantly stronger allergic reaction than reconstituted control animals (Feehley et al. 2019). Microbiome analysis was used to compare the stool samples of healthy children to those suffering from milk allergy. Samples of healthy children were enriched in bacteria of the *Lachnospiraceae* family. Interestingly, colonizing germ-free mice with a bacterial species from this family were also protective. A study using a mouse model for peanut allergy showed similar results. Here, monocolonization with *Clostridium* spp. protected the animals from sensitization to food allergens. The study also showed that reconstitution induces interleukin-22 (IL-22) production, IgA secretion, and the expansion of regulatory T lymphocytes (Treg), which could synergistically promote oral tolerance (Stefka et al. 2014). Other studies have connected bacterial metabolites to food allergy. Some bacteria species such as *Bifidobacteria* convert dietary fiber into small chain fatty acids (SCFAs). Experiments in mouse models suggest that SCFAs protect animals from food allergy by promoting Treg function

(Lyons et al. 2010). Another concept is the so-called gut-lung axis, suggesting that the intestinal microbiome can affect pathologies in the lung via bacterial metabolites or influence on the immune system (Schroeder and Bäckhed 2016). For example, neonatal mice treated with the antibiotic vancomycin had an increased inflammatory response in an asthma model (Russell et al. 2012). As antibiotic therapy influences the intestinal microbiome, the results of these studies suggest that increased antibiotic consumption during early childhood might increase the risk of allergic disease by altering the intestinal microbiome during a time when immune tolerance is established.

6 Microbiome and Therapy

There are numerous clinical approaches to influence the microbiome with pre-, pro- and symbiotics. Early clinical studies have shown that topical application of the bacterium *Roseomonas mucosa* can reduce the symptoms of AE and reduce the need for steroid therapy (Myles et al. 2018). A double-blind, placebo-controlled randomized trial using the probiotic *Lactobacillus rhamnosus* in combination with peanut oral immunotherapy in food allergic children showed that co-administration was associated with reduced responses in skin prick tests and reduced peanut-specific IgE levels (Tang et al. 2015). Despite these encouraging results, many underlying molecular mechanisms of the microbiome remain poorly understood. Researching whether, or how, the microbiome can be altered, and whether this change is beneficial to the patient, is therefore an important goal in microbiome research. Due to the multifactorial nature of allergic diseases, manipulation of the microbiome as therapy or prevention can only be part of a multi-modal treatment approach to allergic diseases.

	Skin	Respiratory tract
Healthy microbiome (commensals)	Bacteria – *Corynebacterium* spp. – *Staphylococcus* spp. – *Dermabacteraceae* – *Micrococcus* spp. – *Cutibacterium acnes* Fungi – *Malassezia* spp. – *Candida* spp. – *Aspergillus* spp. – *Penicillium* spp.	Bacteria – *Streptococcus* spp. – *Neisseria* spp. – *Haemophilus* spp. Anaerobic bacteria – *Prevotella* spp. – *Veillonella* spp. – *Fusobacterium* spp. Fungi – *Candida* spp.
Spatial distribution	Body region specific microbiome (i.e., skin regions rich in sebaceous glands: *Cutibacterium acnes*)	Microbiome of the nasopharynx differs significantly from the lower respiratory tract
Dysbiosis	Atopic eczema ↑ *Staphylococcus aureus* ↑ *Malassezia* spp.	Asthma and allergic rhinitis ↑ Proteobacteria ↑ Microbiome diversity

(continued)

References	Altunbulakli et al. (2018), Byrd et al. (2017), Costello et al. (2009), Glatz et al. (2015), Harada et al. (2015), Kong et al. (2012)	Dickson et al. (2015), Dickson and Huffnagle (2015), Findley et al. (2013), Hilty et al. (2010), Hooks and O'Malley (2017), Krause et al. (2016), Le Ta et al. (2018), Marri et al. (2013)

References

The Integrative Human Microbiome Project (2019) Nature 569:641–648. https://doi.org/10.1038/s41586-019-1238-8

Altunbulakli C, Reiger M, Neumann AU, Garzorz-Stark N, Fleming M, Huelpuesch C, Castro-Giner F, Eyerich K, Akdis CA, Traidl-Hoffmann C (2018) Relations between epidermal barrier dysregulation and staphylococci-dominated microbiome dysbiosis in atopic dermatitis. J Allergy Clin Immunol. https://doi.org/10.1016/j.jaci.2018.07.005

Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, Khan MT, Zhang J, Li J, Xiao L, Al-Aama J, Zhang D, Lee YS, Kotowska D, Colding C, Tremaroli V, Yin Y, Bergman S, Xu X, Madsen L, Kristiansen K, Dahlgren J, Wang J (2015) Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 17:852. https://doi.org/10.1016/j.chom.2015.05.012

Bibel DJ, Lovell DJ (1976) Skin flora maps: a tool in the study of cutaneous ecology. J Invest Dermatol 67:265–269. https://doi.org/10.1111/1523-1747.ep12513459

Bray JR, Curtis JT (1957) An ordination of the upland Forest communities of southern Wisconsin. Ecol Monogr 27:325–349. https://doi.org/10.2307/1942268

Byrd AL, Deming C, Cassidy SKB, Harrison OJ, Ng WI, Conlan S, Nisc Comparative Sequencing Program, Belkaid Y, Segre JA, Kong HH (2017) *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. Sci Transl Med 9. https://doi.org/10.1126/scitranslmed.aal4651

Cahenzli J, Köller Y, Wyss M, Geuking MB, McCoy KD (2013) Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. Cell Host Microbe 14:559–570. https://doi.org/10.1016/j.chom.2013.10.004

Callahan BJ, McMurdie PJ, Holmes SP (2017) Exact sequence variants should replace operational taxonomic units in marker-gene data analysis. ISME J 11:2639–2643. https://doi.org/10.1038/ismej.2017.119

Chakravorty S, Helb D, Burday M, Connell N, Alland D (2007) A detailed analysis of 16S ribosomal RNA gene segments for the diagnosis of pathogenic bacteria. J Microbiol Methods 69:330–339. https://doi.org/10.1016/j.mimet.2007.02.005

Chu DM, Ma J, Prince AL, Antony KM, Seferovic MD, Aagaard KM (2017) Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat Med 23:314–326. https://doi.org/10.1038/nm.4272

Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R (2009) Bacterial community variation in human body habitats across space and time. Science 326:1694–1697. https://doi.org/10.1126/science.1177486

Cruaud P, Rasplus J-Y, Rodriguez LJ, Cruaud A (2017) High-throughput sequencing of multiple amplicons for barcoding and integrative taxonomy. Sci Rep 7:2045. https://doi.org/10.1038/srep41948

Dickson RP, Huffnagle GB (2015) The lung microbiome: new principles for respiratory bacteriology in health and disease. PLoS Pathog 11:e1004923. https://doi.org/10.1371/journal.ppat.1004923

Dickson RP, Erb-Downward JR, Freeman CM, McCloskey L, Beck JM, Huffnagle GB, Curtis JL (2015) Spatial variation in the healthy human lung microbiome and the adapted island model of lung biogeography. Ann Am Thorac Soc 12:821–830. https://doi.org/10.1513/AnnalsATS.201501-029OC

Dominguez-Bello MG, Jesus-Laboy KMD, Shen N, Cox LM, Amir A, Gonzalez A, Bokulich NA, Song SJ, Hoashi M, Rivera-Vinas JI, Mendez K, Knight R, Clemente JC (2016) Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 22:250–253. https://doi.org/10.1038/nm.4039

Escherich T (1989) The intestinal bacteria of the neonate and breast-fed infant. 1885. Rev Infect Dis 11:352–356. https://doi.org/10.1093/clinids/11.2.352

Feehley T, Plunkett CH, Bao R, Choi Hong SM, Culleen E, Belda-Ferre P, Campbell E, Aitoro R, Nocerino R, Paparo L, Andrade J, Antonopoulos DA, Berni Canani R, Nagler CR (2019) Healthy infants harbor intestinal bacteria that protect against food allergy. Nat Med 25:448–453. https://doi.org/10.1038/s41591-018-0324-z

Findley K, Oh J, Yang J, Conlan S, Deming C, Meyer JA, Schoenfeld D, Nomicos E, Park M, Kong HH, Segre JA (2013) Topographic diversity of fungal and bacterial communities in human skin. Nature 498:367–370. https://doi.org/10.1038/nature12171

Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P (2015) The role of *Malassezia* spp. in atopic dermatitis. J Clin Med 4:1217–1228. https://doi.org/10.3390/jcm4061217

Goffau MCD, Lager S, Salter SJ, Wagner J, Kronbichler A, Charnock-Jones DS, Peacock SJ, Smith GCS, Parkhill J (2018) Recognizing the reagent microbiome. Nat Microbiol 3:851–853. https://doi.org/10.1038/s41564-018-0202-y

Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T, Rupp S, Uchimura Y, Li H, Steinert A, Heikenwalder M, Hapfelmeier S, Sauer U, McCoy KD, Macpherson AJ (2016) The maternal microbiota drives early postnatal innate immune development. Science 351:1296–1302. https://doi.org/10.1126/science.aad2571

Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, Demain J, Portnoy J, Lv H (2013) The biodiversity hypothesis and allergic disease: world allergy organization position statement. World Allergy Organ J 6:3. https://doi.org/10.1186/1939-4551-6-3

Hannigan GD, Zheng Q, Meisel JS, Minot SS, Bushman FD, Grice EA (2017) Evolutionary and functional implications of hypervariable loci within the skin virome. PeerJ 5:e2959. https://doi.org/10.7717/peerj.2959

Harada K, Saito M, Sugita T, Tsuboi R (2015) *Malassezia* species and their associated skin diseases. J Dermatol 42:250–257. https://doi.org/10.1111/1346-8138.12700

Harter K, Hammel G, Krabiell L, Linkohr B, Peters A, Schwettmann L, Ring J, Johar H, Ladwig K-H, Traidl-Hoffmann C (2019) Different psychosocial factors are associated with seasonal and perennial allergies in adults – cross-sectional results of the KORA FF4 study. Int Arch Allergy Immunol (4):179, 262–272

Herbst T, Sichelstiel A, Schär C, Yadava K, Bürki K, Cahenzli J, McCoy K, Marsland BJ, Harris NL (2011) Dysregulation of allergic airway inflammation in the absence of microbial colonization. Am J Respir Crit Care Med 184:198–205. https://doi.org/10.1164/rccm.201010-1574OC

Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, Davies J, Ervine A, Poulter L, Pachter L, Moffatt MF, Cookson WOC (2010) Disordered microbial communities in asthmatic airways. PLoS One 5:e8578. https://doi.org/10.1371/journal.pone.0008578

Hooks KB, O'Malley MA (2017) Dysbiosis and its discontents. MBio 8. https://doi.org/10.1128/mBio.01492-17

Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DYM, Muraro A, Fleisher TA (2017) 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 139:1099–1110. https://doi.org/10.1016/j.jaci.2017.02.007

Janda JM, Abbott SL (2007) 16S rRNA gene sequencing for bacterial identification in the diagnostic laboratory: pluses, perils, and pitfalls. J Clin Microbiol 45:2761–2764. https://doi.org/10.1128/JCM.01228-07

Jo J-H, Kennedy EA, Kong HH (2017) Topographical and physiological differences of the skin mycobiome in health and disease. Virulence 8:324–333. https://doi.org/10.1080/21505594.2016.1249093

Jost L (2007) Partitioning diversity into independent ALPHA and BETA components. Ecology 88:2427–2439. https://doi.org/10.1890/06-1736.1

Khan R, Petersen FC, Shekhar S (2019) Commensal bacteria: an emerging player in defense against respiratory pathogens. Front Immunol 10:1203. https://doi.org/10.3389/fimmu.2019.01203

Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE (2011) Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci U S A 108(Suppl 1):4578–4585. https://doi.org/10.1073/pnas.1000081107

Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, Nomicos E, Polley EC, Komarow HD, Murray PR, Turner ML, Segre JA (2012) Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 22:850–859. https://doi.org/10.1101/gr.131029.111

Kong HH, Andersson B, Clavel T, Common JE, Jackson SA, Olson ND, Segre JA, Traidl-Hoffmann C (2017) Performing skin microbiome research: a method to the madness. J Investig Dermatol 137:561–568. https://doi.org/10.1016/j.jid.2016.10.033

Kozik AJ, Huang YJ (2019) The microbiome in asthma: role in pathogenesis, phenotype, and response to treatment. Ann Allergy Asthma Immunol 122:270–275. https://doi.org/10.1016/j.anai.2018.12.005

Krause R, Moissl-Eichinger C, Halwachs B, Gorkiewicz G, Berg G, Valentin T, Prattes J, Högenauer C, Zollner-Schwetz I (2016) Mycobiome in the lower respiratory tract – a clinical perspective. Front Microbiol 7:2169. https://doi.org/10.3389/fmicb.2016.02169

Le Ta DH, Yap GC, Tay CJX, Lim ASM, Huang C-H, Chu CW, de Sessions PF, Shek LP, Goh A, van Bever HPS, Teoh OH, Soh JY, Thomas B, Ramamurthy MB, Goh DYT, Lay C, Soh S-E, Chan YH, Saw S-M, Kwek K, Chong Y-S, Godfrey KM, Hibberd ML, Lee BW (2018) Establishment of the nasal microbiota in the first 18 months of life: correlation with early-onset rhinitis and wheezing. J Allergy Clin Immunol 142:86–95. https://doi.org/10.1016/j.jaci.2018.01.032

Lim ES, Zhou Y, Zhao G, Bauer IK, Droit L, Ndao IM, Warner BB, Tarr PI, Wang D, Holtz LR (2015) Early life dynamics of the human gut virome and bacterial microbiome in infants. Nat Med 21:1228–1234. https://doi.org/10.1038/nm.3950

Lozupone C, Knight R (2005) UniFrac: a new phylogenetic method for comparing microbial communities. Appl Environ Microbiol 71:8228–8235. https://doi.org/10.1128/AEM.71.12.8228-8235.2005

Lyons A, O'Mahony D, O'Brien F, MacSharry J, Sheil B, Ceddia M, Russell WM, Forsythe P, Bienenstock J, Kiely B, Shanahan F, O'Mahony L (2010) Bacterial strain-specific induction of Foxp3+ T regulatory cells is protective in murine allergy models. Clin Exp Allergy 40:811–819. https://doi.org/10.1111/j.1365-2222.2009.03437.x

Marchesi JR, Ravel J (2015) The vocabulary of microbiome research: a proposal. Microbiome 3:8. https://doi.org/10.1186/s40168-015-0094-5

Marri PR, Stern DA, Wright AL, Billheimer D, Martinez FD (2013) Asthma-associated differences in microbial composition of induced sputum. J Allergy Clin Immunol 131:346–352.e1-3. https://doi.org/10.1016/j.jaci.2012.11.013

Marsh RL, Kaestli M, Chang AB, Binks MJ, Pope CE, Hoffman LR, Smith-Vaughan HC (2016) The microbiota in bronchoalveolar lavage from young children with chronic lung disease includes taxa present in both the oropharynx and nasopharynx. Microbiome 4:37. https://doi.org/10.1186/s40168-016-0182-1

Metzler S, Frei R, Schmaußer-Hechfellner E, Ev M, Pekkanen J, Karvonen AM, Kirjavainen PV, Dalphin J-C, Divaret-Chauveau A, Riedler J, Lauener R, Roduit C (2019) Association between

antibiotic treatment during pregnancy and infancy and the development of allergic diseases. Pediatr Allergy Immunol 30:423–433. https://doi.org/10.1111/pai.13039

Ev M, Schmid S (2006) The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe. Allergy 61:407–413. https://doi.org/10.1111/j.1398-9995.2006.01009.x

Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T (2018) Cutaneous barriers and skin immunity: differentiating a connected network. Trends immunol 39(4):315–327. https://doi.org/10.1016/j.it.2018.02.004. Epub 2018 Mar 15. PMID: 29551468

Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, Saleem A, Fontecilla NM, Welch PA, Darnell DA, Barnhart LA, Sun AA, Uzel G, Datta SK (2018) First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. JCI Insight 3. https://doi.org/10.1172/jci.insight.120608

Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, Deming C, Quinones M, Koo L, Conlan S, Spencer S, Hall JA, Dzutsev A, Kong H, Campbell DJ, Trinchieri G, Segre JA, Belkaid Y (2012) Compartmentalized control of skin immunity by resident commensals. Science 337:1115–1119. https://doi.org/10.1126/science.1225152

Park S-C, Won S (2018) Evaluation of 16S rRNA databases for taxonomic assignments using Mock Community. Genomics Inform 16:e24. https://doi.org/10.5808/GI.2018.16.4.e24

Pashley CH, Fairs A, Free RC, Wardlaw AJ (2012) DNA analysis of outdoor air reveals a high degree of fungal diversity, temporal variability, and genera not seen by spore morphology. Fungal Biol 116:214–224. https://doi.org/10.1016/j.funbio.2011.11.004

Pei Z, Bini EJ, Yang L, Zhou M, Francois F, Blaser MJ (2004) Bacterial biota in the human distal esophagus. Proc Natl Acad Sci 101:4250–4255. https://doi.org/10.1073/pnas.0306398101

Ranganathan S, Gribskov MR, Nakai K, Schönbach C (eds) (2019) Encyclopedia of bioinformatics and computational biology. Elsevier, Amsterdam

Roduit C, Scholtens S, JCD J, Wijga AH, Gerritsen J, Postma DS, Brunekreef B, Hoekstra MO, Aalberse R, Smit HA (2009) Asthma at 8 years of age in children born by caesarean section. Thorax 64:107–113. https://doi.org/10.1136/thx.2008.100875

Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, Gill N, Blanchet M-R, Mohn WW, McNagny KM, Finlay BB (2012) Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep 13:440–447. https://doi.org/10.1038/embor.2012.32

Schroeder BO, Bäckhed F (2016) Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 22:1079–1089. https://doi.org/10.1038/nm.4185

Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 14:e1002533. https://doi.org/10.1371/journal.pbio.1002533

Shendure J, Balasubramanian S, Church GM, Gilbert W, Rogers J, Schloss JA, Waterston RH (2017) DNA sequencing at 40: past, present and future. Nature 550:345–353. https://doi.org/10.1038/nature24286

Sinha R, Abnet CC, White O, Knight R, Huttenhower C (2015) The microbiome quality control project: baseline study design and future directions. Genome Biol 16:207. https://doi.org/10.1186/s13059-015-0841-8

Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, Tjota MY, Seo G-Y, Cao S, Theriault BR, Antonopoulos DA, Zhou L, Chang EB, Fu Y-X, Nagler CR (2014) Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A 111:13145–13150. https://doi.org/10.1073/pnas.1412008111

Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299:1259–1260. https://doi.org/10.1136/bmj.299.6710.1259

Tang MLK, Ponsonby A-L, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S (2015) Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 135:737–744.e8. https://doi.org/10.1016/j.jaci.2014.11.034

Traidl S, Kienlin P, Begemann G, Jing L, Koelle DM, Werfel T, Roesner LM (2018) Patients with atopic dermatitis and history of eczema herpeticum elicit herpes simplex virus-specific type

2 immune responses. J Allergy Clin Immunol 141:1144–1147.e5. https://doi.org/10.1016/j.jaci.2017.09.048

Wagner BD, Grunwald GK, Zerbe GO, Mikulich-Gilbertson SK, Robertson CE, Zemanick ET, Harris JK (2018) On the use of diversity measures in longitudinal sequencing studies of microbial communities. Front Microbiol 9:461. https://doi.org/10.3389/fmicb.2018.01037

Walker AW, Martin JC, Scott P, Parkhill J, Flint HJ, Scott KP (2015) 16S rRNA gene-based profiling of the human infant gut microbiota is strongly influenced by sample processing and PCR primer choice. Microbiome 3:440. https://doi.org/10.1186/s40168-015-0087-4

Williams MR, Costa SK, Zaramela LS, Khalil S, Todd DA, Winter HL, Sanford JA, O'Neill AM, Liggins MC, Nakatsuji T, Cech NB, Cheung AL, Zengler K, Horswill AR, Gallo RL (2019) Quorum sensing between bacterial species on the skin protects against epidermal injury in atopic dermatitis. Sci Transl Med 11. https://doi.org/10.1126/scitranslmed.aat8329

von Mutius E, Schmid S (2006) PASTURE study group. The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe. Allergy 61(4):407–413. https://doi.org/10.1111/j.1398-9995.2006.01009.x. PMID: 16512801

Zipperer A, Konnerth MC, Laux C, Berscheid A, Janek D, Weidenmaier C, Burian M, Schilling NA, Slavetinsky C, Marschal M, Willmann M, Kalbacher H, Schittek B, Brotz-Oesterhelt H, Grond S, Peschel A, Krismer B (2016) Human commensals producing a novel antibiotic impair pathogen colonization. Nature 535:511–516. https://doi.org/10.1038/nature18634

Zou S, Caler L, Colombini-Hatch S, Glynn S, Srinivas P (2016) Research on the human virome: where are we and what is next. Microbiome 4:142. https://doi.org/10.1186/s40168-016-0177-y

Zuo T, Lu X-J, Zhang Y, Cheung CP, Lam S, Zhang F, Tang W, Ching JYL, Zhao R, Chan PKS, Sung JJY, Yu J, Chan FKL, Cao Q, Sheng J-Q, Ng SC (2019) Gut mucosal virome alterations in ulcerative colitis. Gut 68:1169–1179. https://doi.org/10.1136/gutjnl-2018-318131

Part III

Symptoms and Diseases

A Current Perspective of Allergic Asthma: From Mechanisms to Management

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Abstract

Asthma is a result of heterogenous, complex gene–environment interactions with variable clinical phenotypes, inflammation, and remodeling. It affects more than 330 million of people worldwide throughout their educational and working lives, while exacerbations put a heavy cost/burden on productivity. Childhood asthma is characterized by a predominance of allergic sensitization and multimorbidity, while in adults polysensitization has been positively associated with asthma occurrence. Despite significant improvements in recent decades, asthma management remains challenging. Recently, a group of specialists suggested that the term "asthma" should be preferably used as a descriptive term for symptoms. Moreover, type 2 inflammation has emerged as a pivotal disease mechanism including overlapping endotypes of specific IgE production, while type 2-low asthma includes several disease endotypes. Optimal asthma control requires both appropriate pharmacological interventions, tailored to each patient, as well as trigger avoidance measures. Regular monitoring for maintenance of symptom control, preservation of lung function, and detection of treatment-related adverse effects are warranted. Allergen-specific immunotherapy and the advent of new targeted therapies for patients with difficult to control asthma offer diverse treatment options. The current review summarizes up-to-date knowledge on epidemiology, definitions, diagnosis, and current therapeutic strategies.

Keywords

Allergy · Asthma · Asthma treatment

1 Definition

Both "allergy" and "asthma" have been challenging to define. The current definition of asthma, according to most recently published guidelines, incorporates persistent and/or recurrent symptoms, such as wheeze, cough, and difficulty in breathing, associated with reversible airflow obstruction and airway hyperresponsiveness (GINA report 2017). In addition, diagnostic guidelines highlight the importance of using objective measurements to support asthma diagnosis, including assessment of lung function by spirometry and/or impulse oscillometry, airway hyperresponsiveness (AHR) by bronchoprovocation tests, and inflammation by exhaled fractional nitric oxide (NICE, GINA, etc.) (Papi et al. 2018). Nevertheless, asthma is a result of heterogenous, complex gene–environment interactions with

variable clinical phenotypes, inflammation, and remodeling. Recently, a group of specialists suggested that the term "asthma" should be preferably used as a descriptive term for symptoms, without taking into account the distinct underlying pathophysiologic mechanisms, which are linked to fundamentally different patterns of the disease between subjects (Pavord et al. 2018). Instead, identification of well-defined, measurable, and potentially modified/cured treatable traits, i.e. airflow limitation, airway inflammation, etc. are proposed as realistic management targets. On the other hand, clear definitions for allergy and consequently "allergic asthma" have been proposed (Johansson et al. 2004); however, they are not uniformly followed and different approaches have been used in the literature. Recently, there have been proposals for re-scoping the definition (Ring et al. 2018). Particularly in regard to asthma, overlapping endotypes of specific IgE production or "type-2" cytokine expression can be classified in different ways: "allergic asthma" may include asthma triggered by allergens, or asthma mediated through an immune mechanism, or asthma in which IgE antibodies play a central role. In most cases, these subgroups overlap, they are however not identical, explaining part of the discrepancies in relation to epidemiology, diagnosis, and/or treatment responses.

2 Epidemiology

Asthma affects more than 330 million people worldwide throughout their educational and working lives, while exacerbations put a heavy cost/burden on productivity (Vos et al. 2012). The prevalence of self-reported asthma varies considerably between countries, ranging from 0–2% in China up to 21% in Australia, with a mean rate of 4.5% globally (To et al. 2012). More pronounced variations were recorded in the International Study of Asthma and Allergies in Childhood (ISAAC) study for children and teenagers, with an overall prevalence of 10% in the European Union and North America (European Respiratory Society 2013). Although data from epidemiological studies present conflicting data, it is well accepted that asthma prevalence is increasing steadily in developing countries that adopt a more westernized lifestyle, while same trends are noted in several European countries and Australia (Anandan et al. 2010; European Respiratory Society 2013).

Due to heavy economic and morbidity burden of chronic respiratory diseases, a public health policy document towards the Council of the European Union including initiatives regarding early detection, prevention, efficient care, and new therapeutic targets for allergic diseases and asthma was released (Samolinski et al. 2012).

Childhood asthma is characterized by a predominance of allergic sensitization and multimorbidity more so in males, although this gender pattern begins to reverse at adolescence (Gabet et al. 2016). Recently, an overview of systematic reviews in allergy epidemiology identified asthma as the most commonly reviewed allergic disease (Genuneit et al. 2017). During the last two decades, major increases have been recorded with respect to allergic sensitization in children, potentially resulting in enhanced allergic asthma prevalence in the forthcoming years (Ronmark et al. 2009). In addition, indoor allergen exposure, allergic multimorbidity, and/or

polysensitization have been strongly associated with asthma development and persistence (Murray et al. 2001). In several pediatric cohort studies, co-existence of other allergic diseases was significantly associated with increased asthma risk later in life (Gough et al. 2015). Causal network analysis in school-aged children has shown that allergen sensitization, allergic inflammation, and rhinitis activity explained over half of the variance in asthma severity (Liu et al. 2016).

In adults, the prevalence of allergic asthma has increased from 1996 to 2006 and further to 2016, while the prevalence of non-allergic asthma has remained stable (Backman et al. 2017). In addition, polysensitization has been positively associated with asthma occurrence (Toppila-Salmi et al. 2015), while more recently adult-onset asthma was positively associated with the number of allergic multi-morbidities in a dose-dependent manner, more so in younger ages (Toppila-Salmi et al. 2019).

The importance of exposure to specific environmental factors on asthma and allergy development, i.e. indoor allergens, dampness, mold, has also been demonstrated in special population settings such as immigrants and farming communities (Radhakrishnan et al. 2019). More recently, the importance of in utero and/or early life exposures on asthma and sensitization occurrence has been documented (Lundback et al. 2016).

3 Mechanisms

The link between asthma and inflammation has been established for more than 50 years now (Mosmann et al. 1986). The currently considered "classical" immunopathogenic concept in asthma was based on the recognition of $CD4^+$ Th2 cells as the cardinal cells of adaptive immune response, contributing to eosinophilic airway inflammation by the induction of interleukins (IL)-4, IL-5, IL-13 in response to specific allergen stimulation (Kuruvilla et al. 2019). IL-4, which acts as a regulatory cytokine upstream from Type 2 effector cytokines, binds to the IL-4R α receptor, thus modulating Th0 differentiation to Th2 and T-regulatory proliferation upon signaling (Gandhi et al. 2017). IL-5 orchestrates eosinophil development, maturation, and activation in the bone marrow, as well as subsequent mobilization and survival, while also modulates the development and function of mast cells and basophils (Rosenberg et al. 2007). Moreover, IL-13 has a multifunctional role in asthma pathogenesis, including B-cell isotype switching, mucus hypersecretion, goblet cell hyperplasia, subepithelial fibrosis, and AHR (Akdis et al. 2016). This concept evolved resulting in the classification of asthma into T2 high (eosinophilic) and Th2 low (non-eosinophilic) endotypes (Sterk and Lutter 2014). These Th2 high and low phenotypes may show differential responses to available therapies, while patients with non-Th2-driven asthma may be less responsive to steroids. Subsequent studies have shown significant heterogeneity and impact of various inflammatory pathways on the asthma endotypes. Recently, asthma nomenclature has acknowledged that cytokines in Th2 high endotype are secreted by numerous cell types including invariant T cells, natural killer cells, eosinophil/basophil progenitor cells, Th1 cells under certain conditions, and Type 2 innate lymphoid cells (ILCs)

(Robinson et al. 2017). As a result, type-2 inflammation has emerged as a pivotal disease mechanism, while type 2-low asthma includes several disease endotypes, each affecting relatively small subgroups of patients.

A novel subset of innate immune cells has been described, named innate lymphoid cells (ILCs). Three clusters of ILCs have been described: ILC1 and ILC3 mainly produce interferons and IL-17/IL-22, respectively. ILC2 induces large amounts of $CD4^{+}$Th2 like ILs, such as IL-4, IL-5, and IL-13, further activating mast cell, basophil, and eosinophils, as well as IgE antibody production, resulting in allergic airway inflammation (Annunziato et al. 2015; Halim et al. 2012). ILC2 lacks antigen-specific receptors; however, they are activated by mediators deriving from epithelial cells in response to proteases, such as interleukin IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), termed alarmins (Peebles and Aronica 2019). In specific, IL-33 not only plays a major role in cytokine production by ILC2, but also induces antigen-specific IL-5^{+} CD^{+} T cells, independent of IL-4, and promotes pro-allergic inflammatory properties of CD4 T cells (Morita et al. 2017). In asthmatic patients, levels of IL-33 and TSLP were inversely associated with lung function as assessed by spirometry (Momen et al. 2017), while increased IL-25 mRNA expression from airway brushings was significantly associated with bronchial hyperresponsiveness and eosinophilic activation (Cheng et al. 2014). Moreover, viral IL-33 and IL-25 ILC2 responses have been identified as major determinants and potential therapeutic targets during virus-induced asthma exacerbations, which constitute the most important element of asthma morbidity (Andreakos and Papadopoulos 2014; Jackson et al. 2014).

Another important pathway in asthma pathogenesis includes CD4 Th17 cells that produce IL-17A and IL-17F. These in turn induce the production of cytokines and chemokines promoting the chemotaxis and survival of neutrophils in the airway and the lung (Veldhoen 2017). Studies in animal models and clinical settings have shown that IL-17A increases Th2-mediated airway responsiveness and inflammation and airway smooth muscle proliferation, while significant correlation is noted with respect to asthma activity (Barlow et al. 2011; Chang et al. 2012).

In addition, another class of lipid mediator, eicosanoids, mainly prostaglandins (PG) such as PGD2, cysteinyl leukotrienes (LTs), and thromboxanes are also involved in asthma pathogenesis (Kytikova et al. 2019). These are generated through metabolism of arachidonic acid, deriving from the cell membrane of degranulated mast cells and basophils, and promote smooth muscle constriction and inflammation that propagate allergic responses. PGDP2 is the major mast cell and eosinophil derived prostanoid and has positively been associated with the level of asthma control, number of exacerbations and markers of Th2 inflammation (Fajt et al. 2013). Currently studies are underway evaluating the role of PGD2 antagonists on uncontrolled asthma management (Erpenbeck et al. 2016).

Cysteinyl LTs are formed mainly from eosinophils, basophils, mast cells, macrophages, and basophils, following specific stimuli, such as IgE, IgG complexes, endotoxin, and phagocytosis (Sirois 2019). Binding of LTs on their respective receptors induces bronchoconstriction, mucus secretion, airway edema, thus increasing pulmonary resistance and decreasing lung compliance.

Recent advances in lipidomics technology have identified and described the biological actions of a newly identified bioactive metabolome with pro-resolving capacities, such as maresins, lipoxins, resolvins, and protectins (Serhan and Levy 2018). These are known to contribute to homeostasis, following inflammation in the airway diseases and are now studied as new immune-resolvent therapies (Kytikova et al. 2019).

Mechanisms of persistence and remodeling in allergic asthma are largely unexplored. In vitro and in vivo studies have emphasized the importance of atopy and allergic inflammation in the induction and perpetuation of respiratory allergic diseases. Early in vitro models demonstrated that infections by human rhinovirus (hRV), which are the main triggers of asthma exacerbations, modulate epithelial responses by delaying epithelial repair (Bossios et al. 2005). Moreover, hRV infections promote airway remodeling by inducing angiogenesis, mediated through vascular endothelial growth factor (VEGF), an effect also enhanced in the presence of atopy (Psarras et al. 2006), while similar responses were observed for other pro-fibrotic factors, such as fibroblast growth factor 2 (Skevaki et al. 2012) and transforming growth factor (TGF)-β (Bielor et al. 2017). In clinical settings, it was shown that hRV-induced asthma exacerbations are more prevalent in the presence of high IgE titers to relevant allergens, indicating the important role of the host's atopic status (Soto-Quiros et al. 2012). Moreover, the duration of airway hyperresponsiveness, an indirect marker of asthma severity and inflammation, is significantly prolonged only in atopics presenting an increased number of colds, possibly contributing to perpetuation of inflammation and persistence of asthma symptoms (Xepapadaki et al. 2005). Based on the above, the hypothesis that repeated, acute infection-mediated events may reprogram the innate, adaptive and/or regulatory immune responses towards a chronic inflammation pattern has been evaluated in the context of an EU-funded project, PreDicta (www.predicta.eu). Data from the PreDicta childhood cohort indicate that a differential humoral response exists in asthmatic and healthy controls, resulting in altered protection to different RV species (Megremis et al. 2018).

More recently, the complex role of airway and gut microbiome has been acknowledged in the development and severity of asthma (Sullivan et al. 2016). Studies have shown that the type of colonization during early life is strongly associated with asthma diagnosis in the preschool years (Bisgaard et al. 2007), while the airway bacterial burden is closely related to asthma phenotypes, disease activity, and airway hyperresponsiveness (Durack et al. 2017). In addition, the role of virome is also explored in asthma pathogenesis and exacerbations (Megremis et al. 2018).

4 Diagnosis

Current diagnostic algorithms emphasize the importance of an accurate history and physical examination, but as equal important the use of objective confirmatory tests for assessing lung function, airway inflammation, and hyperresponsiveness [https://www.nice.org.uk/guidance/ng80]. Incorporation of objective assessments has been

shown to minimize misdiagnosis in a significant proportion of children and adults and avoid inappropriate asthma prescription medications (MacNeil et al. 2016). Alternatively, effort independent lung function tests such as impulse oscillometry are currently tested in specialized centers with positive results (Knihtila et al. 2018). Nevertheless, certain limitations must be considered: interpretation of lung function results varies even among specialists, while there is a lack of lower "normal" value limit at different ages. Moreover, children usually preserve normal lung function, irrespective of severity (Teague et al. 2018), while positive bronchodilation response might only be documented during asthma attacks and for limited time periods (Konstantinou et al. 2013). Additionally, in mild asthmatics, airway obstruction is often not present during investigation by spirometry, thus leading to diagnostic uncertainty (Schneider et al. 2009). Several factors such as variability of disease activity and airflow limitation, lack of positive bronchodilation responses in spirometry and the complexity of asthma phenotypes contribute to asthma over and underdiagnosis (Saglani and Menzie-Gow 2019).

AHR is a cardinal pathophysiological feature of asthma, and its measurement is an important tool in asthma diagnosis. In specialized centers, an indirect bronchial provocation test, with pharmacological and non-pharmacological agents can be used to assess hyperresponsiveness (Nair et al. 2017a). Direct cholinergic agents have been primarily used to exclude an asthma diagnosis, with a reasonable certainty while indirect challenges show significant correlation with the underlying eosinophilic inflammation and potentially exercise induced bronchoconstriction (Comberiati et al. 2018). It should be noted that AHR is highly dynamic depending on disease activity and persistence (Xepapadaki et al. 2005), exposure to specific triggers and allergens and treatment, although a certain element reflecting smooth muscle function represents a more stable component (Leuppi 2014).

5 Phenotypes

The complexity of the asthma syndrome has led to the necessity of classifying patients according to observable characteristics with no necessary direct relationship to underlying disease process; these categories are named "phenotypes" (Skloot 2016). Current approaches on asthma stratification primarily rely on identifying phenotypes, since the level of understanding required to establish distinct mechanistic pathways (endotypes) has, in general, not yet been achieved. The primary target of stratification is to facilitate personalized management as indicated by individual characteristics (Chung 2015). Commonly described asthma phenotypes are based on (a) inflammatory profiles such as allergic and non-allergic or more recently T2 and non-T2 asthma, (b) triggers: virus, exercise, and/or allergen induced asthma (c) epidemiology such as early and late onset, transient or persistent (d) comorbidities, such as obesity related asthma (Bacharier et al. 2008; Wenzel 2012).

By contrast, the term "endotype" is used to describe distinct disease entities which may be present in clusters of phenotypes, but each is defined by a specific biological/molecular mechanism (Stokes and Casale 2016). The most commonly

used classification, based on cellular profiles, is eosinophilic and neutrophilic asthma. Certain limitations when phenotypes and endotypes are used need to be considered. Prospective studies showed that there is significant transition between phenotypes and endotypes, both in children and adults, suggesting that repeated measures to assess biomarkers' fluctuations are required (Kupczyk et al. 2014; Oksel et al. 2019). Moreover, in clinical settings, where subjective sub-types are identified using predefined or hypothesized criteria, significant overlap has been observed between phenotypes, whereas less obvious or rare patterns may be missed (Xepapadaki et al. 2018).

More sophisticated approaches like machine learning and latent class analysis have been used in order to incorporate several pathophysiological characteristics deriving from large, longitudinal datasets into phenotypes, thus revealing new categories/trajectories in asthmatic subjects (Saglani and Custovic 2019). However, conclusions drawn from cross-sectional analyses of longitudinal data might not accurately reflect longitudinal trajectories within individuals.

In order to determine endotype clusters that drive the airway inflammation, complex technologies, such as the omics in the context of U_BIOPRED and SARP study, combined with gene expression data have been used (Jarjour et al. 2012; Lefaudeux et al. 2017). However, the effect of several other factors, such as environmental, infectious, and therapeutic, on endotype manifestation, needs to be addressed. Moreover, lack of data replication from the aforementioned studies and overlap/instability in time represent the major limitations (Bush 2019).

6 Biomarkers

Any objectively measured process that relates to disease diagnosis, response to therapy, and monitoring can be defined as biomarker (Biomarkers Definitions Working Group 2001). The first key question is whether simple and single biomarker assessments are adequate, since asthma phenotypes, i.e. the eosinophilic and non-eosinophilic are quite unstable. Several biomarkers have been proposed for monitoring type 2 airway inflammation, e.g. eosinophil counts or levels of eosinophilic cationic protein in sputum, tryptase levels in nasal fluid; however, these have not been included in clinical algorithms yet (Amat and Labbe 2018). Below we provide data for the most studied/promising biomarkers in asthma management.

6.1 Exhaled Fractional Nitric Oxide (FeNO)

Measurement of the fraction of exhaled nitric oxide has been established as a non-invasive marker of airway inflammation, which can easily be assessed even in preschoolers. High levels of FeNO are typically considered as a marker of airway eosinophilic inflammation and are associated with asthma control deterioration (Pijnenburg 2019). A recent systematic review and meta-analysis showed that FeNO measurements, with a suggested cut-off value of 50 ppb has a high specificity

for asthma diagnosis and concurrently predicts positive inhaled corticosteroid responsiveness (Karrasch et al. 2017). Although it is still debated whether FeNO could be used for ICS dose adjustment and asthma management (Turner 2015), the most recent NICE guidelines have incorporated FeNO determination into the asthma management algorithm, based on recent evidence that such a strategy prevents severe asthma exacerbations (Ferraro et al. 2018).

6.2 Sputum and Blood Eosinophils

Currently, assessment of sputum eosinophils is only indicated in the management of severe adult asthmatics, but not for diagnostic purposes. Several limitations, such as challenges in obtaining and analyzing the sample, especially in children, limit its usefulness in clinical practice (Westerhof et al. 2015). Recent data show moderate correlation of sputum eosinophils and other non-invasive markers such as exhaled nitric oxide, blood eosinophils, total serum IgE, suggesting that no single biomarker can accurately predict asthma diagnosis (Korevaar et al. 2015). Respective data in children are even more scarce.

On the contrary, assessment of blood eosinophils is an easy point-of-care test, in all clinical settings and has been used as a marker of steroid and anti-eosinophilic monoclonal antibody responsive patients. In children several factors have to be considered such as the elevated eosinophil count in the healthy state, thus altering the cut-off normal limit, the impact atopy per se and steroid treatment have on peripheral eosinophil count and the disease activity (Aldrimer et al. 2013; FitzGerald et al. 2018; Ullmann et al. 2013). Recently, the utility of blood eosinophils in predicting steroid responsiveness has been documented in preschoolers with asthma (Fitzpatrick et al. 2016).

6.3 Exhaled Breath Condensate

Exhaled breath condensate collection is an easy non-invasive technique, where several biomarkers can be assessed such as pH, markers of oxidative stress (including hydrogen peroxide), microRNA profiles, lipoxins, cytokines, and leukotrienes (Konstantinidi et al. 2015). Although initially pH reductions have been associated with asthma activity and symptom exacerbation, subsequent studies did not verify those findings. Moreover, H_2O_2, a marker of oxidative stress, has been associated with the level of asthma control and lung function indices such as FEV1, but only in adults (Davis and Montpetit 2018). The biggest issue remains a lack of standardization regarding EBC collection, preservation, processing, and analysis, thus the method is still only used in research (Bannier et al. 2019).

6.4 Exhaled Breath Temperature

Exhaled breath temperature (EBT) reflects the loss of heat in the airways and has been proposed as a non-invasive method to detect inflammatory processes in the airways because of increased blood flow within the airways (Popov et al. 2017). Studies involving either adults or/and children demonstrated that EBT is increased in patients with uncontrolled asthma (Ntontsi et al. 2018). We have previously showed that EBT values increase during a virus-induced asthma exacerbation and such increase correlated well with other markers of inflammation (Xepapadaki et al. 2010). Current devices include microsensors and provide accurate, simple, and acceptable non-invasive and user-friendly way of assessing EBT.

6.5 Serum Periostin

Periostin is induced by IL-4 and IL-13 in airway epithelial cells and lung fibroblasts and serves as a surrogate marker of Th2 inflammation both in animal and human studies (Blanchard et al. 2008). Serum periostin in asthmatic patients correlates well with blood eosinophil count, serum IgE, and eosinophilic cationic protein levels (Matsumoto 2014). With regard to treatment, periostin is a useful biomarker for responsiveness to inhaled corticosteroid therapy and may help identify patients as suitable candidates for anti-IL13 treatment (Hanania et al. 2015).

6.6 Volatile Organic Compounds

VOCs are products of metabolic activity taking place in the body; hence, they directly reflect the current state of cells, tissues, and the microbiome – providing a rich source of valuable information about the health of an individual. VOCs represent a highly innovative biomarker, since they have been studied only recently for asthma diagnosis and monitoring (Rufo et al. 2016).

Studies showed that increased VOCs levels can discriminate asthmatics from patients with other respiratory diseases and healthy controls. Moreover, significant correlations were noted in studies, with respect to severity of airway obstruction and airway inflammation and potentially as predictors of asthma exacerbations (van Vliet et al. 2017).

7 Asthma Management

The goals of asthma management and treatment may be divided into two domains: asthma control and reduction of future risk related to the complications of the disease itself and the medications used. The achievement and maintenance of good asthma control involves reduction of asthma-related daytime and nighttime symptoms, optimization of lung function, infrequent use of short-acting b2-agonists (SABAs)

as rescue inhalers and maintenance of normal daily activities. Minimization of the risk of asthma-related mortality, asthma exacerbations, suboptimal lung development (for children) or function (for adults), and adverse effects of the medications used in the treatment of asthma is another important consideration when managing a patient with asthma. As a chronic condition, asthma management requires continuous assessments, adjustments of treatment, and reviews of response (Selroos et al. 2015). Patient's preferences and practical issues should also be taken into account. Therefore, all international guidelines recommend a stepwise approach in treating patients with asthma, i.e. "stepping-up" treatment when asthma control is not achieved or maintained for sufficient time and "stepping-down" treatment when there is good asthma control and ideally no exacerbations. Of note, treatment adherence, inhaler technique, and comorbidities should always be assessed before changes in the treatment plan are made.

As new evidence stemming from well-designed research is accumulating, there are modifications in the recommended treatment strategies. The recent report by the Global Initiative for Asthma (GINA) published in 2019 stressed the importance of using an inhaled corticosteroid-containing controller medication either on an as-needed basis or regularly in adults and adolescents with asthma (GINA report 2019). An increase in ICS dose or the addition of other medications are the preferred next steps. In addition, SABAs are no longer the preferred reliever medication. In children 6–11 years old, daily low-dose ICS is the preferred initial treatment and the addition of other medications or an increased ICS dose may be considered further on. In younger children ($\leq$5 years), the diagnosis of asthma remains challenging. In this age group, there is currently lack of understanding regarding the role of the different phenotypes and endotypes as well as the association of preschool wheeze, a hallmark of pediatric asthma, with later development of asthma (Papadopoulos et al. 2019). ICSs in escalating doses are the preferred controller medications in these patients (GINA report 2019).

Therefore, the medications used to treat asthma may be divided into two categories: controller and reliever medications and are summarized below.

7.1 Controller Medications

7.1.1 Inhaled Corticosteroids

Inhaled corticosteroids constitute the current gold standard of maintenance treatment, being the most effective anti-inflammatory medication for most patients with asthma across all age and disease severity groups. The device types include pressurized metered-dose inhalers (pMDIs) with or without a spacer, dry powder inhalers (DPIs), and nebulizers and the choice of the most appropriate device in clinical practice depends on the level of patient's respiratory function, age, preferences, and ability of device handling. Optimal inhaler technique, which requires proper education and regular reevaluation, as well as treatment adherence are considered the most important factors in reducing the risk of asthma exacerbations and controlling symptoms. However, in a recent systematic review

investigators concluded that although there are interventions which may improve inhaler technique in some circumstances, the evidence is inadequate to discern which are the most effective interventions for clinicians to use and what is the measurable impact on clinical outcomes (Normansell et al. 2017). The relative efficacy of ICSs has been examined in numerous RCTs. Fluticasone administered either at the same or at half the daily dose of budesonide or beclomethasone led to slight improvements in some measures of lung function, and this effect applied to all drug doses, age groups, and device types (Adams et al. 2007). No difference was observed with regard to asthma exacerbations, b2-agonist use or asthma symptoms (Adams et al. 2007). Guidelines recommend a daily low dose of ICS in adults and children with persistent asthma. No clinically significant differences in lung function, risk of asthma exacerbation, use of rescue medications, or symptom control were observed between patients who received a low or moderate and a high initial starting dose of ICS (Powell and Gibson 2004). Dose escalation or the addition of another controller medication are the two options available for patients who fail to achieve asthma control. On the other hand, the evidence is sparse regarding the optimal timing of stepping down the dose of ICSs in adult patients with well-controlled asthma (Crossingham et al. 2017). The administration of ICSs at the beginning of an exacerbation in school-aged children with asthma and preschoolers with recurrent wheezing has been the focus of various studies and review articles. Children with intermittent ICS use did not differ significantly in their risk of oral corticosteroid use or other serious health events compared to those with regular ICS use. However, daily ICS use resulted in improved markers of lung function, asthma control, and airway inflammation (Chauhan et al. 2013). A major concern about corticosteroids is their potential adverse effects and although ICSs have fewer and less severe unfavorable reactions, the fact that they are usually administered for long time periods increases the risk of systemic effects, especially in children and the elderly. Inhaled corticosteroids have both local (e.g., oral candidiasis, hoarseness) and systemic (e.g., adrenal suppression, cataracts, osteoporosis) adverse effects. It appears that ICS use is associated with a small decrease in linear growth velocity in children and this effect follows a dose-response curve (Pruteanu et al. 2014; Zhang et al. 2014). Of note, the presence of comorbidities such as allergic rhinitis or atopic dermatitis may further increase the cumulative dose of corticosteroids via different routes of administration. Therefore, patients using high ICS doses for prolonged periods should regularly be monitored for early detection of adverse effects.

7.1.2 ICS/LABA Combination

Long-acting b2-agonists (LABAs) approved for use in patients with asthma include salmeterol, formoterol, and the ultra-long acting (24 h duration of action) vilanterol. Indacaterol and olodaterol are currently approved for use in patients with COPD. They are recommended in combination with ICS, as the next step of treatment in patients aged >5 years with inadequately controlled asthma while receiving a low-to-medium dose of ICS (GINA report 2019). The combination of ICS and LABAs reduced the risk of asthma exacerbations and improved lung function and asthma symptoms compared to the same dose of ICS in adults with asthma

(Ducharme et al. 2010). On the contrary, the addition of a LABA to ICS in children has not been shown to be associated with a reduction in exacerbations requiring systemic steroids compared to ICS monotherapy, but it improved other measures of asthma control (Chauhan et al. 2015). The therapeutic option of a single inhaler both as controller and reliever medication, referred to as "Single Inhaler Therapy" (SiT) or "Single Maintenance and Reliever Therapy" (SMART) has gained popularity in recent years due to its convenience and the potential of improved treatment adherence. In adults and adolescents, the combination of budesonide and formoterol as SiT decreased the risk of asthma exacerbations requiring systemic steroids or hospital admission compared to higher ICS dose/LABA combination inhalers and as-needed SABA (Kew et al. 2013). Three recently published RCTs examined the use of budesonide/formoterol combination as needed in adults and adolescents with mild asthma (Bateman et al. 2018; O'Byrne et al. 2018; Beasley et al. 2019). Similar exacerbation rates were observed in the as-needed budesonide/formoterol and the budesonide maintenance/as needed SABA (albuterol or terbutaline) groups, but daily budesonide offered superior asthma symptom control. Compared to albuterol or terbutaline used as needed, patients who received budesonide/formoterol as needed experienced fewer exacerbations and had improved asthma symptom control. Of note, budesonide/formoterol combination resulted in lower glucocorticoid exposure. Based on the aforementioned RCTs, GINA now recommends as-needed ICS/formoterol as the preferred reliever medication in all levels of asthma severity in adults and adolescents (GINA report 2019). LABAs should not be administered as monotherapy in patients with asthma due to concerns about increased morbidity and mortality. However, accumulating evidence from the current use of fixed-dose combination inhalers has been reassuring and the US Food and Drug Administration concluded that ICS/LABA combination is not associated with an increased risk of serious asthma-related adverse events compared to ICS monotherapy (FDA Drug Safety Communication 2018).

7.1.3 Leukotriene Modifiers

Leukotriene modifiers include three leukotriene receptor antagonists (LTRAs) (montelukast, zafirlukast, pranlukast) and one 5-lipoxygenase inhibitor (zileuton). Availability varies across countries worldwide, but montelukast is by far the most frequently used agent, while zafirlukast is used to a smaller extent in the USA. Leukotriene modifying agents are administered in patients with mild asthma as an alternative to ICS and in patients with more severe disease, as an alternative to an increase in ICS dose or to the addition of LABAs (GINA report 2019). In adults and adolescents with predominantly mild persistent asthma, administration of LTRAs as monotherapy was superior to placebo in reducing the risk of asthma exacerbations and in improving measures of asthma control and quality of life (Miligkos et al. 2015). However, LTRAs are generally considered less effective than ICS treatment in both adults and children. LTRA monotherapy resulted in more asthma exacerbations requiring oral corticosteroids and worse outcomes in lung function, asthma symptoms, and quality of life (Chauhan and Ducharme 2012). The addition of LTRAs to ICS compared with the same, an increased or a tapering dose of ICS in

adults and adolescents with asthma was assessed by Chauhan and colleagues. LTRAs as add-on treatment compared with the same dose of ICS reduced the risk of an asthma exacerbation requiring oral corticosteroids by half and improved most measures of lung function and asthma control, whereas no statistically significant difference was observed for any outcome measure when LTRAs were compared to a higher or a tapering dose of ICS (Chauhan et al. 2017). LTRAs as second-line treatment in adults and children aged >6 years were inferior to LABAs in lung function tests and resulted in a statistically significant, though comparable, increase in asthma exacerbation risk (Chauhan and Ducharme 2014). In preschool children with asthma or recurrent wheezing, maintenance treatment with LTRAs appears less effective than ICS (Castro-Rodriguez and Rodriguez-Martinez 2018). The safety profile of LTRAs in the published RCTs is comparable to either placebo or active drugs (Chauhan and Ducharme 2012; Miligkos et al. 2015). The advantage of once- or twice-daily oral dosing and the theoretical good response in patients with specific characteristics (e.g., concomitant allergic rhinitis, young children) constitutes leukotriene modifying agents a useful therapeutic option mainly in patients who are unwilling or cannot tolerate ICS.

7.1.4 Long-Acting Muscarinic Antagonists

Long-acting muscarinic antagonists (LAMAs) are currently indicated for the treatment of difficult-to-control asthma as add-on medications to ICSs and as an alternative to the combination of ICS/LABA. Tiotropium, administered via a mist inhaler, has been approved for use in patients with asthma aged ≥6 years. The combination of tiotropium/ICS reduced the risk of asthma exacerbations and improved lung function compared to the same ICS dose in 5 RCTs of 2,563 adult patients with asthma, though the evidence for other important measures of efficacy remains inconclusive (Anderson et al. 2015). The addition of tiotropium to ICS did not reduce the risk of asthma exacerbations compared to the addition of salmeterol or formoterol to ICS in around 2,000 adult patients with asthma, but it conferred small though statistically significant improvements in some measures of lung function (Kew et al. 2015). Tiotropium administration as an add-on treatment to the combination of ICS/LABA has also been investigated in adults with asthma, showing small added benefits (Kew and Dahri 2016).

7.1.5 Biologicals

Several targeted therapies are currently available and there are more under development for patients with uncontrolled asthma, despite optimal treatment with inhalers. Omalizumab was the first monoclonal antibody directed against IgE that received marketing authorization approval approximately 15 years ago and as adjunctive treatment to ICS it has been shown to reduce the exacerbation rate and improve symptom control and quality of life in children ≥6 years old and adults with severe uncontrolled asthma (Normansell et al. 2014). In addition, the potential of concurrent treatment of other coexisting allergy-associated conditions, such as allergic rhinitis and severe food allergy, renders omalizumab as an appealing therapeutic option (Humbert et al. 2019). Three more monoclonal antibodies directed against

IL-5 or the IL-5 receptor are approved for use in adults, adolescents (reslizumab, benralizumab), and children >6 years old (mepolizumab) with severe eosinophilic asthma. All of these treatments are able to reduce the number of severe exacerbations, and improve lung function and other markers of asthma control compared to placebo (Pavord et al. 2012; Ortega et al. 2014; Castro et al. 2015; Bleecker et al. 2016; FitzGerald et al. 2016). Of note, both mepolizumab and benralizumab have shown oral corticosteroid-sparing effect in patients relying on systemic corticosteroids to control their asthma (Bel et al. 2014; Nair et al. 2017b). In early 2019, another monoclonal antibody directed against the IL-4 receptor, dupilumab, was approved for adolescents and adults with moderate-to-severe eosinophilic asthma or dependent on oral corticosteroids. Patients who received dupilumab experienced on average fewer severe exacerbations and demonstrated improved lung function and asthma control compared to placebo, with the most prominent effect observed in patients with high eosinophil count at baseline (Castro et al. 2018). In oral corticosteroid-dependent patients, dupilumab administration resulted in significantly reduced use of oral steroids compared to placebo (Rabe et al. 2018). Although the available evidence is limited, no clinically significant adverse events have been observed to date and therefore the aforementioned biologics constitute an important therapeutic option for patients with severe uncontrolled asthma characterized mainly by Th2 inflammation. However, there remains a substantial group of patients with non-Th2 inflammation who do not respond adequately to standard treatment and may also fail current targeted therapies. Various other agents directed against other interleukins (e.g., brodalumab, tezepelumab, RGN3500), inhibitors of prostaglandin D2 receptor (fevipiprant), and inhibitors of the proto-oncogene receptor tyrosine kinase – KIT (imatinib) are currently evaluated in phase 2 or 3 trials and the early promising results remain to be replicated (Corren 2019).

7.1.6 Systemic Corticosteroids

Systemic corticosteroids remain the mainstay of therapy of moderate to severe asthma exacerbations. However, patients with uncontrolled asthma despite optimal treatment and adherence may require regular administration of oral corticosteroids. Long-term corticosteroid therapy is associated with clinically significant and potentially serious adverse effects, and their routine use should be avoided.

7.1.7 Other

Controller medications with limited use nowadays include theophylline and cromones (nedocromil and cromoglycate). Theophylline is an oral bronchodilator with inferior efficacy to ICSs (Dahl et al. 2002) or LABAs (Tee et al. 2007) and increased risk of adverse effects, including life-threatening cardiovascular and neurologic toxicity (Cooling 1993). Cromones are inhaled medications with a favorable safety profile, though they are considered less effective than low-dose ICS in both adults and children with asthma (Guevara et al. 2006; Sridhar and McKean 2006).

7.2 Allergen Immunotherapy

Allergen immunotherapy (AIT) is a procedure inducing tolerance to a specific allergen, by repetitive administration of the implicated allergen and there is increasing need for treatment modalities, which will benefit patients with allergic asthma. In 2019, the European Academy of Allergy and Clinical Immunology (EAACI) published a practice guideline for the use of house dust mites (HDM) AIT as add-on treatment for HDM-driven allergic asthma in children and adults (Agache et al. 2019). The currently available routes of administration evaluated in the guideline included the subcutaneous (SCIT) and the sublingual (SLIT) immunotherapy. HDM-SCIT is recommended for children and adults with controlled HDM-driven allergic asthma as an add-on treatment to decrease symptoms and medication use, though the absence of solid evidence regarding the exacerbation rate and markers of asthma control and lung function precluded any recommendation about these important outcomes (Agache et al. 2019). Likewise, HDM-SLIT drop preparations are recommended for children with controlled HDM-driven allergic asthma as an adjunctive treatment to control symptoms and decrease drugs utilization (Agache et al. 2019). Based on moderate quality evidence, the guideline recommends the use of HDM-SLIT tablets for adults with controlled or partially controlled HDM-driven asthma as an add-on treatment to regular pharmacotherapy, to reduce the risk of exacerbations and improve asthma control (Agache et al. 2019). Due to lack of safety data in patients with uncontrolled asthma, HDM-AIT is contraindicated in those patients. Overall, AIT has shown significant benefits in selected patients with allergen-triggered asthma (Dhami et al. 2017). However, the increased risk of publication bias and adverse events as well the amount of clinical (e.g., different kinds of allergens, monosensitized vs. polysensitized patients) and methodological heterogeneity (e.g., absence of validated symptom assessment tools) observed in the published systematic reviews reduces generalizability of the conclusions (Abramson et al. 2010; Dhami et al. 2017).

7.3 Reliever Medications

Rapid-acting b2-agonists were until recently the preferred treatment option for patients with acute respiratory symptoms, including short-acting agents such as salbutamol, terbutaline and the long-acting b2-agonist, formoterol. Traditionally, short-acting b2-agonists (SABAs) were prescribed to every patient with a diagnosis of asthma to be used on an as-needed basis in order to relieve symptoms due to bronchospasm. In addition, for patients with intermittent asthma (i.e., asthma symptoms less than twice a month, no nighttime awakening in the past month and no exacerbation in the previous year) SABAs were the only recommended medication (GINA report 2018; NAEPP EPR3 on the Diagnosis and Management of Asthma 2007). However, the fact that patients with even mild asthma may have severe exacerbations or progressive loss of lung function and the observed overconsumption of SABA by a significant proportion of patients caused a paradigm shift in

recent guidelines (GINA report 2019). In summary, SABAs are not any more considered as the best choice as single inhalers for patients with intermittent asthma and they are currently not the preferred reliever medication for all other patients. Formoterol, due to its rapid onset of action compared to other LABAs, is now recommended in combination with ICS as needed in patients with either intermittent or persistent disease (GINA report 2019). Ipratropium, an anticholinergic agent, is frequently administered in patients with acute asthma in the hospital setting, though the presence of incremental benefit to SABA therapy is questioned (Vezina et al. 2014).

7.4 Non-pharmacological Interventions

As with every chronic condition, a variety of factors interplay and contribute to a disease flare-up. Therefore, in addition to pharmacological treatments, there are other strategies to be considered where relevant, though strong evidence for most of them is lacking. These include but are not limited to smoke, allergen or occupational exposure avoidance, medication avoidance (e.g., NSAIDs), adoption of a healthy lifestyle (e.g., healthy diet, normal weight, regular physical activity), and vaccinations, especially for the prevention of pneumococcal disease and influenza. Bronchial thermoplasty is indicated for cautiously selected adult patients with difficult-to-control asthma despite adequate pharmacotherapy and it involves treatment of the airways with radiofrequency pulses.

References

Abramson MJ, Puy RM, Weiner JM (2010) Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 8:CD001186. https://doi.org/10.1002/14651858.CD001186.pub2

Adams N, Lasserson TJ, Cates CJ, Jones PW (2007) Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Cochrane Database Syst Rev 4: CD002310. https://doi.org/10.1002/14651858.CD002310.pub4

Agache I, Lau S, Akdis CA et al (2019) EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. Allergy 74:855–873. https://doi.org/10.1111/all.13749

Akdis M, Aab A, Altunbulakli C et al (2016) 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 138:984–1010. https://doi.org/10.1016/j.jaci.2016.06.033

Aldrimer M, Ridefelt P, Rodoo P et al (2013) Population-based pediatric reference intervals for hematology, iron and transferrin. Scand J Clin Lab Invest 73:253–261. https://doi.org/10.3109/00365513.2013.769625

Amat F, Labbe A (2018) Biomarkers for severe allergic asthma in children: could they be useful to guide disease control and use of omalizumab? Expert Rev Respir Med 12:475–482. https://doi.org/10.1080/17476348.2018.1475233

Anandan C, Nurmatov U, van Schayck OC, Sheikh A (2010) Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy 65:152–167. https://doi.org/10.1111/j.1398-9995.2009.02244.x

Anderson DE, Kew KM, Boyter AC (2015) Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. Cochrane Database Syst Rev 8:CD011397. https://doi.org/10.1002/14651858.CD011397.pub2

Andreakos E, Papadopoulos NG (2014) IL-25: the missing link between allergy, viral infection, and asthma? Sci Transl Med 6:256fs38. https://doi.org/10.1126/scitranslmed.3010273

Annunziato F, Romagnani C, Romagnani S (2015) The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol 135:626–635. https://doi.org/10.1016/j.jaci.2014.11.001

Bacharier LB, Boner A, Carlsen KH et al (2008) Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 63:5–34. https://doi.org/10.1111/j.1398-9995.2007.01586.x

Backman H, Raisanen P, Hedman L et al (2017) Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016-results from three population surveys. Clin Exp Allergy 47:1426–1435. https://doi.org/10.1111/cea.12963

Bannier M, Rosias PPR, Jobsis Q, Dompeling E (2019) Exhaled breath condensate in childhood asthma: a review and current perspective. Front Pediatr 7:150. https://doi.org/10.3389/fped.2019.00150

Barlow JL, Flynn RJ, Ballantyne SJ, McKenzie AN (2011) Reciprocal expression of IL-25 and IL-17A is important for allergic airways hyperreactivity. Clin Exp Allergy 41:1447–1455. https://doi.org/10.1111/j.1365-2222.2011.03806.x

Bateman ED, Reddel HK, O'Byrne PM et al (2018) As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 378:1877–1887. https://doi.org/10.1056/NEJMoa1715275

Beasley R, Holliday M, Reddel HK et al (2019) Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 380:2020–2030. https://doi.org/10.1056/NEJMoa1901963

Bel EH, Wenzel SE, Thompson PJ et al (2014) Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 371:1189–1197. https://doi.org/10.1056/NEJMoa1403291

Bielor C, Sopel N, Maier A et al (2017) Role of TGF-beta in anti-rhinovirus immune responses in asthmatic patients. J Allergy Clin Immunol 140:283–286 e10. https://doi.org/10.1016/j.jaci.2016.10.049

Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69:89–95. https://doi.org/10.1067/mcp.2001.113989

Bisgaard H, Hermansen MN, Buchvald F et al (2007) Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med 357:1487–1495. https://doi.org/10.1056/NEJMoa052632

Blanchard C, Mingler MK, McBride M et al (2008) Periostin facilitates eosinophil tissue infiltration in allergic lung and esophageal responses. Mucosal Immunol 1:289–296. https://doi.org/10.1038/mi.2008.15

Bleecker ER, FitzGerald JM, Chanez P et al (2016) Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 388:2115–2127. https://doi.org/10.1016/S0140-6736(16)31324-1

Bossios A, Psarras S, Gourgiotis D et al (2005) Rhinovirus infection induces cytotoxicity and delays wound healing in bronchial epithelial cells. Respir Res 6:114. https://doi.org/10.1186/1465-9921-6-114

Bush A (2019) Pathophysiological mechanisms of asthma. Front Pediatr 7:68. https://doi.org/10.3389/fped.2019.00068

Castro M, Zangrilli J, Wechsler ME et al (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3:355–366. https://doi.org/10.1016/S2213-2600(15)00042-9

Castro M, Corren J, Pavord ID et al (2018) Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378:2486–2496. https://doi.org/10.1056/NEJMoa1804092

Castro-Rodriguez JA, Rodriguez-Martinez CE (2018) Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: a systematic review. Pediatr Pulmonol 53:1670–1677. https://doi.org/10.1002/ppul.24176

Chang Y, Al-Alwan L, Risse PA et al (2012) Th17-associated cytokines promote human airway smooth muscle cell proliferation. FASEB J 26:5152–5160. https://doi.org/10.1096/fj.12-208033

Chauhan BF, Ducharme FM (2012) Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev 5:Cd002314. https://doi.org/10.1002/14651858.CD002314.pub3

Chauhan BF, Ducharme FM (2014) Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 1:Cd003137. https://doi.org/10.1002/14651858.CD003137.pub5

Chauhan BF, Chartrand C, Ducharme FM (2013) Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. Cochrane Database Syst Rev 2:CD009611. https://doi.org/10.1002/14651858.CD009611.pub3

Chauhan BF, Chartrand C, Ni Chroinin M et al (2015) Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 11:Cd007949. https://doi.org/10.1002/14651858.CD007949.pub2

Chauhan BF, Jeyaraman MM, Singh Mann A et al (2017) Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma. Cochrane Database Syst Rev 3:Cd010347. https://doi.org/10.1002/14651858.CD010347.pub2

Cheng D, Xue Z, Yi L et al (2014) Epithelial interleukin-25 is a key mediator in Th2-high, corticosteroid-responsive asthma. Am J Respir Crit Care Med 190:639–648. https://doi.org/10.1164/rccm.201403-0505OC

Chung KF (2015) Targeting the interleukin pathway in the treatment of asthma. Lancet 386:1086–1096. https://doi.org/10.1016/S0140-6736(15)00157-9

Comberiati P, Katial RK, Covar RA (2018) Bronchoprovocation testing in asthma: an update. Immunol Allergy Clin N Am 38:545–571. https://doi.org/10.1016/j.iac.2018.06.010

Cooling DS (1993) Theophylline toxicity. J Emerg Med 11:415–425

Corren J (2019) New targeted therapies for uncontrolled asthma. J Allergy Clin Immunol Pract 7:1394–1403. https://doi.org/10.1016/j.jaip.2019.03.022

Crossingham I, Evans DJ, Halcovitch NR, Marsden PA (2017) Stepping down the dose of inhaled corticosteroids for adults with asthma. Cochrane Database Syst Rev 2:CD011802. https://doi.org/10.1002/14651858.CD011802.pub2

Dahl R, Larsen BB, Venge P (2002) Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. Respir Med 96:432–438

Davis MD, Montpetit AJ (2018) Exhaled breath condensate: an update. Immunol Allergy Clin N Am 38:667–678. https://doi.org/10.1016/j.iac.2018.06.002

Dhami S, Kakourou A, Asamoah F et al (2017) Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy 72:1825–1848. https://doi.org/10.1111/all.13208

Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ (2010) Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 5:Cd005535. https://doi.org/10.1002/14651858.CD005535.pub2

Durack J, Lynch SV, Nariya S et al (2017) Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. J Allergy Clin Immunol 140:63–75. https://doi.org/10.1016/j.jaci.2016.08.055

Erpenbeck VJ, Popov TA, Miller D et al (2016) The oral CRTh2 antagonist QAW039 (fevipiprant): a phase II study in uncontrolled allergic asthma. Pulm Pharmacol Ther 39:54–63. https://doi.org/10.1016/j.pupt.2016.06.005

European Respiratory Society (2013) The European lung white book. Respiratory health and disease in Europe. European Respiratory Society Publications, Sheffield

Fajt ML, Gelhaus SL, Freeman B et al (2013) Prostaglandin D(2) pathway upregulation: relation to asthma severity, control, and TH2 inflammation. J Allergy Clin Immunol 131:1504–1512. https://doi.org/10.1016/j.jaci.2013.01.035

FDA Drug Safety Communication (2018) FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-no-significant-increase-risk-serious-asthma-outcomes

Ferraro V, Carraro S, Bozzetto S et al (2018) Exhaled biomarkers in childhood asthma: old and new approaches. Asthma Res Pract 4:9. https://doi.org/10.1186/s40733-018-0045-6

FitzGerald JM, Bleecker ER, Nair P et al (2016) Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 388:2128–2141. https://doi.org/10.1016/S0140-6736(16)31322-8

FitzGerald JM, Bleecker ER, Menzies-Gow A et al (2018) Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med 6:51–64. https://doi.org/10.1016/S2213-2600(17)30344-2

Fitzpatrick AM, Jackson DJ, Mauger DT et al (2016) Individualized therapy for persistent asthma in young children. J Allergy Clin Immunol 138:1608–1618 e12. https://doi.org/10.1016/j.jaci.2016.09.028

Gabet S, Just J, Couderc R et al (2016) Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. Pediatr Allergy Immunol 27:831–837. https://doi.org/10.1111/pai.12622

Gandhi NA, Pirozzi G, Graham NMH (2017) Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 13:425–437. https://doi.org/10.1080/1744666X.2017.1298443

Genuneit J, Seibold AM, Apfelbacher CJ et al (2017) Overview of systematic reviews in allergy epidemiology. Allergy 72:849–856. https://doi.org/10.1111/all.13123

Global Initiative for Asthma (2017) Global strategy for asthma management and prevention. www.ginasthma.org

Global Initiative for Asthma (2018) Global strategy for asthma management and prevention. www.ginasthma.org

Global Initiative for Asthma (2019) Global strategy for asthma management and prevention. www.ginasthma.org

Gough H, Grabenhenrich L, Reich A et al (2015) Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr Allergy Immunol 26:431–437. https://doi.org/10.1111/pai.12410

Guevara JP, Ducharme FM, Keren R et al (2006) Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Cochrane Database Syst Rev 2:CD003558. https://doi.org/10.1002/14651858.CD003558.pub2

Halim TY, Krauss RH, Sun AC, Takei F (2012) Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. Immunity 36:451–463. https://doi.org/10.1016/j.immuni.2011.12.020

Hanania NA, Noonan M, Corren J et al (2015) Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. Thorax 70:748–756. https://doi.org/10.1136/thoraxjnl-2014-206719

Humbert M, Bousquet J, Bachert C et al (2019) IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. J Allergy Clin Immunol Pract 7:1418–1429. https://doi.org/10.1016/j.jaip.2019.02.030

Jackson DJ, Makrinioti H, Rana BM et al (2014) IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. Am J Respir Crit Care Med 190:1373–1382. https://doi.org/10.1164/rccm.201406-1039OC

Jarjour NN, Erzurum SC, Bleecker ER et al (2012) Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. Am J Respir Crit Care Med 185:356–362. https://doi.org/10.1164/rccm.201107-1317PP

Johansson SG, Bieber T, Dahl R et al (2004) Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 113:832–836. https://doi.org/10.1016/j.jaci.2003.12.591

Karrasch S, Linde K, Rucker G et al (2017) Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 72:109–116. https://doi.org/10.1136/thoraxjnl-2016-208704

Kew KM, Dahri K (2016) Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev 1:CD011721. https://doi.org/10.1002/14651858.CD011721.pub2

Kew KM, Karner C, Mindus SM, Ferrara G (2013) Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev 12:Cd009019. https://doi.org/10.1002/14651858.CD009019.pub2

Kew KM, Evans DJW, Allison DE, Boyter AC (2015) Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. Cochrane Database Syst Rev 6:CD011438. https://doi.org/10.1002/14651858.CD011438.pub2

Knihtila H, Kotaniemi-Syrjanen A, Pelkonen AS et al (2018) Small airway function in children with mild to moderate asthmatic symptoms. Ann Allergy Asthma Immunol 121:451–457. https://doi.org/10.1016/j.anai.2018.07.026

Konstantinidi EM, Lappas AS, Tzortzi AS, Behrakis PK (2015) Exhaled breath condensate: technical and diagnostic aspects. Sci World J 2015:435160. https://doi.org/10.1155/2015/435160

Konstantinou GN, Xepapadaki P, Manousakis E et al (2013) Assessment of airflow limitation, airway inflammation, and symptoms during virus-induced wheezing episodes in 4- to 6-year-old children. J Allergy Clin Immunol 131:87–93 e1-5. https://doi.org/10.1016/j.jaci.2012.10.033

Korevaar DA, Westerhof GA, Wang J et al (2015) Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med 3:290–300. https://doi.org/10.1016/S2213-2600(15)00050-8

Kupczyk M, Dahlen B, Sterk PJ et al (2014) Stability of phenotypes defined by physiological variables and biomarkers in adults with asthma. Allergy 69:1198–1204. https://doi.org/10.1111/all.12445

Kuruvilla ME, Lee FE, Lee GB (2019) Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 56:219–233. https://doi.org/10.1007/s12016-018-8712-1

Kytikova O, Novgorodtseva T, Denisenko Y et al (2019) Pro-resolving lipid mediators in the pathophysiology of asthma. Medicina 55:284. https://doi.org/10.3390/medicina55060284

Lefaudeux D, De Meulder B, Loza MJ et al (2017) U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. J Allergy Clin Immunol 139:1797–1807. https://doi.org/10.1016/j.jaci.2016.08.048

Leuppi JD (2014) Bronchoprovocation tests in asthma: direct versus indirect challenges. Curr Opin Pulm Med 20:31–36. https://doi.org/10.1097/MCP.0000000000000009

Liu AH, Babineau DC, Krouse RZ et al (2016) Pathways through which asthma risk factors contribute to asthma severity in inner-city children. J Allergy Clin Immunol 138:1042–1050. https://doi.org/10.1016/j.jaci.2016.06.060

Lundback B, Backman H, Lotvall J, Ronmark E (2016) Is asthma prevalence still increasing? Expert Rev Respir Med 10:39–51. https://doi.org/10.1586/17476348.2016.1114417

MacNeil J, Loves RH, Aaron SD (2016) Addressing the misdiagnosis of asthma in adults: where does it go wrong? Expert Rev Respir Med 10:1187–1198. https://doi.org/10.1080/17476348.2016.1242415

Matsumoto H (2014) Serum periostin: a novel biomarker for asthma management. Allergol Int 63:153–160. https://doi.org/10.2332/allergolint.13-RAI-0678

Megremis S, Niespodziana K, Cabauatan C et al (2018) Rhinovirus species-specific antibodies differentially reflect clinical outcomes in health and asthma. Am J Respir Crit Care Med 198:1490–1499. https://doi.org/10.1164/rccm.201803-0575OC

Miligkos M, Bannuru RR, Alkofide H et al (2015) Leukotriene-receptor antagonists versus placebo in the treatment of asthma in adults and adolescents: a systematic review and meta-analysis. Ann Intern Med 163:756–767. https://doi.org/10.7326/M15-1059

Momen T, Ahanchian H, Reisi M et al (2017) Comparison of interleukin-33 serum levels in asthmatic patients with a control group and relation with the severity of the disease. Int J Prev Med 8:65. https://doi.org/10.4103/ijpvm.IJPVM_179_16

Morita H, Nakae S, Saito H, Matsumoto K (2017) IL-33 in clinical practice: size matters? J Allergy Clin Immunol 140:381–383. https://doi.org/10.1016/j.jaci.2017.03.042

Mosmann TR, Cherwinski H, Bond MW et al (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136:2348–2357

Murray CS, Woodcock A, Custovic A (2001) The role of indoor allergen exposure in the development of sensitization and asthma. Curr Opin Allergy Clin Immunol 1:407–412. https://doi.org/10.1097/01.all.0000011053.76412.14

Nair P, Martin JG, Cockcroft DC et al (2017a) Airway hyperresponsiveness in asthma: measurement and clinical relevance. J Allergy Clin Immunol Pract 5:649–659 e2. https://doi.org/10.1016/j.jaip.2016.11.030

Nair P, Wenzel S, Rabe KF et al (2017b) Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 376:2448–2458. https://doi.org/10.1056/NEJMoa1703501

National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma (2007) Expert Panel Report 3: guidelines for the diagnosis and management of asthma. National Heart, Lung, and Blood Institute, Bethesda. https://www.ncbi.nlm.nih.gov/books/NBK7232/

Normansell R, Walker S, Milan SJ et al (2014) Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 1:CD003559. https://doi.org/10.1002/14651858.CD003559.pub4

Normansell R, Kew KM, Mathioudakis AG (2017) Interventions to improve inhaler technique for people with asthma. Cochrane Database Syst Rev 3:CD012286. https://doi.org/10.1002/14651858.CD012286.pub2

Ntontsi P, Bakakos P, Papathanasiou E et al (2018) Exhaled breath temperature in optimally treated asthmatics: severity and underlying mechanisms. J Breath Res 12:026013. https://doi.org/10.1088/1752-7163/aa9d46

O'Byrne PM, FitzGerald JM, Bateman ED et al (2018) Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 378:1865–1876. https://doi.org/10.1056/NEJMoa1715274

Oksel C, Granell R, Haider S et al (2019) Distinguishing wheezing phenotypes from infancy to adolescence: a pooled analysis of five birth cohorts. Ann Am Thorac Soc 16:868–876. https://doi.org/10.1513/AnnalsATS.201811-837OC

Ortega HG, Liu MC, Pavord ID et al (2014) Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 371:1198–1207. https://doi.org/10.1056/NEJMoa1403290

Papadopoulos NG, Custovic A, Cabana MD et al (2019) Pediatric asthma: an unmet need for more effective, focused treatments. Pediatr Allergy Immunol 30:7–16. https://doi.org/10.1111/pai.12990

Papi A, Brightling C, Pedersen SE, Reddel HK (2018) Asthma. Lancet 391:783–800. https://doi.org/10.1016/S0140-6736(17)33311-1

Pavord ID, Korn S, Howarth P et al (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 380:651–659. https://doi.org/10.1016/S0140-6736(12)60988-X

Pavord ID, Beasley R, Agusti A et al (2018) After asthma: redefining airways diseases. Lancet 391:350–400. https://doi.org/10.1016/S0140-6736(17)30879-6

Peebles RS, Aronica MA (2019) Proinflammatory pathways in the pathogenesis of asthma. Clin Chest Med 40:29–50. https://doi.org/10.1016/j.ccm.2018.10.014

Pijnenburg MW (2019) The role of FeNO in predicting asthma. Front Pediatr 7:41. https://doi.org/10.3389/fped.2019.00041

Popov TA, Kralimarkova TZ, Labor M, Plavec D (2017) The added value of exhaled breath temperature in respiratory medicine. J Breath Res 11:034001. https://doi.org/10.1088/1752-7163/aa7801

Powell H, Gibson PG (2004) High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database Syst Rev 2:CD004109. https://doi.org/10.1002/14651858.CD004109.pub2

Pruteanu AI, Chauhan BF, Zhang L et al (2014) Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Cochrane Database Syst Rev 7:CD009878. https://doi.org/10.1002/14651858.CD009878.pub2

Psarras S, Volonaki E, Skevaki CL et al (2006) Vascular endothelial growth factor-mediated induction of angiogenesis by human rhinoviruses. J Allergy Clin Immunol 117:291–297. https://doi.org/10.1016/j.jaci.2005.11.005

Rabe KF, Nair P, Brusselle G et al (2018) Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 378:2475–2485. https://doi.org/10.1056/NEJMoa1804093

Radhakrishnan D, Guttmann A, To T et al (2019) Generational patterns of asthma incidence among immigrants to Canada over two decades. A population-based cohort study. Ann Am Thorac Soc 16:248–257. https://doi.org/10.1513/AnnalsATS.201803-187OC

Ring J, Jutel M, Papadopoulos N et al (2018) Provocative proposal for a revised nomenclature for allergy and other hypersensitivity diseases. Allergy 73:1939–1940. https://doi.org/10.1111/all.13561

Robinson D, Humbert M, Buhl R et al (2017) Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. Clin Exp Allergy 47:161–175. https://doi.org/10.1111/cea.12880

Ronmark E, Bjerg A, Perzanowski M et al (2009) Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. J Allergy Clin Immunol 124:357–63 e1-15. https://doi.org/10.1016/j.jaci.2009.05.011

Rosenberg HF, Phipps S, Foster PS (2007) Eosinophil trafficking in allergy and asthma. J Allergy Clin Immunol 119:1303–1310. ; quiz 1311-2. https://doi.org/10.1016/j.jaci.2007.03.048

Rufo JC, Madureira J, Fernandes EO, Moreira A (2016) Volatile organic compounds in asthma diagnosis: a systematic review and meta-analysis. Allergy 71:175–188. https://doi.org/10.1111/all.12793

Saglani S, Custovic A (2019) Childhood asthma: advances using machine learning and mechanistic studies. Am J Respir Crit Care Med 199:414–422. https://doi.org/10.1164/rccm.201810-1956CI

Saglani S, Menzie-Gow AN (2019) Approaches to asthma diagnosis in children and adults. Front Pediatr 7:148. https://doi.org/10.3389/fped.2019.00148

Samolinski B, Fronczak A, Kuna P et al (2012) Prevention and control of childhood asthma and allergy in the EU from the public health point of view: Polish Presidency of the European Union. Allergy 67:726–731. https://doi.org/10.1111/j.1398-9995.2012.02822.x

Schneider A, Gindner L, Tilemann L et al (2009) Diagnostic accuracy of spirometry in primary care. BMC Pulm Med 9:31. https://doi.org/10.1186/1471-2466-9-31

Selroos O, Kupczyk M, Kuna P et al (2015) National and regional asthma programmes in Europe. Eur Respir Rev 24:474–483. https://doi.org/10.1183/16000617.00008114

Serhan CN, Levy BD (2018) Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest 128:2657–2669. https://doi.org/10.1172/JCI97943

Sirois P (2019) Leukotrienes: one step in our understanding of asthma. Respir Investig 57:97–110. https://doi.org/10.1016/j.resinv.2018.12.003

Skevaki CL, Psarras S, Volonaki E et al (2012) Rhinovirus-induced basic fibroblast growth factor release mediates airway remodeling features. Clin Transl Allergy 2:14. https://doi.org/10.1186/2045-7022-2-14

Skloot GS (2016) Asthma phenotypes and endotypes: a personalized approach to treatment. Curr Opin Pulm Med 22:3–9. https://doi.org/10.1097/MCP.0000000000000225

Soto-Quiros M, Avila L, Platts-Mills TA et al (2012) High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J Allergy Clin Immunol 129:1499–1505 e5. https://doi.org/10.1016/j.jaci.2012.03.040

Sridhar AV, McKean M (2006) Nedocromil sodium for chronic asthma in children. Cochrane Database Syst Rev 3:CD004108. https://doi.org/10.1002/14651858.CD004108.pub2

Sterk PJ, Lutter R (2014) Asthma phenotyping: TH2-high, TH2-low, and beyond. J Allergy Clin Immunol 133:395–396. https://doi.org/10.1016/j.jaci.2013.10.008

Stokes JR, Casale TB (2016) Characterization of asthma endotypes: implications for therapy. Ann Allergy Asthma Immunol 117:121–125. https://doi.org/10.1016/j.anai.2016.05.016

Sullivan A, Hunt E, MacSharry J, Murphy DM (2016) The microbiome and the pathophysiology of asthma. Respir Res 17:163. https://doi.org/10.1186/s12931-016-0479-4

Teague WG, Phillips BR, Fahy JV et al (2018) Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. J Allergy Clin Immunol Pract 6:545–554 e4. https://doi.org/10.1016/j.jaip.2017.05.032

Tee AKH, Koh MS, Gibson PG et al (2007) Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. Cochrane Database Syst Rev 3:CD001281. https://doi.org/10.1002/14651858.CD001281.pub2

To T, Stanojevic S, Moores G et al (2012) Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 12:204. https://doi.org/10.1186/1471-2458-12-204

Toppila-Salmi S, Huhtala H, Karjalainen J et al (2015) Sensitization pattern affects the asthma risk in Finnish adult population. Allergy 70:1112–1120. https://doi.org/10.1111/all.12670

Toppila-Salmi S, Chanoine S, Karjalainen J et al (2019) Risk of adult-onset asthma increases with the number of allergic multimorbidities and decreases with age. Allergy 74:2406–2416. https://doi.org/10.1111/all.13971

Turner S (2015) Exhaled nitric oxide and the management of childhood asthma--yet another promising biomarker “has been” or a misunderstood gem. Paediatr Respir Rev 16:88–96. https://doi.org/10.1016/j.prrv.2014.07.005

Ullmann N, Bossley CJ, Fleming L et al (2013) Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. Allergy 68:402–406. https://doi.org/10.1111/all.12101

van Vliet D, Smolinska A, Jobsis Q et al (2017) Can exhaled volatile organic compounds predict asthma exacerbations in children? J Breath Res 11:016016. https://doi.org/10.1088/1752-7163/aa5a8b

Veldhoen M (2017) Interleukin 17 is a chief orchestrator of immunity. Nat Immunol 18:612–621. https://doi.org/10.1038/ni.3742

Vezina K, Chauhan BF, Ducharme FM (2014) Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev 7:CD010283. https://doi.org/10.1002/14651858.CD010283.pub2

Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2

Wenzel SE (2012) Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 18:716–725. https://doi.org/10.1038/nm.2678

Westerhof GA, Korevaar DA, Amelink M, de Nijs SB, de Groot JC, Wang J, Weersink EJ, ten Brinke A, Bossuyt PM, Bel EH (2015) Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. Eur Respir J 46:688–696. https://doi.org/10.1183/09031936.00012415

Xepapadaki P, Papadopoulos NG, Bossios A et al (2005) Duration of postviral airway hyperresponsiveness in children with asthma: effect of atopy. J Allergy Clin Immunol 116:299–304. https://doi.org/10.1016/j.jaci.2005.04.007

Xepapadaki P, Xatziioannou A, Chatzicharalambous M et al (2010) Exhaled breath temperature increases during mild exacerbations in children with virus-induced asthma. Int Arch Allergy Immunol 153:70–74. https://doi.org/10.1159/000301581

Xepapadaki P, Bachert C, Finotto S et al (2018) Contribution of repeated infections in asthma persistence from preschool to school age: design and characteristics of the PreDicta cohort. Pediatr Allergy Immunol 29:383–393. https://doi.org/10.1111/pai.12881

Zhang L, Prietsch SOM, Ducharme FM (2014) Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database Syst Rev 7:CD009471. https://doi.org/10.1002/14651858.CD009471.pub2

Allergic Conjunctivitis: An Update

Arthur Mueller

Contents

Abstract

Conjunctivitis is a frequent disease of the eye with the typical clinical sign being the "red eye" and comprises a very heterogeneous group with different causes. In general, infectious conjunctivitis must be strictly differentiated from non-infectious conjunctivitis. Allergic conjunctivitis is a subtype of non-infectious conjunctivitis and imposes as an acute, intermittent or chronic, inflammation which is most frequently caused by airborne allergens. The leading clinical sign is chemosis, and patients typically complain about itching. Allergic conjunctivitis is often a reaction to topical and systemic drugs or cosmetics as well as animal hairs from cats and/or dogs. Allergic conjunctivitis is sub-classified into the following forms: seasonal allergic conjunctivitis (also termed: hay fever conjunctivitis), atopic conjunctivitis, vernal conjunctivitis, upper limbal (kerato-) conjunctivitis, and conjunctivitis associated with various oculomucocutaneous syndromes. In each form, there are distinctive features in: clinical appearance, generating agent(s), as well as treatment as listed here.

Keywords

Allergy · Atopic conjunctivitis · Conjunctivitis · Eye · Hay fever conjunctivitis · Seasonal allergic conjunctivitis · Vernal conjunctivitis

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Conjunctivitis is a frequent disease of the eye. It affects everyone at least once in his/her lifetime. The typical clinical sign of conjunctivitis is the "red eye" which results from an increase of blood filling the conjunctival vessels (hyperemia). Conjunctivitis may also be accompanied by symptoms such as secretion and chemosis (swelling of the conjunctiva). The secretion is either watery, mucous, or purulent and chemosis is usually mild to moderate. During allergic conditions chemosis can manifest as a massive protrusion to such a degree that the affected patient is unable to close his eye lids. The presence or absence of chemosis as well as the type of secretion is distinctive and helps identifying the different causes of conjunctivitis (Grehn 2012).

Infectious conjunctivitis should be strictly distinguished from non-infectious conjunctivitis. However, in some cases non-infectious conjunctivitis can be superinfected by infectious agents. In the case of primarily infectious or secondarily superinfected conjunctivitis, effective therapy must include antibiotic, antiviral and/or antimycotic drugs based on the clinical findings and microbiological results. However, any "overtreatment" (e.g., topically administered antibiotics when not indicated) may substantially complicate any type of conjunctivitis because the antibiotics themselves as well as the preservatives in eye drops or ointments can induce or complicate allergic reactions.

Within the group of non-infectious conjunctivitis, two major types may be differentiated: unspecific conjunctivitis and allergic conjunctivitis. Unspecific conjunctivitis most often results from lack of tears ("dry eye syndrome") or other forms of dyslacrimia. Other less frequent causes include various external conditions such as extensive exposure of the eyes to smoke, dust, heat, cold, wind, and ultraviolet light or other physical eye issues. Moreover, multiple other conditions can lead to unspecific conjunctivitis. These conditions include lid anomalies, uncorrected refractive errors, disorders of binocular vision, as well as stress, lack of sleep, and strenuous overnight work. A relatively frequent cause of unspecific conjunctivitis is overworn contact lenses or the use of dirty and otherwise compromised contact lenses. All these causes of unspecific conjunctivitis are often termed "allergic," which is misleading because the immune system is not activated in any of these.

In contrast to the aforementioned type, true allergic conjunctivitis is an acute, intermittent or chronic, non-infectious inflammation which is most frequently caused by airborne allergens (Ono and Abelson 2005). Allergic conjunctivitis is a type-I-hypersensitive reaction. Patients with multiple allergies are especially prone to the development of allergic conjunctivitis. In contrast to other forms of conjunctivitis, patients with allergic conjunctivitis often complain about itching. In addition, chemosis is the leading clinical sign. The appearance of chemosis is usually transparent with either little or no watery discharge. Allergic conjunctivitis is often a reaction to topical and systemic drugs or cosmetics. Animal hairs (cats, dogs) can be another source for allergic reaction. In case of animal "hair-induced" allergic conjunctivitis the causing agent for allergic reaction are not the hairs themselves, but instead the animal's saliva that is adhered to the hairs (Friedlaender 1998).

Allergic conjunctivitis is sub-classified into the following forms. If possible, for each form the distinctive features in clinical appearance, causing agent(s), as well as treatment are listed.

(a) Seasonal allergic conjunctivitis (hay fever conjunctivitis)

Seasonal allergic conjunctivitis is an allergic reaction to pollen and other plant derived allergens. It is most prevalent at the time of blooming for grasses and plants and is, therefore, most common during spring and early fall. Seasonal allergic conjunctivitis is typically accompanied by a watery rhinitis with patients experiencing intensive tearing and sneezing. In addition, chemosis and foreign body sensation are frequent symptoms. Whenever possible, the patients should get general desensitization against the causing grasses and plants. Local therapy includes astringent eye drops, and in extreme cases local steroids may be used for a limited time. For recurrent cases, prophylactic treatment with eye drops containing chromoglycinacid, lodoxamid, or olopatadin (preferably without conserving agents) is helpful to prevent exacerbation of seasonal conjunctivitis, because these agents inhibit mast cell degranulation (Anderson 2001).

(b) Atopic conjunctivitis, (kerato-) conjunctivitis eccematosa, and phlyctaenulosa

Atopic conjunctivitis is particularly found among atopic children and results from an allergy against bacterial toxins, dust, mites, or animal dandruff. It is often found in children who are undernourished or living in less hygienic conditions. The symptoms are typically present throughout the entire year. The conjunctiva is affected with little knots which may also be found on the cornea and can lead to corneal scarring. During the acute phase, the patients are largely affected by bright light and by intensive tearing. Conjunctivitis phlyctaenulosa is often associated with tuberculosis which must be first ruled out, and then in acute phases, local antibiotics and steroids are administered. In case of corneal scarring, a keratoplasty might become necessary, but should only by carried out when no acute inflammation is present.

(c) Vernal Conjunctivitis

Vernal conjunctivitis is a bilateral severe allergic reaction which affects mainly boys and male teenagers. It can either occur isolated or with a general atopic condition such as asthma, eczema, or general seasonal allergies. Vernal conjunctivitis is exacerbated often during springtime. In this disease, an IGE-associated immune reaction plays a major role. There are three clinical types: tarsal or conjunctival, limbal, and a type in which corneal complications are most prevalent. In case of the conjunctival or tarsal type the upper tarsus shows square, flat, gray to reddish appearing paving-stone like papillae, where in the limbal type the pericorneal conjunctiva is hypertrophic with a grayish color, and in 3–11% of cases corneal ulcers develop. For all three types, steroid eye drops are helpful, and to prevent

reoccurrences, eye drops containing chromoglycinacid, lodoxamid, or olopatadin should also be administered in the disease-free interval. The latter eye drops should also be used continuously as a prophylaxis. This reduces recurrent exacerbation of vernal conjunctivitis and, thus, less or no corticosteroid eye drops are necessary in the acute phase.

(d) Upper Limbal (Kerato-) Conjunctivitis

Upper limbal keratoconjunctivitis is a chronic inflammation associated with thyroid diseases and mostly affects women.

(e) Oculomucocutaneous Syndromes

A group of rare but especially severe and complicated forms of allergic conjunctivitis are associated with the so-called oculomucocutaneous syndromes (e.g., Stevens-Johnson syndrome, Lyell syndrome, ocular cicatrizing conjunctival pemphigoid). The name "oculomucocutaneous syndromes" indicates that the manifestation of these potentially life-threatening diseases is not confined to the eye but affects various other mucous tissues (ear, nose, throat, and others) as well as the skin.

Stevens-Johnson syndrome, also termed "erythema exudativum multiforme" leads to a toxic hyperergic membranous conjunctivitis. Its characteristic features are the development of chemosis and subsequently the formation of a symblepharon. Stevens-Johnson syndrome is a severe and life-threatening allergic reaction to different systemically administered drugs, mostly antibiotics. Another oculomucocutaneous syndrome is the Lyell syndrome, also named "toxic epidermal necrolysis," which is ophthalmologically characterized by an allergic membranous conjunctivitis and the development of a symblepharon. The skin of the affected patients often resembles a generalized burn injury. The third very rare form in this group of oculocutaneomucous syndromes is the ocular cicatrizing conjunctival pemphigoid. This is a severe chronic autoimmune disease of the cornea that mostly affects elder women. In this disease, the conjunctiva grows across the corneal limbus, and in the final stage of the disease, the entire cornea becomes covered with a pannus, and the eyelids stick to surface of the eye. Thus, the development of a symblepharon is characteristic. A biopsy of the conjunctiva would show immunglobulins in the basic membrane of the conjunctiva and the complement.

In summary, conjunctivitis comprises a very heterogeneous group of different causes for the patient's "red eye." The specific case history of the patient as well as a careful interview of the symptoms is crucial in sub-classifying the exact form. This is especially true for allergic conjunctivitis. Any unspecific treatment attempts in allergic conjunctivitis, e.g. antibiotics if not indicated, often complicate the disease substantially and can lead to chronic cases which may burden the patients for many weeks or even months.

References

Anderson DF (2001) Management of seasonal allergic conjunctivitis (SAC): current therapeutic strategies. Clin Exp Allergy 31(6):823–826

Friedlaender MH (1998) The current and future therapy of allergic conjunctivitis. Curr Opin Ophthalmol 9(4):54–58

Grehn F (2012) Augenheilkunde. Springer, Heidelberg

Ono SJ, Abelson MB (2005) Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 115(1):118–122

Atopic Eczema: Pathophysiological Findings as the Beginning of a New Era of Therapeutic Options

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Contents

Abstract

Atopic eczema (AE) is a chronic inflammatory disease hallmarked by intense pruritus and eczematous lesions. It depicts one of the most common skin diseases affecting a major part of children and several percentages of adults.

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Both pathogenesis and pathophysiology are based on complex orchestrated interactions of skin barrier defects, immunological changes, the environment, and an abundance of other contributing factors. Frequently, AE displays the starting point for other allergic diseases such as allergic asthma and rhinoconjunctivitis. Additionally, the risk of developing food allergy is increased. Furthermore, the disease is accompanied by a susceptibility to bacterial, fungal, and viral infections. The development of new therapies received great impetus by an ample research of the pathophysiological mechanisms, leading to a new era in the treatment of severe atopic eczema due to targeted treatments, e.g. the IL-4R alpha specific monoclonal antibody dupilumab.

This article provides an overview of the causative and pathophysiological characteristics, the clinical and diagnostic aspects as well as current and future therapeutical possibilities focusing allergic aspects contributing to the course of the disease.

Keywords

Atopic eczema · Atopy · Pathophysiology · Type 2 immune response

1 Introduction

Atopic eczema (AE), also known as atopic dermatitis, depicts one of the most common chronic inflammatory skin diseases affecting nearly one in five individuals in industrialized countries (Weidinger and Novak 2016; Flohr and Mann 2014; Werfel et al. 2016). The disease was first described by Robert Willan in 1808 and characterized in detail by Ernest Henri Besnier in 1892 (Besnier 1892). The term "atopic" classifies AE as a disease belonging with allergic asthma, allergic rhinoconjunctivitis, and food allergy to the spectrum of atopic diseases, first described in 1922 by the allergists Arthur F. Coca and Robert A. Cooke (1923).

Regarding the disease prevalence, an increase has become apparent in the last decades, especially in industrialized countries. As in most countries, over 20% of the children are affected at least during a period of their lives. In adulthood the prevalence ranges from 1 to 10% considering distinct regional variations and based on the definition of AE in the data collection (Flohr and Mann 2014; Dizon et al. 2018). Around 60% of all cases manifest within the first year and additionally 85% before the age of five; however, AE can emerge lifelong (Garmhausen et al. 2013; Vakharia and Silverberg 2019; Abuabara et al. 2019). Large birth cohort studies revealed that most of the children affected by AE have a mild disease severity; however, moderate to severe AE can persist into adulthood in individual cases, particularly in children early and severely affected and that are sensitized to various allergens in infancy and early childhood. Register studies are needed to investigate the persistence of AE beyond the youth (Bieber et al. 2020).

Combined with other allergic diseases, AE impacts the socioeconomics heavily (Chung and Simpson 2019). However, the intense burden is reported not only for the economy but also for the life quality, especially in patients with severe AE, as, e.g.,

levels of anxiety and depression are higher in those patients (de Bruin-Weller et al. 2020).

2 Pathogenesis and Pathophysiology

The pathogenesis of AE is orchestrated by a complex interaction between genetic predisposition and the environmental aspects (Gilles et al. 2018).

2.1 Genetics

The genetic burden depicts a major factor for developing AE, which is emphasized by a concordance of 80% in monozygous twins and 20% in heterogenous ones. Genetic analyses of AE patients have revealed a multitude of different mutations, especially in genes of barrier proteins and immunological pathways. In 2015, Paternoster et al. identified additional 10 risk loci maximizing the number to 31, e.g. in the filaggrin gene, in cytokine molecules and receptors like IL-13 and IL6R, and in signaling proteins as STAT3 (Paternoster et al. 2015). However, less than 20% of the estimated heritability can be explained by the identified susceptibility loci (Weidinger and Novak 2016). The most prominent risk factors are loss-of-function mutations in the filaggrin gene. This gene encodes a protein which is essential not only for a functional skin barrier but also for the homoeostasis of the epidermis. A filaggrin loss-of-function mutation increases the risk for AE by a factor of 3.12–4.78 (Irvine et al. 2011; van den Oord and Sheikh 2009). Noteworthy, roughly 60% of mutation carriers in the whole population do not develop AE (Weidinger and Novak 2016; Irvine et al. 2011).

2.2 Environment

The impact of environmental and social factors is underlined by investigations showing an increased risk due to treatment with antibiotics in pregnancy and early childhood (Penders et al. 2014), smaller families and classes of higher socioeconomic status (Ofenloch et al. 2019), and a reduced diversity of the microbiota in the gut (Wang et al. 2008). Additionally, indoor (Kim et al. 2015; Kwon et al. 2015; Lee et al. 2011) and outdoor air pollution (Huang et al. 2015) as well as psychosocial stress may contribute to an increased risk for AE (Gilles et al. 2018). Concerning the development of allergies, the skin exposure with peanut proteins in household dust may elevate the risk of developing a peanut allergy in children with AE or those carrying a filaggrin loss-of-function mutation (Brough et al. 2015).

2.3 Pathophysiology

Pathophysiologically, these aspects, combined with a complex interaction of skin barrier defects and an inadequate immune response, are assumed to lead to the clinical picture of AE (Weidinger and Novak 2016). The immunological hallmark of AE lesions is a Th2 polarized inflammation infiltrate. Type 2 skewing of Th cells and other immune cells (cytotoxic T lymphocytes, innate lymphoid cells) are induced by different factors. Keratinocytes produce augmented amounts of thymic stromal lymphopoietin (TSLP) in AE skin priming naïve T cells toward Th2 via dendritic cells (Oyoshi et al. 2010). Furthermore, pollen, which can penetrate the disrupted skin barrier easily, contribute to a type 2 cytokine milieu, among others by inhibiting IL-12 production (Aglas et al. 2018; Traidl-Hoffmann et al. 2005).

Concerning the skin, different abnormalities are reported in AE: an increased transepidermal water lass (TEWL) (Flohr et al. 2010), changes in lipid composition and stucture (Ishikawa et al. 2010; Janssens et al. 2012), and elevated activity of skin serine proteases (Weidinger and Novak 2016; Voegeli et al. 2009). Further, changes of the skin microbiome are present, especially a reduced skin microbiome diversity and augmented amounts of Staphylococcus aureus (S. aureus) colonizing the surface (Reiger et al. 2019). Recently, it was shown that the abundance of, Staphylococcus aureus (S. aureus) correlates with the expression of skin barrier proteins, revealing the importance of the skin microbiome in the pathophysiology of AE (Altunbulakli et al. 2018). However, not just the skin microbiome, but also the gut bacteria seem to contribute to the pathophysiology of AE. Bifidobacterium counts are lower in AE patients and, additionally, Faecalibacterium prausnitzii subspecies are highly related to AE (Watanabe et al. 2003; Song et al. 2016; Reiger et al. 2020). Several studies revealed that the aberrations of the gut microbiome precede the onset of AE. It is part of ongoing research to which extension the altered gut microbiome contributes to the development of the disease and a Th2 skewing of cutaneous inflammation.

The immunological hallmarks of AE led to a dichotomic subgrouping into an intrinsic ("non-allergic") and extrinsic ("allergic") form of the disease. The latter was defined by an increased total IgE in serum, detectable allergen-specific IgE antibodies against aero- and food allergens, and association with IgE mediated clinical reactions and other atopic diseases (Novak and Bieber 2003; Johansson et al. 2001). Contrarily, 16–45% of adult patients with AE reveal neither specific sensitizations nor elevated total IgE and thus suffer from the intrinsic form (Schmid-Grendelmeier et al. 2001). Notably, in infants (age 0–2 years) the prevalence of the intrinsic form approaches 60% (Park et al. 2006), suggesting that normal total IgE and lack of allergen-specific IgE antibodies, respectively, may only be present in the inception of the disease. Therefore, this dichotomic approach has become blurred and the concept of the differentiation of endotypes of the disease has risen (Eyerich et al. 2019; Czarnowicki et al. 2019).

Besides IgE against environmental allergens, a multitude of IgE reactive to self-proteins was described under the term "autoallergy" (Hradetzky et al. 2014; Roesner and Werfel 2019). Autoallergic phenomena appear specific in AE and may contribute to the inflammation (Hradetzky et al. 2015). T cells reactive to autoallergens

produce, besides the common type 2 cytokines IL-4 and IL-13, type 1 inflammation proteins such as IFN-γ and other cytokines such as IL-17 and IL-22 (Hradetzky et al. 2014; Roesner et al. 2016).

Interestingly, not just a type 2 polarized inflammation can be detected in AE lesions, but Th1 cytokines are upregulated in subacute and chronic lesions of adult patients as well (Werfel et al. 1996). In the lesional skin of children, Brunner et al. showed additionally to the Th2 profile an increase of Th17 and Th22 cytokines (Brunner et al. 2018). Additionally, alterations can be detected concerning different ethnical backgrounds, as the Asian AE can be hallmarked, besides a Th2 profile, by a pronounced Th17 inflammation providing some characteristics known from psoriasis (Noda et al. 2015).

In conclusion, a myriad of different aspects concerning genetics, immunology, environment, and skin barrier and their interaction have been identified to contribute to the complex picture of AE's pathogenesis and pathophysiology so far.

3 Clinical Symptoms

The clinical manifestations of AE are diverse. In addition to scratch induced excoriations and crustae caused by pruritus, the disease is characterized by inflammatory lesions with epidermal involvement "eczematous" skin lesions. In most patients these lesions do not occur before the age of two months (Weidinger and Novak 2016). The distribution pattern of lesions on the integument varies with age, leading to the differentiation of three phases: In infancy eczematous lesions are predominant in the face and capillitium and, furthermore, frequently combined with exudative crusted erosions, which are associated with superinfections caused most prominently by S. aureus (Alexander et al. 2020). The diseases hallmarks in childhood are focused at the cubital and popliteal folds being less exudative than in infants (Traidl and Werfel 2019). In the adulthood, the accented areas are symmetrical around the head, neck, and flexure folds (Fig. 1a, b) (Coors 2016). Furthermore, acute lesions are accompanied by oozing, as chronic AE lesions provide the picture of lichenification, meaning coarsening of the skin markings (Finlay et al. 1980).

The disease is characterized by recurrent flares induced by a multitude of factors, e.g. stress or bacterial skin infections. Double-blinded, placebo-controlled studies revealed an exacerbation of the disease due to aeroallergens and food allergens in sensitized patients (Werfel et al. 2015; Wassmann-Otto et al. 2018).

4 Diagnosis

Due to the fact that laboratory markers are not available, the diagnosis of AE can only be based on clinical features. The diagnostic criteria of Jon M. Hanifin and Georg Rajka published in 1980 are still the basis for the diagnosis and most frequently used in clinical trials (Vakharia et al. 2018; Hanifin and Rajka 1980).

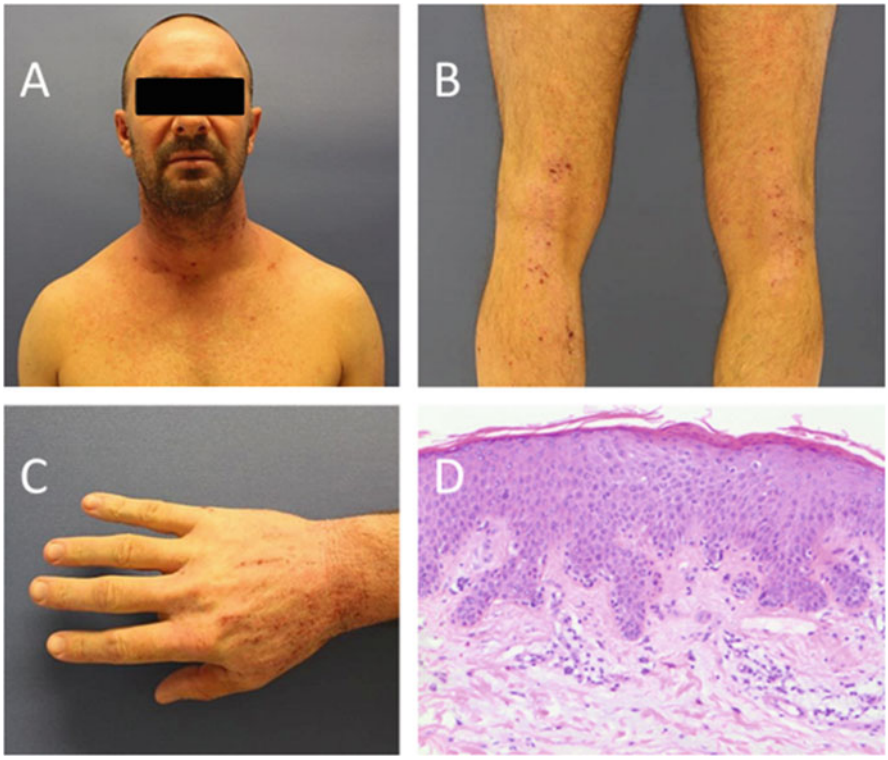

Fig. 1 Skin manifestations of AE and histological abnormalities. (**a**) Typical head and neck involvement in an adult male AE patient. (**b**) Flexural papules with scratch excoriations and lichenification. (**c**) AE affecting the hand characterized by intense pruritic, eczematous lesions. (**d**) Histological changes of AE: The biopsy reveals parakeratosis, moderate acanthosis, spongiosis, and an assorted infiltrate with several eosinophils and melanophages (Image **d** is kindly provided by PD Dr. med. V. Schacht)

The major criteria involve pruritus, eczematous lesions (Fig. 1c) on the disease and age typical spots, a chronic or relapsing course of disease, and a personal or family history of atopic diseases. Additionally, 23 minor criteria exist, such as elevated total IgE or the Dennie-Morgan infraorbital fold (Braun-Falco et al. 2005). Both exemplary minor criteria represent the allergic aspect of the disease, as they can be found in patients with allergic rhinoconjunctivitis as well. The diagnosis of AE can be made based on at least three major criteria accompanied by three minor criteria (Hanifin and Rajka 1980). In 1994 the U.K. Working Party published their refinement of the Hanifin and Rajka criteria containing a minimum of criteria for the AE diagnosis (Williams et al. 1994). Therefore, a detailed history combined with the skin inspection and an IgE measurement is the key point for the diagnosis. Additionally, the latter is important, as sensitizing against aero- and food allergens can lead to flares of the AE (Werfel et al. 2015; Wassmann-Otto et al. 2018). Whilst food allergies in young AE children, e.g. to hen's egg, milk, and

wheat, depict the most common ones, in adults cross allergy to, e.g., nuts due to sensitization against aeroallergens are more prevalent (Wassmann and Werfel 2015). Consequently, there is a shift from food allergens to aeroallergens from young to adult AE patients, which is, however, not obligate, since some adult patients with AE can still suffer from food allergies and some young children can already develop inhalant allergies. Several double-blinded, placebo-controlled studies emphasized the deteriorative effect of allergens to sensitized patients measured by clinical skin scores as SCORAD and EASI (Werfel et al. 2015; Breuer et al. 2004; Werfel and Kapp 1998).

Histological analysis of skin biopsies showing spongiosis, mild acanthosis, orthokeratosis, and a lymphohistiocytic infiltrate with eosinophils and several melanophages can complete the diagnosis. Dermatohistopathology is, however, of minor importance for the diagnosis of AE compared to other clinical features in clear presentations of symptoms (Fig. 1d).

Different scores are suitable for measuring the clinical severity of AE: Eczema Area and Severity Index (EASI), Patient-oriented Eczema Measure (POEM), and Severity Scoring of Atopic Dermatitis (SCORAD) index (Schmitt et al. 2007). Regarding the SCORAD, besides the distribution of the affected body surface, erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and xerosis are assessed for objective scores, while the extent of pruritus and sleeplessness are measured as subjective parameters. The EASI score focuses on the objective parameters such as erythema, edema and papulation, lichenification, and excoriation allocated with the four areas head, upper extremities, body, and lower extremities (Kunz et al. 1997). To focus on subjective parameters of the disease, the Patient-Oriented Eczema Measures for Eczema (POEM) is frequently used. All three scores, SCORAD, POEM, and EASI, are currently applied in clinical trials.

5 Comorbidities and Complications: From Allergy to Infections

As mentioned before, AE depicts one of the four diseases of the atopic circle. Gustafsson et al. investigated the development of other atopic diseases of AE affected children. 94 children were examined for seven years, revealing that nearly 90% of the patients experienced an improvement of the skin manifestations; however, 43% developed allergic asthma and 45% allergic rhinoconjuncitivits (Gustafsson et al. 2000). Interestingly, an early onset of AE is associated with an increased risk of a sensitization against aeroallergens. Additionally, 5,729 patients born in 1961 were followed up until 2004 by Martin et al. (Martin et al. 2011). It was shown that manifesting an AE before the age of seven increases the risk to develop an allergic asthma in adulthood and that the disease persists beyond childhood when developing an asthma as a child. It is hypothesized that the barrier defects, which are caused, among others, by the insufficient expression of filaggrin, allow a sensitization against aeroallergens. The German multicenter allergy study (MAS), observing 1,314 newborns until the age of twenty, showed an increased risk of developing

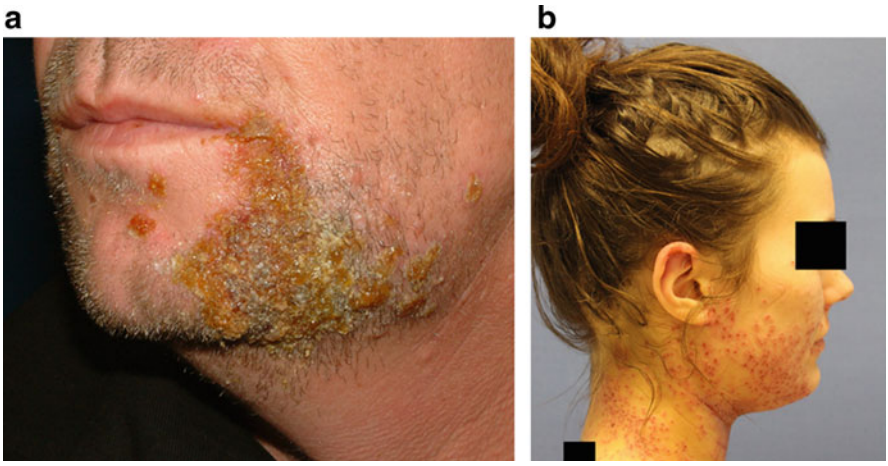

Fig. 2 Infectious complications of AE patients. (**a**) Staphylococcal superinfection of AE lesion. (**b**) Eczema herpeticum: grouped scattered erythematous erosions and vesicles presented in a young female AE patient

allergies and allergic disease if at least two closer family members suffer from AE, another atopic manifestation or an increased IgE in the cord blood (Lau et al. 2002). Interestingly, eczema was still present in 10% of all young women and 4 % in young men at the age of 20 in members of this atopic birth cohort (Gough et al. 2015).

In conclusion, AE often depicts the first step of an allergic burden, followed by allergic rhinoconjunctivitis and allergic asthma as well as food allergy. This development is called "atopic march."

Additionally, AE patients are prone to viral and bacterial infections. Bacterial infections with especially group A Streptococcus inducing impetigo contagiosa (see Fig. 2a) and S. aureus superinfections are common in those subjects.

Concerning viral susceptibility, disseminated clinical manifestations of herpes simplex virus (HSV), molluscum contagiosum virus (MCV), human papillomavirus (HPV), and vaccinia virus can appear. Most prominently, the spread of herpes vesiculae known as eczema herpeticum (EH) (see Fig. 2b) can be accompanied by systemic symptoms such as fever and malaise and may lead to life-threatening complications when HSV affects the brain (herpes encephalitis) and liver (herpes hepatitis) (Traidl et al. 2018, 2021; Seegräber et al. 2020).

These viral disseminations affect around 7–10% of AE patients (Beck et al. 2009). Noteworthy, AE is defined as a contraindication for the vaccination with vaccinia virus due to the viral susceptibility (Grabenstein and Winkenwerder 2003). Additionally, not only skin affecting viral diseases but also extra dermal diseases are more prevalent in AE, as high-risk HPV is more common in AE in cervical cytology (Morgan et al. 2015).

Beside somatic comorbidities, a high number of studies focused on psychiatric comorbidities in AE patients. Schmitt et al. analyzed large cohorts of patients, investigating the prevalence of attention-deficit/hyperactivity disorder (ADHD) in

600,000 German children and adolescents. They showed that the prevalence in AE patients was significantly increased with 5.2% compared to 3.4% in healthy individuals (Schmitt et al. 2009). An increased prevalence of ADHD in AE was confirmed by a couple of other independent studies from different countries. Further prospective data revealed that infants with AE suffer from an elevated risk for mental health problems at age 10. Importantly, despite clearing after the age of two years, AE may cause persistent emotional and behavioral complications (Schmitt et al. 2010). There is a significant correlation of earlier use of antihistamines and ADHD symptoms (OR 1.88; 95%-CI: 1.04–3.39) (Schmitt et al. 2018). However, not just ADHD, but also depression (1.81; 95% CI, 1.33–2.46), anxiety (1.77; 95% CI, 1.36–2.29), conduct disorder (1.87; 95% CI, 1.46–2.39), and autism (3.04; 95% CI, 2.13–4.34) were found to be significantly increased in AE (Yaghmaie et al. 2013). Additionally, AE is associated with an increased prevalence of suicidal ideation in children and adults (OR 4.32; 95% CI, 1.93–9.66).

6 Therapy

Based on the chronic relapsing character of the disease, the treatment of AE can be challenging.

The use of moisturizers displays the basis of all therapeutical concepts for AE. As most cases of AE are mild, moisturizers supported by topical steroids, calcineurin inhibitors and, only approved in the USA, topical phosphodiesterase 4 inhibitors are sufficient to control the disease. Additionally, a proactive use, meaning a long-term, low-dose intermittent application of topical steroids or calcineurin inhibitor twice per week even if no active lesions are visible, has proven to reduce exacerbations (Berth-Jones et al. 2003; Wollenberg and Ehmann 2012). Furthermore, AE patients should be educated regarding the benefit of topical and systemic treatments and the avoidance of trigger factors of the disease. Controlled studies revealed not just an increase of the quality of life by patient education intervention but also a significant disease improvement in children, adolescents, and adults taking part in structured patient education programs for AE such as Arbeitsgemeinschaft Neurodermitisschulung (AGNES) or Arbeitsgemeinschaft Neurodermitisschulung für Erwachsene (ARNE) (Heratizadeh et al. 2017; Staab et al. 2006). As AE is more prevalent in children, educational concepts training children and their caregivers are of importance (for a differentiated view on this topic, see: Handbook of Experimental Pharmacology on Allergy: Patient/Relative Education).

However, for chronic or frequently recurrent moderate to severe forms of AE topical treatment alone may be insufficient. For those patients, additional systemic therapy is needed. Until 2017, systemic steroids and ciclosporin were the only approved therapy options in AE (Schmitt et al. 2017). The off-label use of other immune suppressive treatments, e.g. methotrexate, mycophenolate mofetil, or azathioprine was rare. With the approval of dupilumab, a human monoclonal IgG4 antibody targeting the a-chain of the IL-4 and IL-13 receptor, the first biological is available for the treatment of AE. It has a comprehensive label by the EMA as it

"[. . .] is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy" (European Medicines Agency 2018). In the dupilumab phase III studies 1,379 patients with moderate to severe atopic dermatitis were treated with 300 mg subcutaneous every week, every other week or placebo (Simpson et al. 2016). The primary endpoint of total or nearly complete remission after 16 weeks was achieved by 36–38% of the patients in the intervention groups intervention groups. An EASI-75, meaning an improvement of the EASI score compared to baseline of at least 75%, was prevalent in 44–51% of patients after 16 weeks of treatment with dupilumab. Data from the German registry on adult patients with AE ("TREATgermany") recently confirmed comparable efficacy of dupilumab in the "real world." (Abraham et al. 2020) In comparison, the EASI-75 of ciclosporin after 12 weeks was shown to be around 34% in this registry before (Schmitt et al. 2017). The most common adverse event of dupilumab is conjunctivitis. Interestingly, this is a disease specific side effect, as it is not observed in the dupilumab studies in asthma or polyposis nasi patients (Castro et al. 2018; Bachert et al. 2016). It should be mentioned that the risk of eczema herpeticum is reduced under the treatment with dupilumab probably due to its positive effect on the overall skin condition (Fleming and Drucker 2018).

Of note, dupilumab depicts just the beginning of a new era of innovative treatment options for moderate to severe AE patients who cannot be treated sufficiently with topical applications and phototherapy. Besides monocloncal antibodies against major type 2 inflammation associated cytokines, e.g. IL-13, IL-22, and IL-31, other molecules are targeted such as OX-40 and TSLP by antibodies or small molecules (Honstein and Werfel 2020). Additionally, cytokine receptor associated kinases, namely Janus kinases, are inhibited by several promising drugs leading to the interruption of different cytokine pathways. Most recently, the histamine (H) 4 receptor was identified as a potential target and positive effect concerning the disease severity on blocking the receptor was revealed in a clinical proof of concept trial with nearly 100 patients with AE (Schaper-Gerhardt et al. 2018; Werfel et al. 2019).

7 Resume and Outlook

The research of AE has received great impetus over the last decades. The improved understanding of the pathophysiology, the involved cells, and cytokines in addition to the increasing prevalence led to a multiplicity of different new therapy options in the pipeline. In the last years it has become more and more clear that the disease, besides the quite uniform clinical manifestation, consists of different disease endotypes. It will be important to use the new and upcoming research techniques to identify different endotypes of the disease and provide a tailored therapy for the individual patient. Due to the rising prevalence of allergies and the connection of AE with atopic comorbidities an all-embracing therapeutical approach is needed.

However, even more important is a preventive view on the disease. Especially the intervention in early childhood in high-risk infants seems to be fundamental.

In conclusion, AE is a disease with a high socioeconomic and individual impact and can be accompanied by a multitude of comorbidities and complications. A sufficient treatment, especially with new therapeutically possibilities, is needed. Therefore, further research is important to have the ability to tailor the treatment to the patient's endotype.

References

Abraham S, Haufe E, Harder I et al (2020) Implementation of dupilumab in routine care of atopic eczema: results from the german national registry TREATgermany. Br J Dermatol 183 (2):382–384

Abuabara K, Ye M, McCulloch CE, Sullivan A, Margolis DJ, Strachan DP, Paternoster L, Yew YW, Williams HC, Langan SM (2019) Clinical onset of atopic eczema: results from 2 nationally representative British birth cohorts followed through midlife. J Allergy Clin Immunol 144 (3):710–719. https://doi.org/10.1016/j.jaci.2019.05.040. Epub 2019 Jun 28. PMID: 31260715; PMCID: PMC6721832

Aglas L, Gilles S, Bauer R et al (2018) Context matters: TH2 polarization resulting from pollen composition and not from protein-intrinsic allergenicity. J Allergy Clin Immunol 142 (3):984–987.e6

Alexander H, Paller AS, Traidl-Hoffmann C, Beck LA, De Benedetto A, Dhar S, Girolomoni G, Irvine AD, Spuls P, Su J, Thyssen JP, Vestergaard C, Werfel T, Wollenberg A, Deleuran M, Flohr C (2020) The role of bacterial skin infections in atopic dermatitis: expert statement and review from the international eczema council skin infection group. Br J Dermatol 182(6):1331–1342. https://doi.org/10.1111/bjd.18643

Altunbulakli C, Reiger M, Neumann AU et al (2018) Relations between epidermal barrier dysregulation and staphylococcus species-dominated microbiome dysbiosis in patients with atopic dermatitis. J Allergy Clin Immunol 142(5):1643–1647.e12

Bachert C, Mannent L, Naclerio RM et al (2016) Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 315(5):469–479

Beck LA, Boguniewicz M, Hata T et al (2009) Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. J Allergy Clin Immunol 124(2):260–269.e7

Berth-Jones J, Damstra RJ, Golsch S et al (2003) Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ 326(7403):1367

Besnier E (1892) Premi`ere note et observations pr´eliminaires pour servir d'introduction `a l'´etude des prurigos diath´esiques (dermatites multiformes prurigineuses chroniques exacerbantes et paroxystiques, du type du prurigo de hebra). Ann Dermatol Syphil 3:634–648

Bieber T, Traidl-Hoffmann C, Schappi G, Lauener R, Akdis C, Schmid-Grendlmeier P (2020) Unraveling the complexity of atopic dermatitis: the CK-CARE approach toward precision medicine. Allergy 75(11):2936–2938

Braun-Falco O, Plewig G, Wolff HH, Burgdorf W, Landthaler M (eds) (2005) Braun-falco's dermatologie, venerologie und allergologie, 5th edn. Springer, Heidelberg

Breuer K, Heratizadeh A, Wulf A et al (2004) Late eczematous reactions to food in children with atopic dermatitis. Clin Exp Allergy 34(5):817–824

Brough HA, Liu AH, Sicherer S et al (2015) Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. J Allergy Clin Immunol 135(1):164–170

Brunner PM, Israel A, Zhang N et al (2018) Early-onset pediatric atopic dermatitis is characterized by TH2/TH17/TH22-centered inflammation and lipid alterations. J Allergy Clin Immunol 141 (6):2094–2106

Castro M, Corren J, Pavord ID et al (2018) Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378(26):2486–2496
Chung J, Simpson EL (2019) The socioeconomics of atopic dermatitis. Ann Allergy Asthma Immunol 122(4):360–366
Coca AF, Cooke RA (1923) On the classification of the phenomena of hypersensitiveness. J Immunol 8(3):163–182
Coors E (2016) Atopische dermatitis. In: Moll I (ed) Dermatologie, vol 8. Thieme, Stuttgart, pp 189–193
Czarnowicki T, He H, Krueger JG, Guttman-Yassky E (2019) Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 143(1):1–11
de Bruin-Weller M, Gadkari A, Auziere S, Simpson EL, Puig L, Barbarot S, Girolomoni G, Papp K, Pink AE, Saba G, Werfel T, Eckert L (2020) The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada. J Eur Acad Dermatol Venereol 34(5):1026–1036. https://doi.org/10.1111/jdv.16003. Epub 2020 Jan 14. PMID: 31587373; PMCID: PMC7318704
Dizon MP, Yu AM, Singh RK et al (2018) Systematic review of atopic dermatitis disease definition in studies using routinely collected health data. Br J Dermatol 178(6):1280–1287
European Medicines Agency (2018) Dupixent. https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent. Accessed 02/09, 2019
Eyerich K, Brown SJ, Perez White BE et al (2019) Human and computational models of atopic dermatitis: a review and perspectives by an expert panel of the international eczema council. J Allergy Clin Immunol 143(1):36–45
Finlay AY, Nicholls S, King CS, Marks R (1980) The 'dry' non-eczematous skin associated with atopic eczema. Br J Dermatol 103(3):249–256
Fleming P, Drucker AM (2018) Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol 78(1):62–69.e1
Flohr C, Mann J (2014) New insights into the epidemiology of childhood atopic dermatitis. Allergy 69(1):3–16
Flohr C, England K, Radulovic S et al (2010) Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. Br J Dermatol 163(6):1333–1336
Garmhausen D, Hagemann T, Bieber T et al (2013) Characterization of different courses of atopic dermatitis in adolescent and adult patients. Allergy 68(4):498–506
Gilles S, Akdis C, Lauener R et al (2018) The role of environmental factors in allergy: a critical reappraisal. Exp Dermatol 27(11):1193–1200
Gough H, Grabenhenrich L, Reich A et al (2015) Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr Allergy Immunol 26(5):431–437
Grabenstein JD, Winkenwerder W Jr (2003) US military smallpox vaccination program experience. JAMA 289(24):3278–3282
Gustafsson D, Sjoberg O, Foucard T (2000) Development of allergies and asthma in infants and young children with atopic dermatitis – a prospective follow-up to 7 years of age. Allergy 55(3):240–245
Hanifin J, Rajka G (1980) Diagnostic features of atopic dermatitis. Acta Derm Venereol 92:44–47
Heratizadeh A, Werfel T, Wollenberg A et al (2017) Effects of structured patient education in adults with atopic dermatitis: multicenter randomized controlled trial. J Allergy Clin Immunol 140(3):845–853.e3
Honstein T, Werfel T (2020) The show must go on: an update on clinical experiences and clinical studies on novel pharmaceutical developments for the treatment of atopic dermatitis. Curr Opin Allergy Clin Immunol 20(4):386–394. https://doi.org/10.1097/ACI.0000000000000652. PMID: 32452891
Hradetzky S, Roesner LM, Balaji H et al (2014) Cytokine effects induced by the human autoallergen alpha-NAC. J Invest Dermatol 134(6):1570–1578

Hradetzky S, Roesner LM, Heratizadeh A et al (2015) Differential cytokine induction by the human skin-associated autoallergen thioredoxin in sensitized patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol 135(5):1378–80.e1-5

Huang CC, Wen HJ, Chen PC, Chiang TL, Lin SJ, Guo YL (2015) Prenatal air pollutant exposure and occurrence of atopic dermatitis. Br J Dermatol 173(4):981–988

Irvine AD, McLean WH, Leung DY (2011) Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 365(14):1315–1327

Ishikawa J, Narita H, Kondo N et al (2010) Changes in the ceramide profile of atopic dermatitis patients. J Invest Dermatol 130(10):2511–2514

Janssens M, van Smeden J, Gooris GS et al (2012) Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. J Lipid Res 53(12):2755–2766

Johansson SG, Hourihane JO, Bousquet J et al (2001) A revised nomenclature for allergy. an EAACI position statement from the EAACI nomenclature task force. Allergy 56(9):813–824

Kim EH, Kim S, Lee JH et al (2015) Indoor air pollution aggravates symptoms of atopic dermatitis in children. PLoS One 10(3):e0119501

Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A (1997) Clinical validation and guidelines for the SCORAD index: consensus report of the European task force on atopic dermatitis. Dermatology 195(1):10–19

Kwon JH, Kim E, Chang MH et al (2015) Indoor total volatile organic compounds exposure at 6 months followed by atopic dermatitis at 3 years in children. Pediatr Allergy Immunol 26 (4):352–358

Lau S, Nickel R, Niggemann B et al (2002) The development of childhood asthma: lessons from the German multicentre allergy study (MAS). Paediatr Respir Rev 3(3):265–272

Lee CH, Chuang HY, Hong CH et al (2011) Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis. Br J Dermatol 164(3):483–489

Martin PE, Matheson MC, Gurrin L et al (2011) Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades. J Allergy Clin Immunol 127(6):1473–9.e1

Morgan TK, Hanifin J, Mahmood M et al (2015) Atopic dermatitis is associated with cervical high risk human papillomavirus infection. J Low Genit Tract Dis 19(4):345–349

Noda S, Suarez-Farinas M, Ungar B et al (2015) The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol 136(5):1254–1264

Novak N, Bieber T (2003) Allergic and nonallergic forms of atopic diseases. J Allergy Clin Immunol 112(2):252–262

Ofenloch RF, Schuttelaar ML, Svensson A et al (2019) Socioeconomic status and the prevalence of skin and atopic diseases in five European countries. Acta Derm Venereol 99(3):309–314

Oyoshi MK, Larson RP, Ziegler SF, Geha RS (2010) Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. J Allergy Clin Immunol 126(5):976–984. 984.e1-5

Park JH, Choi YL, Namkung JH et al (2006) Characteristics of extrinsic vs. intrinsic atopic dermatitis in infancy: correlations with laboratory variables. Br J Dermatol 155(4):778–783

Paternoster L, Standl M, Waage J et al (2015) Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat Genet 47 (12):1449–1456

Penders J, Gerhold K, Thijs C et al (2014) New insights into the hygiene hypothesis in allergic diseases: mediation of sibling and birth mode effects by the gut microbiota. Gut Microbes 5 (2):239–244

Reiger M, Schwierzeck V, Traidl-Hoffmann C (2019) Atopisches Ekzem und Mikrobiom [Atopic eczema and microbiome]. Hautarzt 70(6):407–415. German. https://doi.org/10.1007/s00105-019-4424-6. PMID: 31111169

Reiger M, Traidl-Hoffmann C, Neumann AU (2020) The skin microbiome as a clinical biomarker in atopic eczema: promises, navigation, and pitfalls. J Allergy Clin Immunol 145(1):93–96
Roesner LM, Werfel T (2019) Autoimmunity (or not) in atopic dermatitis. Front Immunol 10:2128
Roesner LM, Heratizadeh A, Wieschowski S et al (2016) Alpha-NAC-specific autoreactive CD8+ T cells in atopic dermatitis are of an effector memory type and secrete IL-4 and IFN-gamma. J Immunol 196(8):3245–3252
Schaper-Gerhardt K, Rossbach K, Nikolouli E, Werfel T, Gutzmer R, Mommert S (2018) The role of the histamine H4 receptor in atopic dermatitis and psoriasis. Br J Pharmacol 177(3):490–502
Schmid-Grendelmeier P, Simon D, Simon HU, Akdis CA, Wuthrich B (2001) Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). Allergy 56(9):841–849
Schmitt J, Langan S, Williams HC (2007) European Dermato-Epidemiology Network. What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol 120(6):1389–1398
Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W (2009) Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. JAMA 301(7):724–726
Schmitt J, Apfelbacher C, Chen CM et al (2010) Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (german infant nutrition intervention plus). J Allergy Clin Immunol 125(2):404–410
Schmitt J, Abraham S, Trautmann F et al (2017) Usage and effectiveness of systemic treatments in adults with severe atopic eczema: first results of the german atopic eczema registry TREATgermany. J Dtsch Dermatol Ges 15(1):49–59
Schmitt J, Buske-Kirschbaum A, Tesch F et al (2018) Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. Allergy 73 (3):615–626
Seegräber M, Worm M, Werfel T, Svensson A, Novak N, Simon D, Darsow U, Augustin M, Wollenberg A (2020) Recurrent eczema herpeticum - a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. J Eur Acad Dermatol Venereol 34(5):1074–1079. https://doi.org/10.1111/jdv.16090. Epub 2020 Jan 30. PMID: 31733162
Simpson EL, Bieber T, Guttman-Yassky E et al (2016) Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 375(24):2335–2348
Song H, Yoo Y, Hwang J, Na YC, Kim HS (2016) Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. J Allergy Clin Immunol 137(3):852–860
Staab D, Diepgen TL, Fartasch M et al (2006) Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: Multicentre, randomised controlled trial. BMJ 332(7547):933–938
Traidl S, Werfel T (2019) Atopic dermatitis and general medical comorbidities. Internist (Berl) 60 (8):792–798
Traidl S, Kienlin P, Begemann G et al (2018) Patients with atopic dermatitis and history of eczema herpeticum elicit herpes simplex virus-specific type 2 immune responses. J Allergy Clin Immunol 141(3):1144–1147.e5
Traidl S, Roesner L, Zeitvogel J, Werfel T (2021) Eczema herpeticum in atopic dermatitis. Allergy. https://doi.org/10.1111/all.14853. Epub ahead of print. PMID: 33844308
Traidl-Hoffmann C, Mariani V, Hochrein H et al (2005) Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. J Exp Med 201(4):627–636
Vakharia PP, Chopra R, Silverberg JI (2018) Systematic review of diagnostic criteria used in atopic dermatitis randomized controlled trials. Am J Clin Dermatol 19(1):15–22

Vakharia PP, Silverberg JI (2019) Adult-onset atopic dermatitis: characteristics and management. Am J Clin Dermatol 20(6):771–779. https://doi.org/10.1007/s40257-019-00453-7. PMID: 31140066

van den Oord RA, Sheikh A (2009) Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ 339:b2433

Voegeli R, Rawlings AV, Breternitz M, Doppler S, Schreier T, Fluhr JW (2009) Increased stratum corneum serine protease activity in acute eczematous atopic skin. Br J Dermatol 161(1):70–77

Wang M, Karlsson C, Olsson C et al (2008) Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol 121(1):129–134

Wassmann A, Werfel T (2015) Atopic eczema and food allergy. Chem Immunol Allergy 101:181–190

Wassmann-Otto A, Heratizadeh A, Wichmann K, Werfel T (2018) Birch pollen-related foods can cause late eczematous reactions in patients with atopic dermatitis. Allergy 73(10):2046–2054

Watanabe S, Narisawa Y, Arase S et al (2003) Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol 111(3):587–591

Weidinger S, Novak N (2016) Atopic dermatitis. Lancet 387(10023):1109–1122

Werfel T, Kapp A (1998) Environmental and other major provocation factors in atopic dermatitis. Allergy 53(8):731–739

Werfel T, Morita A, Grewe M et al (1996) Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. J Invest Dermatol 107(6):871–876

Werfel T, Heratizadeh A, Niebuhr M et al (2015) Exacerbation of atopic dermatitis on grass pollen exposure in an environmental challenge chamber. J Allergy Clin Immunol 136(1):96–103.e9

Werfel T, Allam JP, Biedermann T et al (2016) Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol 138(2):336–349

Werfel T, Layton G, Yeadon M et al (2019) Efficacy and safety of the histamine H4 receptor antagonist ZPL-3893787 in patients with atopic dermatitis. J Allergy Clin Immunol 143 (5):1830–1837.e4

Williams HC, Burney PG, Hay RJ et al (1994) The U.K. working party's diagnostic criteria for atopic dermatitis. I. derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 131(3):383–396

Wollenberg A, Ehmann LM (2012) Long term treatment concepts and proactive therapy for atopic eczema. Ann Dermatol 24(3):253–260

Yaghmaie P, Koudelka CW, Simpson EL (2013) Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 131(2):428–433

The Classification, Pathogenesis, Diagnostic Workup, and Management of Urticaria: An Update

Marcus Maurer, Torsten Zuberbier, and Martin Metz

Contents

Abstract

Wheals and angioedema are the signature signs of urticaria, and itch is the key symptom. Urticaria, in most patients, is acute and resolves within days (acute urticaria, AU). Chronic urticaria (CU) can be of long duration and results not only in severely impaired quality of life but also has a socioeconomic impact due to work productivity impairment. In some patients with CU, the wheals and angioedema are induced exclusively by defined and definite triggers (chronic

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inducible urticaria, CIndU). In most patients with CU, wheals and angioedema develop unprompted, spontaneously (chronic spontaneous urticaria, CSU). The management of CU aims for the complete control and absence of its signs and symptoms. This is achieved, in most patients, by prophylactic treatment until spontaneous remission occurs. Modern, second-generation H1-antihistamines are the first-line therapy, with the option of updosing to fourfold, and omalizumab is used when this fails.

Keywords

Angioedema · Chronic · Hives · Inducible · Itch · Mast Cell · Pruritus · Spontaneous · Urticaria · Wheals

1 Definition

Urticaria is a mast cell-mediated condition characterized by itchy wheals, angioedema, or both (Church et al. 2018; Zuberbier et al. 2018). The wheals in patients with urticaria are short-lived transient superficial itchy skin swellings. Initially pale in color (Fig. 1), they progressively take on a reddish hue and develop a surrounding flare (erythema, Fig. 1) and then resolve fully over the course of minutes to hours without obvious subsequent skin alterations. Wheals in patients with urticaria are usually itchy, but may also come with skin burning, pain, or stinging. Angioedema is a rapid swelling of the dermis and subcutis or of the mucosa and submucosa (Fig. 1). Angioedema in patients with urticaria most commonly occurs in the face (lips, eyes), and it does not occur in the gastrointestinal tract or the airways.

2 Classification

Urticaria is commonly classified, based on its duration, as acute and chronic. In acute urticaria (AU), wheals and/or angioedema occur for less than 6 weeks. In chronic urticaria (CU), wheals and/or angioedema occur for more than 6 weeks (Zuberbier et al. 2018). Urticaria is further subclassified as spontaneous or inducible. In patients with spontaneous urticaria, acute or chronic, the development of wheals and angioedema is unprompted and unpredictable. In patients with inducible urticaria, wheals and/or angioedema occur only in response to specific and definite triggers acting on the skin (Magerl et al. 2016) (Fig. 2). These triggers can be physical stimuli, in forms of physical urticaria, or urticariogens, for example in contact urticaria and aquagenic. The triggers of physical urticaria include skin exposure to cold and heat (cold urticaria, heat urticaria), friction, pressure and vibration (symptomatic dermographism, pressure urticaria, vibratory angioedema), and ultraviolet or visible light (solar urticaria). In patients with cholinergic urticaria, symptoms are triggered by exercise or passive warming (e.g., hot showers, exercise, spicy food). Some patients have more than one subtype of urticaria, for example chronic spontaneous urticaria (CSU) together with symptomatic dermographism.

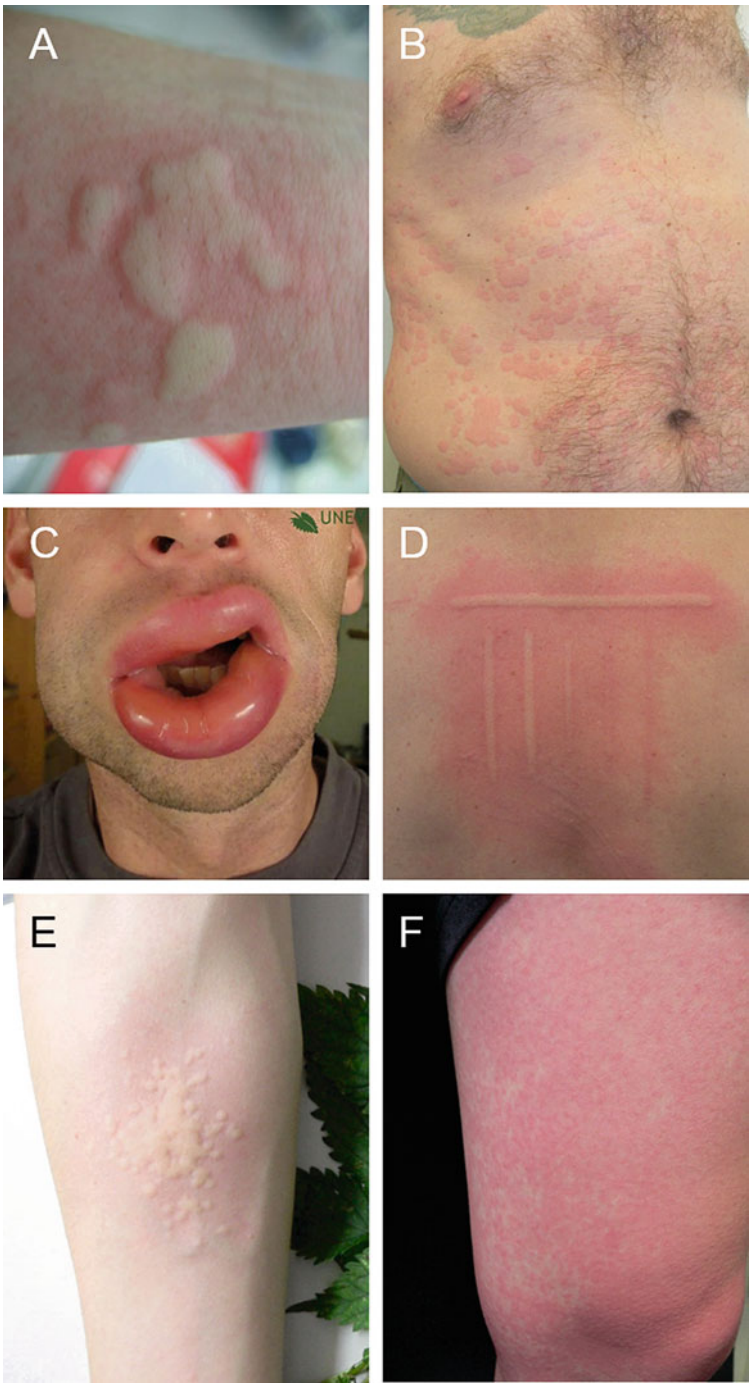

Fig. 1 Wheals and angioedema in urticaria. (**a**) Wheals at an early stage of development in a patient with chronic spontaneous urticaria. (**b**) Wheals of several hours duration in a patient with chronic spontaneous urticaria. (**c**) Angioedema in a patient with chronic spontaneous urticaria. (**d**)

3 Epidemiology

Urticaria is a very common condition, experienced by virtually everyone, at one point during his or her life, as acute urticaria or after touching urticariogenic plants such as stinging nettles or animals, for example jellyfish (Fig. 1). The lifetime prevalence of acute spontaneous urticaria is estimated to be up to 20% (Maurer et al. 2011a; Zuberbier et al. 2010). Urticaria, in patients with acute spontaneous urticaria, rarely progresses to CSU. Acute inducible urticaria is rare. CSU, which is held to be at least twice as common as CIndU, has an estimated point prevalence of 1%, in both children and adults (Maurer et al. 2011a; Balp et al. 2018). CSU can occur at any age and often starts between the 20th and the 40th year of life. Women are affected twice or three times as often as men (Maurer et al. 2011a; Siebenhaar et al. 2018).

4 Pathogenesis

Urticaria is a mast cell-driven disease, i.e. in all patients with urticaria, the wheals and angioedema are due to the degranulation of skin mast cells and the effects of histamine and other proinflammatory mediators released by this process (Church et al. 2018). Skin mast cells are mainly localized around cutaneous blood vessels and sensory nerves (Siebenhaar et al. 2018), in both the upper papillary dermis and the deep dermis and subcutis. When mast cells are triggered to degranulate, they discharge cytoplasmic granules. These granules contain histamine, proteases, and other mediators of inflammation that activate sensory skin nerves (itch, skin burning, pain), dilate skin blood vessels (erythema, hyperthermia), and induce plasma extravasation (edema and influx of basophils, neutrophils, eosinophils, and other immune cells). The action of histamine on its H_1 receptor plays a crucial role in the development of urticaria signs and symptoms. Following their degranulation, skin mast cells produce and secrete prostaglandins, leukotrienes, and platelet activating factor as well as several cytokines. These mediators, together with infiltrating immune cells, are held to contribute to the inflammatory response induced by degranulation and to prime the skin including skin mast cells for subsequent whealing and angioedema formation.

In patients with CSU, the degranulation of skin mast cells is not due to classical allergic activation, i.e. the binding of environmental allergens to specific IgE bound to cell surface IgE receptors. Instead, mast cells are degranulated by autoantibodies including IgG autoantibodies to IgE or its receptor, FcεRI, (Grattan et al. 1991; Hide et al. 1993) and IgE autoantibodies directed against autoantigens (autoallergens) such as thyreoperoxidase (TPO) (Altrichter et al. 2011; Sanchez et al. 2019),

Fig. 1 (continued) Wheals induced by scratching of the skin, in a patient with symptomatic dermographism. (**e**) Wheals induced by skin contact with a stinging nettle (contact urticaria). (**f**) Wheals with pronounced erythema, in a patient with cholinergic urticaria

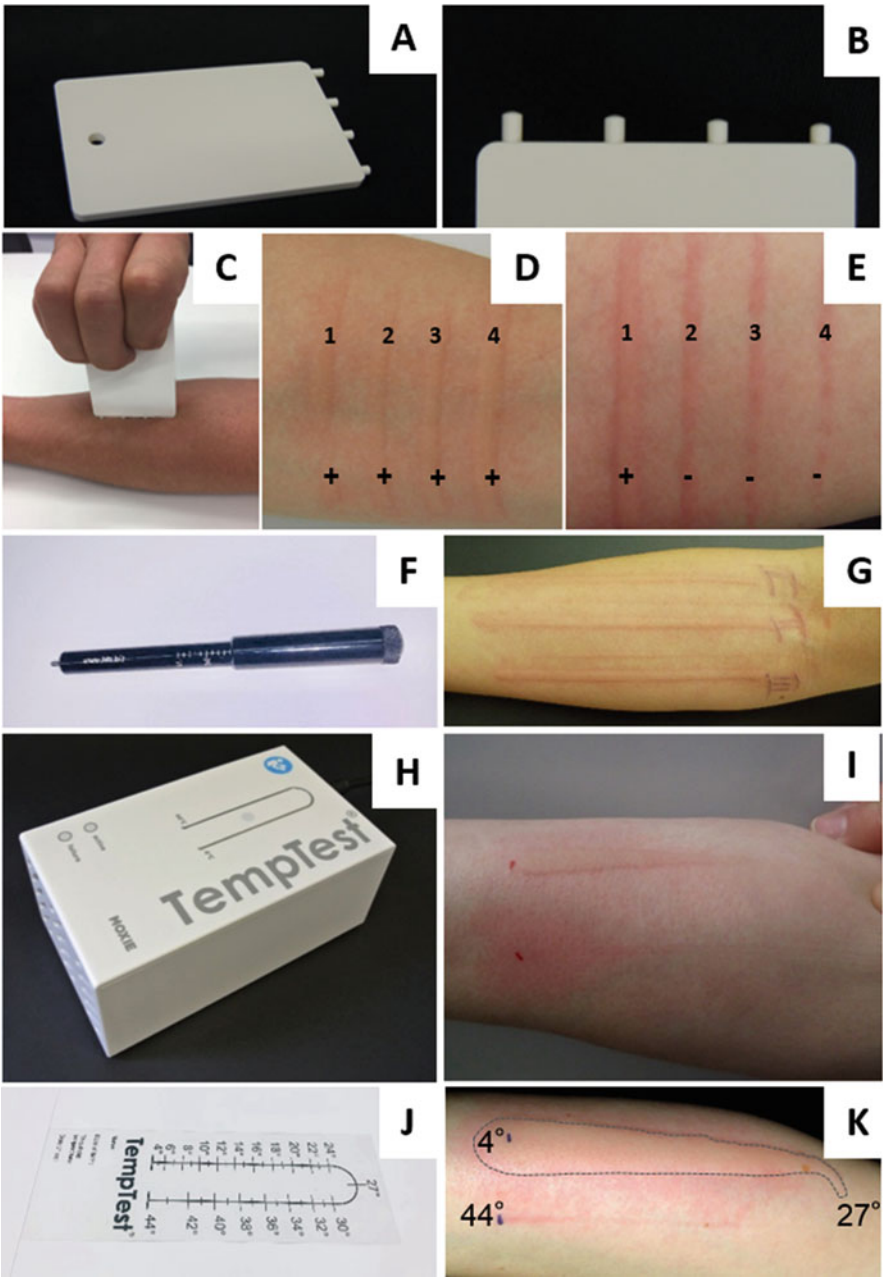

Fig. 2 Provocation and threshold testing in patients with chronic inducible urticaria. FricTest® (**a**–**c**) is a dermographometer used for provocation testing and threshold testing in patients with symptomatic dermographism. The instrument has four pins of different lengths (**b**). Provocation tests with FricTest ® (Moxie, Berlin, Germany) are done by placing the four pins on the skin and then moving them horizontally across the skin test site. By stroking with these four pins, the skin is exposed to four defined trigger strengths (**c**). The test result is positive, when an itchy wheal develops at the provocation site within 10 min. In patients with severe symptomatic

double-stranded DNA (Hatada et al. 2013), or interleukin-24 (Schmetzer et al. 2018). Additional signals that are held to have important effects on mast cells in CSU include complement components such as C5a (Ferrer et al. 1999) and neuropeptides, for example substance P (Metz et al. 2014; Vena et al. 2018), some of which may act via the receptor MRGPRX2, which has been reported to be upregulated in skin mast cells of patients with CSU (Fujisawa et al. 2014) and can be induced by interleukin-33 (Wang et al. 2019).

5 Clinical Picture

5.1 Acute Spontaneous Urticaria

Acute spontaneous urticaria (AU) resolves within a few days to several weeks. The causes of AU include viral infections of the upper airways (the common cold) or gastrointestinal tract, IgE-mediated food allergy, and the intake of non-steroidal anti-inflammatory drugs such as ibuprofen, diclofenac, and acetylsalicylic acid. In many patients with AU, the cause cannot be identified. The clinical picture is variable in patients with AU, ranging from a few transient wheals to severe angioedema of several days' duration with hundreds of simultaneous and sometimes confluent wheals that affect large body areas and come with systemic impairment.

5.2 Chronic Spontaneous Urticaria

Wheals and angioedema can occur together or alone in patients with CSU. About 50% of CSU patients develop both, wheals and angioedema. About 40% and 10% of patients experience solely wheals and solely angioedema, respectively (Maurer et al. 2011a). CSU is of long duration in most patients and shows spontaneous remission in virtually all patients. About 50% of patients with CSU are affected for more than 10 years (van der Valk et al. 2002), and the average duration of CSU ranges from 4 to 7 years. In most patients with moderate or severe CSU, wheals and/or angioedema

Fig. 2 (continued) dermographism, all four pins of Frictest® induce a positive response (**d**). In patients with mild symptomatic dermographism, only the longest pin results in a positive response (**e**). In (**d**) and (**e**), numbers indicate the four pins with 1 = the longest pin and 4 = the shortest pin; +, positive response; −, negative response. A pen-shaped dermographic tester with a spring-loaded tip is also used to assess trigger thresholds in patients with symptomatic dermographism (F, HTZ Limited, Vulcan Way, New Addington, Croydon, Surrey, UK). (**g**) shows three positive skin provocation test results induced by scratching with the dermographic tester set to three different trigger strength. The TempTest® cold and heat provocation instrument (H, Courage & Khazaka, Köln, Germany). (**i**) Positive test result in a patient with cold urticaria tested with TempTest®. (**j**) The see-through assessment template is placed on the test reaction to assess the trigger threshold, i.e. the highest temperature that produces a wheal. (**k**) Temperature threshold of 27°C determined by TempTest® in a patient with cold urticaria and high disease activity

occur every day or almost every day (Weller et al. 2011). Disease activity can change markedly over time in the same patient, with periods of weeks and months in which no symptoms occur and other times in which disease activity is high. In some patients, unspecific triggers such as stress or infections can sporadically lead to the exacerbation of CSU.

5.3 Chronic Inducible Urticaria

In patients with CIndU, wheals and angioedema are induced by specific triggers, such as cold in cold urticaria and scratching in symptomatic dermographism. These triggers are definite triggers, i.e. exposure to the relevant trigger always induces wheals and/or angioedema, and wheals and/or angioedema only occur after trigger exposure. This makes CIndU a more predictable disease than CSU in terms of its clinical picture. In terms of its duration, CIndU is as unpredictable as CSU. There are, currently, no biomarkers or other indicators that can predict, in individual patients, the duration of their CIndU. Like CSU, CIndU goes into remission in all or almost all patients after several years (Maurer et al. 2011a). CIndU is often of longer duration as compared to CSU. The wheals in patients with CIndU are often of shorter duration than the wheals in patients with CSU.

In patients with CIndU, high frequency trigger exposure and a low trigger threshold result in high disease activity, i.e. wheals and/or angioedema develop often and are severe. Trigger thresholds, i.e. the sensitivity to symptom-inducing triggers, are rather constant in most patients with CIndU. The signs and symptoms of CIndU typically occur where the skin is exposed to the relevant trigger. Skin sites such as the hands and the face, which are exposed to cold and friction and UV light more often than other skin sites, are more commonly affected. Systemic reactions including anaphylaxis may occur and are held to be due to the effects of histamine and other mediators released by skin mast cells after trigger exposure.

6 Diagnostics

6.1 Acute Spontaneous Urticaria

Patients with ASU, in most cases, do not need a diagnostic workup with the exception of taking the patient's history. The disease is self-limited, and diagnostic test, when performed, often fails to identify the cause. There is one exception to this rule: In patients where ASU is suspected to be due to an allergy, based on the patient's history, an allergy to food for example, allergy tests and patient education can help to avoid subsequent exposure to the causative allergen.

6.2 Chronic Spontaneous Urticaria

In patients with CSU, the diagnostic workup can have several aims such as the exclusion of a severe inflammatory condition and of differential diagnoses, the search for the underlying cause and relevant aggravators, the evaluation of disease activity, impact, and control, the assessment of comorbidities, and the characterization of predictors of the course of the disease or the response to treatment. Physicians should be clear, in their communication with patients, which diagnostic tests are done and why.

In all patients with CSU, the erythrocyte sedimentation rate and/or C-reactive protein should be measured, and a differential blood count should be done. This is to rule out severe inflammatory conditions including autoinflammatory differential diagnoses.

Patients with long-standing CSU and/or high disease activity may benefit from tests that are aimed at the investigation of the underlying cause or of relevant aggravators. This search should be based on clues from the patient's history, and it should focus on common causes of CSU such as autoimmunity and autoallergy as well as common aggravating conditions such as chronic infections, stress and intolerance to food components.

Autoimmunity and autoallergy are harmful responses of the body to itself, and they involve IgG autoantibodies and IgE autoantibodies, respectively (Maurer et al. 2018a). Both have been linked to CSU and are held by many to be the underlying cause in most patients with CSU. Autoimmune CSU (aiCSU) does not come with distinct clinical features, but high disease activity, angioedema, poor response to antihistamines and omalizumab therapy, and autoimmune comorbidities have been described to be more frequent in patients with aiCSU. Also, elevated levels of anti-TPO and ANA and low levels of IgE have been reported to be more common in patients with aiCSU. The tests performed for aiCSU include the autologous serum skin test, cellular activation tests such as the basophil histamine release test or the basophil activation test, and assays for IgG autoantibodies to IgE or FcϵRI. Autoallergic CSU (aaCSU) comes with IgE autoantibodies to autoallergens such as thyreoperoxidase (TPO) (Altrichter et al. 2011; Sanchez et al. 2019), double-stranded DNA (Hatada et al. 2013), or interleukin-24 (Schmetzer et al. 2018). Like aiCSU, aaCSU does not come with distinct clinical features. High normal or elevated total IgE levels and a fast and good response to omalizumab treatment have been reported to be linked to aaCSU (Kolkhir et al. 2017a; Kolkhir et al. 2017b; Maurer et al. 2011b). As of now, tests to diagnose aaCSU, i.e. assays for IgE autoantibodies or total auto-IgE, are not commercially available.

Bacterial infections, for example of the gastrointestinal tract by *Helicobacter pylori* or chronic ear nose or throat infections, as well as viral infections can aggravate CSU. However, most studies indicate that eradication of *Helicobacter pylori* has no discernible effect on CSU beyond that of standard CSU therapy (Curth et al. 2015; Kim et al. 2019). Still, it may not be irrelevant, as one recent study showed that inflammation linked to *Helicobacter pylori* infection can lead to reflux and that patients who are successfully treated for reflux, but not those who are not,

can experience remission of their CSU (Zheleznov et al. 2018). Many patients with CSU suspect that their condition is due to what they eat and drink, and food intolerance, for example to preservatives or to naturally occurring aromatic compounds, has been linked to CSU in about one out of three patients (Magerl et al. 2010; Zuberbier et al. 1995). In a small study with 45 CSU patients and 45 healthy controls, stress has been described to aggravate CSU and to contribute to high levels of disease activity (Varghese et al. 2016). Assessing patients with CSU for the relevance of these known aggravators can help with the management of their disease.

The diagnostic workup, in all patients with CSU, should aim to assess and monitor disease activity, impact on quality of life, and disease control (Weller et al. 2015). The urticaria activity score, UAS, is the gold standard for measuring disease activity in patients with CSU (Mlynek et al. 2008). The UAS is based on the daily documentation, usually once daily for seven consecutive days (UAS7), of the number of wheals and the intensity of pruritus during the previous 24 h (Hawro et al. 2018; Hollis et al. 2018). It uses a 0–3 point scale for wheals (0 for none, 1 for <20, 2 for 20–50, and 3 for >50) and a 0–3 point scale for pruritus (0 for none, 1 for mild, 2 for moderate, and 3 for intense). The sum of the daily totals of these wheal and itch scores is the value of the UAS7, it ranges from 0 (no disease activity) to 42 (maximum disease activity). The UAS does not assess angioedema. Thus, in patients with CSU with angioedema, with or without wheals, the angioedema activity score (AAS) should be used to assess disease activity (Weller et al. 2013).

In addition to the activity of their disease, patients with CSU should be assessed for the impact of the disease on their lives including its effects on their quality of life. The CU-Q_2oL (Chronic Urticaria Quality of Life Questionnaire) and the AE-QoL (Angioedema Quality of Life Questionnaire) are disease-specific instruments to assess the impairment in quality of life in patients with CSU who have wheals and angioedema, respectively (Baiardini et al. 2005; Mlynek et al. 2009; Weller et al. 2012, 2016).

The guideline-recommended tool for assessing disease control in patients with CSU is the urticaria control test (UCT) (Weller et al. 2014). The UCT consists of four items, and it has a defined cut off for "well-controlled" (12 points or more) vs. "poorly controlled" CSU (11 points or less).

The diagnostic workup of patients with CSU should include their evaluation for comorbidities. Autoimmune diseases, for example, are well recognized to be more common in patients with CSU (Kolkhir et al. 2016, 2017a, b, c). There is increasing evidence that mental disorders are also more prevalent and under-recognized. Some comorbidities including mental disorders and CIndU add to the burden of CSU and to the impairment of quality of life in patients with CSU (Staubach et al. 2011). Concomitant CIndU and autoimmune thyroid disease have been linked to longer CSU duration and progression from ASU to CSU. In some cases, CSU has been reported to show remission or improvement after the treatment of comorbid malignancy, infections or hyper- and hypothyroidism (Kolkhir et al. 2017c, 2018a; Larenas-Linnemann et al. 2018). For all of these reasons, patients with CSU should be assessed for comorbidities.

Finally, it is useful to assess patients with CSU for predictors of the course of their disease and for their response to treatment. Higher age at onset of CSU, being female, long CSU duration and aspirin/NSAID hypersensitivity have been reported to be linked to severe CSU and a long time to spontaneous remission. In addition, comorbidity of CIndU and the occurrence of angioedema may point to longer CSU duration, whereas a positive autologous serum skin test appears to be linked to higher disease activity (Sanchez et al. 2019). Patients with CSU, who are non-responders to antihistamine treatment, have higher C-reactive protein levels as compared to responders (Kolkhir et al. 2018b). Serum autoreactivity as assessed by basophil histamine release or autologous serum skin testing and low levels of IgE and failure of IgE to increase after the start of treatment have been reported to predict poor or slow treatment responses in patients treated with omalizumab (Ertas et al. 2018; Marzano et al. 2018; Nettis et al. 2018; Weller et al. 2018a).

6.3 Inducible Urticarias

The diagnostic workup, in patients with CIndU, should exclude differential diagnoses, aim to identify and characterize the relevant elicitation trigger(s), and evaluate disease activity, impact and control (Magerl et al. 2016). A search for underlying causes is not recommended as these are currently not known.

In symptomatic dermographism, formerly also called urticaria factitia or dermographic urticaria, scratching of the skin is the relevant wheal-inducing trigger. Provocation tests are done by stroking the skin with a smooth and blunt object such as a closed ballpoint pen or, preferably, a dermographometer (Magerl et al. 2016; Schoepke et al. 2015). Two types of dermographometers are available: (1) FricTest® (Moxie, Berlin, Germany, Fig. 2) is used for simultaneous testing of four defined trigger strengths. (2) A pen-shaped dermographic tester with a spring-loaded tip is used to test individual triggers strengths (HTZ Limited, Vulcan Way, New Addington, Croydon, Surrey, UK, Fig. 2). Both of these dermographometers are used for provocation testing by placing them on the skin and then moving them vertically across the skin test site. The test result is positive, when an itchy wheal develops at the provocation site within 10 min. Positive provocation tests should be followed up by threshold testing (Magerl et al. 2016) (Fig. 2). Patients with symptomatic dermographism should be monitored for their disease activity, response to treatment, and control of the disease by threshold testing and use of the UCT at every visit.

In delayed pressure urticaria, skin exposure to vertical pressure is the relevant trigger, e.g. pressure from the shoulder straps of heavy bags, tight shoes, or prolonged sitting. Patients with delayed pressure urticaria typically develop erythematous angioedema-like swellings, not wheals, and these swellings develop hours after exposure to pressure with a delay of 4–8 h, rather than fast. Also, these swellings typically persist for several hours, in some patients for several days. Provocation and threshold testing for delayed pressure urticaria is done with

weighted rods or a dermographic tester, and the test result is considered to be positive when a red palpable swelling is present 6 h after testing.

In vibratory angioedema, skin exposure to vibration is the relevant trigger, and this results in cutaneous swellings that occur within minutes after exposure at exposed skin sites. Provocation testing can be done with a laboratory vortex mixer.

In cold urticaria, skin exposure to cold is the relevant trigger. Patients with cold urticaria show itchy wheal and flare type skin reactions or angioedema at exposed skin sites, typically within minutes after cold contact (cold air, cold liquids or objects). Provocation testing is done with a melting ice cube in a thin plastic bag, and the test is considered positive when the test site shows a palpable wheal. Patients with cold urticaria should be evaluated for their individual temperature and/or stimulation time thresholds, for example by using a TempTest® instrument (Courage & Khazaka, Köln, Germany) (Magerl et al. 2015, 2016; Maurer et al. 2018a, b, c, d) (Fig. 2). Threshold measurements and use of the UCT at every visit allow patients and physicians to monitor disease activity, the therapeutic response, and disease control.

In heat urticaria, wheals develop within minutes and resolve within a few hours at skin areas exposed to heat. Provocation testing for heat urticaria is done by applying temperatures of up to 44°C to the skin, for example by TempTest® or metal/glass cylinders filled with hot water. Patients with heat urticaria show whealing after provocation testing and should be assessed for their temperature thresholds to determine and monitor disease activity.

In solar urticaria, exposure to UV and/or visible light is the relevant trigger, and skin responses are characterized by itchy wheals that occur within minutes at exposed skin sites. Provocation testing for solar urticaria is done with solar simulators or monochromators, and the test result is positive when a palpable wheal develops. Patients should be threshold tested for their lowest urticaria-triggering dose of radiation.

In cholinergic urticaria, sweating is the relevant trigger and results in itching and whealing, typically within minutes and for less than 1 h. Provocation testing for cholinergic urticaria is done by first subjecting patients to moderate physical exercise to make them sweat. When this test is positive, patients are exposed in a second test to a warm bath, which also leads to whealing in cholinergic urticaria patients, but not in patients with exercise-induced anaphylaxis. Threshold testing is done by pulse-controlled ergometry to assess disease activity, together with the cholinergic urticaria activity score, CholUAS (Altrichter et al. 2014). Disease control and impact are assessed by use of the UCT and the cholinergic urticaria quality of life questionnaire (CholU-QoL), respectively (Ruft et al. 2018).

7 Therapy

7.1 Acute Spontaneous Urticaria

In the management of ASU, the therapeutic goal is to control and prevent the development of urticarial lesions until the condition resolves by itself. Future exposure to known and circumventable elicitors should be avoided. Patients with minimal or mild ASU may not require treatment or respond to an oral non-sedating H_1-antihistamine, which should be used until the recurrence of wheals subsides. In patients with moderate and severe ASU, the dose of the H_1-antihistamine may need to be increased up to fourfold the standard dose, and the addition of an oral steroid should be considered.

7.2 Chronic Spontaneous Urticaria

In CSU, the aim of treatment is to stop the reoccurrence of wheals and/or angioedema. In most patients, the use of prophylactic medication rather than attempts to eliminate suspected causes or aggravators is the strategy of choice.

The first-line symptomatic treatment for CSU is a second generation, non-sedating H_1-antihistamine (Zuberbier et al. 2018). The response to this treatment should be monitored by the use of the UAS and/or AAS as well as the UCT. In patients where this does not prevent the occurrence of wheals and angioedema and does not control the disease after 2–4 weeks, the dose of the non-sedating H_1-antihistamine should be increased to up to four times the standard dosage. This is more effective than standard-dosed antihistamine treatment, and it is safe and well tolerated with antihistamines that are non-sedating at higher than standard doses (Gimenez-Arnau et al. 2009; Staevska et al. 2010; Weller et al. 2018b). Patients who fail to achieve control of their CSU with a higher than standard-dosed H_1-antihistamine are treated with add-on omalizumab, best given at 300 mg every 4 weeks. The efficacy and safety of omalizumab in the treatment of patients with CSU has been demonstrated in clinical trials and real life (Gimenez-Arnau et al. 2016; Zhao et al. 2016). Multiple mechanisms have been suggested to contribute to the therapeutic effects of omalizumab in patients with CSU as well as for the heterogeneity of their clinical responses experienced by patients (Chang et al. 2015; Gericke et al. 2017; Metz et al. 2017a, 2019). Patients with complete control of their signs and symptoms should be assessed for spontaneous remission of their CSU every 6–12 months.

7.3 Chronic Inducible Urticaria

The management of CIndU aims to control the disease, completely, and to prevent the induction of wheals and angioedema for as long as it takes, i.e. until spontaneous remission occurs. To this end, patients should be advised to monitor trigger

thresholds and to document the activity, impact, and control of their CIndU, to avoid or mitigate relevant triggers, and to use prophylactic medication. All CIndU patients should know that modifying or stopping the exposure to relevant triggers can help, and they should be made familiar with strategies to do so. Patients with DPU, for example, should avoid, if possible, tight fitting shoes, if wearing them results in swelling of their feet, and give preference to soft and loose-fitting ones. Importantly, CIndU can have devastating effects on patients' quality of life when trigger thresholds are low and trigger avoidance interferes with daily routines and a normal daily life.

In patients with CIndU, a second-generation non-sedating H_1-antihistamine at standard and higher than standard dose is the first-line and the second-line treatment, respectively (Maurer et al. 2018b; Dressler et al. 2018). Higher than standard antihistamine doses are more effective than standard-dosed treatment, and they are often needed to prevent whealing and angioedema and to achieve disease control (Abajian et al. 2016; Krause et al. 2013; Magerl et al. 2012). Omalizumab, although off label, is the recommended treatment for patients with antihistamine-resistant CIndU, based on controlled trials and clinical experience (Maurer et al. 2017, 2018d; Metz et al. 2017b). In patients with CIndU who fail to respond to omalizumab treatment, other therapies that have been reported to be of benefit should be considered. Examples include cyclosporine A or antibiotic treatment with doxycycline for cold urticaria (Gorczyza et al. 2017), UVB light therapy for symptomatic dermographism (Borzova et al. 2008), the humanized interleukin-5 antagonist monoclonal antibody reslizumab (Maurer et al. 2018c) or anti-TNFα (Magerl et al. 2007) in delayed pressure urticaria, and afamelanotide, a synthetic peptide and analogue of α-melanocyte stimulating hormone, for solar urticaria (Haylett et al. 2011).

In some types of CindU such as solar urticaria, cold urticaria, and cholinergic urticaria, desensitization to the eliciting trigger is possible. But this treatment is often not tolerated well and patient compliance is poor. Patient compliance, however, is crucial for this treatment to be successful, because daily exposure of the patients to their specific trigger (e.g., daily cold showers in patients with cold urticaria) is needed to achieve and maintain the depletion of urticaria-eliciting mediators and the protection from trigger-induced wheals and angioedema.

References

Abajian M, Curto-Barredo L, Krause K et al (2016) Rupatadine 20 mg and 40 mg are effective in reducing the symptoms of chronic cold urticaria. Acta Derm Venereol 96(1):56–59

Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M (2011) IgE mediated autoallergy against thyroid peroxidase – a novel pathomechanism of chronic spontaneous urticaria? PLoS One 6(4):e14794

Altrichter S, Salow J, Ardelean E, Church MK, Werner A, Maurer M (2014) Development of a standardized pulse-controlled ergometry test for diagnosing and investigating cholinergic urticaria. J Dermatol Sci 75(2):88–93

Baiardini I, Pasquali M, Braido F et al (2005) A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy 60 (8):1073–1078

Balp MM, Weller K, Carboni V et al (2018) Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. Pediatr Allergy Immunol 29(6):630–636

Borzova E, Rutherford A, Konstantinou GN, Leslie KS, Grattan CE (2008) Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism: a pilot study. J Am Acad Dermatol 59(5):752–757

Chang TW, Chen C, Lin CJ, Metz M, Church MK, Maurer M (2015) The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 135(2):337–342

Church MK, Kolkhir P, Metz M, Maurer M (2018) The role and relevance of mast cells in urticaria. Immunol Rev 282(1):232–247

Curth HM, Dinter J, Nigemeier K, Kutting F, Hunzelmann N, Steffen HM (2015) Effects of helicobacter pylori eradication in chronic spontaneous urticaria: results from a retrospective cohort study. Am J Clin Dermatol 16(6):553–558

Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer M (2018) Chronic inducible urticaria: a systematic review of treatment options. J Allergy Clin Immunol 141(5):1726–1734

Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M (2018) The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy 73(3):705–712

Ferrer M, Nakazawa K, Kaplan AP (1999) Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol 104(1):169–172

Fujisawa D, Kashiwakura J, Kita H et al (2014) Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. J Allergy Clin Immunol 134 (3):622–633.e629

Gericke J, Metz M, Ohanyan T et al (2017) Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol 139 (3):1059–1061.e1051

Gimenez-Arnau A, Izquierdo I, Maurer M (2009) The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. J Eur Acad Dermatol Venereol 23(9):1088–1091

Gimenez-Arnau AM, Toubi E, Marsland AM, Maurer M (2016) Clinical management of urticaria using omalizumab: the first licensed biological therapy available for chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 30(Suppl 5):25–32

Gorczyza M, Schoepke N, Krause K, Hawro T, Maurer M (2017) Patients with chronic cold urticaria may benefit from doxycycline therapy. Br J Dermatol 176(1):259–261

Grattan CE, Francis DM, Hide M, Greaves MW (1991) Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 21 (6):695–704

Hatada Y, Kashiwakura J, Hayama K et al (2013) Significantly high levels of anti-dsDNA immunoglobulin E in sera and the ability of dsDNA to induce the degranulation of basophils from chronic urticaria patients. Int Arch Allergy Immunol 161(Suppl 2):154–158

Hawro T, Ohanyan T, Schoepke N et al (2018) The urticaria activity score-validity, reliability, and responsiveness. J Allergy Clin Immunol Pract 6(4):1185–1190.e1181

Haylett AK, Nie Z, Brownrigg M, Taylor R, Rhodes LE (2011) Systemic photoprotection in solar urticaria with alpha-melanocyte-stimulating hormone analogue [Nle4-D-Phe7]-alpha-MSH. Br J Dermatol 164(2):407–414

Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW (1993) Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 328(22):1599–1604

Hollis K, Proctor C, McBride D et al (2018) Comparison of urticaria activity score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: results from the ASSURE-CSU study. Am J Clin Dermatol 19(2):267–274

Kim HJ, Kim YJ, Lee HJ et al (2019) Systematic review and meta-analysis: effect of helicobacter pylori eradication on chronic spontaneous urticaria. Helicobacter 24(6):e12661

Kolkhir P, Pogorelov D, Olisova O, Maurer M (2016) Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus – a systematic review. Clin Exp Allergy 46(2):275–287

Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M (2017a) Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev 16 (12):1196–1208

Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M (2017b) Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol 139 (6):1772–1781.e1771

Kolkhir P, Metz M, Altrichter S, Maurer M (2017c) Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. Allergy 72(10):1440–1460

Kolkhir P, Pereverzina N, Olisova O, Maurer M (2018a) Comorbidity of viral hepatitis and chronic spontaneous urticaria: a systematic review. Allergy 73(10):1946–1953

Kolkhir P, Altrichter S, Hawro T, Maurer M (2018b) C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. Allergy 73 (4):940–948

Krause K, Spohr A, Zuberbier T, Church MK, Maurer M (2013) Up-dosing with bilastine results in improved effectiveness in cold contact urticaria. Allergy 68(7):921–928

Larenas-Linnemann D, Saini SS, Azamar-Jacome AA, Maurer M (2018) Chronic urticaria can be caused by cancer and resolves with its cure. Allergy 73(7):1562–1566

Magerl M, Philipp S, Manasterski M, Friedrich M, Maurer M (2007) Successful treatment of delayed pressure urticaria with anti-TNF-alpha. J Allergy Clin Immunol 119(3):752–754

Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M (2010) Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial. Allergy 65(1):78–83

Magerl M, Pisarevskaja D, Staubach P, Martus P, Church MK, Maurer M (2012) Critical temperature threshold measurement for cold urticaria: a randomized controlled trial of H(1)-antihistamine dose escalation. Br J Dermatol 166(5):1095–1099

Magerl M, Abajian M, Krause K, Altrichter S, Siebenhaar F, Church MK (2015) An improved Peltier effect-based instrument for critical temperature threshold measurement in cold- and heat-induced urticaria. J Eur Acad Dermatol Venereol 29(10):2043–2045

Magerl M, Altrichter S, Borzova E et al (2016) The definition, diagnostic testing, and management of chronic inducible urticarias – the EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy 71(6):780–802

Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, Ferrucci S, Pepe P, Liberati S, Pigatto PD, Offidani A, Martina E, Girolomoni G, Rovaris M, Foti C, Stingeni L, Cristaudo A, Canonica GW, Nettis E, Asero R (2019) Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. J Eur Acad Dermatol Venereol 33 (5):918–924. https://doi.org/10.1111/jdv.15350. Epub 2018 Dec 7. PMID: 30451325

Maurer M, Weller K, Bindslev-Jensen C et al (2011a) Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. Allergy 66(3):317–330

Maurer M, Altrichter S, Bieber T et al (2011b) Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. J Allergy Clin Immunol 128 (1):202–209.e205

Maurer M, Schutz A, Weller K et al (2017) Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. J Allergy Clin Immunol 140 (3):870–873.e875

Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M (2018a) Immunoglobulin E-mediated autoimmunity. Front Immunol 9:689

Maurer M, Fluhr JW, Khan DA (2018b) How to approach chronic inducible urticaria. J Allergy Clin Immunol Pract 6(4):1119–1130

Maurer M, Altrichter S, Metz M, Zuberbier T, Church MK, Bergmann KC (2018c) Benefit from reslizumab treatment in a patient with chronic spontaneous urticaria and cold urticaria. J Eur Acad Dermatol Venereol 32(3):e112–e113

Maurer M, Metz M, Brehler R et al (2018d) Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. J Allergy Clin Immunol 141 (2):638–649

Metz M, Krull C, Hawro T et al (2014) Substance P is upregulated in the serum of patients with chronic spontaneous urticaria. J Invest Dermatol 134(11):2833–2836

Metz M, Staubach P, Bauer A et al (2017a) Clinical efficacy of omalizumab in chronic spontaneous urticaria is associated with a reduction of FcepsilonRI-positive cells in the skin. Theranostics 7 (5):1266–1276

Metz M, Schutz A, Weller K et al (2017b) Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. J Allergy Clin Immunol 140(3):864–867.e865

Metz M, Torene R, Kaiser S et al (2019) Omalizumab normalizes the gene expression signature of lesional skin in patients with chronic spontaneous urticaria: a randomized, double-blind, placebo-controlled study. Allergy 74(1):141–151

Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M (2008) How to assess disease activity in patients with chronic urticaria? Allergy 63(6):777–780

Mlynek A, Magerl M, Hanna M et al (2009) The German version of the chronic urticaria quality-of-life questionnaire: factor analysis, validation, and initial clinical findings. Allergy 64 (6):927–936

Nettis E, Cegolon L, Di Leo E et al (2018) Omalizumab chronic spontaneous urticaria: efficacy, safety, predictors of treatment outcome, and time to response. Ann Allergy Asthma Immunol 121(4):474–478

Ruft J, Asady A, Staubach P et al (2018) Development and validation of the cholinergic urticaria quality-of-life questionnaire (CholU-QoL). Clin Exp Allergy 48(4):433–444

Sanchez J, Sanchez A, Cardona R (2019) Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. Allergy Asthma Immunol Res 11(1):29–42

Schmetzer O, Lakin E, Topal FA et al (2018) IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 142(3):876–882

Schoepke N, Abajian M, Church MK, Magerl M (2015) Validation of a simplified provocation instrument for diagnosis and threshold testing of symptomatic dermographism. Clin Exp Dermatol 40(4):399–403

Siebenhaar F, Redegeld FA, Bischoff SC, Gibbs BF, Maurer M (2018) Mast cells as drivers of disease and therapeutic targets. Trends Immunol 39(2):151–162

Staevska M, Popov TA, Kralimarkova T et al (2010) The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. J Allergy Clin Immunol 125(3):676–682

Staubach P, Dechene M, Metz M et al (2011) High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol 91(5):557–561

van der Valk PG, Moret G, Kiemeney LA (2002) The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. Br J Dermatol 146(1):110–113

Varghese R, Rajappa M, Chandrashekar L et al (2016) Association among stress, hypocortisolism, systemic inflammation, and disease severity in chronic urticaria. Ann Allergy Asthma Immunol 116(4):344–348.e341

Vena GA, Cassano N, Di Leo E, Calogiuri GF, Nettis E (2018) Focus on the role of substance P in chronic urticaria. Clin Mol Allergy 16:24

Wang Z, Guhl S, Franke K, Artuc M, Zuberbier T, Babina M (2019) IL-33 and MRGPRX2-triggered activation of human skin mast cells-elimination of receptor expression on chronic exposure, but reinforced degranulation on acute priming. Cells 8(4)

Weller K, Ziege C, Staubach P et al (2011) H1-antihistamine up-dosing in chronic spontaneous urticaria: patients' perspective of effectiveness and side effects – a retrospective survey study. PLoS One 6(9):e23931

Weller K, Groffik A, Magerl M et al (2012) Development and construct validation of the angioedema quality of life questionnaire. Allergy 67(10):1289–1298

Weller K, Groffik A, Magerl M et al (2013) Development, validation, and initial results of the angioedema activity score. Allergy 68(9):1185–1192

Weller K, Groffik A, Church MK et al (2014) Development and validation of the urticaria control test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol 133(5):1365–1372. 1372.e1–6

Weller K, Zuberbier T, Maurer M (2015) Chronic urticaria: tools to aid the diagnosis and assessment of disease status in daily practice. J Eur Acad Dermatol Venereol 29(Suppl 3):38–44

Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M (2016) The angioedema quality of life questionnaire (AE-QoL) – assessment of sensitivity to change and minimal clinically important difference. Allergy 71(8):1203–1209

Weller K, Ohanyan T, Hawro T et al (2018a) Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy 73(12):2406–2408

Weller K, Church MK, Hawro T et al (2018b) Updosing of bilastine is effective in moderate to severe chronic spontaneous urticaria: a real-life study. Allergy 73(10):2073–2075

Zhao ZT, Ji CM, Yu WJ et al (2016) Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. J Allergy Clin Immunol 137 (6):1742–1750.e1744

Zheleznov S, Urzhumtseva G, Petrova N et al (2018) Gastritis can cause and trigger chronic spontaneous urticaria independent of the presence of helicobacter pylori. Int Arch Allergy Immunol 175(4):246–251

Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM (1995) Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol 75(6):484–487

Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M (2010) Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol 35(8):869–873

Zuberbier T, Aberer W, Asero R et al (2018) The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 73(7):1393–1414

AIT: New Avenues in Allergen Immunotherapy

Wolfgang Pfützner and Christian Möbs

Contents

Abstract

During the last decades a substantial increase of allergic diseases has been noticed including allergic asthma and rhinoconjunctivitis as well as food allergies. Since efficient avoidance of airborne – and often hidden – food allergens is not possible, allergen immunotherapy (AIT) is the only causative treatment with the goal of inducing allergen tolerance in affected individuals. Efficacy as well as safety of AIT significantly depends on how the allergen is presented to the immune system, meaning both the route and the form of its application. Here, new ways of allergen administration have lately been explored, some of which are auspicious candidates for successful implementation in the therapeutic management of immediate-type allergies. While the first oral AIT has been approved recently by the FDA for the treatment of peanut allergy, further interesting routes of allergen application include either epicutaneous, intradermal, intranasal, or intralymphatic delivery. Besides, rather the immunologically relevant peptides

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instead of whole allergen may be administered to develop tolerance. In this chapter, we will describe these new and promising avenues of allergen application in the field of AIT. In addition, we will discuss their potential for future treatment of IgE-mediated allergic diseases enhancing therapeutic efficiency while further minimizing the risks of adverse events.

Keywords

Allergen immunotherapy · Allergy · EPIT · ILIT · OIT

Abbreviations

AIT	Allergen immunotherapy
APC	Antigen-presenting cell
Breg cells	Regulatory B cells
EPIT	Epicutaneous immunotherapy
IDIT	Intradermal immunotherapy
ILIT	Intralymphatic immunotherapy
LNIT	Local nasal immunotherapy
OIT	Oral immunotherapy
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
Th cell	T helper cell
Treg cells	Regulatory T cells

Allergen immunotherapy (AIT) describes the establishment of immune – and hereby clinical – tolerance to an allergen, achieved by different cellular and humoral immune responses. Mechanisms involved in the induction of tolerance are, e.g., the promotion of both regulatory T (Treg) and B (Breg) cells, a diminished T helper (Th) 2 cell reactivity and the production of allergen-blocking IgG antibodies (Shamji and Durham 2017; Wambre 2015; Möbs et al. 2008). This requires successful delivery of allergen to antigen-presenting cells (APC) capable of initiating an immunoregulatory cross-talk between various T and B cell subsets. Depending on the specific circumstances of how and where to the allergen is applied, it can be recognized and taken up by different APC, encompassing either epidermal Langerhans cells (in skin or mucosa), cutaneous dermal or lymphatic follicular dendritic cells (Kashem et al. 2017), potentially influencing the outcome of tolerance induction. Potential routes of AIT comprise subcutaneous and sublingual allergen transfer, both of which are well-established and routinely used. In addition, allergen can be administered via oral, epicutaneous, intradermal, nasal, and intralymphatic routes, which have been and still are the focus of intense investigation for their therapeutic potential (Fig. 1). In the following, we will highlight and discuss these

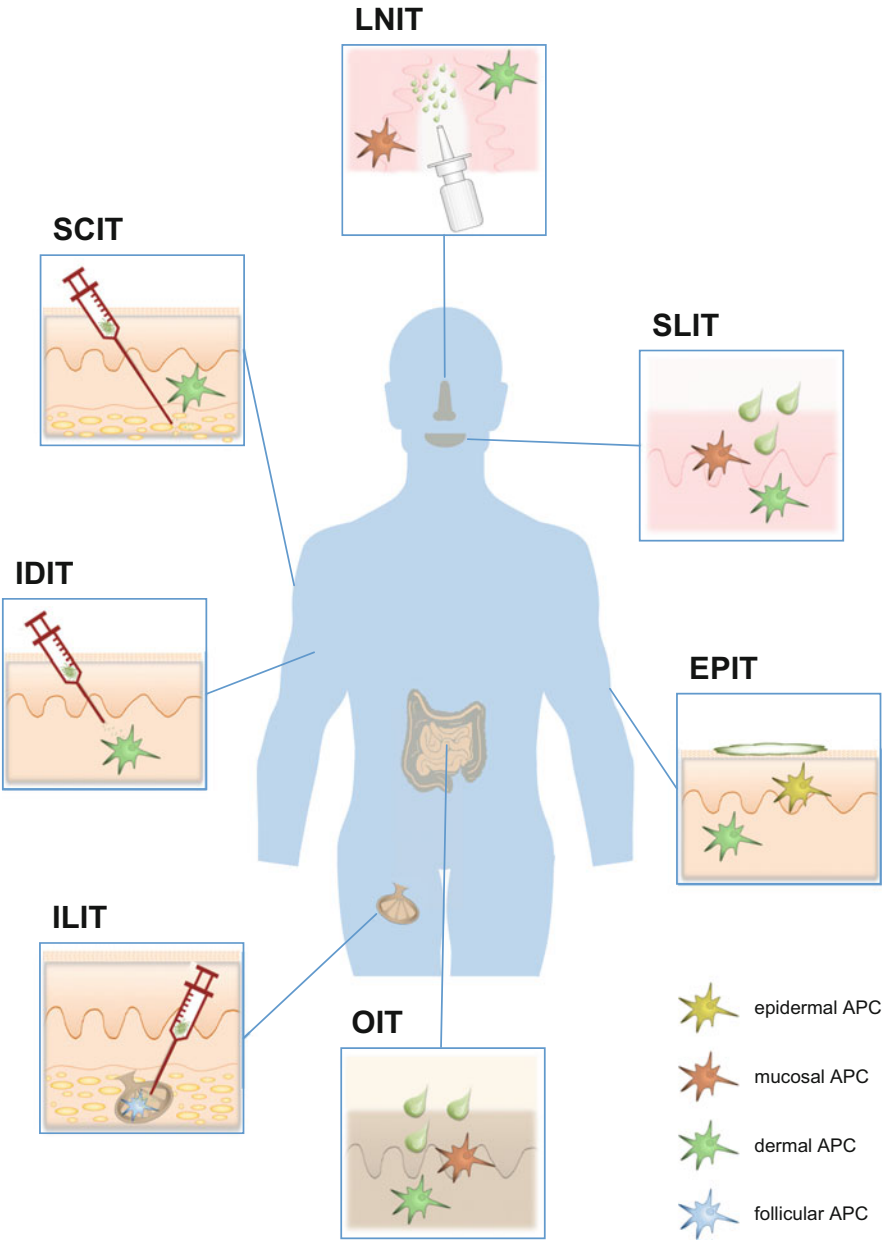

Fig. 1 Different routes of allergen immunotherapy. *APC* antigen-presenting cells

novel approaches, several of which may serve as promising alternatives for future AIT applications in routine practice.

Due to its easy accessibility, the skin constituted the primary venue for delivery of foreign antigens to elicit an immune response, with Edward Jenner performing the first successful vaccination in 1793 by scratching cowpox virus into the skin. Subsequently, the outer epithelium encompassing its deeper layers have been explored and utilized in various ways for the therapeutic application of antigens, not only to establish a protective immune response against infectious pathogens but later on also to induce tolerance against allergens. Here, in 1911 Leonard Noon described the treatment of patients suffering from hay fever by subcutaneous inoculation of increasing doses of grass pollen extract (Noon 1911). Inspired by his and John Freeman's work, who in 1930 published the first rush protocol of grass pollen AIT (Freeman 1930), injection of allergens into the subcutis became the conventional form of AIT, also termed subcutaneous immunotherapy (SCIT). Nevertheless, very soon after Noon's pivotal report, other routes of allergen application have been explored aiming

- to optimize the efficiency of allergen uptake and presentation to the immune system,
- to minimize the risk of systemic side effects by inadvertent vascular delivery, and,
- to establish a convenient, less cumbersome way of delivering the allergen, preferably by self-administration.

For example, as an alternative method topical application of allergens on scarified skin was reported showing clinical efficacy in patients with pollen or animal dander allergy, respectively (Vallery-Radot and Hangenau 1921; Blamoutier et al. 1959). Another, more gentle approach was studied by application of the allergen onto slightly rubbed skin (Pautrizel et al. 1957). In 1986, sublingual administration (SLIT) was proven to be an effective, non-invasive and safe treatment route of house dust mite allergy (Scadding and Brostoff 1986). While initially viewed with skepticism whether SLIT might be as efficacious as SCIT, by now it has been established as an appropriate alternative of allergen delivery in patients suffering from IgE-mediated respiratory allergies like allergic rhinoconjunctivitis and bronchial asthma (Muraro et al. 2018).

As research efforts continued to investigate further routes of allergen application, both clinical studies and animal models have been performed to improve the efficacy and/or safety of AIT. This is exemplified by new forms of treatment including oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), intradermal immunotherapy (IDIT), local nasal immunotherapy (LNIT), and intralymphatic immunotherapy (ILIT), which we will present here in more detail.

1 Oral Immunotherapy (OIT)

OIT aims to convey protection against anaphylactic reactions to food allergens by inducing allergen tolerance through controlled ingestion of incremental doses of the respective aliment (Wood 2017; Freeland et al. 2017). First reported in 1908 by successful treatment of an egg-allergic child (Shofield 1908), numerous observational and controlled studies of different OIT approaches, both in adults and children, have been presented since then with a broad variety of currently performed clinical trials (Tordesillas et al. 2017a). In general, OIT comprises three phases starting with an initial 1–2 day (rush OIT) dose escalation step to achieve a minimal dose, which is expected to be safely consumed without an increased risk of systemic reactions (Scurlock 2018). This is followed by a build-up phase of several months increasing the amount of applied allergen every (other) week until the target dose (usually between 300 and 4,000 mg of food protein) is reached. Thereafter, the maintenance phase continues, which entails the steady consumption of the attained allergen dose for months to years. The objective is to not only build up a state of desensitization, defined as a transient tolerability of the aliment which has to be constantly renewed by regular allergen intake. Rather, the ultimate goal is to achieve sustained unresponsiveness meaning a long-term allergen tolerance which lasts even when OIT is discontinued.

Most of the studies investigating the immunological or clinical effects of OIT have been performed with cow's milk, hen's egg, and peanuts. Both animal and pre-clinical trials have demonstrated pronounced immune alterations associated with the development of food tolerance, namely a loss of allergen-specific Th2 cells, presumably as a result of either Th2 cell anergy or deletion (Tordesillas and Berin 2018; Ryan et al. 2016). While Treg cells are seen as a central player in mediating allergen tolerance, their significance in OIT is controversially discussed (Tordesillas et al. 2017a). Alterations in different subsets, for example $Foxp3^+$ TGF-β- or IL-10-secreting Treg cells, have been observed in OIT-treated patients (Syed et al. 2014; Smaldini et al. 2015), however, others have failed to certify their appearance (Bedoret et al. 2012; Ryan et al. 2016). This might be due to a more local activity at the intestinal side of allergen contact and/or a generally rather transitional role of Treg cells in promoting AIT-specific immunoregulatory processes (Chinthrajah et al. 2016; Möbs et al. 2012). Furthermore, OIT-induced Treg cells may be established on a Th2 cell-like phenotype being rather instable and prone to lose their regulatory capability, which also might explain why food tolerance quite often vanishes after stopping treatment (Noval Rivas et al. 2015). Humoral immune mechanisms have been reported as a delayed decline of allergen-specific IgE (both in peripheral blood and on the surface of effector cells like basophils) and the development of memory B cells producing IgG (namely IgG4) and IgA antibodies, which steadily increase during treatment and can compete with IgE for allergen binding (Tordesillas et al. 2017a; Chinthrajah et al. 2016). It has been shown that OIT-induced IgG antibodies display a high rate of somatic mutations suggesting enhanced allergen affinity compared to IgE and that this antibody subclass can block basophil and mast cell

activation by binding to the inhibitory FcγRII receptor (Hoh et al. 2016; Burton et al. 2014).

From the beginning of this century, a variety of clinical OIT studies have been performed mainly with egg, milk, or peanuts, but a few of them also with other foods like wheat, tree nuts, or fish, and most of these studies have been conducted in children and adolescents (Wood 2017; Scurlock 2018). Randomized, placebo-controlled trials have shown that desensitization can be achieved in about 70 to up to 90% of the participants (with a range of 30–100%), reaching tolerated doses of around 1–4 g. However, many will lose their tolerance after stopping OIT with only around 30–40% showing sustained unresponsiveness. Nevertheless, there have been studies with even 90% still being protected when off OIT, as has been demonstrated in very small children of 9–36 months of age successfully treated with peanuts (Vickery et al. 2017). Thus, the management of adverse reactions is still a major challenge in OIT. About 50% of the patients are affected and drop-out rates of 10–20% (in some studies even up to one third of the participants) are very common (Wood 2017, Scurlock 2018). Most of them represent local events like abdominal pain, but systemic reactions are also not uncommon. While the majority of symptoms are rather moderate including urticaria, wheezing, and vomiting, severe anaphylaxis may be possible. Predisposing risk factors are asthma and allergic rhinitis as well as concurrent co-factors like illness, physical stress, or menses. However, for patients with a high risk of food anaphylaxis, OIT represents a very promising therapy to achieve tolerance at least against inadvertent ingestion of the eliciting allergen. Notably, in 2020 the first OIT product has been approved by the Food and Drug Administration in the USA for treatment of peanut allergy in 4–17 years old patients (https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treatment-peanut-allergy-children; Table 1).

2 Epicutaneous Immunotherapy (EPIT)

EPIT describes the induction of allergen tolerance by topical application of allergens on intact or pre-treated skin (Esposito et al. 2018; Bird et al. 2018). Early reports about its employment date back up to 100 years ago administering the allergen onto either (non-bleeding) scarified or simply rubbed skin (Vallery-Radot and Hangenau 1921; Pautrizel et al. 1957; Blamoutier et al. 1959). Pre-clinical studies in peanut sensitized animals have demonstrated its efficacy by prevention of esophageal inflammation or food anaphylaxis applying the allergen onto intact skin of piglets or mice, respectively (Tordesillas et al. 2017b; Mondoulet et al. 2017). Mouse experiments also shed light onto the responsible immune mechanisms showing a delayed allergen uptake over 48 h by epidermal dendritic cells, which migrated to local lymph nodes (Dioszeghy et al. 2011). Both humoral and T-cellular effects have been noticed in peanut-allergic EPIT models encompassing the synthesis of allergen-specific IgG2a antibodies (without effecting IgE levels), a diminished Th2 cell response and the induction of TGF-β-secreting Treg cells. Interestingly, this Treg cell subset expressed homing receptors not only for the skin but also for the intestinal

Table 1 Summarizing overview of different forms of allergen immunotherapy

Therapy	Schedule		Efficacy	Continued tolerance after stopping therapy	Safety		Compliance
	Up-dosing	Duration			Local AE	Systemic AE	
Approved, routinely prescribed							
SCIT	Yes	Several years	High	Yes (majority)	Common (local swelling)	Rarely (depends on allergen)	Relatively good
SLIT	No	Several years	High	Yes (majority)	Common (oral swelling, itching)	No (anecdotal events)	Relatively good
One product approved in 2020							
OIT	Yes	Several years	High	Small fraction (≈ 30%)	Common (abdominal pain)	Frequently	Hampered
Investigational trials (including phase III studies)							
EPIT	No	Several years	Variable[a]	?	Variable (local eczema)	Rarely (depends on allergen)	Relatively good
Investigational trials							
IDIT	No	Weeks to years	Low[b]	?	Common (local swelling)	No	?
ILIT	No	2 months (3 injections)	High[c]	Yes	Seldom	Rarely	Relatively good
Investigational trials (in use in some countries)							
LNIT	No	Repeatedly	High	No	Seldom	No	?

AE adverse events
[a]Compared to OIT rather small increases of tolerated food dosage
[b]Compared to placebo
[c]Only few trials with mostly low numbers of patients

allergic effector organs enabling them to execute local immunoregulatory functions (Tordesillas et al. 2017b; Dioszeghy et al. 2017). The decisive role of these Treg cells, which display a CTLA-4-dependent immunosuppressive activity, was demonstrated by both abrogation of the protective effect after depletion of $CD25^+$ cells and its conveyance to peanut-allergic mice through adoptive cell transfer.

Clinical studies include double-blind, placebo-controlled EPIT trials in patients (both adults and children) suffering either from allergic rhinoconjunctivitis or food allergies (Esposito et al. 2018). In three studies with grass pollen-allergic adults, the skin was pre-treated either by tape stripping or by abrasion of the corneal layer to enhance the epidermal uptake of allergen. Grass pollen extract solved in either petrolatum or glycerin was administered at weekly intervals for 8 or 48 h under a patch, at dosages of 3–30 μg of the major grass pollen allergen Phl p 5 (Senti et al. 2009; Senti et al. 2012b; Senti et al. 2015). Significant changes were observed for allergen-treated individuals by a reduction of clinical symptoms assessed by visual analogue scale during pollen season, but not by nasal provocation test or a decreased consumption of symptomatic medication. Clinical effects were dose-dependent requiring single allergen dosages of 21–30 μg (cumulative dose of 126 to 252 μg). In another trial with children, patches with 11.25 μg of Phl p 5 were applied at weekly intervals (cumulative dose of 135 μg) for 24 h onto intact skin. Here, a significant improvement in rhinorrhea, nasal obstruction, dyspnea, and ocular tearing was noticed in verum-treated subjects. In contrast, ocular itching rather increased in the verum group, while the use of anti-allergic drugs reduced (Agostinis et al. 2010). Whereas in the children's study no local or systemic events were observed, the majority of EPIT-treated adults reported local reactions, mostly eczema at the patch test area (in up to more than 70%). The frequency of local reactions was related to both allergen dosage and duration of application. Systemic events included pruritus, rhinitis, conjunctivitis, and even asthma, most frequent in patients with abraded application sites.

EPIT trials treating food hypersensitivity utilized patches containing dry powder of allergen, which were placed onto intact skin. Serving as a condensation chamber, the epidermal water loss was herein captured leading to allergen solubilization and hydration of the stratum corneum, thereby promoting epidermal penetration without mechanical skin disruption. While a study in a small number of children treated for a short time of 3 months with single allergen dosages of 1 mg skimmed cow's milk (cumulative dose of 36 mg) failed to demonstrate a significant effect compared to placebo (Dupont et al. 2010), a larger trial in peanut-allergic patients aged 6–55 years showed an increase in tolerated peanut protein [from $\leq$300 mg (corresponding to roughly one peanut kernel) to up to $\geq$1,000 mg or 10 times baseline amount, verified by oral food challenge] in about 50% of patients treated with 250 μg of peanut protein daily over 52 weeks (Sampson et al. 2017). The highest response rate was noticed in children $<$12 years old (53.6% compared to 19.4% in the placebo group). Peanut-specific IgG4 antibodies increased fivefold. A second study in 4–25 years old subjects yielded similar results, again with the highest success among younger children (Jones et al. 2017). In general, treatment with EPIT was tolerated well, with local skin reactions occurring as the most

frequent side effect and absence of systemic adverse events. However, patients with severe peanut anaphylaxis were excluded from participation in these studies. For comparison, a recent published phase III trial of OIT in patients with severe peanut allergy reacting already at doses of ≤100 mg peanut protein yielded protection in 67% of individuals tolerating at least 600 mg protein. Notably, protection was only realized in patients between 4 and 17 years, but not in adults (Palisade Group of Clinical Investigators 2018).

3 Intradermal Immunotherapy (IDIT)

Already in 1926, successful treatment of allergic rhinitis was reported by intradermal grass pollen injection (Philipps 1926). Based on this observation and the finding that low-dose intradermal allergen inoculation – as it is known from conventional SCIT – suppresses allergen-induced cutaneous late-phase responses (Rotiroti et al. 2012), a double-blind, randomized phase II trial of IDIT with grass pollen extract was conducted. However, seven pre-seasonal injections of extract containing 7 ng of the major grass pollen allergen Phl p 5 did neither result in improvement of clinical symptoms nor in reduction of symptomatic medication (Slovick et al. 2017). Instead a Th2-priming effect was noticed associated with a trend for worsening of nasal and asthmatic symptoms compared to placebo-treated patients. Another IDIT study treating cat-allergic subjects with peptides encompassing different T cell epitopes of the major cat allergen Fel d 1 at first yielded promising results. Here, the authors could show a significant reduction of nasal and ocular symptoms evaluated by a cat allergen challenge in an environmental exposure chamber (Patel et al. 2013). However, a clinical phase III trial failed to demonstrate efficacy due to an equally high response rate in the placebo group of nearly 60% reduction of the combined total rhinoconjunctivitis score (https://www.circassia.com/wp/wp-content/uploads/2016/06/CIR-PR-17_CATALYST-results-final.pdf). Similar results were obtained by IDIT with peptides of the major house dust mite allergen Der p 1 (https://www.circassia.com/wp/wp-content/uploads/2017/04/CIR-PR-20_HDM-SPIRE-results-final.pdf). Even though different reasons have to be considered for these failures, they have essentially terminated the current interest in IDIT. Besides, intradermal allergen application carries the unpleasant side effect of (sometimes very painful) large local swellings, up to 10 cm diameter, which – although substantiating the immunogenic potential of IDIT – hampers treatment adherence of the patients (Slovick et al. 2017).

4 Intralymphatic Immunotherapy (ILIT)

ILIT describes a very recently proposed concept of allergen delivery transferring the allergen directly into lymphatic tissue by injection into a lymph node, instead of choosing a peripheral route. Increased efficacy in initiating an immunoregulatory response is assumed due to allergen uptake and presentation by follicular dendritic

cells in an immunogenic environment densely populated by T and B lymphocytes (Senti et al. 2011). Thereby, the encounter of allergen-specific T and B cells is highly probable. Methodically, this is achieved by ultrasound-guided administration of the allergen extract into an inguinal lymph node, usually for a total of three injections in intervals of 4 weeks (thus requiring only 2 months of treatment). Human and animal studies mostly have demonstrated immune responses similar to what is known from conventional immunotherapy. Especially the induction of ($Foxp3^+$) IL-10-secreting T cells associated with increased production or affinity maturation of allergen-specific IgG4 antibodies, which at least partly were able to block allergen binding by IgE, has been observed in relation to this route of allergen administration (Senti et al. 2012a; Freiberger et al. 2016; Hylander et al. 2016; Kim et al. 2017).

From 2008 until 2019, eight clinical ILIT trials have been performed, either as placebo-controlled or open studies in patients suffering from allergic rhinoconjunctivitis, with the majority conducted in subjects with grass or birch pollen, but also house dust mite, cat, or dog allergy (Kim et al. 2017; Senti et al. 2019). Except for one trial, all proved to be clinically effective. One of them even showed a long-term benefit for up to 3 years analyzing 58 ILIT-treated individuals (Senti et al. 2008). However, most of these studies were executed in small numbers (between 7 and 21 patients) assessing a wide variety of evaluation methods, like different forms of symptom or use-of-medication scores, quality-of-life questionnaires, and nasal provocation tests. One study utilizing a combined score of symptoms and rescue medication – considered as gold standard of testing – failed to show clinical improvement in grass pollen-allergic patients (Witten et al. 2013). It has been proposed that shortening of the injection intervals down to 2 weeks might have been the reason compromising the formation and affinity maturation of IgG-producing allergen-specific memory B cells (Senti et al. 2019), although profound immunological changes like synthesis of allergen-specific IgG4 (as well as IgE) and secretion of IL-10 (as well as IL-4) were noticed (Witten et al. 2013). In terms of safety aspects, injections were mostly tolerated very well, both locally and systemically, even though anaphylactic reactions are possible (Kim et al. 2017).

5 Local Intranasal Immunotherapy (LNIT)

In contrast to the former AIT routes, which aim at treating distant organ or systemic allergic reactions, LNIT focusses on establishing allergen tolerance on the side of allergen application, i.e. the nose as the effector organ in allergic rhinitis (Passalacqua and Canonica 2006). Indeed, clinical benefit is limited to improvement of local symptoms. Introduced in 1951, clinical efficacy of LNIT has been demonstrated in multiple studies conducted mostly in adults since the seventies of the last century (Passalacqua and Canonica 2006; Ascione et al. 2003). Allergens comprised mainly out of various pollen extracts, initially applied as aqueous solutions, which proved to be effective but also resulted in inconvenient local adverse reactions. Utilization of dry powder pump sprays consisting out of granules of 40–50 μm diameter, which were homogeneously deposited at the nasal mucosa,

led to substantially better tolerability. Notably, systemic side effects are virtuously absent underlining the solely stationary impact (Passalacqua et al. 2003). This is further underscored by immunological data revealing local but not systemic production of allergen-specific IgG and IgA antibodies, in conjunction with a decreased allergen-specific T cell response (Giannarini and Maggi 1998; Piazza and Bizzaro 1993). However, obviously, this also implies that allergic unresponsiveness is rather short lasting and dependent on continuous allergen application (Passalacqua and Canonica 2006, Ascione et al. 2003). Thus, LNIT has to be constantly re-applied (either pre-seasonally or persistently) to ensure a long-term clinical benefit in patients suffering from either seasonal or perennial allergic rhinitis.

6 Conclusion

Over the last decades new avenues of allergen transfer, in addition to the well-established methods of subcutaneous injection and sublingual application, namely SCIT and SLIT, have been thoroughly investigated exploring their therapeutic potential, immunological mechanisms, clinical efficacy, and safety aspects (Table 1). Among these, OIT has recently been approved for treatment of peanut allergy in children and adolescents underlining the particular potential of this therapy in the treatment of food allergy, which could not be addressed by the so far established methods of AIT. Clinical studies have shown high efficacy of food tolerance induction, however, current limitations are an early loss of tolerance in many patients when off therapy and a high rate of adverse reactions, mostly in the form of abdominal pain. In contrast, EPIT, which has been also investigated for the treatment of food hypersensitivity (in addition to allergic rhinoconjunctivitis), is characterized by a good safety profile and the ease of application. However, therapeutic effects have been modest so far requiring further improvement in providing a topical allergen delivery system, which releases enhanced amounts of allergen into the skin while causing little or no irritation. Future applications might especially target individuals suffering from severe anaphylaxis with a high risk for strong adverse reactions at even low-level allergen exposure, with children probably showing the best response. Another interesting approach is ILIT, which has shown promising results in treating allergic rhinoconjunctivitis, albeit mostly in small numbers of patients. A significant advantage seems to be the low number of injections needed to achieve prolonged allergen tolerance, possibly through direct targeting of the immunoregulatory lymphatic tissue, with a reasonable safety profile. However, this requires appropriate technical experience in ultrasound-guided allergen administration into the (inguinal) lymph nodes. In comparison, LNIT can be easily performed by the patient him- or herself for the treatment of allergic rhinitis without obvious risks for pronounced adverse events. However, unlike SLIT as a routinely used form of mucosal AIT, it shows only temporary benefit necessitating its long-term, regular administration.

In summary, there are several interesting alternative routes of allergen administration, which are characterized by distinct features in regard of their immunological

action, responsive allergic diseases or individuals, and potential side effects. Here, refinements are needed to target current limitations in terms of therapeutic efficacy and/or clinical safety. This also requires the conduction of well-designed multicenter randomized, double-blind, placebo-controlled studies in large number of patients, in particular addressing questions of optimal allergen dosages and composition, treatment schedules, targeted groups, of how to achieve long-term tolerance and of biomarkers indicating potential therapeutic responses and to expected unwanted side effects.

References

Agostinis F, Forti S, Di Berardino F (2010) Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. Allergy 65:410–411

Ascione E, De Lucia A, Imperiali M, Varricchio A, Motta G (2003) Nasal application of immunotherapy. Chem Immunol Allergy 82:89–98

Bedoret D, Singh AK, Shaw V, Hoyte EG, Hamilton R, DeKruyff RH, Schneider LC, Nadeau KC, Umetsu DT (2012) Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. Mucosal Immunol 5:267–276

Bird JA, Sanchez-Borges M, Ansotegui IJ, Ebisawa M, Ortega Martell, J. A. (2018) Skin as an immune organ and clinical applications of skin-based immunotherapy. World Allergy Organ J 11:38

Blamoutier P, Blamoutier J, Guibert L (1959) Treatment of pollinosis with pollen extracts by the method of cutaneous quadrille ruling. Presse Med 67:2299–2301

Burton OT, Logsdon SL, Zhou JS, Medina-Tamayo J, Abdel-Gadir A, Noval Rivas M, Koleoglou KJ, Chatila TA, Schneider LC, Rachid R, Umetsu DT, Oettgen HC (2014) Oral immunotherapy induces IgG antibodies that act through FcgammaRIIb to suppress IgE-mediated hypersensitivity. J Allergy Clin Immunol 134:1310–1317.e6

Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC (2016) Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol 137:984–997

Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou PH, Dupont C (2011) Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. J Immunol 186:5629–5637

Dioszeghy V, Mondoulet L, Puteaux E, Dhelft V, Ligouis M, Plaquet C, Dupont C, Benhamou PH (2017) Differences in phenotype, homing properties and suppressive activities of regulatory T cells induced by epicutaneous, oral or sublingual immunotherapy in mice sensitized to peanut. Cell Mol Immunol 14:770–782

Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH (2010) Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 125:1165–1167

Esposito S, Isidori C, Pacitto A, Salvatori C, Sensi L, Frati F, DI Cara G, Marcucci F (2018) Epicutaneous immunotherapy in rhino-conjunctivitis and food allergies: a review of the literature. J Transl Med 16:329

Freeland DMH, Manohar M, Andorf S, Hobson BD, Zhang W, Nadeau KC (2017) Oral immunotherapy for food allergy. Semin Immunol 30:36–44

Freeman J (1930) "Rush" inoculation, with special reference to hay-fever treatment. Lancet 215:744–747

Freiberger SN, Zehnder M, Gafvelin G, Gronlund H, Kundig TM, Johansen P (2016) IgG4 but no IgG1 antibody production after intralymphatic immunotherapy with recombinant MAT-Feld1 in human. Allergy 71:1366–1370

Giannarini L, Maggi E (1998) Decrease of allergen-specific T-cell response induced by local nasal immunotherapy. Clin Exp Allergy 28:404–412

Hoh RA, Joshi SA, Liu Y, Wang C, Roskin KM, Lee JY, Pham T, Looney TJ, Jackson KJL, Dixit VP, King J, Lyu SC, Jenks J, Hamilton RG, Nadeau KC, Boyd SD (2016) Single B-cell deconvolution of peanut-specific antibody responses in allergic patients. J Allergy Clin Immunol 137:157–167

Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georen S, Winqvist O, Cardell LO (2016) Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Respir Res 17:10

Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, Henning AK, Berin MC, Chiang D, Vickery BP, Pesek RD, Cho CB, Davidson WF, Plaut M, Sampson HA, Wood RA, Consortium of Food Allergy Research (2017) Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 139:1242–1252.e9

Kashem SW, Haniffa M, Kaplan DH (2017) Antigen-presenting cells in the skin. Annu Rev Immunol 35:469–499

Kim ST, Park SH, Lee SM, Lee SP (2017) Allergen-specific intralymphatic immunotherapy in human and animal studies. Asia Pac Allergy 7:131–137

Möbs C, Slotosch C, Löffler H, Pfützner W, Hertl M (2008) Cellular and humoral mechanisms of immune tolerance in immediate-type allergy induced by specific immunotherapy. Int Arch Allergy Immunol 147:171–178

Möbs C, Ipsen H, Mayer L, Slotosch C, Petersen A, Würtzen PA, Hertl M, Pfützner W (2012) Birch pollen immunotherapy results in long-term loss of Bet v 1-specific TH2 responses, transient TR1 activation, and synthesis of IgE-blocking antibodies. J Allergy Clin Immunol 130:1108–1116.e6

Mondoulet L, Kalach N, Dhelft V, Larcher T, Delayre-Orthez C, Benhamou PH, Spergel J, Sampson HA, Dupont C (2017) Treatment of gastric eosinophilia by epicutaneous immunotherapy in piglets sensitized to peanuts. Clin Exp Allergy 47:1640–1647

Muraro A, Roberts G, Halken S, Agache I, Angier E, Fernandez-Rivas M, Gerth Van Wijk R, Jutel M, Lau S, Pajno G, Pfaar O, Ryan D, Sturm GJ, Van Ree R, Varga EM, Bachert C, Calderon M, Canonica GW, Durham SR, Malling HJ, Wahn U, Sheikh A (2018) EAACI guidelines on allergen immunotherapy: executive statement. Allergy 73:739–743

Noon L (1911) Prophylactic inoculation against hay fever. Lancet 177:1572–1573

Noval Rivas M, Burton OT, Wise P, Charbonnier LM, Georgiev P, Oettgen HC, Rachid R, Chatila TA (2015) Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. Immunity 42:512–523

Palisade Group Of Clinical Investigators, Vickery BP, Vereda A, Casale TB, Beyer K, Du Toit G, Hourihane JO, Jones SM, Shreffler WG, Marcantonio A, Zawadzki R, Sher L, Carr WW, Fineman S, Greos L, Rachid R, Ibanez MD, Tilles S, Assa'ad AH, Nilsson C, Rupp N, Welch MJ, Sussman G, Chinthrajah S, Blumchen K, Sher E, Spergel JM, Leickly FE, Zielen S, Wang J, Sanders GM, Wood RA, Cheema A, Bindslev-Jensen C, Leonard S, Kachru R, Johnston DT, Hampel FC Jr, Kim EH, Anagnostou A, Pongracic JA, Ben-Shoshan M, Sharma HP, Stillerman A, Windom HH, Yang WH, Muraro A, Zubeldia JM, Sharma V, Dorsey MJ, Chong HJ, Ohayon J, Bird JA, Carr TF, Siri D, Fernandez-Rivas M, Jeong DK, Fleischer DM, Lieberman JA, Dubois AEJ, Tsoumani M, Ciaccio CE, Portnoy JM, Mansfield LE, Fritz SB, Lanser BJ, Matz J, Oude Elberink HNG, Varshney P, Dilly SG, Adelman DC, Burks AW (2018) AR101 oral immunotherapy for peanut allergy. N Engl J Med 379:1991–2001

Passalacqua G, Canonica GW (2006) Local nasal specific immunotherapy for allergic rhinitis. Allergy Asthma Clin Immunol 2:117–123

Passalacqua G, Fumagalli F, Guerra L, Canonica GW (2003) Safety of allergen-specific sublingual immunotherapy and nasal immunotherapy. Chem Immunol Allergy 82:109–118

Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M, Hafner RP (2013) Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. J Allergy Clin Immunol 131(103–9):e1–e7

Pautrizel R, Cabanieu G, Bricaud H, Broustet P (1957) Allergenic group specificity & therapeutic consequences in asthma; specific desensitization method by epicutaneous route. Sem Hop 33:1394–1403

Philipps EW (1926) Relief of hay-fever by intradermal injections of pollen extract. JAMA 86:182–184

Piazza I, Bizzaro N (1993) Humoral response to subcutaneous, oral, and nasal immunotherapy for allergic rhinitis due to Dermatophagoides pteronyssinus. Ann Allergy 71:461–469

Rotiroti G, Shamji M, Durham SR, Till SJ (2012) Repeated low-dose intradermal allergen injection suppresses allergen-induced cutaneous late responses. J Allergy Clin Immunol 130:918–924.e1

Ryan JF, Hovde R, Glanville J, Lyu SC, Ji X, Gupta S, Tibshirani RJ, Jay DC, Boyd SD, Chinthrajah RS, Davis MM, Galli SJ, Maecker HT, Nadeau KC (2016) Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets. Proc Natl Acad Sci U S A 113:E1286–E1295

Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, Cheema AS, Leonard SA, Pongracic JA, Sauvage-Delebarre C, Assa'ad AH, De Blay F, Bird JA, Tilles SA, Boralevi F, Bourrier T, Hebert J, Green TD, Gerth Van Wijk R, Knulst AC, Kanny G, Schneider LC, Kowalski ML, Dupont C (2017) Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA 318:1798–1809

Scadding GK, Brostoff J (1986) Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy 16:483–491

Scurlock AM (2018) Oral and sublingual immunotherapy for treatment of IgE-mediated food allergy. Clin Rev Allergy Immunol 55:139–152

Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, Mccormack SJ, Simard JJ, Wuthrich B, Crameri R, Graf N, Johansen P, Kundig TM (2008) Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 105:17908–17912

Senti G, Graf N, Haug S, Ruedi N, VON Moos S, Sonderegger T, Johansen P, Kundig TM (2009) Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. J Allergy Clin Immunol 124:997–1002

Senti G, Johansen P, Kundig TM (2011) Intralymphatic immunotherapy: from the rationale to human applications. Curr Top Microbiol Immunol 352:71–84

Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, Steiner M, Hothorn LA, Gronlund H, Tivig C, Zaleska A, Soyer O, Van Hage M, Akdis CA, Akdis M, Rose H, Kundig TM (2012a) Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol 129:1290–1296

Senti G, Von Moos S, Tay F, Graf N, Sonderegger T, Johansen P, Kundig TM (2012b) Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. J Allergy Clin Immunol 129:128–135

Senti G, Von Moos S, Tay F, Graf N, Johansen P, Kundig TM (2015) Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. Allergy 70:707–710

Senti G, Freiburghaus AU, Larenas-Linnemann D, Hoffmann HJ, Patterson AM, Klimek L, DI Bona D, Pfaar O, Ahlbeck L, Akdis M, Weinfeld D, Contreras-Verduzco FA, Pedroza-Melendez A, Skaarup SH, Lee SM, Cardell LO, Schmid JM, Westin U, Dollner R, Kundig TM (2019) Intralymphatic immunotherapy: update and unmet needs. Int Arch Allergy Immunol 178:141–149

Shamji MH, Durham SR (2017) Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol 140:1485–1498

Shofield AT (1908) A case of egg poisoning. Lancet 171:716

Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Hay E, Lam EPS, Kelly J, Peacock JL, Ying S, Shamji MH, Cousins DJ, Durham SR, Till SJ (2017) Intradermal grass pollen immunotherapy

increases TH2 and IgE responses and worsens respiratory allergic symptoms. J Allergy Clin Immunol 139:1830–1839.e13

Smaldini PL, Orsini Delgado ML, Fossati CA, Docena GH (2015) Orally-induced intestinal CD4+ CD25+ FoxP3+ Treg controlled undesired responses towards oral antigens and effectively dampened food allergic reactions. PLoS One 10:e0141116

Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, Berglund JP, Tsai M, Maecker H, O'riordan G, Galli SJ, Nadeau KC (2014) Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol 133:500–510

Tordesillas L, Berin MC (2018) Mechanisms of oral tolerance. Clin Rev Allergy Immunol 55:107–117

Tordesillas L, Berin MC, Sampson HA (2017a) Immunology of food allergy. Immunity 47:32–50

Tordesillas L, Mondoulet L, Blazquez AB, Benhamou PH, Sampson HA, Berin MC (2017b) Epicutaneous immunotherapy induces gastrointestinal LAP(+) regulatory T cells and prevents food-induced anaphylaxis. J Allergy Clin Immunol 139:189–201.e4

Vallery-Radot P, Hangenau J (1921) Asthme d'origine équine. Essai de désensibilisation par des cutiréactions répétées. Bull Soc Méd Hôp Paris 45:1251–1260

Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, Keet CA, Kulis M, Orgel KG, Guo R, Steele PH, Virkud YV, Ye P, Wright BL, Wood RA, Burks AW (2017) Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol 139:173–181.e8

Wambre E (2015) Effect of allergen-specific immunotherapy on CD4+ T cells. Curr Opin Allergy Clin Immunol 15:581–587

Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK (2013) Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy? J Allergy Clin Immunol 132:1248–1252.e5

Wood RA (2017) Oral immunotherapy for food allergy. J Investig Allergol Clin Immunol 27:151–159

Precision Medicine in Chronic Rhinosinusitis: Where Does Allergy Fit In?

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Abstract

Chronic rhinosinusitis (CRS) is a clinical syndrome stemming from persistent inflammation of the sinonasal mucosa. Phenotypically, it is traditionally and widely described according to the presence or absence of polyps. While this distinction is simple to use, it has little bearing on prognosis and treatment, for CRS is essentially an inflammatory disease resulting from dysregulated interaction between a multitude of host and environmental factors. Allergy is merely one of them and, like many of the proposed aetiologies, has been subject to much debate which will be discussed here. As our understanding of CRS continues to evolve, previous so-called conventional wisdom about phenotypes (e.g. CRS with nasal polyps is associated with Type 2 inflammation) is being challenged, and new phenotypes are also emerging. In addition, there is growing interest in defining the endotypes of CRS to deliver precise and personalised treatment, especially pertaining to the development of biologics for the group of severe, difficult-to-treat CRS patients. A proposed model of precision medicine tailored to management of CRS will also be introduced to readers, which can be continually modified to adapt to new discoveries about this exciting condition.

Keywords

Allergy · Chronic rhinosinusitis · Endotype · Precision medicine

1 Introduction

Chronic rhinosinusitis (CRS) in adults is defined as symptoms of sinonasal inflammation (nasal obstruction/congestion/blockage, nasal drainage, facial pain/pressure/fullness and decreased or loss of sense of smell) for more than 12 weeks, accompanied by objective evidence (nasoendoscopy showing purulent discharge, nasal polyps or oedema; or radiological imaging showing inflammation or mucosal changes within the sinuses). Conventionally, CRS is broadly categorised into two groups based on phenotype, which is the presence or absence of nasal polyps [CRS with nasal polyposis (CRSwNP) and CRS without polyposis (CRSsNP) respectively]. This classification is simple and widely adopted, but imprecise as it does not reflect the underlying pathophysiology, implicate management or prognosticate outcome. This is especially so when considering the complex pathophysiology of

CRS, which is a dysregulated interaction between host and environmental factors. This phenotype-based classification also does not discern from conditions with distinctive phenotypes such as Non-Steroidal Anti-inflammatory Drug (NSAID)-Exacerbated Respiratory Disease (N-ERD) that would otherwise fall under the umbrella group of CRSwNP.

As such, there are attempts to move towards defining CRS by endotype: molecular mechanisms that drive the disease process. In recent years, the terms eosinophilic CRS/type 2 CRS and non-eosinophilic CRS/non-type 2 CRS are gaining prominence in the literature to indicate underlying T-helper 2 (Th2)- or T-helper 1 (Th1)-driven inflammation, respectively, due to the observation that eosinophils are reliable biomarkers for Th2 disease (Fokkens and Reitsma 2019). Another emerging method of defining CRS endotypes is via cluster analysis, an impartial statistical tool that has the ability to analyse a variety of molecular markers to uncover groups that share similar characteristics, which are subsequently correlated with phenotypes and treatment outcomes (Cao et al. 2019).

The challenge in defining endotypes of CRS lies in the heterogeneity of the disease due to the multitude of factors that contribute in varying degrees to inflammation of the sinonasal mucosa. In keeping with the theme of allergy in this publication, this chapter will explore the role of allergy in CRS and discuss the phenotypes that have purported associations with allergy; it must be emphasised that allergy is only one of several factors involved in this complex disease. The pharmacologic management of CRS is presented using a model of precision medicine that escalates treatment options according to disease severity.

2 Role of Allergy in Chronic Rhinosinusitis

The link between allergy and CRS is incompletely understood. From a pathophysiologic standpoint, an association between IgE-mediated allergy and some subgroups of CRS is possible due to a shared Th2-mediated inflammation. There is some evidence of this link via systemic or local mechanisms. In sensitised individuals, allergens are processed by antigen-processing cells which activate antigen-specific effector T-helper cells that in turn release inflammatory cytokines. These cytokines include IL-5, which is a potent chemoattractant for eosinophils. Eosinophils migrate to nasal mucosa via adhesion molecules and chemotactic signals, where inflammatory mediators are released. Increased expression of adhesion molecules and chemotactic cytokines that recruit inflammatory cells has been demonstrated in CRS patients and may be the mechanism by which aeroallergens exacerbate CRS (Jahnsen et al. 1995). Elevated levels of Th2 cytokines, total and allergen-specific IgE, and eosinophilic inflammation in nasal polyp tissue have been identified in both atopic and CRSwNP patients (Bachert et al. 2001). Increased eosinophils have been demonstrated in bilateral maxillary sinus mucosa after unilateral nasal allergen challenge (Baroody et al. 2008).

It is also possible for the allergic process to be limited to the nasal cavity without systemic involvement. Some CRS patients demonstrate IgE production in sinonasal

mucosa in the absence of systemic hypersensitivity – a local mechanism termed local allergic rhinitis (AR) or entopy. Entopy is confirmed with a positive response to a nasal allergen provocation test. However, the mechanism by which allergens are introduced to the sinus cavity is unclear, for inhalation tends not to bring allergens into unoperated sinuses. In the presence of nasal polyps, the middle meatus is often obstructed and further reduces the entry of aeroallergens.

From a clinical perspective, the data linking allergy with CRS have been conflicting. A comprehensive systematic review of 24 articles evaluating the association between allergy and CRS reported nearly equal numbers of studies supporting or refuting this relationship (Wilson et al. 2014). While some studies reported a significant relationship between CRSwNP and perennial allergens, others observed that the presence of allergy did not correlate with polyp size, symptom scores, rate of recurrence or post-operative corticosteroid consumption. Furthermore, while allergen avoidance and allergen immunotherapy (AIT) relieved rhinitis symptoms, they failed to make significant impact on sinonasal disease per se.

Taken together, these findings suggest that IgE-mediated allergy may be a disease-modifying factor in CRS, but a direct cause-effect relationship has not been clearly established. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) states that the evidence for allergy as a cause of CRS is weak and is better viewed as an overlapping issue that contributes to sinonasal inflammation (Fokkens et al. 2020). The International Consensus Statement on Allergy and Rhinology: AR (ICAR:AR) concludes that the aggregate grade of evidence linking allergy to CRSsNP and CRSwNP is grade D (Orlandi et al. 2016). However, some studies have noted that certain CRS subtypes, specifically allergic fungal rhinosinusitis (AFRS) and central compartment atopic disease (CCAD), appear to be more strongly associated with atopy, albeit not without controversy.

2.1 Allergic Fungal Rhinosinusitis

AFRS is a form of non-invasive fungal sinusitis with nasal polyposis and is recognised as a distinctive phenotype of CRSwNP. Bent and Kuhn described their original diagnostic criteria for AFRS in 1994 based on analysis of 15 patients and is still widely quoted today (Bent and Kuhn 1994). These features are: (1) Type 1 hypersensitivity to fungi, (2) nasal polyposis, (3) characteristic CT findings (increased density of material within sinus cavities, expansion or erosion of paranasal sinus bony walls), (4) eosinophilic mucin without fungal invasion, and (5) positive fungal stains.

The preciseness and utility of this diagnostic criteria have been richly debated. Systemic fungal-specific IgE and total IgE levels were not found to be significantly different between patients with AFRS, AR with fungal allergy and CRS without eosinophilic mucin (Pant et al. 2005). The same study also noted that in most AFRS patients, the fungal species to which IgE was elevated often did not match the fungal species identified in the eosinophilic mucin. In addition, elevated fungal-specific IgG3 levels, not IgE, distinguished AFRS from control groups, suggesting a role for

humoral immunity. Moreover, there was no strong evidence for fungal AIT or antifungals in the management of AFRS (Gan et al. 2014). Consequently, the argument for type 1 hypersensitivity as a criterion is weakened. Nasal polyposis is a broad phenotypic description that also applies to non-AFRS subtypes of CRS. Eosinophilic mucin – a tan-brown, tenacious mucous with the consistency of peanut butter or axle grease, consisting of eosinophils and Charcot-Leyden crystals (breakdown products of eosinophils) – is a common finding in eosinophilic CRS without fungal allergy. With highly sensitive techniques of fungal detection, fungi can be found in virtually all normal and CRS patients, and not just AFRS patients (Braun et al. 2003). Ergo, the only feature amongst the Bent-Kuhn criteria that remains unique to AFRS appears to be characteristic CT findings.

Several other notable features which do not belong to any diagnostic criteria for AFRS have been reported. AFRS tends to affect young, immunocompetent individuals. Bony erosion and intraorbital or intracranial extension, but with preservation of the periorbita and dura, respectively, are encountered more frequently compared to other CRS subtypes and are more likely to be seen in males than females. Unilateral sinus involvement is seen in about half of AFRS patients on imaging, as compared to bilateral involvement in all eosinophilic mucin CRS patients (Ferguson 2000). The incidence of co-morbid asthma and aspirin sensitivity is significantly lower in AFRS patients compared to those with eosinophilic mucin CRS. AFRS also reportedly has a geographical predilection for areas with warm and humid climates, such as the southern United States, along the Mississippi Basin and southern Australia (Collins et al. 2003; Ferguson et al. 2000). However, the incidence of AFRS is not significantly increased in other countries with similar climates, such as Malaysia (Goh et al. 2005), Thailand (Aeumjaturapat et al. 2003) and India (Chakrabarti et al. 2015).

Due to ambiguity of the role of fungus and fungal allergy in the pathogenesis in CRS, several modifications of the terminology have been proposed. These include "allergic fungal sinusitis-like", "non-allergic fungal eosinophilic sinusitis", eosinophilic fungal rhinosinusitis" and "eosinophilic mucin rhinosinusitis" to accommodate various permutations of the presence/absence of fungal allergy and fungal hyphae in eosinophilic mucin. The wide variety of opinions probably reflects that the understanding of this disease process remains elusive. Nonetheless, it is clear that this subgroup of CRSwNP is associated with thick tenacious mucous, recurrent nasal polyposis and requires aggressive treatment with surgery and corticosteroids. Type 1 hypersensitivity or an altered immune response to fungi, eosinophilic inflammation and environmental factors may contribute to its pathophysiology to a variable extent.

2.2 Central Compartment Atopic Disease

CCAD is the relatively "new kid on the block" in the CRS phenotype family. It is considered to be a form of IgE-mediated airway inflammation related to antigen contact in the central compartment of the nasal cavity. This entity was first described in 2014, when it was observed that isolated middle turbinate polypoid oedema had a

high positive predictive value for inhalant allergy (White et al. 2014). The term CCAD was subsequently coined in 2017 due to the recognition that this allergic oedema may extend to the superior turbinate and superior septum, resulting in polypoid disease affecting mainly the central structures of the nasal cavity (Brunner et al. 2017; DelGaudio et al. 2017; Hamizan et al. 2017). The aetiology for involvement of these areas is postulated to be related to nasal airflow, which is the highest in the central areas of the nose and presumably prone to higher concentrations of allergen deposition (Wang et al. 2012). Another hypothesis relates to differences in embryologic origin. The middle turbinate arises from the ethmoid bone whereas the inferior turbinate develops from the lateral cartilaginous capsule, which may explain the relative sparing of the inferior turbinate by polyps.

In CCAD, nasal congestion or obstruction was the predominant complaint in nearly all patients. About half of these patients had allergic symptoms, of whom a significant proportion (83–100%) who underwent allergy workup had positive allergy tests (Brunner et al. 2017). House dust mites were the main allergens, followed by grass pollen. Perennial allergens, rather than seasonal ones, were implicated as chronic inflammation was thought to be a requirement to continually drive this condition. Treatment of AR in CCAD patients pre-operatively did not appear to significantly relieve nasal symptoms. Patients seemed to respond well to functional endoscopic sinus surgery (FESS), post-operative topical steroid rinses and treatment of allergies. There is currently no data on the outcome of AIT.

Radiologically, central soft tissue thickening of the middle turbinate, superior turbinate and septum with relative sparing of the roof and lateral sinus cavities is seen on computed tomography. This pattern of sinonasal involvement in CCAD is different from that of other CRSwNP subtypes, which tend to have diffuse sinus disease with relatively little involvement of central compartment structures.

Being a newly described entity, the understanding of this disease is still in its infancy. The current data on CCAD are limited to descriptive case series by the same group of authors, with lack of control groups and long-term data, which is expected with any novel finding. Further research, including from other centres worldwide, is needed to better understand its disease characteristics, pathophysiology, treatment options and outcome.

3 Management of CRS

The four tenets of the healthcare model of precision medicine are patient participation in his care, prediction of treatment success, prevention of disease progression or complications, and personalised care. By adapting this model of precision medicine for CRS, treatment can be stratified into three levels based on severity of disease (Xu et al. 2019). The pharmacotherapy adopted at levels 1–3 is summarised in Table 1.

Table 1 Pharmacologic management of CRS

Management	Intervention	Benefits	Harm
Level 1: Initial pharmacotherapy			
Saline irrigation	High volume nasal saline irrigation as an adjunct to other medical therapies	Improves symptom scores. Well tolerated. No risk of systemic adverse effects. Low cost	Local irritation, headaches, ear pain. Low risk of infection from contaminated rinse bottles
Topical corticosteroids (INCS)	Recommended for CRS, (especially CRSwNP) before and after FESS	Improves symptom and objective scores. Reduces polyp recurrence	Epistaxis, nasal irritation, headache
Oral corticosteroids	Recommended for short-term management of CRSwNP. Lack of evidence for CRSsNP	Significant short-term improvement in symptom & objective scores. Duration of improvement may last 8–12 weeks when used with INCS	Gastrointestinal symptoms, transient adrenal suppression, insomnia. Risks increase with prolonged treatment
Non-macrolide antibiotics	Indicated in acute exacerbations or presence of purulent discharge	Reduces purulent discharge, but not for routine management of CRS	Gastrointestinal symptoms, potential for resistance
Low-dose long-term macrolide antibiotics	Option for patients with CRSsNP	Improves symptom and objective scores, especially in patients with normal IgE levels	Medication interactions, mild adverse events, potential for severe cardiovascular complications
Level 2: Post-FESS pharmacotherapy			
Topical corticosteroids (INCS)	Recommended for CRS after FESS	Improves symptom and objective scores. Reduces polyp recurrence	Epistaxis, nasal irritation, headache
Topical corticosteroids: irrigation	An option after FESS	Unable to statistically confirm therapeutic improvement with present evidence	No evidence of adrenal suppression but cannot be excluded
Oral corticosteroids	Improves post-operative endoscopic scores in CRS and recurrence rates in CRSwNP	Significant short-term improvement in symptom & objective scores. Duration of improvement may last 8–12 weeks when used with INCS	Gastrointestinal symptoms, transient adrenal suppression, insomnia. Risks increase with prolonged treatment
Low-dose long-term macrolide antibiotics	May be beneficial after FESS to reduce recurrence of polyps	Reduced polyp burden in post-FESS patients	Mainly gastrointestinal symptoms. Potential for severe cardiovascular complications

(continued)

Table 1 (continued)

Management	Intervention	Benefits	Harm
Anti-leukotriene therapy	An option instead of, or in addition to INCS	Improved symptom scores, comparable to INCS. May have limited benefit as an adjunct to INCS	Rare neuro-psychiatric events, elevated liver enzymes
Immunotherapy	An option in CRS patients with demonstrated allergy	Theoretically reduces triggers and symptoms of CRS	Local irritation, anaphylaxis, cost
Level 3: Biologics			
Anti-IgE: omalizumab	Approved for severe allergic asthma, chronic spontaneous urticaria. Under phase 3 trial for use in CRS	Reduced symptom, endoscopic scores	Injection site reaction, headache, nasopharyngitis, cardiovascular complications
Anti-IL5: mepolizumab	Approved for severe eosinophilic asthma. Under phase 3 trial for use in CRS	Reduced symptom, endoscopic scores	Headache, injection site reaction, hypersensitivity reactions. Rebound eosinophilia and exacerbation of asthma after cessation of treatment
Anti-IL5: reslizumab	Approved for severe eosinophilic asthma. Under phase 3 trial for use in CRS	Reduced symptom, endoscopic scores	Oropharyngeal pain, increased blood creatine phosphokinase, myalgia
Anti-IL4/-IL13: dupilumab	FDA approved for treatment of CRSwNP	Improved symptom, smell, endoscopic and radiologic scores	Injection site reaction, conjunctivitis, herpes simplex virus reactivation, hypersensitivity, serum sickness

3.1 Level 1 Management

Level 1 management is applied at the time of diagnosis of CRS. First-line treatment is initiated, which includes nasal saline douching, anti-inflammatory medication, culture-directed antibiotics in the presence of purulent nasal discharge and treatment of AR, if present.

At this stage, it is prudent to recognise phenotypes of CRS that will *not* respond well to conventional treatment. One such phenotype is N-ERD, a clinical syndrome characterised by a triad of hypersensitivity to NSAIDs including aspirin, asthma and nasal polyposis. The underlying pathophysiology is NSAID-induced inhibition of cyclooxygenase-1, resulting in depletion of prostaglandin E2 and downstream activation of inflammatory cells such as mast cells, eosinophils, basophils and

platelets. The nasal polyps of N-ERD is more resistant to the usual pharmacologic and surgical treatment and should be managed by experienced otolaryngologists. In addition, NSAID hypersensitivity and asthma must be addressed in concert.

3.1.1 Nasal Saline Irrigation

Nasal saline irrigation is strongly recommended as an adjunct to other medical therapies for CRS. Its favourable safety profile, lack of systemic absorption and low cost make it widely acceptable for many patients. Saline irrigation improves symptoms and quality of life (QoL) outcomes in CRS patients who do not undergo surgery (Bachmann et al. 2000). Large volume isotonic saline irrigation appears to have better outcomes than low volume saline nasal sprays. Isotonic and hypertonic saline solutions have similar effects on patient symptoms and QoL scores.

Adverse effects of saline irrigation are uncommon. Nasal burning and ear plugging can occur with isotonic saline irrigation. Pain and nasal drainage has been associated with hypertonic saline irrigation. Bacterial contamination of saline irrigation bottles has occurred as early as 1 week after use, with the rate of contamination increasing with duration of device use. Although there is no clear evidence linking this to poor sinus outcomes, cleaning after every use and 3-monthly replacement of saline irrigation bottles is recommended (Psaltis et al. 2012).

3.1.2 Topical Corticosteroids

Intranasal corticosteroid sprays (INCSs) are the mainstay of treatment for CRSsNP and CRSwNP due to inflammation being a major driver of CRS. The mechanism of action is a combination of anti-inflammatory effects and suppression of the production of pro-inflammatory mediators, cell chemotactic factors and adhesion molecules. The use of INCS is well studied especially in CRSwNP and is proven to improve symptom scores, polyp size, polyp recurrence and nasal airflow compared to placebo (Wei et al. 2013).

The commonest adverse effects of INCS are epistaxis, local irritation and headache. There is no evidence of systemic immunosuppression. In fact, the safety profile of second-generation INCS (e.g. fluticasone propionate, mometasone furoate, fluticasone furoate) is particularly favourable, with systemic bioavailability of less than 1% (Sastre and Mosges 2012).

3.1.3 Oral Corticosteroids

Oral corticosteroids are recommended in the short-term management of mild CRSwNP or eosinophilic CRS with limited disease burden. Short courses (7–14 days) of oral corticosteroids have been shown to improve nasal obstruction, olfaction, nasal endoscopy scores and reduce eosinophil count (Hissaria et al. 2006). The efficacy of such short oral corticosteroid courses, followed by maintenance with INCS, lasts 8 to 12 weeks following completion of the oral steroid course. Oral steroids have also been shown to significantly improve the quality of the surgical field, reduce blood loss and operative time when given prior to FESS (Pundir et al. 2016).

Patients with non-eosinophilic CRS do not respond to oral corticosteroids as well as those with eosinophilic CRS. The commonest adverse effect of oral corticosteroids is gastrointestinal effects. Other potential side effects include transient adrenal suppression, mood changes, insomnia, hyperglycaemia, raised intraocular pressure, avascular necrosis of the hip and osteoporosis. Longer-term or frequent use of corticosteroids for CRSwNP is not recommended and carries an increased risk of harm.

3.1.4 Oral Non-macrolide Antibiotics

Culture-directed antibiotics, or broad-spectrum antibiotics such as amoxicillin-clavulanate in the absence of culture results, are recommended during an acute exacerbation of CRS. The American Academy of Otolaryngic Allergy (AAOA) recommends reserving antibiotics for patients with evidence of purulent sinus drainage (Marple et al. 2009). Non-macrolide antibiotics are not recommended in routine management of CRS due to risks of gastrointestinal adverse effects, the theoretical development of antimicrobial resistance and lack of evidence for benefits. However, surveys of otolaryngologists indicated that more than 90% use antibiotics as part of medical management, which may be due to conventional association of CRS with bacterial infection (Dubin et al. 2007).

3.1.5 Oral Low-Dose Macrolides (>12 Weeks)

Macrolides have anti-inflammatory, immunomodulatory properties when administered in low daily doses. They decrease production of pro-inflammatory cytokines including IL-8, inhibit neutrophil recruitment and reduce nasal fibroblast proliferation in way that corticosteroids cannot. The use of long-term (12 weeks or more) low-dose macrolides has been shown to benefit patients with lower airway inflammatory diseases, such as asthma, chronic obstructive pulmonary disease and cystic fibrosis. They may have a role in the treatment of CRSsNP, which is traditionally associated with predominantly non-eosinophilic inflammation.

There are two placebo-controlled randomised trials that compared the effects of 12 weeks low-dose macrolides in non-operated CRS patients versus placebo. One reported that patients with CRSsNP who were treated with roxithromycin, especially those with normal serum IgE, had significant improvement in disease-specific QoL, nasoendoscopy scores, saccharine transit time and IL-8 levels compared to placebo (Wallwork et al. 2006). These benefits were not sustained following cessation of treatment. However, the other study did not observe any significant benefits of azithromycin over placebo in terms of subjective or objective measures in patients with CRSsNP and CRSwNP (Videler et al. 2011). A systemic review of these two studies concluded that there was no clinically significant improvement in disease-specific QoL measures with long-term low-dose macrolides for CRS (Pynnonen et al. 2013).

One randomised controlled trial (RCT) compared 12 weeks low-dose clarithromycin with 12 weeks INCS in CRSsNP patients prior to FESS (Zeng et al. 2011). It reported significant reduction in total symptom scores, overall burden scores, mucosal swelling and nasal discharge scores in both groups, seen as early as

4 weeks after commencement of treatment. However, there were no significant differences in symptom or endoscopic scores between both groups at any time point post-treatment.

Therefore, the evidence for the benefits of long-term low-dose macrolides in the treatment of pre-operative CRS is unclear. The EPOS 2020 recommends reserving long-term macrolides for CRSsNP patients, especially those with normal serum IgE, in whom INCS and saline irrigation have failed to improve symptoms (Fokkens et al. 2020). The ICAR: Chronic Rhinosinusitis (CR) states that macrolides are an option for patients with CRSsNP, without making a differentiation for pre- or post-FESS patients (Orlandi et al. 2016). There is no evidence for the use of low-dose long-term macrolides in the management of pre-FESS CRSwNP patients.

The commonest side effects of macrolides are gastrointestinal disorders, such as mild diarrhoea and abdominal discomfort. In non-CRS studies, macrolides are associated with ototoxicity, liver dysfunction, ventricular arrhythmia and cardiac arrest.

3.1.6 Allergy Testing and Avoidance

The EPOS 2020 management scheme for CRSsNP and CRSwNP recommends taking a history for allergic symptoms and if positive, to do allergy testing (Fokkens et al. 2020). The ICAR:CR guidelines state that allergy testing and treatment are optional in CRS, as there are theoretical benefits of identifying inflammatory triggers and the risk of harm is low (Orlandi et al. 2016).

If there is suspicion of CCAD, allergy testing is warranted due to the purported association of this condition with atopy. In AFRS, a positive allergy test to fungal allergens is part of the Bent-Kuhn criteria, but fungal-specific AIT has not been conclusively down to significantly affect the outcome.

3.2 Level 2 Management

Level 2 management is instituted for severe CRS that is suboptimally managed with level 1 care. The aim is to prevent disease progression and complications. At this stage, surgery is often necessary, along with requisite post-operative pharmacotherapy.

3.2.1 Surgery: Functional Endoscopic Sinus Surgery

Surgery is generally indicated when symptoms persist despite medical therapy or when complications of CRS arise. Once polypoid changes have occurred, INCS is unlikely to resolve the remodeling that has occurred. The principles of FESS are mucosal preservation, widening of the natural sinus drainage pathways to relieve sinus outflow obstruction, decrease the inflammatory burden and improve post-operative topical drug delivery to the sinuses.

Attempts have been made to determine the appropriate duration or courses of medication before surgical intervention is warranted. However, the definition of this so-called maximal medical therapy is vague and is probably inappropriate, as it

implies that all medical treatment options should be exhausted before exploring surgery as an option. Chronic inflammation in sinonasal mucosa leads to epithelial remodelling, a process that results in poorly proliferating basal cells that fail to form a proper epithelial barrier (Zhao et al. 2017). These changes are not reversed by steroid treatment and are unlikely to revert to a functional respiratory epithelium by the time some of these patients undergo FESS.

3.2.2 Surgery: Adenoidectomy

Whilst not commonly encountered in adults, adenoid hypertrophy deserves brief mention here due to its association with AR, mainly in children. Treatment of adenoid hypertrophy plays a role in paediatric CRS but generally not adult CRS. Adenoids are reservoirs for bacteria and adenoid cultures have a high correlation with lateral nasal wall cultures. A meta-analysis of nine studies investigating the efficacy of adenoidectomy in paediatric CRS patients who failed medical therapy noted significant improvement in caregiver-reported symptoms of sinusitis (Brietzke and Brigger 2008).

In the American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) Guidelines Task Force for paediatric CRS, there was strong consensus for adenoidectomy as a first-line surgical procedure for children with CRS up to 6 years old. Less consensus was arrived at for children aged 6–12 years old (Brietzke et al. 2014). There was no consensus reached on whether adenoidectomy was effective for those aged 13 years and older due to lack of supporting evidence.

3.2.3 Post-FESS: Intranasal Corticosteroid Sprays

A strong recommendation is made for INCS following FESS to control post-operative mucosal inflammation. Topical nasal steroid sprays following FESS minimises mucosal inflammation and optimises clinical outcomes. A systemic review and meta-analysis of 11 RCTs comparing the use of INCS with placebo in post-FESS patients noted significant improvement in the INCS group in terms of endoscopic scores at 6 and 12 months, symptoms scores and recurrence rate of polyps (Fandino et al. 2013).

The limitation of INCS is that it provides good nasal cavity contact but poor sinus delivery. Topical steroids from nasal sprays are well-distributed to the septum, inferior turbinate, and head of the middle turbinate, but less so to the middle and superior meatus (Lam et al. 2013).

3.2.4 Post-FESS: Topical Corticosteroids – Irrigation

Nasal irrigation of corticosteroids has been thought to deliver topical steroids more effectively to post-operative sinuses compared to INCS. The efficacy of topical corticosteroids, commonly budesonide, in nasal saline irrigation for post-operative patients with CRSwNP or eosinophilic CRS is reported in several studies (Kanowitz et al. 2008; Snidvongs et al. 2012). Large volume irrigations (>100 ml) achieve significantly more optimal drug delivery to post-operative sinuses than low volume delivery devices. A literature review of 11 articles on topical corticosteroid

irrigations concluded that large volume corticosteroid irrigations improved QoL by symptom control and objective clinical findings when used in tandem with complete sinus surgery (Grayson and Harvey 2019).

Nasal irrigation of corticosteroids has been recommended as part of first-line therapy in management of post-FESS CRS based on level 1 evidence of their benefit over INCS (Grayson and Harvey 2019). The ICAR:CS states that non-standard delivery of topical corticosteroids, such as via nasal irrigation, is an option in post-FESS CRSwNP patients, based on aggregate evidence grade B (Orlandi et al. 2016). There is no evidence on the efficacy of topical corticosteroid irrigation in non-eosinophilic CRS. There is also no evidence to suggest systemic absorption.

3.2.5 Post-FESS: Oral Corticosteroids

In the immediate post-operative period, a short course of oral corticosteroids minimises mucosal inflammation during the healing period and improve olfaction. In AFRS, an RCT on 24 patients reported that tapering doses of oral corticosteroids over 12 weeks resulted in significant subjective and objective improvement of patients with AFRS and prevented early recurrence (Rupa et al. 2010).

Subsequently, just as patients with asthma on inhaled corticosteroids may need oral corticosteroids as "rescue" medication during periods of exacerbation, CRS patients may likewise require short courses of oral corticosteroids to manage exacerbations of eosinophilic airway inflammation when locally-delivered corticosteroids do not suffice.

3.2.6 Post-FESS: Oral Low-Dose Macrolides (>12 Weeks)

There are two RCTs comparing low-dose macrolides versus placebo in post-FESS patients. One RCT reported that 12 weeks low-dose erythromycin had statistically significant improvement in nasoendoscopy scores compared to placebo (Haxel et al. 2015). Moreover, CRSsNP patients showed a tendency towards improved parameters compared to CRSwNP patients. The other RCT reported that 12 weeks low-dose azithromycin resulted in significantly improved symptom scores and percentage change in scores after treatment compared to placebo; however, this improvement was not clinically significant (Amali et al. 2015). A systematic review on the pooled data from these two studies concluded that symptom and endoscopic scores in the macrolide group did not significantly differ from that of the placebo group (Lasso et al. 2017).

One RCT compared 24 weeks low-dose clarithromycin and INCS, 12 weeks low-dose clarithromycin and INCS, and INCS alone in CRSwNP patients who had undergone FESS (Varvyanskaya and Lopatin 2014). This open-label study found that both macrolide groups had significant improvement in symptom, nasoendoscopy and imaging scores, rhinomanometry and saccharin transit time compared to INCS alone. It concluded that long-term low-dose macrolides may have a role in controlling eosinophilic inflammation and preventing early relapse of nasal polyps after FESS. Therefore, long-term low-dose macrolide is an option for patients with CRSsNP based on aggregate grade B of evidence (Orlandi et al. 2016). It may also be beneficial when used with INCS in CRSwNP patients after FESS.

3.2.7 Post-FESS: Anti-fungal Therapy

A small number of studies with small sample sizes have looked at anti-fungal treatment in patients who fulfil the Bent and Kuhn criteria of AFRS. In an RCT of 24 AFRS patients, post-operative oral steroids combined with oral itraconazole and INCS resulted in significant improvement in subjective and objective scores, and reduced early recurrence of disease compared to itraconazole and INCS alone (Rupa et al. 2010). Another RCT compared oral followed by topical steroids for 6 months with oral itraconazole alone for 6 months post-operatively in 60 AFRS patients, and noted that the oral itraconazole group had better symptom relief and endoscopic clearance of disease (Rojita et al. 2017). However, a Cochrane review of topical and systemic anti-fungal therapies in all CRS patients, including AFRS, failed to demonstrate any clear benefit due to low quality of evidence (Head et al. 2018).

3.2.8 Post-FESS: Anti-leukotriene Therapy

Cysteinyl leukotrienes are inflammatory mediators produced by eosinophils and mast cells through breakdown of arachidonic acid. The cysteinyl leukotriene pathway promotes bronchoconstriction, mucous profusion and oedema, and is upregulated in several conditions of the airway such as CRSwNP, asthma and AR. Cysteinyl leukotrienes inhibitors are commonly prescribed as adjuncts in treatment of asthma and AR due to their steroid-sparing, anti-inflammatory properties.

There is moderate evidence suggesting that leukotriene antagonists (LTAs) such as montelukast and zileuton are effective adjuncts when used in combination with topical and/or oral steroids to treat CRSwNP. A systematic review on the use of LTAs in CRSwNP reported improved symptoms compared to placebo, but no significant difference when compared to INCS (Wentzel et al. 2013). The review concluded that LTAs had limited benefits as adjunctive therapy, but could be considered in patients who were unable to tolerate or did not respond to INCS. Montelukast alone did not appear to be as effective as INCS in preventing polyp recurrence following FESS.

There are no studies evaluating LTAs in the treatment of CRSsNP. The adverse effects of LTAs are generally low. There are rare reports of rashes, neuro-psychiatric events and tremors with montelukast. Zileuton has been associated with elevated liver enzymes.

3.2.9 Allergen Immunotherapy (AIT)

AIT modifies the basic allergic mechanism by inducing desensitisation and an anergy state. While AIT is recommended in the treatment of AR, its role in the management of CRS is uncertain. Currently, there is no clear evidence that AIT alleviates CRS, including AFRS, although it may improve superimposed rhinitis symptoms. A systemic review of patients with atopic CRS and had undergone AIT noted that symptom scores and objective endoscopic findings improved with AIT when used as an adjunctive treatment, particularly in the post-operative period (DeYoung et al. 2014). However, the evidence to support the use of AIT was deemed weak due to the small number and low quality of studies.

A systematic review of AIT in AFRS noted that AIT appeared to reduce mucosa inflammation, but the evidence was weakened by small sample sizes, lack of standardised control groups and inclusion of other medical treatments (Gan et al. 2014). The EPOS 2020 noted that subcutaneous AIT improved short-time outcomes in AFRS, but the long-term benefits were unclear (Fokkens et al. 2020). The ICAR: CS stated that AIT had an equal degree of benefit and harm and was thus an option in post-operative refractory AFRS based on aggregate grade C of evidence (Orlandi et al. 2016). The role of AIT in CCAD has not been investigated currently, but has been described as a treatment option.

3.3 Level 3 Management

Level 3 management is reserved for severe, uncontrolled or refractory CRS. At this level, endotype-driven treatment in the form of biologics is implemented. At present, omalizumab and dupilumab are approved in the European Union for treatment of CRSwNP, whereas only dupilumab is approved by the Food and Drug Administration (FDA) for treatment of CRSwNP in the United States. The list may continue to evolve with emerging evidence from further phase 3 studies on other biologics.

3.3.1 Anti-IgE

IgE is a key atopic inflammatory mediator responsible for mast cell activation. It is significantly elevated in inflammatory airway conditions such as CRS and asthma. Omalizumab is a humanised monoclonal antibody that blocks IgE from binding to its receptor that is located on mast cells and basophils. It is approved in the United States for treatment of severe allergic asthma and chronic spontaneous urticaria. It is additionally approved by the European Commission recently as add-on treatment with INCS for the treatment severe CRSwNP for whom INCS does not provide adequate disease control based on the outcome of two randomised phase 3 trials (Gevaert et al. 2020).

Adverse effects with omalizumab include headache, injection site reactions, nasopharyngitis and cardiovascular complications, including deep vein thrombosis and myocardial infarction.

3.3.2 Anti-IL-5

IL-5 is a type 2 cytokine and key mediator in eosinophil growth, recruitment and activation. Mepolizumab and reslizumab are humanised monoclonal antibodies that bind to and block the function of circulating IL-5, thus preventing binding of IL-5 to its receptor. Both are approved in the European Union and the United States for the treatment of severe eosinophilic asthma. Two randomised, double-blind, placebo-controlled trials reported that mepolizumab significantly reduced nasal polyp size, improved symptom scores and reduced the need for sinus surgery (Bachert et al. 2017; Gevaert et al. 2011). Elevated nasal IL-5 levels at baseline were noted to predict positive responsiveness to reslizumab. Both biologics are currently undergoing phase 3 clinical trials to determine their efficacy in treating CRSwNP.

Mepolizumab is generally well tolerated, with adverse effects of headaches, injection site reaction and hypersensitivity reactions. Rebound eosinophilia and exacerbation of asthma after cessation of treatment have been reported. Common side effects associated with reslizumab are oropharyngeal pain, raised blood creatine phosphokinase and myalgia.

3.3.3 Anti-IL-4/-IL-13

IL-4 and IL-13 are key regulators of the type 2 inflammatory pathway in airway disease responsible for Th2 cell differentiation, IgE synthesis, recruitment of eosinophils and mast cells which contribute to airway remodeling. Dupilumab is a humanised monoclonal antibody that binds specifically to IL-4Rα, inhibiting signaling of both IL-4 and IL-13. It is approved in the European Union, the United States and Japan for moderate-to-severe atopic dermatitis in adults. Dupilumab is recently approved in the United States and European Union for the treatment of inadequately-controlled CRSwNP based on two pivotal trials, the 24-week SINUS-24 and 52-week SINUS-52 that are part of the Phase 3 LIBERTY clinical trial (Bachert et al. 2019; Han et al. 2019). Two-weekly administration of dupilumab with mometasone furoate nasal spray was compared with placebo injection plus mometasone furoate nasal spray. At 24 weeks, both trials demonstrated significant improvement in nasal congestion, nasal polyp score, sinus opacification and sense of smell compared to placebo. In the 52-week SINUS-52 trial, patients continued to do well throughout the treatment period. Dupilumab has been associated with injection site reactions, conjunctivitis, serum sickness and ocular and orofacial reactivation of herpes simplex virus.

4 Conclusion

CRS is an umbrella term that encompasses a spectrum of sinonasal inflammatory conditions, of which the causes are diverse and often overlapping. This concept should be reflected in the management of CRS, which is moving away from a simple CRSsNP/CRSwNP approach towards one that is directed against the underlying inflammatory mechanism. Despite an overlap of immunologic pathways and symptoms, there is lack of definitive conclusion about the association between atopy and nasal polyposis due to conflicting data in the literature. Well-designed, prospective studies with transparent inclusion and exclusion criteria could shed additional light on this relationship.

Conflict of Interest The authors declared that no conflict of interest exists.

References

Aeumjaturapat S, Saengpanich S, Isipradit P, Keelawat S (2003) Eosinophilic mucin rhinosinusitis: terminology and clinicopathological presentation. J Med Assoc Thai 86(5):420–424

Amali A, Saedi B, Rahavi-Ezabadi S, Ghazavi H, Hassanpoor N (2015) Long-term postoperative azithromycin in patients with chronic rhinosinusitis: a randomized clinical trial. Am J Rhinol Allergy 29(6):421–424. https://doi.org/10.2500/ajra.2015.29.4244

Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P (2001) Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol 107 (4):607–614. https://doi.org/10.1067/mai.2001.112374

Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME, Kariyawasam HH, Gilbert J, Austin D, Maxwell AC, Marshall RP, Fokkens WJ (2017) Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. J Allergy Clin Immunol 140(4):1024–1031.e1014. https://doi.org/10.1016/j.jaci.2017.05.044

Bachert C, Desrosiers M, Mullol J, Hellings P, Cervin A, Sher L, Bosso J, Lee S, Maspero J, Fujieda S (2019) A randomized phase 3 study, Sinus-52, evaluating the efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 143(2)

Bachmann G, Hommel G, Michel O (2000) Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol 257 (10):537–541

Baroody FM, Mucha SM, Detineo M, Naclerio RM (2008) Nasal challenge with allergen leads to maxillary sinus inflammation. J Allergy Clin Immunol 121(5):1126–1132.e1127. https://doi.org/10.1016/j.jaci.2008.02.010

Bent JP 3rd, Kuhn FA (1994) Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 111(5):580–588. https://doi.org/10.1177/019459989411100508

Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H (2003) 'Eosinophilic fungal rhinosinusitis': a common disorder in Europe? Laryngoscope 113(2):264–269. https://doi.org/10.1097/00005537-200302000-00013

Brietzke SE, Brigger MT (2008) Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol 72(10):1541–1545. https://doi.org/10.1016/j.ijporl.2008.07.008

Brietzke SE, Shin JJ, Choi S, Lee JT, Parikh SR, Pena M, Prager JD, Ramadan H, Veling M, Corrigan M, Rosenfeld RM (2014) Clinical consensus statement: pediatric chronic rhinosinusitis. Otolaryngol Head Neck Surg 151(4):542–553. https://doi.org/10.1177/0194599814549302

Brunner JP, Jawad BA, McCoul ED (2017) Polypoid change of the middle turbinate and paranasal sinus polyposis are distinct entities. Otolaryngol Head Neck Surg 157(3):519–523. https://doi.org/10.1177/0194599817711887

Cao PP, Wang ZC, Schleimer RP, Liu Z (2019) Pathophysiologic mechanisms of chronic rhinosinusitis and their roles in emerging disease endotypes. Ann Allergy Asthma Immunol 122(1):33–40. https://doi.org/10.1016/j.anai.2018.10.014

Chakrabarti A, Rudramurthy SM, Panda N, Das A, Singh A (2015) Epidemiology of chronic fungal rhinosinusitis in rural India. Mycoses 58(5):294–302. https://doi.org/10.1111/myc.12314

Collins MM, Nair SB, Wormald PJ (2003) Prevalence of noninvasive fungal sinusitis in South Australia. Am J Rhinol 17(3):127–132

DelGaudio JM, Loftus PA, Hamizan AW, Harvey RJ, Wise SK (2017) Central compartment atopic disease. Am J Rhinol Allergy 31(4):228–234. https://doi.org/10.2500/ajra.2017.31.4443

DeYoung K, Wentzel JL, Schlosser RJ, Nguyen SA, Soler ZM (2014) Systematic review of immunotherapy for chronic rhinosinusitis. Am J Rhinol Allergy 28(2):145–150. https://doi.org/10.2500/ajra.2014.28.4019

Dubin MG, Liu C, Lin SY, Senior BA (2007) American Rhinologic Society member survey on "maximal medical therapy" for chronic rhinosinusitis. Am J Rhinol 21(4):483–488

Fandino M, Macdonald KI, Lee J, Witterick IJ (2013) The use of postoperative topical corticosteroids in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. Am J Rhinol Allergy 27(5):e146–e157. https://doi.org/10.2500/ajra.2013.27.3950

Ferguson BJ (2000) Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. Laryngoscope 110(5 Pt 1):799–813. https://doi.org/10.1097/00005537-200005000-00010

Ferguson BJ, Barnes L, Bernstein JM, Brown D, Clark CE 3rd, Cook PR, DeWitt WS, Graham SM, Gordon B, Javer AR, Krouse JH, Kuhn FA, Levine HL, Manning SC, Marple BF, Morgan AH, Osguthorpe JD, Skedros D, Rains BM 3rd, Ramadan HH, Terrell JE, Yonkers AJ (2000) Geographic variation in allergic fungal rhinosinusitis. Otolaryngol Clin North Am 33 (2):441–449

Fokkens WJ, Reitsma S (2019) Proposal for an algorithm on the management of chronic rhinosinusitis. Allergy. https://doi.org/10.1111/all.13797

Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M (2020) European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 58(Suppl S29):1–464

Gan EC, Thamboo A, Rudmik L, Hwang PH, Ferguson BJ, Javer AR (2014) Medical management of allergic fungal rhinosinusitis following endoscopic sinus surgery: an evidence-based review and recommendations. Int Forum Allergy Rhinol 4(9):702–715. https://doi.org/10.1002/alr.21352

Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, De Ruyck N, Blomme K, Sousa AR, Marshall RP, Bachert C (2011) Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol 128(5):989–995.e981–988. https://doi.org/10.1016/j.jaci.2011.07.056

Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, Kaufman D, Ligueros-Saylan M, Howard M (2020) Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol 146(3):595–605

Goh BS, Gendeh BS, Rose IM, Pit S, Samad SA (2005) Prevalence of allergic fungal sinusitis in refractory chronic rhinosinusitis in adult Malaysians. Otolaryngol Head Neck Surg 133 (1):27–31. https://doi.org/10.1016/j.otohns.2005.03.028

Grayson JW, Harvey RJ (2019) Topical corticosteroid irrigations in chronic rhinosinusitis. Int Forum Allergy Rhinol 9(S1):S9–S15. https://doi.org/10.1002/alr.22331

Hamizan AW, Christensen JM, Ebenzer J, Oakley G, Tattersall J, Sacks R, Harvey RJ (2017) Middle turbinate edema as a diagnostic marker of inhalant allergy. Int Forum Allergy Rhinol 7 (1):37–42. https://doi.org/10.1002/alr.21835

Han JK, Bachert C, Desrosiers M, Laidlaw TM, Hopkins C, Fokkens WJ, Paggiaro P, Cho SH (2019) Efficacy and safety of Dupilumab in patients with chronic rhinosinusitis with nasal polyps: results from the randomized phase 3 Sinus-24 study. J Allergy Clin Immunol 143(2): AB422

Haxel BR, Clemens M, Karaiskaki N, Dippold U, Kettern L, Mann WJ (2015) Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. Laryngoscope 125(5):1048–1055. https://doi.org/10.1002/lary.25052

Head K, Sharp S, Chong LY, Hopkins C, Philpott C (2018) Topical and systemic antifungal therapy for chronic rhinosinusitis. Cochrane Database Syst Rev 9:CD012453. https://doi.org/10.1002/14651858.CD012453.pub2

Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, Kette F (2006) Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol 118(1):128–133. https://doi.org/10.1016/j.jaci.2006.03.012

Jahnsen FL, Haraldsen G, Aanesen JP, Haye R, Brandtzaeg P (1995) Eosinophil infiltration is related to increased expression of vascular cell adhesion molecule-1 in nasal polyps. Am J Respir Cell Mol Biol 12(6):624–632. https://doi.org/10.1165/ajrcmb.12.6.7539273

Kanowitz SJ, Batra PS, Citardi MJ (2008) Topical budesonide via mucosal atomization device in refractory postoperative chronic rhinosinusitis. Otolaryngol Head Neck Surg 139(1):131–136. https://doi.org/10.1016/j.otohns.2008.03.009

Lam K, Tan BK, Lavin JM, Meen E, Conley DB (2013) Comparison of nasal sprays and irrigations in the delivery of topical agents to the olfactory mucosa. Laryngoscope 123(12):2950–2957. https://doi.org/10.1002/lary.24239

Lasso A, Masoudian P, Quinn JG, Cowan J, Labajian V, Bonaparte JP, Kilty S (2017) Long-term low-dose macrolides for chronic rhinosinusitis in adults – a systematic review of the literature. Clin Otolaryngol 42(3):637–650. https://doi.org/10.1111/coa.12787

Marple BF, Stankiewicz JA, Baroody FM, Chow JM, Conley DB, Corey JP, Ferguson BJ, Kern RC, Lusk RP, Naclerio RM, Orlandi RR, Parker MJ, American Academy of Otolaryngic Allergy Working Group on Chronic R (2009) Diagnosis and management of chronic rhinosinusitis in adults. Postgrad Med 121(6):121–139. https://doi.org/10.3810/pgm.2009.11.2081

Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, Batra PS, Bernal-Sprekelsen M, Bhattacharyya N, Chandra RK, Chiu A, Citardi MJ, Cohen NA, DelGaudio J, Desrosiers M, Dhong HJ, Douglas R, Ferguson B, Fokkens WJ, Georgalas C, Goldberg A, Gosepath J, Hamilos DL, Han JK, Harvey R, Hellings P, Hopkins C, Jankowski R, Javer AR, Kern R, Kountakis S, Kowalski ML, Lane A, Lanza DC, Lebowitz R, Lee HM, Lin SY, Lund V, Luong A, Mann W, Marple BF, McMains KC, Metson R, Naclerio R, Nayak JV, Otori N, Palmer JN, Parikh SR, Passali D, Peters A, Piccirillo J, Poetker DM, Psaltis AJ, Ramadan HH, Ramakrishnan VR, Riechelmann H, Roh HJ, Rudmik L, Sacks R, Schlosser RJ, Senior BA, Sindwani R, Stankiewicz JA, Stewart M, Tan BK, Toskala E, Voegels R, Wang DY, Weitzel EK, Wise S, Woodworth BA, Wormald PJ, Wright ED, Zhou B, Kennedy DW (2016) International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol 6 (Suppl 1):S22–S209. https://doi.org/10.1002/alr.21695

Pant H, Kette FE, Smith WB, Wormald PJ, Macardle PJ (2005) Fungal-specific humoral response in eosinophilic mucus chronic rhinosinusitis. Laryngoscope 115(4):601–606. https://doi.org/10.1097/01.mlg.0000161341.00258.54

Psaltis AJ, Foreman A, Wormald PJ, Schlosser RJ (2012) Contamination of sinus irrigation devices: a review of the evidence and clinical relevance. Am J Rhinol Allergy 26(3):201–203. https://doi.org/10.2500/ajra.2012.26.3747

Pundir V, Pundir J, Lancaster G, Baer S, Kirkland P, Cornet M, Lourijsen ES, Georgalas C, Fokkens WJ (2016) Role of corticosteroids in functional endoscopic sinus surgery – a systematic review and meta-analysis. Rhinology 54(1):3–19. https://doi.org/10.4193/Rhin15.079

Pynnonen MA, Venkatraman G, Davis GE (2013) Macrolide therapy for chronic rhinosinusitis: a meta-analysis. Otolaryngol Head Neck Surg 148(3):366–373. https://doi.org/10.1177/0194599812470427

Rojita M, Samal S, Pradhan P, Venkatachalam VP (2017) Comparison of steroid and Itraconazole for prevention of recurrence in allergic fungal rhinosinusitis: a randomized controlled trial. J Clin Diagn Res 11(4):MC01–MC03. https://doi.org/10.7860/JCDR/2017/23488.9610

Rupa V, Jacob M, Mathews MS, Seshadri MS (2010) A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. Eur Arch Otorhinolaryngol 267(2):233–238. https://doi.org/10.1007/s00405-009-1075-8

Sastre J, Mosges R (2012) Local and systemic safety of intranasal corticosteroids. J Investig Allergol Clin Immunol 22(1):1–12

Snidvongs K, Pratt E, Chin D, Sacks R, Earls P, Harvey RJ (2012) Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. Int Forum Allergy Rhinol 2(5):415–421. https://doi.org/10.1002/alr.21047

Varvyanskaya A, Lopatin A (2014) Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. Int Forum Allergy Rhinol 4 (7):533–541. https://doi.org/10.1002/alr.21318

Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, Menger DJ, Lehtonen MT, Toppila-Salmi SK, Vento SI, Hytonen M, Hellings PW, Kalogjera L, Lund VJ, Scadding G, Mullol J, Fokkens WJ (2011) Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy 66(11):1457–1468. https://doi.org/10.1111/j.1398-9995.2011.02693.x

Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A (2006) A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope 116(2):189–193. https://doi.org/10.1097/01.mlg.0000191560.53555.08

Wang DY, Lee HP, Gordon BR (2012) Impacts of fluid dynamics simulation in study of nasal airflow physiology and pathophysiology in realistic human three-dimensional nose models. Clin Exp Otorhinolaryngol 5(4):181–187. https://doi.org/10.3342/ceo.2012.5.4.181

Wei CC, Adappa ND, Cohen NA (2013) Use of topical nasal therapies in the management of chronic rhinosinusitis. Laryngoscope 123(10):2347–2359. https://doi.org/10.1002/lary.24066

Wentzel JL, Soler ZM, DeYoung K, Nguyen SA, Lohia S, Schlosser RJ (2013) Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review. Am J Rhinol Allergy 27(6):482–489. https://doi.org/10.2500/ajra.2013.27.3976

White LJ, Rotella MR, DelGaudio JM (2014) Polypoid changes of the middle turbinate as an indicator of atopic disease. Int Forum Allergy Rhinol 4(5):376–380. https://doi.org/10.1002/alr.21290

Wilson KF, McMains KC, Orlandi RR (2014) The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol 4(2):93–103. https://doi.org/10.1002/alr.21258

Xu X, Ong YK, Wang Y (2019) Novel findings in immunopathophysiology of chronic rhinosinusitis and their role in a model of precision medicine. Allergy. https://doi.org/10.1111/all.14044

Zeng M, Long XB, Cui YH, Liu Z (2011) Comparison of efficacy of mometasone furoate versus clarithromycin in the treatment of chronic rhinosinusitis without nasal polyps in Chinese adults. Am J Rhinol Allergy 25(6):e203–e207. https://doi.org/10.2500/ajra.2011.25.3728

Zhao L, Li YY, Li CW, Chao SS, Liu J, Nam HN, Dung NTN, Shi L, Wang DY (2017) Increase of poorly proliferated p63(+) /Ki67(+) basal cells forming multiple layers in the aberrant remodeled epithelium in nasal polyps. Allergy 72(6):975–984. https://doi.org/10.1111/all.13074

Part IV

From Environmental Trigger to Disease Management

Treatment Approaches to Food Allergy

Barbara Bohle and Thomas Werfel

Contents

Abstract

IgE-mediated food allergies affect both children and adults and are associated with dramatic decreases in the quality of life. In the majority of cases, food allergens have to be avoided which may be difficult, particularly in patients who suffer from life-threatening symptoms following the ingestion of minimal doses of food allergens. Several novel therapeutic approaches have been studied during the recent past and are summarized in this review. Therapies with novel therapeutic monoclonal antibodies, innovative allergen-specific immunotherapies using subcutaneous, sublingual, or epicutaneous routes, and oral

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immunotherapies leading to increases of individual thresholds of tolerable foods upon their continuous ingestion showed promising results which may change future management strategies in moderate to severe food allergy.

Keywords

Allergen-specific immunotherapy · Apple · IgE-mediated food allergy · Peanut

1 Introduction

According to the position paper from the European Academy of Allergy and Clinical Immunology (EAACI) food allergy is an immune-mediated non-toxic adverse reaction to foods including immunoglobulin (Ig)E-mediated immediate hypersensitivity reactions, delayed non-IgE-mediated reactions, and disorders with contributions from both IgE-mediated and non-IgE-mediated immune pathways (Fig. 1) (Bruijnzeel-Koomen et al. 1995).

The most common form of food allergy is mediated by IgE antibodies and reflects an immediate-type ("type 1 hypersensitivity") reaction, i.e. acute onset of symptoms after ingestion or inhalation of foods. During the phase of sensitization the immune system produces IgE antibodies directed against food allergens which bind to the high affinity receptor FcεRI expressed on the surface of mast cells and basophils. Following re-exposure to the respective food allergen, cross-linking of surface-bound IgE antibodies triggers the release of preformed mediators, such as histamine, tryptase, and tumor necrosis factor. These mediators cause the acute phase of allergic symptoms which appear within a few minutes up to 2 h after contact with the offending food. The allergic reactions may be confined to the site of contact with the food, such as the oral allergy syndrome (OAS) which comprises pruritus, tingling, and angioedema of the lips, tongue, palate, and throat, occasionally also a sensation of tightness in the ears or in the throat, or both. Apart from the gastrointestinal tract (nausea, laryngeal edema, stomach cramps, vomiting, flatulence,

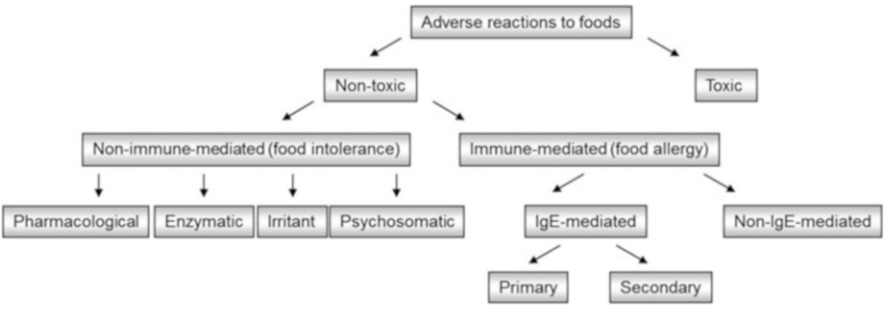

Fig. 1 Classification of adverse reactions to foods according to the pathophysiology (Bruijnzeel-Koomen et al. 1995). Adverse reactions to foods comprise toxic and non-toxic reactions. The latter reactions are either non-immune-mediated or immune-mediated. IgE-mediated reactions constitute primary and secondary food allergies

diarrhea) allergic reactions may manifest in the skin (urticaria, angioedema) and/or the respiratory tract (rhinoconjunctivitis, bronchospasm). Anaphylaxis, the maximum variant of an IgE-mediated allergic reaction, is a life-threatening condition which affects two or more organ systems.

In addition to the release of preformed mediators, IgE-induced activation of mast cells triggers the de novo synthesis of agents, e.g. leukotrienes, prostaglandins, and cytokines. These mediators start the recruitment of neutrophils, eosinophils, and basophils which are involved in the allergic late-phase reaction. Thus, mast cells are generally regarded as central players in both, allergic immediate and late-phase reactions because they attract and activate inflammatory cells (Galli 2016). Beyond this, allergenic food proteins activate special subsets of T lymphocytes which are involved in T-cell B-cell interactions and the induction of specific antibodies and also contribute to the late-phase inflammation in sensitized individuals. In fact, they can cause late-phase reactions independently from earlier IgE-mediated mast cell activation. For example, patients with milk allergy may develop isolated late asthmatic reactions after the ingestion of milk (Papageorgiou et al. 1983). Moreover, patients suffering from birch pollen-related food allergy may develop a worsening of atopic eczema after symptom-free ingestion of the offending food (Bohle et al. 2006; Wassmann-Otto et al. 2018). Nevertheless, the general prevalence of biphasic reactions after food ingestion is low (Jarvinen et al. 2009).

2 Primary and Secondary Food Allergy

IgE-mediated food allergy can be further classified into primary and secondary food allergy on the basis of the affected patients (children or adults), clinical appearance, the disease-eliciting food allergens, and the underlying immune mechanisms (Fig. 1).

Primary food allergy starts in early life and often represents the first manifestation of the "atopic syndrome," a term summarizing all clinical manifestations connected to the atopic constitution. The eight most common allergenic foods include cow's milk, hen's egg, fish, shellfish, peanuts, soybean, tree nuts, and wheat. Often, primary food allergens do not only elicit allergic reactions in the gastrointestinal (GI) tract but cause or influence urticaria, atopic dermatitis as well as bronchial obstruction. With a few exceptions (peanut and fish) most children outgrow primary food allergy within the first 3–6 years of life.

In primary food allergy, sensitization typically occurs via the oral route. Usually, oral tolerance is the default response to ingested antigens in food which has been demonstrated in animal models (Commins 2015) and humans (Husby et al. 1994). The latter study has reported that daily administration of 50 mg of the neoantigen keyhole limpet hemocyanin (KLH) per os to adult volunteers for 10 days prior to subcutaneous immunization with KLH induced systemic T-cell tolerance and higher titers of KLH-specific antibodies compared to the non-fed control group (Husby et al. 1994). The induction of oral tolerance is an active process and involves the generation of regulatory T (reg) cells, the suppression of T helper (Th)2 cells, a

decreased production of IgE and increased IgA and IgG4 production, suppression of effector T-cell migration to tissues, induction of IL-10–producing DCs, and suppression of basophil, eosinophil, and mast cell activation (Sampson et al. 2018). Recently, a new subset of regulatory innate lymphoid cells (ILC) has been identified in the intestine that inhibits inflammation (Wang et al. 2017).

Oral tolerance protects from inappropriate immune responses to the *plethora* of foreign antigens in food normally encountered in the gastrointestinal tract. Primary food allergy may be regarded as a failure to establish or to maintain oral tolerance against innocuous antigens. The fact that the immunosuppressive intestinal environment is controlled by a complex network of immunological interactions between epithelial cells, antigen-presenting cells, and lymphocytes makes it difficult to unravel the precise mechanisms that trigger food allergy. A dysfunction of any of the steps of the complex interplay may cause disease in susceptible individuals. Moreover, the establishment of immune homeostasis depends on windows of opportunity during which innate and adaptive immunity are coordinated by antigen-presenting cells orchestrated by microbial products and dietary constituents. In particular, the neonatal period is critical for the induction of the necessary homeostatic mechanisms because the mucosal epithelial barrier and the immunoregulatory network are poorly developed in newborns. Although the precise reasons for a failure to develop oral tolerance in allergic patients still remain to be elucidated, various factors that damage the epithelial barrier have been considered to promote allergic sensitization (Lozano-Ojalvo et al. 2019). Growing evidence suggests that allergy development is influenced by the composition and metabolic activity of certain microbiota in the gut (Stephen-Victor and Chatila 2019). A reduced microbial diversity early in life (3 months of age) accompanied by diminished *Bacteroidaceae* species and an enriched *Enterobacteriaceae* species could be associated with an increased likelihood of food-sensitization later in life (12 months of age) (Azad et al. 2015). Moreover, children with milk allergy displayed an altered composition of their microbiome and if enriched with *Firmicutes* and *Clostridia* species in early life tended to resolve their milk allergy at the age of 8 years (Bunyavanich et al. 2016). The relevance of the gut microbiome was further underlined by the transfer of food allergy through transfer of microbiota from food allergy-prone mice to wild-type animals (Noval Rivas et al. 2013). Commensals of the order *Clostridiales* and *Bacteroidales* drive the differentiation of Treg cells which have been implicated in establishing tolerance to luminal antigens in the gut (Esterhazy et al. 2019). Thus, dysbiosis of the gut microbiome seems to contribute to the development of food allergy.

In addition to sensitization via the oral route, the clinical evidence for sensitization to food allergens through the skin is growing. A dysfunction of the skin barrier has been considered to explain the association between atopic dermatitis and food allergy. For example, peanut protein levels in household dust and positive peanut skin prick tests showed an exposure-response relationship (Brough et al. 2018). The effect was even more prominent in children with severe atopic dermatitis and in patients with associated skin barrier defects (e.g., with filaggrin loss-of-function mutations), underlining that environmental exposure through an impaired skin

Table 1 Secondary food allergy

Primary allergen source	Possible cross-reaction to	Risk
Birch pollen	Stone-fruits, kiwi, tree nuts, celery, carrot, soy, peanut, fresh fig,	Very high
Ficus benjamina	Fig (fresh and dried), occasionally also kiwi, papaya, banana	High
Bird feathers	Egg yolk	High
Mugwort pollen	Celery, carrot, chamomile, honey, lychee, mango, spices (caraway, anise, curry, coriander, cumin)	Moderate
Profilin	Melon, banana, tomato, pepper, mango	Moderate
Rubber latex	Kiwi, avocado, banana, pepper, fig	Moderate
House dust mite	Crustaceae	Low
Cat dander	Pork	Very low

barrier is a plausible route for sensitization and allergy development. Similar to peanut allergy, eczema was strongly associated with egg allergy development and the association increased with increasing eczema severity as recently described on the pan-European EuroPrevall birth cohort on more than 12.000 infants (Grimshaw et al. 2020). Here past or current eczema was significantly associated with egg allergy (adjusted odds ratio, 9.21; 95% CI, 2.65–32.04). Interestingly, increasing eczema severity was associated with an increasing likelihood of egg allergy and egg allergy started with an average 3.6 ± 0.5 months after eczema. Occupational exposure to proteins of animals and plants present in aerosolized foods during food processing frequently induces IgE-mediated reactions (Jeebhay et al. 2019). Respiratory sensitization as initiator of food allergy was also reported for adult bird owners exposed to millet in bird food who developed severe anaphylactic reactions when ingesting food containing millet (Bohle et al. 2003a). However, it is still an open question whether the non-oral sensitization process is associated with a dysbiosis of the microbiota in the lung and skin.

In 2009, the carbohydrate galactose-α-1,3-galactose (α-Gal) was first reported to cause delayed allergic reactions to red meat (Commins et al. 2009). Today, the "α-Gal syndrome" is established as a common form of food allergy affecting adults and children (Platts-Mills et al. 2020). In stark contrast to other food allergies the α-Gal syndrome is not induced by a protein but a carbohydrate and characterized by a delayed onset of allergic reactions after consumption of red meat (Levin et al. 2019; Hodzic et al. 2019). Furthermore, this atypical form of food allergy is considered to be initiated by tick bites (Cabezas-Cruz et al. 2019).

Secondary food allergy is the most abundant food allergy in adolescent and adult individuals but also affects children (Werfel et al. 2015). This food allergy is a consequence of primary sensitization to a non-food allergen, e.g. certain allergens in pollens, house dust mites, animal dander, or rubber latex (Table 1). Clinically, the majority of the individuals develop hypersensitivity reactions to food after the manifestation of the primary allergy. Immunologically, the food proteins themselves

are not able to initiate IgE-production but are recognized by IgE antibodies initially produced against a non-food allergen. This humoral cross-reaction which is often due to structural homology of both proteins then results in immediate allergic reactions to the food.

The risk to develop secondary food allergy depends on the sensitizing allergen. For example, individuals allergic to birch pollen and the major allergen Bet v 1 in particular are at high risk to experience allergic reactions to foods which contain Bet v 1-homologous proteins. Table 1 provides an overview on typical secondary food allergies, the sensitizing allergen source, and the risk to develop food allergy.

Already in 1948 it has been observed that birch pollen-allergic patients may develop oral symptoms to hazelnuts (Juhlin-Dannfelt 1948). In the late 1970s research has started to investigate the cause for the clinical observation that a high percentage of birch pollen-allergic patients develop allergic reactions to certain foods, most often tree nuts and stone-fruits (Hannuksela and Lahti 1977; Eriksson et al. 1982; Dreborg and Foucard 1983). Birch pollen-related food allergy (BPRFA), and apple-induced BRPFA in particular, evolved into a broadly used disease model to elucidate the pathophysiology of secondary food allergy. One important reason for this development was the availability of Bet v 1 as recombinant protein (Breiteneder et al. 1989) allowing its detailed structural and immunological characterization (Gajhede et al. 1996; Mogensen et al. 2002; Spangfort et al. 2003; Radauer et al. 2008; Jahn-Schmid et al. 2005). In 1995, recombinant (r) Mal d 1, the Bet v 1-homolog in apple, became available (Vanek-Krebitz et al. 1995) and represented a stable substitute for the very labile natural protein which is easily destroyed when isolated from apples (Vieths and Schoning 1996). Recently, rMal d 1 was successfully applied to solve its 3-dimensional structure, composed of a seven-stranded antiparallel beta-sheet and three alpha-helices forming a large internal cavity, and confirmed the high structural similarity with Bet v 1 and other cross-reactive food allergens from the pathogenesis-related (PR) protein family 10 (Ahammer et al. 2017; Fernandes et al. 2013).

Recombinant Bet v 1 and Mal d 1 served as essential tools for the characterization of epitopes involved in IgE cross-reactivity of both proteins (Holm et al. 2001; Ma et al. 2006; Klinglmayr et al. 2009). Notably, most relevant IgE epitopes on these allergens are conformational, i.e. they depend on proper protein folding resulting in the correct 3-dimensional structure. In experimental settings, gastrointestinal enzymes rapidly degrade Mal d 1 and other Bet v 1-homologous food allergens in fragments which are not recognized by IgE antibodies from individuals with BPRFA (Schimek et al. 2005). The destruction of their 3-dimensional structure by gastrointestinal proteases may imply that Bet v 1-related food proteins do not reach the gut-associated lymphoid tissue (GALT) in their natural conformation. The demonstration of the rapid gastrointestinal degradation of Bet v 1-homologous food proteins also provided an explanation for the fact that BPRFA usually manifests as OAS. However, in the case that the proteolytic activity of gastrointestinal proteases is impaired, e.g. by the rise of the gastric pH, birch pollen-related foods may induce more severe, anaphylactic reactions (Schulten et al. 2011). In this respect, the consumption of soy-based foods and particularly of soy drinks containing the Bet

v 1-homolog Gly m 4 has been defined as risky for birch pollen-allergic individuals (Kleine-Tebbe et al. 2002; De Swert et al. 2012; Kosma et al. 2011; Treudler et al. 2008). Severe systemic reactions may occur because drinking soy milk enhances the gastric pH, thereby hindering the proteolytic activity of pepsin and enabling the absorption of non-digested IgE-reactive Bet v 1-related food allergens (Schulten et al. 2011). To make individuals at risk aware of these rare but serious complications, BPRFA should be reliably diagnosed.

Recombinant Bet v 1 and Mal d 1 also allowed the first demonstration of T-cell cross-reactivity between an aeroallergen and a food protein (Fritsch et al. 1998). In contrast to the conformational epitopes recognized by IgE antibodies, T cells are activated by linear peptides resulting from allergen degradation by antigen-processing cells prior to loading onto MHC-class II molecules. Based on the knowledge of the amino acid sequences of Bet v 1 various distinct T-cell epitopes could be identified (Jahn-Schmid et al. 2005). Several of the corresponding regions in the amino acid sequences of Bet v 1-related food proteins displayed sufficient homology to activate Bet v 1-specific T cells (Bohle et al. 2003b, 2005; Kitzmuller et al. 2015; Zulehner et al. 2017). In particular, T cells specific for the highly conserved immunodominant epitope Bet v $1_{142–156}$ were shown to respond to various Bet v 1-related food allergens (Jahn-Schmid et al. 2005). Moreover, gastrointestinal degradation of Bet v 1-related food allergens resulted in fragments which were still able to induce proliferative and cytokine responses of Bet v 1-specific T cells (Schimek et al. 2005). Similarly, heat-treated Bet v 1-homologous allergens still displayed T-cell-stimulating activity despite lacking IgE-reactivity due to the destruction of conformational IgE epitopes by thermal processing (Bohle et al. 2006). T lymphocytes are important key players in late eczematous reactions, and Bet v 1-specific T-cell responses have been detected in the lesional skin of birch pollen-allergic patients (Reekers et al. 1999). Together, the detailed in vitro analysis of the cellular cross-reactivity between Bet v 1 and its homologs in foods explained how ingestion of birch pollen-related food can cause the exacerbation of skin lesions in birch pollen-allergic patients with atopic dermatitis (Wassmann-Otto et al. 2018) and why these cutaneous late-phase reactions may also occur after symptom-free consumption of cooked birch pollen-related foods (Bohle et al. 2006). Consequently, (cooked) birch pollen-related food may represent an underestimated provocation factor for a subgroup of birch pollen-allergic patients with atopic dermatitis.

In the past decades, the clinical and immunological insights about birch pollen-related food allergy accumulated and markedly contributed to a better understanding of the pathophysiology of secondary food allergy. It is expected that the immune processes of less common secondary food allergies are similar, e.g. those associated with respiratory allergy to mugwort pollen, natural latex, or house dust mites (Table 1) (Werfel et al. 2015).

3 Immunotherapy for Food Allergy

More than 17 million people suffer from food allergy in Europe, out of which 3.5 million are younger than 25 years. Food allergies significantly impair the quality of life (QoL), affecting both work and leisure time which has also a negative economic impact for the society in general. A recent questionnaire-based study revealed that food allergic adolescents are affected more than younger children (based on parental report) in terms of QoL including emotional, dietary, and social aspects (Miller et al. 2020).

Upon diagnosis of food allergy performed by taking the patient's history, proven IgE-mediated sensitizations, and showing their clinical relevance by elimination diets and subsequent challenge tests, usually a therapeutical long-lasting elimination diet is indicated (Muraro et al. 2014). That means that currently, food allergies are mostly managed by strict avoidance of the allergenic food and if severe, the provision of an emergency plan and medications, e.g. self-injectable epinephrine, for the treatment of accidental ingestions. In addition, patients need to be educated as most fatal reactions occur when foods are consumed or prepared outside the home. Proper information also includes the family, close relatives, friends, and caregivers, in particular when children are concerned. This complex situation demands for effective treatment strategies for food allergy.

As for respiratory allergies, allergen-specific immunotherapy (AIT) is an option to treat food allergy because it alters the disease-eliciting pathophysiology and thus, has long-term clinical benefit (Pajno et al. 2018). The major goal of AIT is to achieve sustained unresponsiveness, which is defined as the ability to ingest an offending food without symptoms regardless of long avoidance periods or irregular consumption. The redirection of the allergic response requires the repetitive administration of increasing doses of the food allergen in order to modify the IgE-mediated immune response. Prior to becoming tolerant, patients are desensitized, a process which strictly depends on the regular exposure to the allergenic food. Nevertheless, when the regular food exposure is withdrawn, allergic symptoms to the offending foods return. Up to now, the indications for AIT of food allergy are still poorly defined and standardized protocols how to perform AIT with foods are lacking. The latter together with a high risk of adverse reactions currently implies that AIT with food allergens are not yet to be implemented into normal clinical practice but can only be performed at specialized centers with expert staff and adequate equipment. Therefore, strategies for improving the safety and efficacy of AIT for food allergy are needed. First attempts to cure primary food allergy by conventional subcutaneous AIT had to be abandoned due to an unacceptable risk of severe anaphylactic reactions. To increase the safety of AIT with food allergens other routes than subcutaneously, e.g. sublingually, epicutaneously and orally, have been assessed.

3.1 Sublingual Allergen Immunotherapy (SLIT)

The food protein is delivered under the tongue, held for 2 min and then swallowed. SLIT has been tested with milk, peanut, hazelnut, and peach (Burks et al. 2015; Enrique et al. 2008; Fernandez-Rivas et al. 2009; Keet et al. 2012; Kim et al. 2019). SLIT has a very good safety profile; however, SLIT with native foods may not be the most effective method to induce clinically significant desensitization or sustained unresponsiveness. Therefore, SLIT may be considered for patients with severe allergy who cannot tolerate oral immunotherapy (OIT). Studies comparing SLIT and OIT suggest that SLIT may have a role not only as a stand-alone therapy, but also as an initial desensitizing therapy to mitigate side effects, followed by OIT for maximum desensitization effect.

3.2 Epicutaneous Immunotherapy (EPIT)

Repeated epicutaneous application of an allergen to intact skin has an acceptable safety profile and is relatively well tolerated (Fleischer et al. 2019; Jones et al. 2017). Primarily mild cutaneous reactions including local erythema or eczema at application sites, and pruritus and flares of atopic dermatitis may occur. Depending on the food allergy, the daily allergen doses vary from 100–500 μg. In 2015 it was concluded that the efficacy of EPIT is similar to SLIT (Chiang and Berin 2015). Correspondingly, EPIT may be applicable prior to OIT to increase the safety of OIT dosing.

3.3 Oral Immunotherapy (OIT)

OIT involves the consumption of a daily maintenance dose of 300–4,000 mg of food allergen typically mixed in some food vehicle. The majority of studies have focused on single-allergen OIT with milk, egg, or peanut (Longo et al. 2008; Skripak et al. 2008; Jones et al. 2016; Vickery et al. 2017). Protocols differ, but several trials have shown that most patients who tolerate OIT can be successfully desensitized; however, sustained unresponsiveness is rarely achieved (Scurlock and Jones 2018). OIT is associated with high rates of adverse reactions with mild abdominal pain being the most common symptom. However, unpredictable more severe reactions may occur even to a previously tolerated dose, particularly during up dosing. To prevent systemic reactions, pretreatment with omalizumab has been proposed. This fully humanized monoclonal antibody selectively binds to IgE. Adjuvant therapy with omalizumab has been extensively used in severe peanut allergy, milk allergy, egg allergy, and multiple food allergy with significant clinical improvements observed in both adults and children (Andorf et al. 2019; Gunawardana and Durham 2018). Nevertheless, some patients relapse after 2–4 months of suspending omalizumab which may suggest that a longer maintenance therapy with omalizumab is needed (Loh and Tang 2018). Standard protocols as well as information on the optimal

duration of adjuvant therapy with omalizumab are still missing. As a consequence, this therapeutic approach has not been incorporated in the most recent EAACI guidelines where a case-by-case evaluation has been proposed (Pajno et al. 2018).

4 Novel Treatment Options for Primary Food Allergy: Peanut Allergy as an Example

Over the last decade, much emphasis has been laid on the development of therapies for primary food allergy and studies have progressed most quickly for the treatment of peanut allergy (Kim et al. 2020). Peanut allergy is a common example of primary food allergy which may cause severe, life-threatening allergic reactions (Capucilli et al. 2020). Moreover, peanut allergy is rarely outgrown and frequently carried into adulthood. Consequently, the risk of accidental anaphylaxis to ingested traces of peanuts poses a significant burden on the quality of life of peanut-allergic individuals and their families (Shaker and Greenhawt 2019).

The number of therapeutic antibodies directed to molecules being involved in allergic inflammation increases. Recently a phase IIa study was performed with anti-IL-33 antibody in 20 peanut-allergic individuals. More than 70% of the treated group but none of the placebo group tolerated 275 mg of peanut protein, which was the food challenge outcome in the study, after 15 days (Chinthrajah et al. 2019a).

As conventional subcutaneous AIT induced fatal reactions (Nelson et al. 1997), other routes of allergen administration have been applied for the treatment of peanut allergy. SLIT with peanut displayed a good safety profile and induced desensitization in the majority of subjects, however, to a lower absolute threshold than peanut OIT (Kim et al. 2020; Zhang et al. 2018). Peanut EPIT was studied in two phase 2 studies and revealed promising results with high adherence rates and an excellent safety profile. However, a large phase 3 follow-up study did not meet the primary endpoint (Waldron and Kim 2020). OIT has been an emerging experimental treatment for peanut allergy although different studies have shown varying results (Vickery et al. 2017; Varshney et al. 2011; Tang et al. 2015; Narisety et al. 2015; Anagnostou et al. 2014; Jones et al. 2009; Bird et al. 2015; Chinthrajah et al. 2019b; Investigators PGoC et al. 2018; Blumchen et al. 2019). OIT rarely achieves tolerance but may increase an individual's reaction threshold to the offending food. It has been estimated that an increase of the peanut threshold from a baseline of $\leq$100 mg peanut protein to 300 mg reduces the risk of experiencing an allergic reaction by 95% for most packaged foods that may contain traces of peanut (Baumert et al. 2018). A similar model using European consumption and peanut contamination data suggested that the increase in peanut threshold achieved with AIT may result in >99% risk reduction for most potential sources of peanut cross-contact (Remington et al. 2018). Still, recent systematic reviews and meta-analyses of the efficacy and safety of OIT in peanut allergy concluded that the treatment regimens require further improvement to reduce the considerable risk of allergic and anaphylactic reactions while clinical efficacy remains unsatisfactory (Chu et al. 2019; Grzeskowiak et al. 2020).

Peanuts contain 16 allergens and have strong allergenic potential (Palladino and Breiteneder 2018). Given the risks of administering intact food allergen to highly allergic patients, research efforts have focused on the development of methods to render allergens into less IgE-binding variants while maintaining their potential to induce tolerance. Along these lines, the vaccine EMP-123 contains the dominant peanut proteins, Ara h 1, Ara h 2, and Ara h 3, which had been modified by amino acid substitutions at major IgE-binding epitopes to reduce their allergenic activity. The rectal administration of these mutated recombinant peanut proteins encapsulated in heat-killed *Escherichia coli* to promote induction of Th1 immunity appeared safe and potentially effective in a mouse model (Li et al. 2003). The results of a first phase 1 study conducted to assess the safety of EMP-123 in peanut-allergic individuals were published in 2013 (Wood et al. 2013). Here, EMP-123 was rectally applied to 10 peanut-allergic adults over 10 weeks from 10 μg to 3,063 μg, followed by three biweekly doses of 3.063 mg (Wood et al. 2013). Although peanut skin test titration and basophil activation were significantly reduced post-treatment, peanut-specific IgE and IgG4 levels pre- and post-treatment did not significantly change. Furthermore, the rectal administration of EMP-123 led to unexpectedly frequent and sometimes even severe allergic reactions.

HAL-MPE1 is an aluminum hydroxide-adsorbed chemically modified peanut extract for subcutaneous administration (van der Kleij et al. 2019). This vaccine contains chemically modified (reduction and alkylation) Ara h 2 and Ara h 6 and partly modified Ara h 1 and Ara h 3 with reduced IgE-binding activity. A double-blind, placebo-controlled phase 1 study included 17 peanut-allergic subjects randomized to receive 15–20 weekly incremental subcutaneous doses of HAL-MPE1 or placebo. Side effects were more prevalent in subjects receiving HAL-MPE1 and included early systemic reactions and grade I late systemic reactions. HAL-MPE1-treated participants showed increased IgG and IgG4 levels for peanut, Ara h 1, Ara h 2, Ara h 3, and Ara h 6 as well as a trend toward reduced basophil histamine release. These results were promising and possible efficacy of HAL-MPE1 is now followed up.

Another novel experimental approach to treat peanut allergy are DNA vaccines. They are based on a bacterial plasmid vector expressing the gene for the protein of interest. Inclusion of the sequence for lysosomal-associated membrane protein-1 (LAMP-1) in DNA plasmids enhances the immunogenicity of the antigen and promotes Th1-like responses. ASP0892 is a DNA plasmid vaccine comprising Ara h 1, Ara h 2, Ara h 3, and LAMP-1, intended for intradermal or subcutaneous administration (Li et al. 2015). So far, mice were sensitized to peanut and then treated with intradermal Ara h 1,2,3-LAMP-Vax or control vector for 4 weeks. After peanut challenge, the vaccine-treated mice displayed 70% lower peanut-specific IgE ($p < 0.05$) and increased peanut-specific IgG2a ($p < 0.02$), had lower symptom scores, higher core body temperature, and lower plasma histamine level after challenge (Li et al. 2015). A phase 1, randomized placebo-controlled trial of ASP0892 for intradermal or intramuscular administration in adults recently completed enrollment (NCT02851277). There is an ongoing trial evaluating intradermal administration in adolescents (NCT03755713).

5 Novel Treatment Options for Secondary Food Allergy: Apple Allergy as an Example

Up to 60% of food allergies in older children, adolescents, and adults are linked with an inhalant allergy (Werfel et al. 2015). IgE antibodies raised against aeroallergens and cross-reactive with homologous proteins in foods are the immunological basis for this type of food allergy. Correspondingly, successful treatment of respiratory allergy was expected to concomitantly benefit secondary food allergy. In fact, AIT exists for many aeroallergens. AIT with birch pollen is clinically effective in approximately 70% of the treated individuals. However, the therapeutic success of AIT with birch pollen on BPRFA fell short among the expectations. Some studies reported the amelioration of mucosal symptoms to apple after successful therapy of pollinosis (Kelso et al. 1995; Asero 1998, 2003, 2004; Bolhaar et al. 2004). However, others reported limited curative effects and in some cases even the onset of BPRFA during AIT (Herrmann et al. 1995; Modrzynski et al. 2002; Bucher et al. 2004; Hansen et al. 2004; Mauro et al. 2011). The varying results from the different trials may be explained by varying protocols and birch pollen-containing vaccines that had been applied. Moreover, these studies relied on prick-to-prick tests, food challenges, or both with fresh apples. These test methods cannot guarantee the use of constant amounts of Mal d 1 for challenges at different time points because its content depends strongly on the cultivar, stage of maturation, and storage conditions (Sancho et al. 2006; Matthes and Schmitz-Eiberger 2009). Moreover, Mal d 1 is easily destroyed during preparation of the test meals because this protein is extremely susceptible to acidic conditions and proteases (Skamstrup Hansen et al. 2001). Nevertheless, a limited curative efficacy of AIT with birch pollen on BPRFA was also the outcome of a randomized placebo-controlled trial evaluating the clinical effects on the associated hazelnut allergy (van Hoffen et al. 2011). The therapeutic efficacy of birch pollen-AIT on BPRFA could also not be improved by SLIT, i.e. the administration of allergen directly at the site of food-induced clinical reactions (Kinaciyan et al. 2007). As a consequence of these studies, it has been speculated that higher doses of the primary allergen than those sufficient to improve respiratory symptoms may be required to reduce secondary food allergy. Along these lines, a hypoallergenic Bet v 1-folding variant of which higher doses can be subcutaneously injected without an increased risk for IgE-mediated side effects (Kahlert et al. 2008) was employed in a double-blind placebo-controlled trial to assess its effects on soy-induced BPRFA (Treudler et al. 2017). Food-induced clinical symptoms before and after treatment were monitored with challenge meals containing consistent levels of soy allergen (Treudler et al. 2016; Holzhauser et al. 2017). This first multicenter component-based trial demonstrated a tendency but no significance of clinical improvement of soy allergy in the treated group compared to the placebo group. In summary, the evidence for a limited curative effect of AIT with the primary sensitizing allergen on secondary food allergy has grown over the past years.

To evaluate OIT as treatment option for secondary food allergy, the clinical effects of daily intake of gradually increasing amounts of fresh apple for an average time interval of 20 weeks were assessed in birch pollen-allergic individuals with

apple allergy (Kopac et al. 2012). Desensitization was achieved in 17 out of 27 patients. Notably, this transient tolerance was neither accompanied by reduced skin reactivity to apple nor enhanced allergen-specific IgG4 levels and referred to treatment-induced exhaustion of local mast cells (Kopac et al. 2012).

Recently, a first sublingual study using rMal d 1 for treatment of secondary food allergy was performed (Kinaciyan et al. 2018). This single center, double-blind placebo-controlled trial included 60 birch pollen-allergic patients with apple allergy randomized into three groups for the daily sublingual application of placebo or 25 μg of either rMal d 1 or rBet v 1 for 16 weeks [ClinicalTrials.gov no NCT01449786 and EudraCT no 2011–001221-24]. 70% of the individuals who received SLIT with rMal d 1 displayed a significant longitudinal improvement of allergic reactions in standardized sublingual challenge tests with the recombinant apple allergen (Kinaciyan et al. 2016). This clinical improvement differed significantly from both the placebo and rBet v 1-treated group and was accompanied by a significant reduction of skin reactivity to rMal d 1. However, the maintenance of tolerance to apples was not evaluated for a longer time period. Therefore, no conclusion on the induction of tolerance can be drawn. On the other hand, participants who received the same regular dose of rBet v 1 experienced a similar extent of treatment-emergent OAS during the course of treatment as those treated with rMal d 1 (Kinaciyan et al. 2018). Thus, despite the exhaustion of sublingual mast cells by rBet v 1, no desensitization to the highly cross-reactive rMal d 1 was achieved. In summary, the results of the pilot studies of OIT with apple and SLIT with rMal d 1 indicate that secondary food allergy can be reduced by regular administration of the secondary food allergen.

Successful tolerance induction has been associated with a modulation of allergen-specific cellular and humoral responses (Bohle et al. 2007; Layhadi et al. 2019). Correspondingly, SLIT with rMal d 1 induced a downregulation of rMal d 1-specific Th2 responses (Kitzmuller et al. 2019) and significantly increased rMal d 1-specific IgG4/IgE ratios (Kinaciyan et al. 2018). Thus, in contrast to OIT with unknown doses of Mal d 1, daily sublingual administration of 25 μg of rMal d 1 resulted in the modulation of the allergen-specific immune response. One hallmark of AIT is the induction of allergen-specific blocking IgG antibodies, essentially IgG4, that compete with IgE for allergen binding and thereby prevent effector cell activation (Shamji et al. 2012). These antibodies are referred to as IgE-blocking antibodies. In basophil activation test, sera collected from individuals who received SLIT with rMal d 1 displayed the ability to inhibit Mal d 1-induced activation of basophils (Acosta et al. 2020). This result is indicative of the presence of IgE-blocking antibodies. The involvement of IgE-blocking antibodies in the reduction of allergic symptoms was recently shown as the administration of two monoclonal blocking Ab specific for distinct conformational epitopes of the major cat allergen Fel d 1 successfully reduced allergen-induced nasal symptoms in cat-allergic patients (Orengo et al. 2018). Similarly, the reduction of Mal d 1-induced OAS could be associated with the presence of IgE-blocking antibodies in post-SLIT sera (Acosta et al. 2020). These results provide evidence that sublingual administration of a recombinant

secondary food allergen induced IgE-blocking antibodies as demonstrated for SLIT with respiratory allergens.

In summary, equal sublingual doses of 2 homologous and highly cross-reactive allergens resulted in different clinical and immunologic responses. The parallel analysis of all parameters induced by either allergen allowed a direct comparison of the effects of SLIT with the primary allergen and the secondary food allergen. SLIT with a standardized dose of rBet v 1 had a limited benefit on the secondary food allergy. This limited improvement matched previous results of a yearlong SLIT with birch pollen extract demonstrating that apple allergy improved in 33%, worsened in 33%, and remained unaffected in 33% of the participants with improved birch pollinosis (Kinaciyan et al. 2007). In another trial, birch pollen SLIT improved apple allergy in only 1/11 individuals but induced food allergy in 3/11 individuals (Hansen et al. 2004). Regarding BPRFA as the best studied example of secondary food allergy, these findings finally confirm that the clinical success of therapy with the primary sensitizer is limited.

6 Concluding Remarks

IgE-mediated food allergies commonly lead to gastrointestinal, cutaneous, respiratory, and/or cardiovascular symptoms. They affect both children and adults and are often associated with significant decreases in QoL. The major tools to draw the proper diagnosis of IgE mediated food allergy are: (1) taking the patient's history, (2) show specific IgE-mediated sensitizations, and (3) proof their clinical relevance. Food allergens usually have to be avoided which may be difficult particularly in those patients who suffer from life-threatening symptoms upon ingesting minimal doses of food allergens. A couple of novel therapeutic approaches have been studied during the last years and are summarized in this review. Therapies with novel therapeutic monoclonal antibodies, innovative allergen-specific immunotherapies using subcutaneous, sublingual, or epicutaneous routes, and oral immunotherapies leading to increases of individual thresholds of tolerable foods upon their continuous ingestion showed promising results which may change future management strategies in moderate to severe food allergy.

References

Acosta GS, Kinaciyan T, Kitzmuller C, Mobs C, Pfutzner W, Bohle B (2020) IgE-blocking antibodies following SLIT with recombinant Mal d 1 accord with improved apple allergy. J Allergy Clin Immunol 146:894–900

Ahammer L, Grutsch S, Kamenik AS, Liedl KR, Tollinger M (2017) Structure of the major apple allergen Mal d 1. J Agric Food Chem 65:1606–1612

Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S et al (2014) Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 383:1297–1304

Andorf S, Purington N, Kumar D, Long A, O'Laughlin KL, Sicherer S et al (2019) A phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued vs discontinued dosing in multifood allergic individuals. EClinicalMedicine 7:27–38

Asero R (1998) Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. Clin Exp Allergy 28:1368–1373

Asero R (2003) How long does the effect of birch pollen injection SIT on apple allergy last? Allergy 58:435–438

Asero R (2004) Effects of birch pollen SIT on apple allergy: a matter of dosage? Allergy 59:1269–1271

Azad MB, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT et al (2015) Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy 45:632–643

Baumert JL, Taylor SL, Koppelman SJ (2018) Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. J Allergy Clin Immunol Pract 6:457–465 e4

Bird JA, Feldman M, Arneson A, Dougherty I, Brown LS, Burk CM et al (2015) Modified peanut oral immunotherapy protocol safely and effectively induces desensitization. J Allergy Clin Immunol Pract 3:433–435 e1-3

Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G et al (2019) Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract 7:479–491 e10

Bohle B, Hirt W, Nachbargauer P, Ebner H, Ebner C (2003a) Allergy to millet: another risk for atopic bird keepers. Allergy 58:325–328

Bohle B, Radakovics A, Jahn-Schmid B, Hoffmann-Sommergruber K, Fischer GF, Ebner C (2003b) Bet v 1, the major birch pollen allergen, initiates sensitization to Api g 1, the major allergen in celery: evidence at the T cell level. Eur J Immunol 33:3303–3310

Bohle B, Radakovics A, Luttkopf D, Jahn-Schmid B, Vieths S, Ebner C (2005) Characterization of the T cell response to the major hazelnut allergen, Cor a 1.04: evidence for a relevant T cell epitope not cross-reactive with homologous pollen allergens. Clin Exp Allergy 35:1392–1399

Bohle B, Zwolfer B, Heratizadeh A, Jahn-Schmid B, Antonia YD, Alter M et al (2006) Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity in vitro and in vivo. J Allergy Clin Immunol 118:242–249

Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C (2007) Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol 120:707–713

Bolhaar ST, Tiemessen MM, Zuidmeer L, van Leeuwen A, Hoffmann-Sommergruber K, Bruijnzeel-Koomen CA et al (2004) Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. Clin Exp Allergy 34:761–769

Breiteneder H, Pettenburger K, Bito A, Valenta R, Kraft D, Rumpold H et al (1989) The gene coding for the major birch pollen allergen Betv1, is highly homologous to a pea disease resistance response gene. EMBO J 8:1935–1938

Brough HA, Kull I, Richards K, Hallner E, Soderhall C, Douiri A et al (2018) Environmental peanut exposure increases the risk of peanut sensitization in high-risk children. Clin Exp Allergy 48:586–593

Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Moneret-Vautrin D et al (1995) Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. Allergy 50:623–635

Bucher X, Pichler WJ, Dahinden CA, Helbling A (2004) Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 59:1272–1276

Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P et al (2016) Early-life gut microbiome composition and milk allergy resolution. J Allergy Clin Immunol 138:1122–1130

Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM et al (2015) Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 135:1240–1248 e1-3

Cabezas-Cruz A, Hodzic A, Roman-Carrasco P, Mateos-Hernandez L, Duscher GG, Sinha DK et al (2019) Environmental and molecular drivers of the alpha-gal syndrome. Front Immunol 10:1210

Capucilli P, Wang KY, Spergel JM (2020) Food reactions during avoidance: focus on peanut. Ann Allergy Asthma Immunol 124:459–465

Chiang D, Berin MC (2015) An examination of clinical and immunologic outcomes in food allergen immunotherapy by route of administration. Curr Allergy Asthma Rep 15:35

Chinthrajah S, Cao S, Liu C, Lyu SC, Sindher SB, Long A et al (2019a) Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 4:22

Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC et al (2019b) Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet 394:1437–1449

Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S et al (2019) Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet 393:2222–2232

Commins SP (2015) Mechanisms of oral tolerance. Pediatr Clin N Am 62:1523–1529

Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD et al (2009) Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 123:426–433

De Swert LF, Gadisseur R, Sjolander S, Raes M, Leus J, Van Hoeyveld E (2012) Secondary soy allergy in children with birch pollen allergy may cause both chronic and acute symptoms. Pediatr Allergy Immunol 23:117–123

Dreborg S, Foucard T (1983) Allergy to apple, carrot and potato in children with birch pollen allergy. Allergy 38:167–172

Enrique E, Malek T, Pineda F, Palacios R, Bartra J, Tella R et al (2008) Sublingual immunotherapy for hazelnut food allergy: a follow-up study. Ann Allergy Asthma Immunol 100:283–284

Eriksson NE, Formgren H, Svenonius E (1982) Food hypersensitivity in patients with pollen allergy. Allergy 37:437–443

Esterhazy D, Canesso MCC, Mesin L, Muller PA, de Castro TBR, Lockhart A et al (2019) Compartmentalized gut lymph node drainage dictates adaptive immune responses. Nature 569:126–130

Fernandes H, Michalska K, Sikorski M, Jaskolski M (2013) Structural and functional aspects of PR-10 proteins. FEBS J 280:1169–1199

Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E et al (2009) Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy 64:876–883

Fleischer DM, Greenhawt M, Sussman G, Begin P, Nowak-Wegrzyn A, Petroni D et al (2019) Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. JAMA 321:946–955

Fritsch R, Bohle B, Vollmann U, Wiedermann U, Jahn-Schmid B, Krebitz M et al (1998) Bet v 1, the major birch pollen allergen, and Mal d 1, the major apple allergen, cross-react at the level of allergen-specific T helper cells. J Allergy Clin Immunol 102:679–686

Gajhede M, Osmark P, Poulsen FM, Ipsen H, Larsen JN, Joost van Neerven RJ et al (1996) X-ray and NMR structure of Bet v 1, the origin of birch pollen allergy. Nat Struct Biol 3:1040–1045

Galli SJ (2016) The mast cell-IgE paradox: from homeostasis to anaphylaxis. Am J Pathol 186:212–224

Grimshaw KEC, Roberts G, Selby A, Reich A, Butiene I, Clausen M et al (2020) Risk factors for hen's egg allergy in europe: europrevall birth cohort. J Allergy Clin Immunol Pract 8:1341–1348 e5

Grzeskowiak LE, Tao B, Knight E, Cohen-Woods S, Chataway T (2020) Adverse events associated with peanut oral immunotherapy in children – a systematic review and meta-analysis. Sci Rep 10:659

Gunawardana NC, Durham SR (2018) New approaches to allergen immunotherapy. Ann Allergy Asthma Immunol 121:293–305

Hannuksela M, Lahti A (1977) Immediate reactions to fruits and vegetables. Contact Dermatitis 3:79–84

Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ (2004) Food allergy to apple and specific immunotherapy with birch pollen. Mol Nutr Food Res 48:441–448

Herrmann D, Henzgen M, Frank E, Rudeschko O, Jager L (1995) Effect of hyposensitization for tree pollinosis on associated apple allergy. J Investig Allergol Clin Immunol 5:259–267

Hodzic A, Mateos-Hernandez L, Leschnik M, Alberdi P, Rego ROM, Contreras M et al (2019) Tick bites induce anti-alpha-gal antibodies in dogs. Vaccines 7:114

Holm J, Baerentzen G, Gajhede M, Ipsen H, Larsen JN, Lowenstein H et al (2001) Molecular basis of allergic cross-reactivity between group 1 major allergens from birch and apple. J Chromatogr B Biomed Sci Appl 756:307–313

Holzhauser T, Franke A, Treudler R, Schmiedeknecht A, Randow S, Becker WM et al (2017) The BASALIT multicenter trial: Gly m 4 quantification for consistency control of challenge meal batches and toward Gly m 4 threshold data. Mol Nutr Food Res 61:1600527

Husby S, Mestecky J, Moldoveanu Z, Holland S, Elson CO (1994) Oral tolerance in humans. T cell but not B cell tolerance after antigen feeding. J Immunol 152:4663–4670

Investigators PGoC, Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G et al (2018) AR101 oral immunotherapy for peanut allergy. N Engl J Med 379:1991–2001

Jahn-Schmid B, Radakovics A, Luttkopf D, Scheurer S, Vieths S, Ebner C et al (2005) Bet v 1142-156 is the dominant T-cell epitope of the major birch pollen allergen and important for cross-reactivity with Bet v 1-related food allergens. J Allergy Clin Immunol 116:213–219

Jarvinen KM, Amalanayagam S, Shreffler WG, Noone S, Sicherer SH, Sampson HA et al (2009) Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. J Allergy Clin Immunol 124:1267–1272

Jeebhay MF, Moscato G, Bang BE, Folletti I, Lipinska-Ojrzanowska A, Lopata AL et al (2019) Food processing and occupational respiratory allergy-a EAACI Position Paper. Allergy 74:1852–1871

Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M et al (2009) Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 124:292–300, e1-97

Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA et al (2016) Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol 137:1117–1127 e10

Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P et al (2017) Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 139:1242–1252 e9

Juhlin-Dannfelt C (1948) About the occurrence of various forms of pollen allergy in Sweden. Acta Med Scand 131:563–577

Kahlert H, Suck R, Weber B, Nandy A, Wald M, Keller W et al (2008) Characterization of a hypoallergenic recombinant Bet v 1 variant as a candidate for allergen-specific immunotherapy. Int Arch Allergy Immunol 145:193–206

Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S et al (2012) The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 129:448–55 e1-5

Kelso JM, Jones RT, Tellez R, Yunginger JW (1995) Oral allergy syndrome successfully treated with pollen immunotherapy. Ann Allergy Asthma Immunol 74:391–396

Kim EH, Yang L, Ye P, Guo R, Li Q, Kulis MD et al (2019) Long-term sublingual immunotherapy for peanut allergy in children: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 144:1320–1326 e1

Kim EH, Patel C, Burks AW (2020) Immunotherapy approaches for peanut allergy. Expert Rev Clin Immunol 16:167–174

Kinaciyan T, Jahn-Schmid B, Radakovics A, Zwolfer B, Schreiber C, Francis JN et al (2007) Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. J Allergy Clin Immunol 119:937–943

Kinaciyan T, Nagl B, Faustmann S, Kopp S, Wolkersdorfer M, Bohle B (2016) Recombinant Mal d 1 facilitates sublingual challenge tests of birch pollen-allergic patients with apple allergy. Allergy 71:272–274

Kinaciyan T, Nagl B, Faustmann S, Frommlet F, Kopp S, Wolkersdorfer M et al (2018) Efficacy and safety of 4 months of sublingual immunotherapy with recombinant Mal d 1 and Bet v 1 in patients with birch pollen-related apple allergy. J Allergy Clin Immunol 141:1002–1008

Kitzmuller C, Zulehner N, Roulias A, Briza P, Ferreira F, Fae I et al (2015) Correlation of sensitizing capacity and T-cell recognition within the Bet v 1 family. J Allergy Clin Immunol 136:151–158

Kitzmuller C, Jahn-Schmid B, Kinaciyan T, Bohle B (2019) Sublingual immunotherapy with recombinant Mal d 1 downregulates the allergen-specific Th2 response. Allergy 74:1579–1581

Kleine-Tebbe J, Vogel L, Crowell DN, Haustein UF, Vieths S (2002) Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1- related PR-10 protein in soybean, SAM22. J Allergy Clin Immunol 110:797–804

Klinglmayr E, Hauser M, Zimmermann F, Dissertori O, Lackner P, Wopfner N et al (2009) Identification of B-cell epitopes of Bet v 1 involved in cross-reactivity with food allergens. Allergy 64:647–651

Kopac P, Rudin M, Gentinetta T, Gerber R, Pichler C, Hausmann O et al (2012) Continuous apple consumption induces oral tolerance in birch-pollen-associated apple allergy. Allergy 67:280–285

Kosma P, Sjolander S, Landgren E, Borres MP, Hedlin G (2011) Severe reactions after the intake of soy drink in birch pollen-allergic children sensitized to Gly m 4. Acta Paediatr 100:305–306

Layhadi JA, Eguiluz-Gracia I, Shamji MH (2019) Role of IL-35 in sublingual allergen immunotherapy. Curr Opin Allergy Clin Immunol 19:12–17

Levin M, Apostolovic D, Biedermann T, Commins SP, Iweala OI, Platts-Mills TAE et al (2019) Galactose alpha-1,3-galactose phenotypes: lessons from various patient populations. Ann Allergy Asthma Immunol 122:598–602

Li XM, Srivastava K, Grishin A, Huang CK, Schofield B, Burks W et al (2003) Persistent protective effect of heat-killed *Escherichia coli* producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. J Allergy Clin Immunol 112:159–167

Li X-M, Song Y, Su Y, Heiland T, Sampson H (2015) Immunization with ARA h1,2,3-LAMP-Vax peanut vaccine blocked IgE mediated-anaphylaxis in a peanut allergic murine model. J Allergy Clin Immunol 135(2):AB167

Loh W, Tang M (2018) Adjuvant therapies in food immunotherapy. Immunol Allergy Clin N Am 38:89–101

Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L et al (2008) Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 121:343–347

Lozano-Ojalvo D, Berin C, Tordesillas L (2019) Immune basis of allergic reactions to food. J Investig Allergol Clin Immunol 29:1–14

Ma Y, Gadermaier G, Bohle B, Bolhaar S, Knulst A, Markovic-Housley Z et al (2006) Mutational analysis of amino acid positions crucial for IgE-binding epitopes of the major apple (Malus domestica) allergen, Mal d 1. Int Arch Allergy Immunol 139:53–62

Matthes A, Schmitz-Eiberger M (2009) Apple (Malus domestica L. Borkh.) allergen Mal d 1: effect of cultivar, cultivation system, and storage conditions. J Agric Food Chem 57:10548–10553

Mauro M, Russello M, Incorvaia C, Gazzola G, Frati F, Moingeon P et al (2011) Birch-apple syndrome treated with birch pollen immunotherapy. Int Arch Allergy Immunol 156:416–422

Miller J, Blackman AC, Wang HT, Anvari S, Joseph M, Davis CM et al (2020) Quality of life in food allergic children: results from 174 quality-of-life patient questionnaires. Ann Allergy Asthma Immunol 124:379–384

Modrzynski M, Zawisza E, Rapiejko P, Przybylski G (2002) Specific-pollen immunotherapy in the treatment of oral allergy syndrome in patients with tree pollen hypersensitivity. Przegl Lek 59:1007–1010

Mogensen JE, Wimmer R, Larsen JN, Spangfort MD, Otzen DE (2002) The major birch allergen, Bet v 1, shows affinity for a broad spectrum of physiological ligands. J Biol Chem 277:23684–23692

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al (2014) EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 69:1008–1025

Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG et al (2015) A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol 135:1275–1282 e1-6

Nelson HS, Lahr J, Rule R, Bock A, Leung D (1997) Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 99:744–751

Noval Rivas M, Burton OT, Wise P, Zhang YQ, Hobson SA, Garcia Lloret M et al (2013) A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol 131:201–212

Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL et al (2018) Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. Nat Commun 9:1421

Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M et al (2018) EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy 73:799–815

Palladino C, Breiteneder H (2018) Peanut allergens. Mol Immunol 100:58–70

Papageorgiou N, Lee TH, Nagakura T, Cromwell O, Wraith DG, Kay AB (1983) Neutrophil chemotactic activity in milk-induced asthma. J Allergy Clin Immunol 72:75–82

Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM (2020) Diagnosis and management of patients with the alpha-gal syndrome. J Allergy Clin Immunol Pract 8:15–23 e1

Radauer C, Lackner P, Breiteneder H (2008) The Bet v 1 fold: an ancient, versatile scaffold for binding of large, hydrophobic ligands. BMC Evol Biol 8:286

Reekers R, Busche M, Wittmann M, Kapp A, Werfel T (1999) Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. J Allergy Clin Immunol 104:466–472

Remington BC, Krone T, Koppelman SJ (2018) Quantitative risk reduction through peanut immunotherapy: safety benefits of an increased threshold in Europe. Pediatr Allergy Immunol 29:762–772

Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA (2018) Mechanisms of food allergy. J Allergy Clin Immunol 141:11–19

Sancho AI, Foxall R, Browne T, Dey R, Zuidmeer L, Marzban G et al (2006) Effect of postharvest storage on the expression of the apple allergen mal d 1. J Agric Food Chem 54:5917–5923

Schimek EM, Zwolfer B, Briza P, Jahn-Schmid B, Vogel L, Vieths S et al (2005) Gastrointestinal digestion of Bet v 1-homologous food allergens destroys their mediator-releasing, but not T cell-activating, capacity. J Allergy Clin Immunol 116:1327–1333

Schulten V, Lauer I, Scheurer S, Thalhammer T, Bohle B (2011) A food matrix reduces digestion and absorption of food allergens in vivo. Mol Nutr Food Res 55:1484–1491

Scurlock AM, Jones SM (2018) Advances in the approach to the patient with food allergy. J Allergy Clin Immunol 141:2002–2014

Shaker M, Greenhawt M (2019) Peanut allergy: burden of illness. Allergy Asthma Proc 40:290–294

Shamji MH, Ljorring C, Francis JN, Calderon MA, Larche M, Kimber I et al (2012) Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. Allergy 67:217–226

Skamstrup Hansen K, Vestergaard H, Stahl Skov P, Sondergaard Khinchi M, Vieths S, Poulsen LK et al (2001) Double-blind, placebo-controlled food challenge with apple. Allergy 56:109–117

Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG et al (2008) A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 122:1154–1160

Spangfort MD, Mirza O, Ipsen H, Van Neerven RJ, Gajhede M, Larsen JN (2003) Dominating IgE-binding epitope of Bet v 1, the major allergen of birch pollen, characterized by X-ray crystallography and site-directed mutagenesis. J Immunol 171:3084–3090

Stephen-Victor E, Chatila TA (2019) Regulation of oral immune tolerance by the microbiome in food allergy. Curr Opin Immunol 60:141–147

Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL et al (2015) Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 135:737–744 e8

Treudler R, Werner M, Thiery J, Kramer S, Gebhardt C, Averbeck M et al (2008) High risk of immediate-type reactions to soy drinks in 50 patients with birch pollinosis. J Investig Allergol Clin Immunol 18:483–484

Treudler R, Franke A, Schmiedeknecht A, Ballmer-Weber BK, Worm M, Werfel T et al (2016) Standardization of double blind placebo controlled food challenge with soy within a multicentre trial. Clin Transl Allergy 6:39

Treudler R, Franke A, Schmiedeknecht A, Ballmer-Weber B, Worm M, Werfel T et al (2017) BASALIT trial: double-blind placebo-controlled allergen immunotherapy with rBet v 1-FV in birch-related soya allergy. Allergy 72:1243–1253

van der Kleij HPM, Warmenhoven HJM, van Ree R, Versteeg SA, Pieters RHH, Dreskin SC et al (2019) Chemically modified peanut extract shows increased safety while maintaining immunogenicity. Allergy 74:986–995

van Hoffen E, Peeters KA, van Neerven RJ, van der Tas CW, Zuidmeer L, van Ieperen-van Dijk AG et al (2011) Effect of birch pollen-specific immunotherapy on birch pollen-related hazelnut allergy. J Allergy Clin Immunol 127:100–101 e1-3

Vanek-Krebitz M, Hoffmann-Sommergruber K, Laimer da Camara Machado M, Susani M, Ebner C, Kraft D et al (1995) Cloning and sequencing of Mal d 1, the major allergen from apple (*Malus domestica*), and its immunological relationship to Bet v 1, the major birch pollen allergen. Biochem Biophys Res Commun 214:538–551

Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P et al (2011) A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 127:654–660

Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI et al (2017) Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol 139:173–181 e8

Vieths S, Schoning B (1996) Characterization of Mal d 1, the 18-kD major apple allergen, at the molecular level. Monogr Allergy 32:63–72

Waldron J, Kim EH (2020) Sublingual and patch immunotherapy for food allergy. Immunol Allergy Clin N Am 40:135–148

Wang S, Xia P, Chen Y, Qu Y, Xiong Z, Ye B et al (2017) Regulatory innate lymphoid cells control innate intestinal inflammation. Cell 171:201–216 e18

Wassmann-Otto A, Heratizadeh A, Wichmann K, Werfel T (2018) Birch pollen-related foods can cause late eczematous reactions in patients with atopic dermatitis. Allergy 73:2046–2054

Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC et al (2015) Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. Allergy 70:1079–1090

Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R et al (2013) A phase 1 study of heat/phenol-killed, E. coli-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy 68:803–808

Zhang W, Sindher SB, Sampath V, Nadeau K (2018) Comparison of sublingual immunotherapy and oral immunotherapy in peanut allergy. Allergo J Int 27:153–161

Zulehner N, Nagl B, Briza P, Roulias A, Ballmer-Weber B, Zlabinger GJ et al (2017) Characterization of the T-cell response to Dau c 1, the Bet v 1-homolog in carrot. Allergy 72:244–251

Drug Allergy and Cutaneous Adverse Reactions

Maja Mockenhaupt

Contents

Abstract

Allergy or hypersensitivity to drugs often affects the skin and sometimes also mucosa. While immediate type reactions show a rather homogeneous pattern, delayed type reactions reveal a high variability. In both cases it may not always be easy to differentiate drug reactions from non-drug-induced skin conditions. Furthermore, the different types of cutaneous adverse reactions may be difficult to distinguish in the beginning. This accounts predominately for delayed hypersensitivity reactions that can occur after a variety of medications and present with

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manifold lesions. Most of these cutaneous adverse reactions are mild, but some are severe with high morbidity and mortality. In the clinical setting, it is important to recognize the signs that point to a more severe condition early on in order to initiate appropriate management. In addition, it is crucial to identify the potentially culprit medication on the basis of a detailed medication history and by evaluating the relevant exposure times of certain drugs that differ substantially between the various reaction types. After the acute stage of the adverse reaction is managed successfully, further allergologic testing may be undertaken to confirm the offending drug.

Keywords

Cutaneous adverse drug reactions · Delayed hypersensitivity · Drug allergy · Immediate hypersensitivity · Severe cutaneous adverse reactions

Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BSA	Body surface area
DRESS	Drug reaction with eosinophilia and systemic symptoms
FDE	Fixed drug eruption
GBFDE	Generalized bullous fixed drug eruption
ICU	Intensive care unit
MPE	Maculopapular exanthema
SCAR	Severe cutaneous adverse reactions
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis

1 Introduction

A variety of skin reactions toward drug ingestion or application are known, which differ in clinical pattern and pathogenesis. Some reactions follow the classical allergic pathway as described by Coombs and Gell, others reveal a different, sometimes unknown mechanism. Urticaria and angioedema may be manifestations of drug hypersensitivity, either IgE-mediated (immediate or type I hypersensitivity) or non-IgE-mediated through direct mast cell activation. Whereas this clinical pattern of immediate hypersensitivity reactions is rather homogeneous, that of delayed cutaneous hypersensitivity reactions (type IV hypersensitivity) is very heterogeneous in terms of lesions, severity, and time course. Some of these delayed drug reactions can be explained through sensitization, for others the mechanism remains unclear (Brockow et al. 2019).

Cutaneous reactions to drugs are common, affecting 2–3% of hospitalized patients, and are a significant cause of outpatient morbidity. It is estimated that 1 in 1,000 hospitalized patients has a serious cutaneous drug reaction (Bigby 2001).

The following chapter will present the various types of drug reactions with focus on delayed and severe hypersensitivity. However, immediate type reactions will be briefly discussed as well.

2 Clinical Reaction Types

2.1 Urticaria and Angioedema

Urticaria is characterized by an eruption of hives (wheals), which are erythematous, circumscribed, raised, pruritic lesions, often with central pallor. Individual lesions may enlarge, coalesce with others, and typically disappear within a few hours. Angioedema is caused by swelling of the deeper dermis and subcutaneous tissue that may be accompanied by urticaria in up to 50% of cases. Angioedema may be disfiguring if it involves the face and lips, or life-threatening if laryngeal edema or tongue swelling leads to airway obstruction.

Antibiotics, esp. penicillins and cephalosporins, are common causes of IgE-mediated drug allergy. However, the infection requiring antibiotic treatment may also induce urticaria.

Other drugs may induce urticaria/angioedema due to direct mast cell activation by a non-IgE mediated mechanism. Most frequently implicated are opiate analgesics like morphine or codeine. The concomitant use of opiates and vancomycin may increase the risk of the so-called red man syndrome, which can be observed after rapid infusion of vancomycin. It is induced by direct mast cell activation and may also present with urticaria (Kanani et al. 2018).

Nonsteroidal anti-inflammatory drugs (NSAIDs) can trigger urticaria/angioedema through direct mast cell activation but also through other mechanisms such as abnormalities of the complement cascade (inherited and acquired abnormalities of complement metabolism) and increased activity of vasodilatory kinin pathways. Angioedema (in the absence of urticaria) has been reported to occur in 2 to 10 of 10,000 new users of angiotensin-converting enzyme (ACE) inhibitors and typically affects mouth and tongue (Stone and Brown 2017). The assumed mechanism is an impaired bradykinin degradation by ACE leading to elevated blood levels of the vasoactive peptide bradykinin.

Despite the name “immediate reaction type” eruptions like urticaria and/or angioedema can also occur accelerated, i.e. hours after exposure, or delayed, i.e. days after exposure.

Anaphylaxis is the most severe and potentially life-threatening form of immediate type I hypersensitivity and includes pruritus, urticaria, angioedema, laryngeal edema, wheezing, nausea, vomiting, tachycardia, and sometimes even shock. Drugs are not the most common cause of anaphylaxis but have been reported as the third frequent trigger (Simons et al. 2013).

2.2 Exanthems

The most frequent cutaneous reactions to drugs are exanthems of various kinds. They represent more than 75% of all drug eruptions. They are described as morbilliform or macular and/or papular eruptions (Bigby 2001; Ardern-Jones and Friedmann 2011). Many frequently prescribed and commonly used medications have been reported as the cause of such cases. Furthermore, it is well known that certain antibiotics, e.g. aminopenicillins, have a higher risk to induce an exanthematous eruption in the presence of a viral infection. In addition, many viral infections show an exanthem and parainfectious eruptions are also frequent. Therefore, the differential diagnosis may be difficult.

2.3 Multiforme-Like Drug Reaction

This eruption is frequently misdiagnosed as erythema (exsudativum) multiforme (E(E)M) or Stevens-Johnson syndrome (SJS). It presents with targetoid lesions that may be confluent (Fig. 1c). The histopathology reveals rather dermal than epidermal

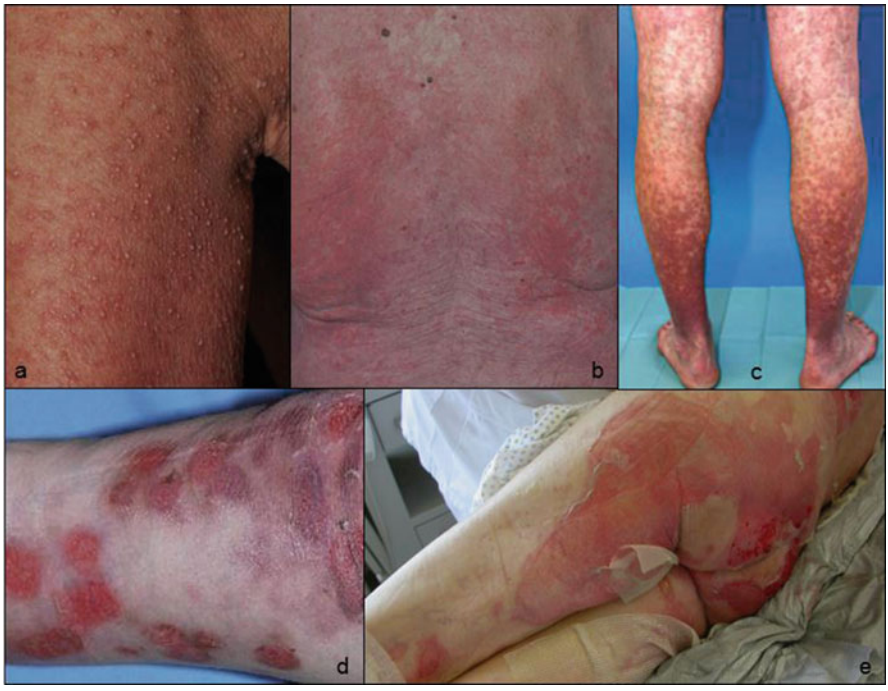

Fig. 1 Various types of cutaneous adverse reactions. (**a**) Acute generalized exanthematous pustulosis (AGEP). (**b**) Drug reaction with eosinophilia and systemic symptoms (DRESS). (**c**) Multiforme-like drug eruption. (**d**) Fixed drug eruption (FDE) with local blisters. (**e**) Generalized bullous fixed drug eruption (GBFDE)

changes, which have been called "the dermal type of EM." Mucosal involvement, if present, is mild and skin blisters may occur due to edema but not due to apoptosis like in EM or SJS/TEN (Roujeau and Mockenhaupt 2019).

Whereas EM minus or majus (with hemorrhagic erosions of mucous membranes) is most frequently (if not always) induced by infection (typically herpes simplex virus or mycoplasma pneumoniae), multiforme-like drug eruption is induced by medication, e.g. NSAIDs and diuretics and has also been observed in the context of targeted therapies (Ziemer et al. 2007).

2.4 Lichenoid Eruption

The violaceous or hyperpigmented, flat-topped, pruritic papules that typically affect the ankles and the volar surface of the wrists in lichen planus may also be seen in lichenoid drug eruptions. This type of reaction usually develops months or even years after beginning of drug use. It may spread over the entire body, but typically spares the mucosa. Beta-blockers, ACE inhibitors, methyldopa, penicillamine, quinidine, antimalarials, and thiazide diuretics have been reported as the most frequent causes (Inoue et al. 2017). Recently, TNF-alpha inhibitors, tyrosine kinase inhibitors, and further targeted therapies have also been observed to induce lichenoid reactions, some with bullous lesions that may imitate Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (Reschke et al. 2019). The mechanism of this reaction pattern remains unknown.

2.5 SDRIFE

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), previously also called baboon syndrome, is an infrequent type of drug-induced eruption (Häusermann and Bircher 2007). It typically occurs a few hours to a few days after the initiation of the offending drug. The eruption presents as a well-demarcated V-shaped erythema in the gluteal-perianal or inguinal-perigenital area, often with involvement of intertriginous folds. Systemic symptoms are not present. In some cases, SDRIFE may resemble a specific pattern of fixed drug eruption, whereas in other cases pustules may occur in the intertriginous areas, which may spread like in AGEP (Brockow et al. 2019; Häusermann and Bircher 2007). Amoxicillin, ceftriaxone, penicillin, clindamycin, and erythromycin have been reported as inducing agents in up to 50% of cases. Iodinate contrast media, pseudoephedrine, acetyl salicylic acid, mitomycin C, phenothiazines, valacyclovir, and many other drugs have also been implicated (Thyssen and Maibach 2008).

2.6 Fixed Drug Eruption

Fixed drug eruption is a distinctive reaction characterized by erythematous and/or edematous plaques with a grayish-violaceous center or bulla in the acute stage and by a dark pigmentation in the chronic phase (Fig. 1d). Affected sites include mouth (lips and tongue), genitalia, face, and acral areas (Brockow et al. 2019). The defining features of this eruption include postinflammatory hyperpigmentation and recurrence of lesions at exactly the same sites with re-exposure of the drug (Brahimi et al. 2010).

Patients with generalized bullous fixed drug eruption (GBFDE) can be misdiagnosed as having SJS/TEN, but in GBFDE mucosal involvement is usually absent or mild and the clinical course is favorable with resolution within 2 weeks after drug discontinuation (Fig. 1e) (Cho et al. 2014). The reaction occurs typically after 1−2 days of taking the inducing medication. Drugs frequently involved include NSAIDs, antibacterial agents, such as sulfamethoxazole, tetracyclines, dapsone, barbiturates, paracetamol (acetaminophen), and metamizole (Mahboob and Haroon 1998).

2.7 Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is a rare disorder characterized by the sudden occurrence of erythema and superficial pustules accompanied by fever. The cutaneous eruption typically starts in the face or intertriginous areas and spreads within a few hours. Small, non-follicular pustules arise on edematous erythema with burning and/or itching and the histopathology reveals spongiosis and subcorneal agglomeration of granulocytes (Fig. 1a). A scoring system was developed that helps to confirm the diagnosis of AGEP or rule it out (Table 1) (Sidoroff et al. 2001).

The time between beginning of drug use and reaction onset is remarkably short with 1−2 days for most of the inducing drugs. However, for other medications the onset of symptoms may be delayed for 1–2 weeks (Momin et al. 2009). Antibiotics, particularly penicillins and macrolides, are thought to play a role in 80% of cases (Sidoroff et al. 2007).

2.8 Drug Reaction with Eosinophilia and Systemic Symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) – in Japan also referred to as drug-induced hypersensitivity syndrome (DIHS) – is a severe reaction characterized by fever (38 to 40°C), malaise, lymphadenopathy, skin eruption, and organ involvement. The latter includes affection of liver, kidney, lung, heart, as well as the presence of hypereosinophilia and/or atypical lymphocytes. A diagnostic scoring system was designed to enable confirmation or exclusion of DRESS. However, it is important to apply it correctly and e.g. only count points for liver

Table 1 Diagnostic score for AGEP (Sidoroff et al. 2001)

Morphology	
Pustules	
Typical	+2
Compatible (with disease)	+1
Insufficient	0
Erythema	
Typical	+2
Compatible (with disease)	+1
Insufficient	0
Distribution pattern	
Typical	+2
Compatible (with disease)	+1
Insufficient	0
Post-pustular desquamation	
Yes	+1
No/insufficient	0
Course	
Mucous membrane involvement	
Yes	–2
No	0
Acute onset ($\leq$10 days)	
Yes	0
No	–2
Resolution ($\leq$15 days)	
Yes	0
No	–4
Fever $\geq$38°C	
Yes	+1
No	0
PNN $\geq$ 7,000/mm^3	
Yes	+1
No	0
Histology	
Other disease	−10
Not representative/no histology	0
Exocytosis of PNN	+1
Subcorneal and/or intraepidermal non-spongiform pustules or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform pustules or NOS pustules without papillary edema	+2
Spongiform subcorneal and/or intra-epidermal pustules with papillary edema	+3

NOS not otherwise specified, *PNN* polynuclear neutrophils
Final score for AGEP: $\leq$0 points: excluded (not AGEP); 1–4 points: possible; 5–7 points: probable; 8–12 points: definite case of AGEP

Table 2 Diagnostic score for DRESS (Kardaun et al. 2007)

Score	−1	0	+1	+2	Min	Max
Fever ≥ 38.5°C	No	Yes			−1	0
Lymphadenopathy		No/U	Yes		0	+1
Eosinophilia Eosinophils % eosinophils if WBC < 4,000			700–1,499/μl 10–19.9%	≥1,500/μl ≥20%	0	+2
Atypical lymphocytes		No/U	Yes		0	+1
Skin involvement Skin rash (% body surface) Rash suggests DRESS Histology suggests DRESS	No No	No/<50% U U	≥50% Yes		−2	+2
Organ involvement[a] Liver Kidneys Lungs Muscle/heart Pancreas Others		No/U	Single organ Yes Yes Yes Yes Yes Yes	2 or more	0	+2
Resolution ≥ 15 days	No	Yes			−1	0
Laboratory					0	+1
Hepatitis A,B, C						
EBV, CMV						
Mycoplasma, chlamydia						
ANA						
Blood culture						
If none positive and ≥ 3 negative			Yes			
Total score					−4	+9

U unknown/unclassifiable, *Min* minimum, *Max* maximum (score points), *WBC* white blood cells, *EBV* Epstein-Barr virus, *CMV* Cytomegalovirus, *ANA* antinuclear antibodies
Final score for DRESS: <2 points: excluded (not DRESS); 2–3 points: possible; 4–5 points: probable; >5 points: definite case of DRESS
[a]After exclusion of other explanations; 1 organ = 1, 2 or more organs = 2

involvement, if the liver enzymes are twofold elevated on at least 2 different dates (Table 2) (Kardaun et al. 2007). The skin eruption is extensive and covers at least 50% of the body surface area (BSA), sometimes even ≥90% (Fig. 1b). In such a state of erythroderma or exfoliative dermatitis, the skin eruption may lead to further complications, such as chills, fluid and protein loss (Ushigome et al. 2013).

In most cases, the reaction begins 2–6 weeks after the initiation of the inducing drugs. Aromatic antiepileptic agents (carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin), allopurinol, antibacterial sulfonamides including sulfasalazine, and vancomycin are the most frequent causes of DRESS (Kardaun et al. 2013).

2.9 Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), nowadays summarized as or called epidermal necrolysis (EN) due to common pathogenesis and causes, is a severe, often life-threatening condition with extensive morbidity and mortality. EN is characterized by epidermal necrosis and sloughing of skin and mucous membranes (Fig. 2 a–e). The amount of skin detachment related to the BSA distinguishes SJS from TEN: detachment is limited to less than 10% in SJS (Fig. 2a) and exceeds 30% in TEN (Fig. 2b) whereas detachment between 10 and 30% defines SJS/TEN-overlap (Table 3) (Bastuji-Garin et al. 1993; Mockenhaupt and Roujeau 2019).

EN is frequently caused by medications. However, approximately 25% of all cases and 50% of pediatric cases are not drug-induced. Most of these may be triggered by infection, predominantly viral respiratory infection and flu-like illness (Mockenhaupt and Roujeau 2019).

The time latency between beginning of drug use and reaction onset varies between 4 days and 4 weeks for different culprit agents. Allopurinol, certain

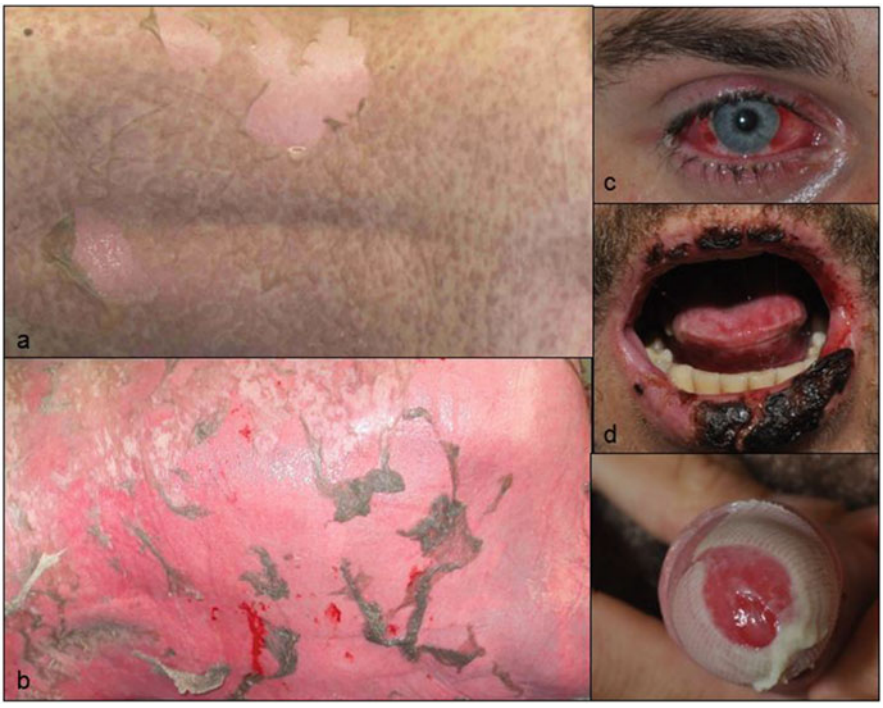

Fig. 2 Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). (**a**) Confluent macules with blister formation in SJS. (**b**) Extensive skin detachment in TEN. (**c**) Eye involvement with conjunctivitis and blepharitis. (**d**) Hemorrhagic erosions of lips and oral mucosa. (**e**) Erosions of genital mucosa in a young man

Table 3 Consensus definition of SJS/TEN (Bastuji-Garin et al. 1993)

Criteria	EM majus	SJS	SJS/TEN overlap	TEN with maculae	TEN on large erythema (without spots)[a]
Skin detachment (%)	<10%	<10%	10–30%	>30%	>10%
Typical target lesions	+	–	–	–	–
Atypical target lesions	Raised	Flat	Flat	Flat	–
Maculae	–	+	+	+	–
Distribution	Mainly limbs	Widespread	Widespread	Widespread	Widespread

EM erythema multiforme, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis
[a]Recently these cases are thought to be forms of generalized bullous fixed drug eruption (GBFDE)

antiepileptic drugs (carbamazepine, lamotrigine, phenobarbital, phenytoin), antibacterial sulfonamides, nevirapine, and oxicam NSAIDs have been shown to carry the highest risk for EN (Mockenhaupt et al. 2008).

AGEP, DRESS, SJS/TEN, and severe cases of GBFDE are referred to as severe cutaneous adverse reactions (SCAR). They are rare, but potentially life-threatening. All age groups may be affected, but elderly patients more frequently.

3 Management of Cutaneous Adverse Reactions

3.1 General Considerations

Most drug reactions are of milder nature, but some are severe and prone to subsequent complications. In the beginning, it can be difficult to differentiate a benign rash from a severe condition. Therefore, the patient should be followed closely and clinical and laboratory investigations may have to be performed repeatedly. Whenever a severe reaction is suspected, basic investigations are recommended, such as assessment of internal organ involvement and comorbidity status through full blood count (FBC), urea and electrolytes (U&E) including magnesium/phosphate/bicarbonate, liver function tests (LFT), coagulation studies, glucose, chest X-ray, HIV, ESR, CRP (Ardern-Jones and Mockenhaupt 2019).

To confirm the diagnosis and exclude differential diagnoses, samples for mycoplasma serology, swabs from lesional skin for virology and bacteriology should be performed when appropriate. Furthermore, a skin biopsy (lesional skin or just adjacent to a blister) should be taken for routine histopathology and in blistering eruptions also direct immunofluorescence to exclude bullous autoimmune disease (Ziemer and Mockenhaupt 2011).

Furthermore, photographs of the skin eruption should be taken to show the specific features and the extent of involvement (Mockenhaupt and Roujeau 2019).

Whenever a skin eruption is considered as being drug-induced, the potentially culprit agent should be identified and withdrawn. The group of SCAR reveals various timelines for onset of symptoms after beginning of drug use with the longest typically seen in DRESS (2–8 weeks) and the shortest in AGEP and GBFDE (1–2 days for most cases), whereas in cases of EN the offending drug is typically started 4–28 days before reaction onset (Fig. 3) (Cho et al. 2014; Mahboob and Haroon 1998; Sidoroff et al. 2007; Kardaun et al. 2013; Mockenhaupt et al. 2008).

The skin eruption of DRESS may be identical to that of a typical benign maculopapular eruption, however, distinct in the systemic features. In addition to the more delayed onset, DRESS usually shows a more florid and extensive eruption, often associated with facial swelling. The mortality of DRESS is mainly due to organ failure (e.g., of the liver) and has been reported as 2–6% (Kardaun et al. 2013). However, long-term morbidity after the acute stage can arise as a consequence of viral reactivation (HHV6/7; EBV; CMV) or induction of autoimmune phenomena (Ushigome et al. 2013).

The occurrence of a non-follicular pustular eruption should point to AGEP. However, numerous small pustules may also be seen in DRESS, but they are mainly follicular. AGEP typically presents as a rapidly arising erythema on which pustules appear, often localized on head, neck, and upper torso and/or predominantly in the body folds. Fever and neutrophilia are present and generalized pustular psoriasis is the main differential diagnosis (Sidoroff et al. 2001; Paulmann and Mockenhaupt 2019).

Blisters leading to epidermal detachment within a skin eruption considered as a hypersensitivity reaction are a key indicator of EN (Bastuji-Garin et al. 1993; Mockenhaupt and Roujeau 2019), but GBFDE should also be considered (Cho et al. 2014). EN, however, is associated with severe hemorrhagic erosions of mucous membranes (typically lips, oral mucosa, eyes, nose, genitalia, and bronchi). Although GBFDE also induces full-thickness epidermal necrosis histologically, the margins of erythematous areas are much more clearly defined than in EN, where detachment can be induced by trauma or friction in skin areas that may not appear affected (positive Nikolsky sign). Furthermore, mucosal involvement is limited and typically does not affect the ocular surface. In addition, mild mucositis may occur as well in DRESS and AGEP (Paulmann and Mockenhaupt 2019).

3.2 Specific Treatments

In AGEP systemic features of fever and neutrophilia are evident, but in most cases they resolve quickly when the culprit drug is withdrawn. Topical or oral corticosteroids may be considered in the acute stage, especially for inflamed or itchy areas of skin. The pustules resolve with a typical post-pustular desquamation, for which emollients can be helpful. Internal involvement, which is reflected by elevation of liver and kidney parameters, has been observed in up to 20% of mainly

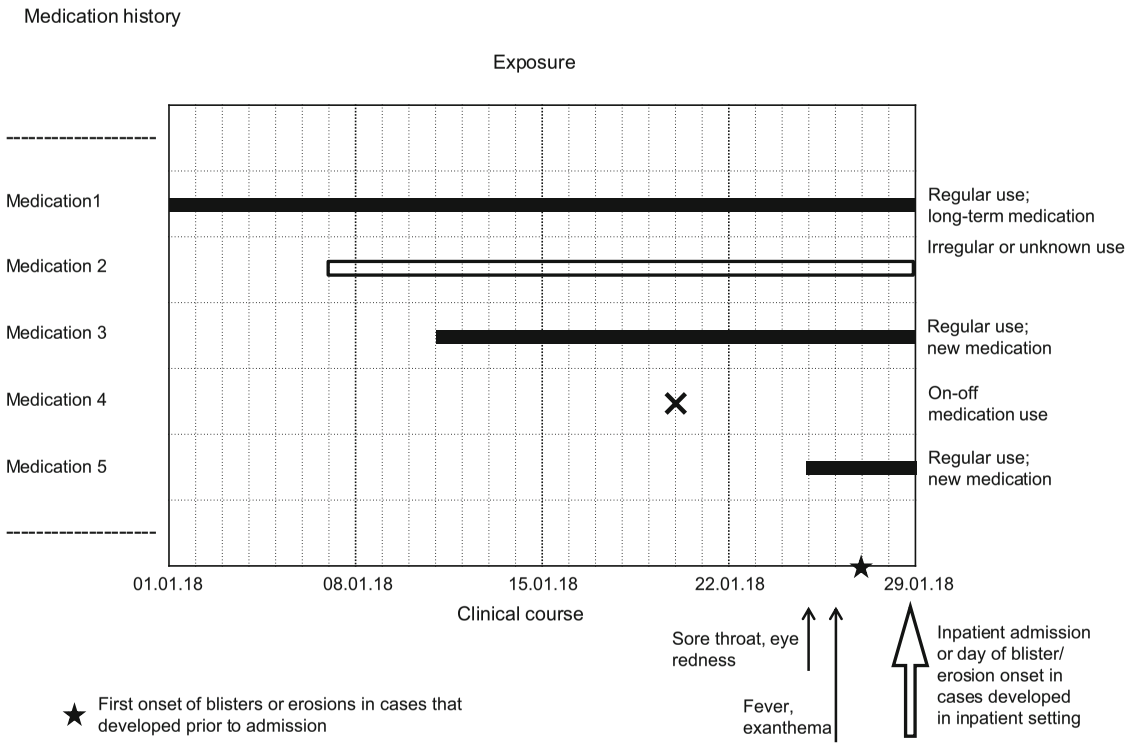

Fig. 3 Timeline of events (X-axis) and medication history (Y-axis) (Paulmann and Mockenhaupt 2019)

Table 4 SCORTEN (Bastuji-Garin et al. 2000)

Factor	Score	Weight/score value[a]
Age	≥40 years	1
Malignancy	Yes	1
Body surface area detached (day 1)	≥10%	1
Tachycardia	≥120/min	1
Serum urea	≥10 mmol/l	1
Serum glucose	≥14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1
	Possible score	0–7

[a]The higher the total score value, the poorer is the prognosis of the patient

elderly patients. However, these elevated values are of transient nature and resolve without specific treatment (Hotz et al. 2013).

Therapy in cases of DRESS should be adjusted to the individual presentation of clinical features and various specialists should be involved accordingly. There is consensus among experts that treatment with corticosteroids is beneficial, topically applied in mild cases, but systemically administered in most cases of DRESS (Funck-Brentano et al. 2015). A dose of 1-2 mg/kg of prednisolone per day is recommended, but the duration of treatment has to be adjusted for each patient. It has been shown that patients who experience reactivation of HHV6/7 (also EBV/CMV) may have a prolonged and complicated course of their disease with repeated flare-ups. Therefore, the corticosteroid dose may have to be tapered very slowly in cases with viral reactivation (Shiohara and Kano 2017). For cases resistant to steroid therapy, successful use of ciclosporin and other immunosuppressants has been reported, whereas IVIG did not proof beneficial (Kirchhof et al. 2016; Joly et al. 2012).

EN can rapidly progress and has the highest mortality of all types of SCAR. Mortality increases with the amount of skin detachment and age of the patient. A useful measurement of prognosis is the "severity score of EN" called SCORTEN (Table 4) (Bastuji-Garin et al. 2000). It should be applied within 24 h after admission, but an analysis of daily scores over the first 5 days revealed that prognostic correlation was best on day 3 (Guégan et al. 2006). Patients with extensive skin detachment should be managed in an intensive care unit (ICU) or burn center, but the precise threshold will be dependent upon local practice. UK guidelines suggest that ICU transfer is appropriate at >10% (Creamer et al. 2016), whereas in Germany the assessment is based on evaluation of the overall medical status and may not be required until detachment of the BSA reaches 30%.

Higher room temperature with increased humidity and pressure relieving mattresses are helpful. Trauma to the affected skin should be minimized, and supportive care includes fluid replacement, nutrition, and analgesia (Mockenhaupt and Roujeau 2019; Creamer et al. 2016). Management of skin detachment may either be conservative (local disinfection and anti-adhesive gauze dressings) or surgical (removal of necrotic or loose skin and the so-called burn-bath). The most common

complication of EN is sepsis secondary to infection most often acquired through catheters and central venous lines. Prophylactic antibiotics are not recommended due to the risk of masking septicemia. Instead, regular microbiological swabbing from multiple sites of the skin and catheters may identify potential pathogenic bacterial organisms, which then can be treated appropriately (Mockenhaupt and Roujeau 2019).

Adequate treatment of affected mucous membranes should involve the relevant specialist with expertise in management of EN. This seems to be of major importance for eye involvement and it has been shown that early intervention with amniotic membrane grafting provides better outcomes (Sharma et al. 2000).

Immunomodulating therapy in EN has been discussed controversially for decades. However, some larger studies could identify a positive effect of short-term steroid use on disease outcome, which was not seen for intravenous immunoglobulins (IVIG) (Schneck et al. 2008; Zimmermann et al. 2017). In recent years different studies and systematic reviews came to the conclusion that ciclosporin A has beneficial effects in terms of disease progression and outcome (Valeyrie-Allanore et al. 2010; González-Herrada et al. 2017; NG et al. 2018).

A randomized controlled trial comparing the TNF-alpha inhibitor etanercept and systemic corticosteroids revealed a better outcome for etanercept. However, this study included mainly mild cases, the steroid therapy was done for as long as 3 weeks, suggesting a higher risk for complications in that group, and the clinical results were not statistically significant (Wang et al. 2018).

Supportive care in GBFDE is essentially the same as that in EN, but immunomodulating treatments have not been evaluated in studies. The majority of cases are less progressive and show a more benign clinical course, but a mortality comparable to that of EN with the same amount of skin detachment has been observed in one study. However, cases of GBFDE with fatal outcome concerned mainly patients who were substantially older and who had a previous event (Lipowicz et al. 2013).

4 Allergologic Testing in SCAR

If the inducing agent has been readily identified by taking a thorough and detailed medication history, no further testing is needed. The drug must be avoided lifelong. In some cases of SCAR the drug history is so complicated that it is impossible to identify the offending medication with any probable likelihood. Causality assessment should be performed by an expert in drug reactions, but one of the problems is that such specialists are often involved weeks, months, or even years after the acute event. As described above, the clinical reaction type with the typical exposure window of inducing medication is of major importance for evaluation of causality.

Skin tests, especially patch test, have been demonstrated to be useful in delayed hypersensitivity reactions. A patch test can also be safely performed in severe reactions, but the correct positive outcome seems to be highly variable. In EN, for example, it provided informative results in no more than 23% of cases. In AGEP and

DRESS the rate of correct positive patch test results was substantially higher but differed between various substances (Barbaud et al. 2013). Allopurinol, a frequent inducer of both DRESS and EN, is not illegible for patch test due to its low lipophilic potency and thus poor skin penetration. This supports the fact that extensive knowledge and specific expertise are required for skin testing in the field of drug reactions (Ardern-Jones and Mockenhaupt 2019). Intradermal testing is routinely used to investigate IgE-mediated drug allergy, when prick test was negative, and is also recommended for use in milder cutaneous adverse reactions. Because severe and even fatal reactions have been reported even when only small doses were applied, intradermal testing in cases of SCAR needs to be done with caution (Brockow et al. 2019; Phillips et al. 2019).

In vitro testing for investigation of SCAR seems to be the ideal approach, but many available tests, e.g. lymphocyte proliferation assay (LPA; syn. lymphocyte transformation test, LTT) and drug-induced cytokine assay (IFN-γ, ELISpot) remain experimental and are not yet used in routine practice. Furthermore, interpretation of the results is often difficult (Trubiano et al. 2018; Porebski 2017).

In recent years a strong association between various HLA-alleles and certain types of SCAR has been identified. Such associations are specific for certain reactions, drugs, and ethnicities. HLA tests are not designed for identification of the culprit drug in adverse reactions but may decrease the risk of SCAR in individuals before taking the decision for certain drug therapy. Thus, the number of carbamazepine-induced EN cases in Hong Kong was substantially reduced when patients tested positive for HLA-B*15:02 were not administered carbamazepine (White et al. 2018).

References

Ardern-Jones MR, Friedmann PS (2011) Skin manifestations of drug allergy. Br J Clin Pharmacol 71(5):672–683

Ardern-Jones M, Mockenhaupt M (2019) Making a diagnosis in severe cutaneous drug reactions. Curr Opin Allergy Clin Immunol 19:283–293. https://doi.org/10.1097/aci.0000000000000546

Barbaud A, Collet E, Milpied B (2013) A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol 3:555–562

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 129(1):92–96

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P (2000) SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 115:149–153

Bigby M (2001) Rates of cutaneous reactions to drugs. Arch Dermatol 137:765

Brahimi N, Routier E, Raison-Peyron N et al (2010) A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol 20:461

Brockow K, Ardern-Jones MR, Mockenhaupt M, Aberer W, Barbaud A, Caubet JC et al (2019) EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy 1:14–27. https://doi.org/10.1111/all.13562

Cho YT, Lin JW, Chen YC et al (2014) Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. J Am Acad Dermatol 70:539

Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK et al (2016) U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. Br J Dermatol 174(6):1194–1227

Funck-Brentano E, Duong TA, Bouvresse S, Bagot M, Wolkenstein P, Roujeau JC et al (2015) Therapeutic management of DRESS: a retrospective study of 38 cases. J Am Acad Dermatol 72 (2):246–252

González-Herrada C, Rodríguez-Martín S, Cachafeiro L, Lerma V, González O, Lorente JA et al (2017) Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. J Invest Dermatol 137:2092–2100

Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E et al (2006) Performance of the SCORTEN during the first five days of hospitalisation to predict the prognosis of epidermal necrolysis. J Invest Dermatol 126:272–276

Häusermann P, Bircher AJ (2007) SDRIFE – another acronym for a distinct cutaneous drug exanthema: do we really need it? Dermatology 214:1–2. https://doi.org/10.1159/000096903

Hotz C, Valeyrie-Allanore L, Haddad C, Bouvresse S, Ortonne N, Duong TA, Ingen-Housz-Oro S, Roujeau JC, Wolkenstein P, Chosidow O (2013) Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. Br J Dermatol 169:1223–1228

Inoue A, Sawada Y, Yamaguchi T et al (2017) Lichenoid drug eruption caused by adalimumab: a case report and literature review. Eur J Dermatol 27:69

Joly P, Janela B, Tetart F, Rogez S, Picard D, D'incan M et al (2012) Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol 148(4):543–544

Kanani A, Betschel SD, Warrington R (2018) Urticaria and angioedema. Allergy Asthma Clin Immunol 14:59

Kardaun SH, Sidoroff A, Valeyrie-Allanore L et al (2007) Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 156:609

Kardaun S, Sekula P, Valeyrie-Allanore L, Liss Y, Chu C, Creamer D et al (2013) Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 169(5):1071–1080

Kirchhof MG, Wong A, Dutz JP (2016) Cyclosporine treatment of drug-induced hypersensitivity syndrome. JAMA Dermatol 152(11):1254–1257

Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A et al (2013) Prognosis of generalized bullous fixed drug eruption: comparison with Stevens–Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 168(4):726–732

Mahboob A, Haroon TS (1998) Drugs causing fixed eruptions: a study of 450 cases. Int J Dermatol 37:833

Mockenhaupt M, Roujeau JC (2019) Epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis). In: Kang S, Amagai M, Bruckner A, Enk AH, Margolis DJ, McMichael AJ, Orringer JS (eds) Fitzpatrick's dermatology, Chapter 44, 9 edn. McGraw Hill Education, New York, pp 733–748

Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A (2008) Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 128(1):35–44

Momin SB, Del Rosso JQ, Michaels B, Mobini N (2009) Acute generalized exanthematous pustulosis: an enigmatic drug-induced reaction. Cutis 83:291

Paulmann M, Mockenhaupt M (2019) Severe skin reactions: clinical picture, epidemiology, etiology, pathogenesis, and treatment. Allergo J Int 28:311–326. https://doi.org/10.1007/s40629-019-00111-8

Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, Lehloenya R, Mockenhaupt M, Peter J, Pirmohamed M, Roujeau JC, Shear NH, Tanno LT, Trubiano J, Valluzzi R, Barbaud A (2019) Controversies in drug allergy: testing for delayed reactions. J Allergy Clin Immunol 143:66–73

Porebski G (2017) In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? Int J Mol Sci 18(8)

Reschke R, Mockenhaupt M, Simon JC, Ziemer M (2019) Severe bullous skin eruptions on checkpoint inhibitor therapy – in most cases severe bullous lichenoid drug eruptions. J Dtsch Dermatol Ges. https://doi.org/10.1111/ddg.13876

Roujeau JC, Mockenhaupt M (2019) Erythema multiforme. In: Kang S, Amagai M, Bruckner A, Enk AH, Margolis DJ, McMichael AJ, Orringer JS (eds) Fitzpatrick's dermatology, Chapter 43, 9 edn. McGraw Hill Education, New York, pp 723–732

Schneck J, Fagot J-P, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M (2008) Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR study. J Am Acad Dermatol 58:33–40

Sharma N, Thenarasun SA, Kaur M et al (2000) Adjuvant role of amniotic membrane transplantation in acute ocular Stevens–Johnson syndrome: a randomized control trial. Ophthalmology 123:484–491

Shiohara T, Kano Y (2017) Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. Expert Opin Drug Saf 16(2):139–147

Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC (2001) Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. J Cutan Pathol 28:113–119

Sidoroff A, Dunant A, Viboud C et al (2007) Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol 157:989

Simons FE, Ardusso LR, Dimov V et al (2013) World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 162:193

Stone C Jr, Brown NJ (2017) Angiotensin-converting enzyme inhibitor and other drug-associated angioedema. Immunol Allergy Clin North Am 37:483

Thyssen JP, Maibach HI (2008) Drug-elicited systemic allergic (contact) dermatitis – update and possible pathomechanisms. Contact Dermatitis 59:195

Trubiano JA, Strautins K, Redwood AJ, Pavlos R, Konvinse KC, Aung AK et al (2018) The combined utility of ex vivo IFN-gamma release enzyme-linked immunospot assay and in vivo skin testing in patients with antibiotic-associated severe cutaneous adverse reactions. J Allergy Clin Immunol Pract 6:1287–1296.e1

Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T (2013) Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. J Am Acad Dermatol 68(5):721–728

Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maître B, Revuz J et al (2010) Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 163:847–853

Ng QX, De Deyn MLZQ, Venkatanarayanan N, Ho CYX, Yeo WS (2018) A meta-analysis of cyclosporine treatment for Stevens–Johnson syndrome/toxic epidermal necrolysis. J Inflammation Res 496 11:135–142

Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH et al (2018) Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. J Clin Invest 128(3):985–996

White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B et al (2018) SJS/TEN 2017: building multidisciplinary networks to drive science and translation. J Allergy Clin Immunol Pract 6(1):38–69

Ziemer M, Mockenhaupt M (2011) Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. In: Khopkar U (ed) Skin biopsy. InTech – Open Access Publisher, London. http://www.intechopen.com/articles/show/title/severe-drug-induced-skin-reactions-clinical-pattern-diagnostics-and-therapy

Ziemer M, Wiesend CL, Vetter R, Weiss J, Blaschke S, Norgauer J, Mockenhaupt M (2007) Cutaneous adverse drug reactions to valdecoxib distinct from Stevens-Johnson syndrome and toxic epidermal necrolysis. Arch Dermatol 143:711–716

Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M et al (2017) Systemic Immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol 153:514–522

Occupational Respiratory Allergy: Risk Factors, Diagnosis, and Management

Monika Raulf

Contents

Abstract

Occupational allergies are among the most common recorded occupational diseases. The skin and the upper and lower respiratory tract are the classical manifestation organs. More than 400 occupational agents are currently documented as being potential "respiratory sensitizers" and new reported causative agents are reported each year. These agents may induce occupational rhinitis (OR) or occupational asthma (OA) and can be divided into high-molecular weight (HMW) and low-molecular weight (LMW) agents. The most common occupational HMW agents are (glycol)proteins found in flour and grains, enzymes, laboratory animals, fish and seafood, molds, and *Hevea brasiliensis* latex. Typical LMW substances are isocyanates, metals, quaternary ammonium persulfate, acid anhydrides, and cleaning products/disinfectants. Diagnosis of occupational respiratory allergy is made by a combination of medical history, physical examination, positive methacholine challenge result or bronchodilator responsiveness,

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determination of IgE-mediated sensitization, and specific inhalation challenge tests as the gold standard. Accurate diagnosis of asthma is the first step to managing OA as shown above. Removal from the causative agent is of central importance for the management of OA. The best strategy to avoid OA is primary prevention, ideally by avoiding the use of and exposure to the sensitizer or substituting safer substances for these agents.

Keywords

Baker's asthma · High-molecular weight agents · Low-molecular weight agents · Occupational allergic asthma · Occupational hypersensitivity pneumonitis · Occupational rhinitis · Prevention

1 Introduction

Occupational allergy refers to those disorders or conditions that are caused by exposure to sensitizers in the work environment. For years occupational allergies have been among the most frequently recorded occupational diseases (Blanc et al. 2019). The classical manifestation organs of occupational allergic diseases are the skin and the upper and lower respiratory tract. The allergic diseases that may be contracted as a consequence of exposure to sensitizing workplace-related agents are rhinitis, conjunctivitis, asthma, eosinophilic bronchitis, hypersensitivity pneumonitis, allergic contact dermatitis, and occupational anaphylaxis. The term "work-exacerbated" allergy is used when the disease is not directly caused by the occupational exposure, but workplace-related stimuli lead aggravating pre-existing rhinitis, asthma, or cough. Occupational skin diseases (OSDs) are the second most common occupational diseases worldwide and comprise irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), contact urticaria, and protein-contact dermatitis (Raulf et al. 2017). The most common form is the so-called acute-toxic contact dermatitis, which results from the direct action of acids, alkalis, or other aggressive chemicals. The second most common cause of occupational skin diseases is allergic contact dermatitis.

In the case of allergy manifestation on the lower respiratory tract as occupational asthma is estimated that 9–15% of all asthmatic diseases in adults have occupational (partial) causes. The prerequisite for the manifestation of an allergic reaction is that sensitization to a specific substance (allergen) has taken place. This means that the immune system has to be introduced to the allergen in a first phase. This sensitization phase runs imperceptibly. Only after the immune system has formed certain cells and/or antibodies that recognize the antigen immediately upon re-contact, an allergic reaction can take place. The main topic of the article concerns on occupational respiratory diseases and additionally some aspects of occupational hypersensitivity pneumonitis (HP) are presented.

2 Different Faces of Occupational Respiratory Allergy: Risk Factors and Workplace Exposure

Inhalation of wide variety of workplace agents can cause the development of sensitizer-induced occupational airway diseases. Both the upper and the lower respiratory tract can be affected. Based on the *united airway disease model* which has been proposed to describe a unique disease with manifestation in different sites of the respiratory system, a strong interaction between the occupational rhinitis (OR) and occupational asthma (OA) exists (Moscato et al. 2009). In occupational setting, it has been demonstrated that a majority of the patients diagnosed with OA also suffer from OR, particularly when high-molecular weight (HMW) agents are involved. Symptoms of OR like nasal congestion, sneezing, rhinorrhea, and/or itching have been reported to develop before those of OA. OA refers to de novo asthma or the recurrence of previously quiescent asthma induced by either sensitization to a specific substance, which is termed allergic or sensitizer-induced OA, or by exposure to an inhaled irritant at work, which is termed irritant-induced OA (Fig. 1). In addition to OA work-related asthma also includes work-exacerbated asthma which is worsened, but not caused, by work exposures (Lau and Tarlo 2019).

The damage to the bronchial system or the upper airways depends on the properties of the substances, e.g. their water solubility and also factors like the individual responsiveness (susceptibility) of the employees. The concentration of the substance (intensity) and the duration of exposure are also decisive factors. The exposure to respiratory sensitizers is usually through aerosols (dusts, mist, fumes) or

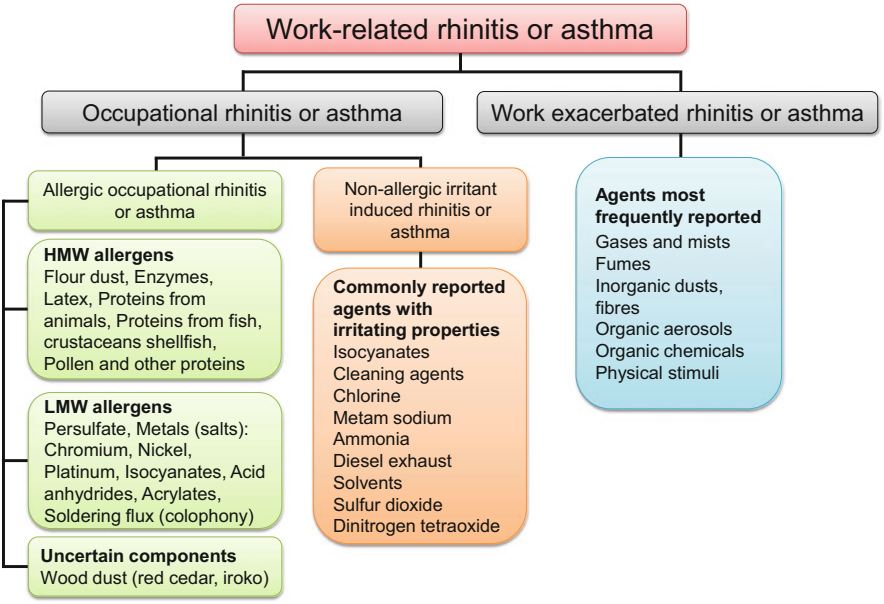

Fig. 1 Causes of work-related rhinitis or asthma

gases. Most of the allergens tend to attach themselves to tiny dust particles (<10 μm) and, thus, get transported easily through air. These tiny particles rarely sediment and can manage to reach deep into the airways during inhalation.

More than 400 occupational agents are currently documented in the scientific literature as being potential "respiratory sensitizers" and new reported causative agents are reported each year (Quirce and Bernstein 2011; Raulf et al. 2018; Tarlo et al. 2017). These agents may induce OR or OA, which can be divided into high-molecular weight (HMW) and low-molecular weight (LMW) agents. The mechanism by which HMW agents, which are proteins or glycoproteins, induce OR or OA is thought to be IgE-mediated similar to that known to cause allergic rhinitis or allergic asthma in the general population. The most common occupational HMW agents are proteins or glycoproteins found in flour and grains, enzymes, laboratory animals, fish and seafood, molds (fungi), and *Hevea brasiliensis* latex. Exposures commonly encountered are in farming, laboratories, office buildings, health care facilities, and food processing and harvesting environments (Kelly and Poole 2019). Regardless of these common workplace-related allergy triggers, it would appear that almost any protein that becomes airborne and inhaled might be a potential cause of occupational asthma. Typical LMW substances are isocyanates, persulfate salts, metals, quaternary ammonium persulfate, acid anhydrides, cleaning products/disinfectants, and medicinal drugs. These substances are usually encountered in painting, industrial, health care, cleaning, and hairdressing work (Kelly and Poole 2019). The pathogenesis of OR or OA caused by LMW agents remains poorly understood but may include both immunologic and non-immunologic mechanisms. An IgE-mediated mechanism has been documented for a few LMW agents such as anhydride acids (used as hardeners in epoxy reins in chemical plants and in powder paints), complex platinum salts (used in platinum refineries or the production of catalysts), and reactive dyes (used in textile manufacture). It is generally assumed that the allergenicity of these LMW or their metabolites results from a mostly covalent interaction with some carrier proteins to build a hapten-carrier complex, because most of them have highly reactive and functional groups (Enoch et al. 2012; Maestrelli et al. 2009). Diisocyanates, characterized by highly reactive NCO groups, are important inducers of occupational asthma especially in industrialized countries. Besides IgE-mediated allergic asthma, isocyanate exposure may also induce irritant asthma, hypersensitivity pneumonitis, and possibly accelerated lung function decline (Pronk et al. 2007). A still existing and in the tendency rising problem represents the occupational exposure to cleaning agents and the resulting increasing frequency of occupational asthma attributed to cleaning agents (Carder et al. 2019; Folletti et al. 2017; Siracusa et al. 2013). Adverse health effects can occur from the individual use of such products and from the mixing or joint application of different products, whether accidental or deliberate. It is attempted to use a "Quantitative Structure Activity Relationship" (QSAR) model to predict the respiratory sensitizing potential of the LMW components of the cleaning agents (Carder et al. 2019).

Several studies have consistently demonstrated that in addition to the inherent sensitizing potency of a given agent (Tarlo and Lemiere 2014) the intensity of workplace exposure to airborne allergens (wheat and rye flour, laboratory animal

allergens, enzymes (e.g., α-amylase, detergent enzymes)) is a major determinant of risk of developing occupational asthma and allergy and for HMW sensitizing agents atopy clearly modifies the risk. Smoking is not an effect modifier for the association between allergen exposure, sensitization and allergic asthma especially for HMW-induced allergy. Therefore, the reduction and avoidance of exposure is highly recommended if symptoms of the upper and lower airways have occurred. Information on exposure-response relationships can be used for risk assessment and will be the input of standard setting procedures in different countries (Raulf et al. 2014).

3 Diagnosis of Occupational Respiratory Allergy

Diagnosis of occupational respiratory allergy is made by a combination of medical history, physical examination, positive methacholine challenge result or bronchodilator responsiveness, determination of IgE-mediated sensitization to HMW allergens (by skin prick testing and/or serologically specific IgE-measurement, and possibly basophil activation testing to LMW chemicals (Vera-Berrios et al. 2019) and HMW allergens). Occupational asthma should be suspected in every adult with new-onset asthma. Therefore, the diagnosis including the question about the occurrence of the respiratory symptoms in connection with the workplace is important. Typically, remission or improvement occurs during weekends and holidays. Rhinitis often accompanies or precedes lower respiratory symptoms, especially when high-molecular-weight agents incite the asthma. Although a thorough clinical and occupational history must be obtained, a compatible history alone is insufficient for diagnosis and has a low positive predictive value. If the patient with asthma-like symptoms is not at work, the specific inhalation challenge (SIC) in the laboratory under controlled conditions to the suspected occupational agents is considered the gold standard. The accuracy of the diagnosis can be improved by the measurement of sputum eosinophils before and after challenge (Quirce et al. 2010). Additionally measurement of the fractional exhaled nitric oxide (FeNO) should be regarded as an additional criterion for the interpretation of SIC with occupational agents, because an increase of FeNO after SIC is highly predictive of occupational asthma (Engel et al. 2018). If the patient is working, serial monitoring of peak expiratory flow (PEF) at work and away from work is also a useful option (Tarlo and Lemiere 2014). In some cases the assessment of eosinophilic airway inflammation by sputum cell count analysis before and after exposure to the offending agent may contribute to an increased diagnostic accuracy for OA (Racine et al. 2017; Engel et al. 2019). If specific inhalation challenge in the laboratory and/or PEF monitoring at work is not possible and occupational asthma is strongly suspected from history, a combination of objective evidence of asthma plus a positive skin test or the verification of specific IgE by serological tests to the suspected agent has a high predictive value for occupational asthma (van Kampen et al. 2008).

4 Examples for Relevant Respiratory Occupational Allergies

Table 1 lists some workplaces/industries and the typical allergen sources. Baker's asthma is one of the oldest recognized occupational diseases described by Bernardino Ramazzini, the father of occupational medicine, in about 1700 and in Western countries it still one of the most common forms of occupational respiratory disease. Case reports from the beginning of the twentieth century established the concept of baker's asthma as an allergic disease because of the observed combination of positive skin tests to flour extracts and respiratory symptoms suggestive of asthma (Brisman 2002). Most studies published later indicate that wheat (*Triticum aestivum*) flour proteins are allergens for 60–70% of symptomatic bakers (Quirce and Diaz-Perales 2013), although other cereals like rye, barley, oats, and corn and non-cereal sources such as buckwheat, soybean flour, or lupine flour, enzymes (like α-amylase, cellulose, xylanase), insects (like flour moth (*Ephestia kuehniella*), flour beetle (*Tribolium confusum*) may be involved because a bakery is a complex environment with a huge amount of potential sensitizers (Brisman 2002). Based on the importance of wheat flour exposure in bakeries, diagnosis of baker's asthma is based on a consistent clinical history, skin prick testing and/or specific IgE antibody tests and inhalation wheat challenges. Nonetheless, this allergic disease is often misdiagnosed, with significant legal, economic, and health consequences for the affected worker. Although specific inhalation challenge with wheat flour is considered as gold standard, it is often difficult to perform (Raulf 2018). Additionally,

Table 1 Examples of workplaces and their typical occupational allergens

Workplace/trade and industry	Allergen source
Agriculture/farming	Cow dander, pollen, storage mites
Bakery/mills	Wheat flour, rye flour, different other grain flours, soy flour, α-amylase, xylanase, storage mites, insects, molds, spices
Food processing industry	Several cereals, plants, vegetables, fruits and spices, seeds, mushrooms, seafood (shellfish and fish), raw coffee beans, farm products (eggs), food additives, enzymes, food contaminants (e.g., mites, insects, molds)
Animal feed production	Soy, phytase
Pharmaceutical industry	Enzymes, *gum arabic*
Laboratory animal facilities/life science faculties of universities	Mouse, rat (urine, dander)
Health care facilities	Disinfectants, natural rubber latex
Veterinary clinics/practice	Cat, dog, guinea pig, rabbit, horse, cow (dander, urine, etc.)
Laundry detergent industry	Enzymes: protease, cellulase, lipase, amylase
Wood processing	Wood dust, mold
Waste handling/compost plants	Molds, bacteria
Offices/schools/day care centers	House dust mites, ubiquitous allergens (e.g., from cat, dog, mouse)

wheat skin prick test extracts are not well characterized and demonstrate a low diagnostic sensitivity (van Kampen et al. 2013a, b). So far 28 *Triticum aestivum* (Tri a) allergens are listed in the WHO/IUIS Allergen Nomenclature database (www.allergen.org), but several studies have shown that in patients with baker's asthma the IgE reaction profiles to *Triticum aestivum* proteins often differ remarkably between individual sera and no major allergen could be identified (Sander et al. 2001, 2011, 2015).

In addition to bakeries also other workplaces with food processing activities where animal and vegetable high-molecular-weight proteins of food were generated in aerosolized form are responsible for a significant number of occupational rhinitis and/or occupational asthma (Jeebhay et al. 2019). Dust particulate or aerosols produced during food processing that are readily inhaled and can act as primary sensitizers in the airways cause a distinct form of respiratory food allergy, usually without any symptoms upon ingestion. The allergenicity of a food protein, allergen exposure levels, and atopy are important risk factors. Exposure assessment, including allergen determination, is a cornerstone for establishing preventive measures. Especially workers in the seafood-processing industries have an increased risk to develop occupational asthma, contact urticaria, and protein-contact dermatitis. During processing activities the workers inhale of airborne seafood particulate matter containing allergens (Bonlokke et al. 2019; Jeebhay and Lopata 2012; Lopata and Jeebhay 2013).

In the 1980s and 1990s in health care facilities where powdered natural rubber latex (NRL) gloves were used NRL allergy reached epidemic proportions in highly exposed populations. In addition to direct skin contact with latex-derived products, the other important route is the inhalation of airborne latex (*Hevea brasiliensis*) proteins (Raulf 2014). The increased recognition of NRL allergy, the enhanced research on allergen characterization and sensitization mechanisms, education about this allergy in health care facilities combined with the introduction of powder-free gloves with reduced protein levels have been associated with a decline in the number of suspected cases of NRL allergies in the late 1990s. For example, in contrast to wheat allergy in patients suffering from baker's asthma where no major allergen could be identified, *Hevea brasiliensis* latex-sensitized patients, e.g. health care workers, recognized major allergens and available recombinant single latex allergens are useful tools in the diagnostic procedure. Therefore, NRL allergy is a very good example, on the one hand, for a "new allergy" that suddenly arises with tremendous health and economic implications and on the other hand for an allergy which becomes a history in a relatively short time period based on successful primary prevention strategies by strict allergen avoidance (Raulf 2014; Vandenplas and Raulf 2017).

Dust of green coffee beans is known to be a relevant cause for occupational allergic respiratory disorders in coffee industry workers and therefore proteins from *Coffea arabica* play a role as occupational allergens (Manavski et al. 2012).

IgE-mediated sensitization and allergy to some wood dusts has been described in case reports (Kespohl et al. 2012) and obeche (*Triplochiton scleroxylon*) wood dust an endochitinase 38 kDa has been characterized as allergen. This allergen was

assigned with the official name Trip s 1 and has been included in the nomenclature list of the International Nomenclature Committee of Allergens (WHO/IUIS) (Kespohl et al. 2005). Especially for the wood allergens (Kespohl et al. 2010) but also for other plants (e.g., like latex) the presence of cross-reactive carbohydrate determinants (CCDs) can negatively influence the specificity of the in vitro diagnostic test. Therefore, it is necessary to exclude glyco-epitopes (with low clinical relevance) responsible for IgE-binding.

Allergy to furred animal is also common in occupational settings, because allergen exposure to furry mammals is found not only in households, where mostly cats and dogs are kept as pets, but also in professional settings, e.g. in farms, laboratory animal facilities, veterinary clinics, and in public places like schools, day care centers, or public transportation vehicles which also represent workplaces for some people (Zahradnik and Raulf 2017). Mammalian allergens belong to few protein families: lipocalins (pheromone binding proteins), serum albumins, secretoglobins, prostatic kallikreins, and latherins. With the exception of serum albumin these allergens are usually present in urine, saliva, and animal dander (Hilger et al. 2017). Laboratory animal allergy (LAA) is an important occupational disease and commonly observed among technicians, animal caretakers, physicians, and scientists who work in laboratory animal facilities at universities, research institutes, and pharmaceutical companies (Jones 2015; Zahradnik and Raulf 2017). Rodents like mice and rats frequently used in animal research are the most common causes of LAA. Urine is the main source of allergenic proteins in both mice and rats, but allergens can be found in dander, hair, saliva, and serum. The major allergens in mouse and rat are lipocalins (Jones 2015). According to a current study LAA can be prevented in modern research units using a multifaceted approach including individually ventilated cages to contain aeroallergen exposure and the judicious use of appropriate respiratory protection (Feary et al. 2019). Dairy farming is a main branch of the agricultural sector in many countries and cattle farmers are occupationally exposed to a variety of bioaerosols of which some components are considerable risk factors for airway diseases. Among them, the lipocalin Bos d 2 is known to be a major respiratory allergen (Böhlandt et al. 2016). Clinical symptoms of the exposed workers can reach from asymptomatic sensitization, rhinitis up to severe asthmatic attacks with lung function impairment leading to a high rate of initial employment disabilities. Due to the passive transport of allergens through work wear, bovine allergens are also detectable in the homes of farmers sometimes at relatively high concentrations (Böhlandt et al. 2016; Zahradnik et al. 2011), although these levels are still much lower than those measured in the stables.

In addition to the mentioned high-molecular-weight (glycol-)protein allergens, polyisocyanates are low-molecular-weight cross-linking agents inducing a broad spectrum of occupational diseases from asthma, reactive airway dysfunction syndrome (RADS) or irritant-induced asthma, hypersensitivity pneumonitis, dermatitis, and pulmonary edema. In many industrialized countries isocyanates represent the most commonly identified cause of occupational asthma. They are highly reactive chemicals used in external coatings and paints or especially the aromatic isocyanates are used to produce flexible foams, adhesives, e.g. in the automobile industry.

Although many efforts to address the pathogenesis of diisocyanate-OA have been made, its nature is heterogeneous in which various immunologic and non-immunologic mechanisms are involved. In only few exposed and symptomatic workers isocyanate-specific IgE-antibodies could be detected.

5 Management and Prevention of Occupational Respiratory Allergy

Accurate diagnosis of asthma is the first step to managing occupational asthma as shown above. Of central importance for the management of occupational asthma is the removal from the causative agent: ideally the removal of the culprit agent; but if it is not possible, this may require changes in the work process or ultimately the removal of the worker from the workplace (Lau and Tarlo 2019). The best prognosis for clearing of asthma has been associated with an early diagnosis and early removal of the trigger, especially if mild asthma is present at the time of diagnosis. The advice to completely avoid the causative sensitizing agent at work can sometimes be achieved relatively simply by changing the material used at work or the formulation of the agent. If this is not feasible, the patient needs to be moved to a different work area or to a different company or job, leading potentially to significant socio-economic impact. Under special circumstances if complete avoidance of exposure to the culprit is not possible reduction of exposure is possible, by installation and use of technical ventilation and/or the use of respiratory protective equipment but not as effective as complete avoidance of exposure.

Primary prevention is the best strategy to avoid occupational asthma, ideally by avoiding the use of and exposure to agents with sensitizing potential or substituting safer substances for these agents (a good example is the ban of powdered latex gloves). Since rates of sensitization are generally greater with higher exposure, obligatory exposure limits for sensitizing chemicals would be expected to reduce the frequency of sensitization. But the relationship is complex if for some of the agents no linear dose-response curves exist there is no consensus of clear exposure thresholds protecting all workers. But environmental control and exposure assessment are cornerstones of prevention strategy. However, due to the lack of standard procedures and equipment for e.g. of occupational allergen exposure quantification, reduction of allergen exposure using appropriate risk management and exposure control strategies is advocated to be best practice.

6 Hypersensitivity Pneumonitis Induced by Occupational Antigens

Hypersensitivity pneumonitis (HP) of exogenous allergic alveolitis (EAA) is an immunologic lung disease resulting from lymphocytic and frequently granulomatous inflammation of the peripheral airways, alveoli, and surrounding interstitial tissue which develops as the result of a delayed non-IgE-mediated allergic reaction

caused by repeated inhalation of antigens (allergens). HP is often triggered by occupational exposure (occupational hypersensitivity pneumonitis (OHP)) (Quirce et al. 2016). A variety of organic materials including animal (especially avian antigens) and plant proteins, fungi/yeasts, bacteria and low-molecular chemical compounds (e.g., acid anhydrides, isocyanates, and metals) are typical HP-inducing antigens. Although agents capable of inducing HP are found in a number of workplaces, HP is an orphan disease and only a minority of exposed individuals develop the disease. Farmer's lung (Sennekamp et al. 2012), humidifier's lung, machine worker's lung, woodworker's lung are typical forms of OHP. Several other forms and inducers are documented only in case reports. According to the EAACI position paper (Quirce et al. 2016) the possibility of OHP should be considered in all cases of interstitial lung disease of unknown etiology and in patients with relapsing respiratory and flu-like symptoms that are work-related. The reason for this is that OHP manifests with a variable spectrum of clinical and radiologic findings that may mimic a wide range of lung diseases. Establishing the diagnosis of HP and the causal role of the workplace is based on a combination of diagnostic tests and requires a multidisciplinary approach. Identification of the offending agent/source of exposure is crucial for establishing a diagnosis of OHP and providing evidence of a causal relationship between the disease and the work environment. An increased serum level of sIgG is one criterion in the diagnostic procedure of HP and crucial for the detection of the triggering antigen for successful avoidance of further exposure (Raulf et al. 2019). Only few antigens causing OHP are well characterized and further diagnostic tools for serological determination of specific IgG and antigen preparations to perform inhalation challenge tests need to be developed and standardized. Conversely, smoking has been consistently associated with a lower prevalence of specific IgG antibodies to organic antigens and clinical HP as compared to nonsmokers (Dalphin et al. 1993). The cornerstone of treatment is early removal from exposure to the eliciting antigen, although the disease may show an adverse outcome even after avoidance of exposure to the causal agent. If a worker in a company is diagnosed with OHP, the co-workers in the work area of the person concerned should be examined promptly. This will allow the early identification and treatment of any other workers who may be affected or ill. In addition, this offers the opportunity to take appropriate preventive measures for safety and health at work. These include technical, organizational, and personal measures (TOP strategy) and occupational hygiene.

References

Blanc PD, Annesi-Maesano I, Balmes JR et al (2019) The occupational burden of nonmalignant respiratory diseases. An Official American Thoracic Society and European Respiratory Society Statement. Am J Respir Crit Care Med 199:1312–1334. https://doi.org/10.1164/rccm.201904-0717ST

Böhlandt A, Schierl R, Heizinger J et al (2016) Cow hair allergen concentrations in dairy farms with automatic and conventional milking systems: from stable to bedroom. Int J Hyg Environ Health 219:79–87. https://doi.org/10.1016/j.ijheh.2015.09.004

Bonlokke JH, Bang B, Aasmoe L et al (2019) Exposures and health effects of bioaerosols in seafood processing workers – a position statement. J Agromedicine 24:1–8. https://doi.org/10.1080/1059924X.2019.1646685

Brisman J (2002) Baker's asthma. Occup Environ Med 59:498–502; quiz 502, 426. https://doi.org/10.1136/oem.59.7.498

Carder M, Seed MJ, Money A et al (2019) Occupational and work-related respiratory disease attributed to cleaning products. Occup Environ Med 76:530–536. https://doi.org/10.1136/oemed-2018-105646

Dalphin JC, Debieuvre D, Pernet D et al (1993) Prevalence and risk factors for chronic bronchitis and farmer's lung in French dairy farmers. Br J Ind Med 50:941–944. https://doi.org/10.1136/oem.50.10.941

Engel J, van Kampen V, Lotz A et al (2018) An increase of fractional exhaled nitric oxide after specific inhalation challenge is highly predictive of occupational asthma. Int Arch Occup Environ Health 91:799–809. https://doi.org/10.1007/s00420-018-1325-4

Engel J, van Kampen V, Gering V et al (2019) Non-invasive tools beyond lung function before and after specific inhalation challenges for diagnosing occupational asthma. Int Arch Occup Environ Health 92:1067–1076. https://doi.org/10.1007/s00420-019-01439-y

Enoch SJ, Seed MJ, Roberts DW et al (2012) Development of mechanism-based structural alerts for respiratory sensitization hazard identification. Chem Res Toxicol 25:2490–2498. https://doi.org/10.1021/tx3003092

Feary JR, Schofield SJ, Canizales J et al (2019) Laboratory animal allergy is preventable in modern research facilities. Eur Respir J 53:1900171. https://doi.org/10.1183/13993003.00171-2019

Folletti I, Siracusa A, Paolocci G (2017) Update on asthma and cleaning agents. Curr Opin Allergy Clin Immunol 17:90–95. https://doi.org/10.1097/ACI.0000000000000349

Hilger C, van Hage M, Kuehn A (2017) Diagnosis of allergy to mammals and fish: cross-reactive- vs. specific markers. Curr Allergy Asthma Rep 17:64. https://doi.org/10.1007/s11882-017-0732-z

Jeebhay MF, Lopata AL (2012) Occupational allergies in seafood-processing workers. Adv Food Nutr Res 66:47–73. https://doi.org/10.1016/B978-0-12-394597-6.00002-1

Jeebhay MF, Moscato G, Bang BE et al (2019) Food processing and occupational respiratory allergy-An EAACI position paper. Allergy 74:1852–1871. https://doi.org/10.1111/all.13807

Jones M (2015) Laboratory animal allergy in the modern era. Curr Allergy Asthma Rep 15:73. https://doi.org/10.1007/s11882-015-0575-4

Kelly KJ, Poole JA (2019) Pollutants in the workplace: effect on occupational asthma. J Allergy Clin Immunol 143:2014–2015. https://doi.org/10.1016/j.jaci.2019.04.013

Kespohl S, Sander I, Merget R et al (2005) Identification of an obeche (Triplochiton scleroxylon) wood allergen as a class I chitinase. Allergy 60:808–814. https://doi.org/10.1111/j.1398-9995.2005.00794.x

Kespohl S, Schlünssen V, Jacobsen G et al (2010) Impact of cross-reactive carbohydrate determinants on wood dust sensitization. Clin Exp Allergy 40:1099–1106. https://doi.org/10.1111/j.1365-2222.2010.03514.x

Kespohl S, Kotschy-Lang N, Tomm JM et al (2012) Occupational IgE-mediated softwood allergy: characterization of the causative allergen. Int Arch Allergy Immunol 157:202–208. https://doi.org/10.1159/000324953

Lau A, Tarlo SM (2019) Update on the management of occupational asthma and work-exacerbated asthma. Allergy Asthma Immunol Res 11:188–200. https://doi.org/10.4168/aair.2019.11.2.188

Lopata AL, Jeebhay MF (2013) Airborne seafood allergens as a cause of occupational allergy and asthma. Curr Allergy Asthma Rep 13:288–297. https://doi.org/10.1007/s11882-013-0347-y

Maestrelli P, Boschetto P, Fabbri LM et al (2009) Mechanisms of occupational asthma. J Allergy Clin Immunol 123:531–542; quiz 543-4. https://doi.org/10.1016/j.jaci.2009.01.057

Manavski N, Peters U, Brettschneider R et al (2012) Cof a 1: identification, expression and immunoreactivity of the first coffee allergen. Int Arch Allergy Immunol 159:235–242. https://doi.org/10.1159/000337461

Moscato G, Vandenplas O, van Wijk RG et al (2009) EAACI position paper on occupational rhinitis. Respir Res 10:16. https://doi.org/10.1186/1465-9921-10-16

Pronk A, Preller L, Raulf-Heimsoth M et al (2007) Respiratory symptoms, sensitization, and exposure response relationships in spray painters exposed to isocyanates. Am J Respir Crit Care Med 176:1090–1097. https://doi.org/10.1164/rccm.200702-215OC

Quirce S, Bernstein JA (2011) Old and new causes of occupational asthma. Immunol Allergy Clin North Am 31:677–698, v. https://doi.org/10.1016/j.iac.2011.07.001

Quirce S, Diaz-Perales A (2013) Diagnosis and management of grain-induced asthma. Allergy Asthma Immunol Res 5:348–356. https://doi.org/10.4168/aair.2013.5.6.348

Quirce S, Lemière C, de Blay F et al (2010) Noninvasive methods for assessment of airway inflammation in occupational settings. Allergy 65:445–458. https://doi.org/10.1111/j.1398-9995.2009.02274.x

Quirce S, Vandenplas O, Campo P et al (2016) Occupational hypersensitivity pneumonitis: an EAACI position paper. Allergy 71:765–779. https://doi.org/10.1111/all.12866

Racine G, Castano R, Cartier A et al (2017) Diagnostic accuracy of inflammatory markers for diagnosing occupational asthma. J Allergy Clin Immunol Pract 5:1371–1377.e1. https://doi.org/10.1016/j.jaip.2017.02.001

Raulf M (2014) The latex story. Chem Immunol Allergy 100:248–255. https://doi.org/10.1159/000358863

Raulf M (2018) Allergen component analysis as a tool in the diagnosis and management of occupational allergy. Mol Immunol 100:21–27. https://doi.org/10.1016/j.molimm.2018.03.013

Raulf M, Buters J, Chapman M et al (2014) Monitoring of occupational and environmental aeroallergens--EAACI position paper. Concerted action of the EAACI IG Occupational Allergy and Aerobiology & Air Pollution. Allergy 69:1280–1299. https://doi.org/10.1111/all.12456

Raulf M, Brüning T, Jensen-Jarolim E et al (2017) Gender-related aspects in occupational allergies – secondary publication and update. World Allergy Organ J 10:44. https://doi.org/10.1186/s40413-017-0175-y

Raulf M, Quirce S, Vandenplas O (2018) Addressing molecular diagnosis of occupational allergies. Curr Allergy Asthma Rep 18:6. https://doi.org/10.1007/s11882-018-0759-9

Raulf M, Joest M, Sander I et al (2019) Update of reference values for IgG antibodies against typical antigens of hypersensitivity pneumonitis – data of a German multicentre study. Allergo J Int 28:192–203

Sander I, Flagge A, Merget R et al (2001) Identification of wheat flour allergens by means of 2-dimensional immunoblotting. J Allergy Clin Immunol 107:907–913. https://doi.org/10.1067/mai.2001.113761

Sander I, Rozynek P, Rihs H-P et al (2011) Multiple wheat flour allergens and cross-reactive carbohydrate determinants bind IgE in baker's asthma. Allergy 66:1208–1215. https://doi.org/10.1111/j.1398-9995.2011.02636.x

Sander I, Rihs H-P, Doekes G et al (2015) Component-resolved diagnosis of baker's allergy based on specific IgE to recombinant wheat flour proteins. J Allergy Clin Immunol 135:1529–1537. https://doi.org/10.1016/j.jaci.2014.11.021

Sennekamp J, Joest M, Sander I et al (2012) Farmerlungen-Antigene in Deutschland (Farmer's lung antigens in Germany). Pneumologie 66:297–301. https://doi.org/10.1055/s-0031-1291676

Siracusa A, de Blay F, Folletti I et al (2013) Asthma and exposure to cleaning products – a European Academy of Allergy and Clinical Immunology task force consensus statement. Allergy 68:1532–1545. https://doi.org/10.1111/all.12279

Tarlo SM, Lemiere C (2014) Occupational asthma. N Engl J Med 370:640–649. https://doi.org/10.1056/NEJMra1301758

Tarlo SM, Malo J-L, de Blay F et al (2017) An Official American Thoracic Society Workshop Report: presentations and discussion of the sixth Jack Pepys workshop on asthma in the workplace. Ann Am Thorac Soc 14:1361–1372. https://doi.org/10.1513/AnnalsATS.201706-508ST

van Kampen V, Rabstein S, Sander I et al (2008) Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. Allergy 63:897–902. https://doi.org/10.1111/j.1398-9995.2008.01646.x

van Kampen V, de Blay F, Folletti I et al (2013a) EAACI position paper: skin prick testing in the diagnosis of occupational type I allergies. Allergy 68:580–584. https://doi.org/10.1111/all.12120

van Kampen V, de Blay F, Folletti I et al (2013b) Evaluation of commercial skin prick test solutions for selected occupational allergens. Allergy 68:651–658. https://doi.org/10.1111/all.12116

Vandenplas O, Raulf M (2017) Occupational latex allergy: the current state of affairs. Curr Allergy Asthma Rep 17:14. https://doi.org/10.1007/s11882-017-0682-5

Vera-Berrios RN, Feary J, Cullinan P (2019) Basophil activation testing in occupational respiratory allergy to low molecular weight compounds. Curr Opin Allergy Clin Immunol 19:92–97. https://doi.org/10.1097/ACI.0000000000000506

Zahradnik E, Raulf M (2017) Respiratory allergens from furred mammals: environmental and occupational exposure. Vet Sci 4:38. https://doi.org/10.3390/vetsci4030038

Zahradnik E, Sander I, Kendzia B et al (2011) Passive airborne dust sampling to assess mite antigen exposure in farming environments. J Environ Monit 13:2638–2644. https://doi.org/10.1039/c1em10430f

Contact Dermatitis: Overcoming Challenges of Specific Patients, Deciphering the Results and Reaching a Correct Diagnosis

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Contents

Abstract

Skin lesions caused by allergic contact dermatitis are an important occupational and environmental disease. Patch testing is the gold-standard procedure used to diagnose allergic contact dermatitis.

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The present chapter summarizes aspects of patch testing for the diagnosis of contact allergy: important working definitions, relevance of treating contact dermatitis, materials, technique, test result and interpretation, and special consideration regarding individual factors which influence the patch test outcome or necessitate special attention.

Performing and interpreting patch tests requires know-how. Knowing how to perform them and the particularities of specific cases is essential to correctly interpret the results. A correct evaluation and diagnosis will significantly impact the natural history of the disease and significantly improve the quality of life of the patient.

Keywords

Contact dermatitis · Eczema · Patch test

1 Introduction

Contact dermatitis is an inflammatory skin reaction to direct contact with noxious agents in the environment (Johansen et al. 2015). It is known for millennia through different names, with reports dating back to the first century AD, when Pliny the Younger noticed individuals experiencing severe itching when cutting pine trees (Fisher et al. 2008). Nowadays, it is a clinically defined entity and a very common skin disease, responsible for 4–7% of all dermatology consultations and with a point prevalence of 15.2% in teenagers and 18.6% in adults (Kostner et al. 2017; Waard-van der Spek et al. 2013).

There are three types of contact dermatitis (Johansen et al. 2015; Nosbaum et al. 2009):

- Allergic contact dermatitis – It is an immune-mediated type IV hypersensitivity reaction. After a sensitization phase, where the immune system learns to recognize a low molecular weight allergen, an allergen-specific T-cell sets in motion an effector phase, which results in the clinical manifestation (usually an eczematous reaction) (Nosbaum et al. 2009; Tan et al. 2014).
- Irritant contact dermatitis – It is a preferentially eczematous reaction in the skin in response to exposure to substances which induce: (1) direct cytotoxic effect on the keratinocytes, or (2) biological epidermal changes, in a dose-dependent way, resulting in the disintegration of the epidermis and inflammation (Fullerton and Serup 1997). It encompasses a large spectrum of reactions: subjective irritant reaction (*pruritus sine materia*), acute irritant reaction (erythema, oedema, inflammation, infiltration and vesiculation; the appearance may vary and is often indistinguishable from acute allergic contact dermatitis), chronic irritant reaction (dryness, fissuring and hyperkeratosis develop in reaction to cumulative and repeated exposure) and chemical burn (Fisher et al. 2008; Nosbaum et al. 2009).

- Mixed contact dermatitis – There is a simultaneous allergen-specific T-cell driven reaction and an inflammatory response of the skin to irritant agents. Frequently the irritant and allergic reaction are caused by different substances (Fisher et al. 2008).

2 The Importance of Diagnosing Allergic Contact Dermatitis

Contact dermatitis is a disease with a significant burden on many levels. Currently, it is the fifth most prevalent skin disease in the USA and has a very high economic cost (Lim et al. 2017). In 2013 in the USA, the estimated direct annual medical cost for contact dermatitis was of 1,529,000,000$; a value that surpasses that of other common skin diseases, like connective tissue diseases (1,375,000,000$), acne (846,000,000$), psoriasis (737,000,000$), urticaria (467,000,000$), and atopic dermatitis (314,000,000$) (Table 1) (Lim et al. 2017).

However, the burden of contact dermatitis goes beyond the number and severity of skin lesions (Skoet et al. 2003). Subjective psychosocial factors, which are a consequence of the former, can cause significant distress and disability to a patient: recalcitrant symptoms such as pain and itch, difficulty in fulfilling personal and familial responsibilities, restraints on leisure activities, absenteeism from work or school, impaired social contact and time-consuming treatments (Skoet et al. 2003; Swietlik and Reeder 2016). These subjective factors, however, do not necessarily correlate with the severity and extent of the skin lesions (Skoet et al. 2003; Swietlik and Reeder 2016). For example, contact dermatitis of the hands may involve less than 5% of the body surface area, but often leads to significant distress and disability (Swietlik and Reeder 2016). For this reason, the indirect costs associated with contact dermatitis are, also, significant (Table 1) (Lim et al. 2017).

By virtue of its subjectivity, self-reported questionnaires are needed to assess the impact on the quality of life (Skoet et al. 2003). There are several validated questionnaires which can be used in skin diseases, some specifically designed to evaluate the quality of life in patients with contact dermatitis: DLQI, DSQL, Skindex, SF-36, Fragrance Quality of Life Index and the Contact Dermatitis Specific Questionnaire (Skoet et al. 2003; Ramirez et al. 2017). All of these have been used to evaluate patients with contact dermatitis (Skoet et al. 2003; Swietlik and Reeder

Table 1 Comparison of prevalence and costs of six frequent cutaneous diseases. Adapted from Ref. (Lim et al. 2017)

	Prevalence (%)	Direct costs	Indirect costs
Contact dermatitis	4.17	1,529,000,000$	699,000,000$
Connective tissue diseases	0.37	1,375,000,000$	122,000,000$
Acne	1.63	846,000,000$	398,000,000$
Psoriasis	0.51	737,000,000$	113,000,000$
Urticaria	0.72	467,000,000$	163,000,000$
Atopic dermatitis	0.99	314,000,000$	128,000,000$

2016; Ramirez et al. 2017; Braunberger et al. 2016). The Fragrance Quality of Life Index specifically was evaluated in a large multicentric European study and showed that fragrance positive patients had a significant impairment in their quality of life, and it was higher than that of fragrance negative patients (after adjusting for age, sex and eczema severity) (Bennike et al. 2019).

With these metrics, two reviews – by Ramirez F et al. and by Skoet R et al. – combined the existing data on contact dermatitis (Skoet et al. 2003; Ramirez et al. 2017). All 10 studies showed that patients had a baseline reduction of the quality of life (mean DLQI scores ranged from 3.6 to 8.0) and that hand involvement, specifically, had a considerable impact on the quality of life (Skoet et al. 2003). The high DLQI scores were also predictive of the development of psychiatric comorbidities like anxiety and depression (Skoet et al. 2003).

Fortunately, evaluation and early diagnosis of contact dermatitis was associated with an improved quality of life (Skoet et al. 2003). In all studies, patch testing improved the quality of life outcomes. Even patients with no positive patch tests showed improvement (Ramirez et al. 2017). This suggests that all patients benefit at least in two ways: (1) by receiving general advice about skin management and barrier protection and (2) by resuming the use of products that they previously avoided because of concerns and by reduction of anxiety (Ramirez et al. 2017).

In summary, when screening patients for allergic contact dermatitis, physicians have many different aims:

- To confirm/exclude that an allergic reaction is the cause of the skin lesion(s);
- To identify an exacerbating factor of a dermatitis, which would prevent from effectively treating it;
- Alleviate the patient's symptoms, provide individualized advice and improve a patient's quality of life.
- To identify which allergenic substances more frequently trigger allergic contact reactions, in order to prevent future widespread sensitizations;

3 When to Refer Patients for Patch Testing?

Because an allergic contact dermatitis can manifest itself in different ways (eczematous lesions, granulomas, polymorph erythema, pigment or purpuric skin eruption) or can simply be an exacerbating factor of another skin disease, it is important to know when to suspect and test for contact dermatitis (Tennstedt 2009). In addition, even when a patch test is positive for an allergen, it is essential to determine if that sensitization is relevant (Johansen et al. 2015).

Patch testing should be performed in the following cases:

- All patients in whom contact allergy is suspected (i.e., history of reaction to a specific cream) or needs to be excluded, regardless of age or anatomical site of dermatitis (Johansen et al. 2015; Beattie et al. 2007).

- Patients with a non-eczematous dermatitis that may represent a contact allergic reaction: erythema multiforme-like; lichenoid eruptions; psoriasis (of the hands); sarcoidal, granulomatous or lymphomatous reactions; photosensitive reactions; pigment or purpuric skin eruptions; ulcerations or erosions; exanthemas; erythroderma; and contact urticaria (Johansen et al. 2015; Tennstedt 2009).
- Patients with a pre-existing eczematous dermatitis: atopic dermatitis, seborrheic dermatitis, nummular eczema, stasis dermatitis, peri-ulcerative dermatitis, dyshidrotic eczema, chronic eczema, hand eczema, feet eczema, face and neck eczema (especially if it affects eyelids and lips) (Johansen et al. 2015; Tennstedt 2009; Beattie et al. 2007).
- Patients with a pre-existing dermatitis which does not improve with treatment, initially improves but then exacerbates, or presents a change in the pattern of the dermatitis (Beattie et al. 2007; Fonacier 2015).
- Patients with mucous membrane reactions (conjunctivitis, stomatitis, or vulvitis) or suspected reaction to implants (Johansen et al. 2015; Tennstedt 2009; Beattie et al. 2007).
- Patients with a dermatitis related to occupational exposures (Johansen et al. 2015; Lazzarini et al. 2013).
- Patients with delayed type drug hypersensitivity reactions (Johansen et al. 2015).

4 How to Perform Patch Tests?

To determine if a patient has an allergic contact dermatitis, the standard procedure for diagnosis is the patch test: the process of applying contact allergens to the skin under occlusion and visually grading the skin inflammatory response (Johansen et al. 2015). Briefly, the allergens are placed in patch test chambers and then placed on the upper back of the patient. This anatomical placement offers a wide flat surface for good occlusion, is less often affected by skin diseases and is not regularly exposed to sun (Johansen et al. 2015). The allergens remain in occlusion for 48 h, after which the chambers are removed, and the first reading is performed. A second reading is performed after 96 h (and sometimes a third on the 7th day) (Fig. 1) (Johansen et al. 2015).

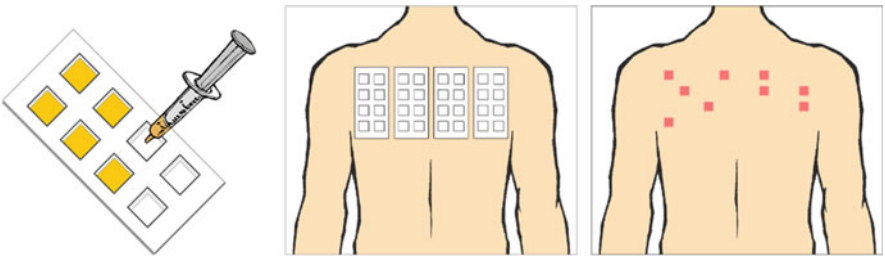

Fig. 1 Schematic of how to perform and place the patch tests

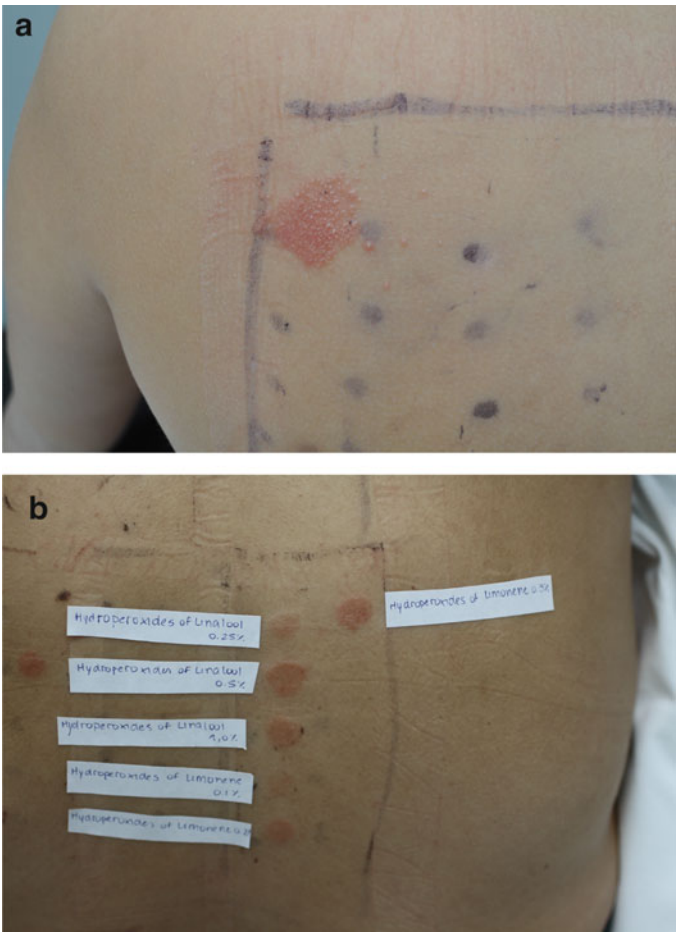

Fig. 2 Positive patch testing assessed after 5 days. (**a**) A three + reaction characterized by erythema, infiltration and vesicles. (**b**) Positive reactions with erythema, one + and with infiltration two ++, induced by different concentrations of Limonene and Linalool hydroperoxides

The morphology of the reaction (erythema, infiltrate, papules and vesicles) is evaluated by the ICDRG criteria, to determine if the reaction is positive (Fig. 2) (Johansen et al. 2015). This determination and differentiation from false-positive reaction is crucial, because it will have prognostic implications for the patient and determine if avoidance of specific substances is warranted (Johansen et al. 2015).

A false-positive is a positive reaction in the absence of contact allergy to the tested substance (Le Coz and Sasseville 2009). It can range from isolated erythema to an exuberant reaction like a purpuric reaction, pustules, pus containing vesicles or necrosis (Le Coz and Sasseville 2009). A false positive can be due to: (1) an irritant reaction to the tested substance (uncommon with standardized extract preparations) (Le Coz and Sasseville 2009); (2) damaged skin or active dermatitis on the patch test

site. In these cases, the threshold to develop an irritant reaction is very low and it is possible to develop generalized positive reactions to many allergens, a condition known as "angry back" (Le Coz and Sasseville 2009); (3) use of an excessive amount of testing material; (55) and (4) close proximity of allergens being tested (Le Coz and Sasseville 2009).

Contrary to false-positives, in false-negative reactions, there is no evident reaction despite the existence of contact allergy (Le Coz and Sasseville 2009). In these cases, the consequences of not identifying the culprit substance are more severe, because we risk the patient's continued exposure to the culprit agent and multiple recurrences (Le Coz and Sasseville 2009). False-negatives can occur due to: (1) excessive dilution of the tested substance (Le Coz and Sasseville 2009), (2) too early reading (some substances like corticosteroids, epoxy resin, metals and some drugs may only provide positive results after 7 days) (Le Coz and Sasseville 2009), (3) absence of the culprit allergen for testing (Le Coz and Sasseville 2009), (4) insufficient occlusion/poorly placed test strips (Le Coz and Sasseville 2009), (5) concomitant treatments/diseases that suppress the positive response (Le Coz and Sasseville 2009).

The existence of these false-reactions is the main reason for having specific recommendations in specific populations (Le Coz and Sasseville 2009).

5 Assessing the Relevance of Positive Patch Test Reactions

Reading patch test results cannot be limited to scoring them as positive or negative. Finding a positive or negative result has no meaning if it is not linked in some way with the medical history of the patient. This interpretation is the most challenging aspect of patch testing.

The physician needs to take into account: the past and present clinical history, exposure patterns of the individual, the dermatitis/lesions which were the cause of the consultation and the morphology and location of the lesions.

Briefly, after determining if the reaction is a true positive, the patient should be assigned to one of the following categories:

- Positive patch test with current/present relevance → When the exposure to the positive allergen putatively explains the patients' current lesions, which were the cause of the consultation. There should be a history of eliciting/worsening of the dermatitis in contact with the allergen, and the distribution pattern of the lesions should be compatible with the allergen exposure.
- Occasionally, the reaction will be caused by a chemically related substance and the chemical relationship between the molecules will help to understand the cross-reactivity patterns. Hence, an allergen might not itself be found relevant or present in a patient's clinical history; but it cross-reacts with the actual culprit.
- Positive patch test with past relevance → When the exposure to the positive allergen putatively explains a past clinical disease, not directly related to the current symptoms. Re-exposure thus poses a risk of recurring symptoms.

- Positive patch test without clinical relevance → When the patient has repeated exposure to the positive allergen, without developing any clinical symptoms. The positive patch test indicates that the patient is sensitized to the allergen; in other words, the patient's immune system recognizes that specific allergen. However, regulatory mechanisms stop the immune system from developing a clinical reaction and the allergen is, thus, tolerated and does not elicit clinical manifestations. When the allergen begins to elicit a reaction, it goes from contact sensitization to contact allergy.

A subsequent evaluation of the patient after instituting eviction of the offending allergens can help confirm the diagnosis.

6 Patch Testing in Special Conditions

It is important to always try to perform patch tests on patients not influenced by confounding factors. However, in real-world conditions, not all patients can be healthy adults, without confounding or influencing factors. In these cases, a medical evaluation of the case is mandatory, to determine if postponing the tests is necessary. In the literature, there are different populations whose characteristics may influence patch test results. They can be organized into four different groups (Fig. 3):

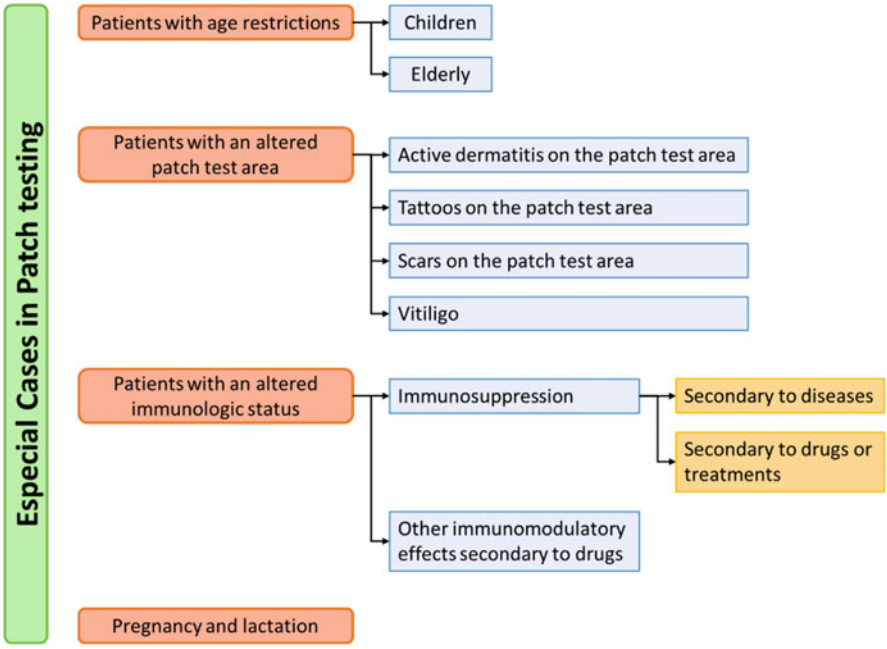

Fig. 3 Special consideration cases in patch testing

6.1 Children

Allergic contact dermatitis was thought to be a rare condition in children for many years (Johansen et al. 2015; Waard-van der Spek et al. 2013; Beattie et al. 2007). In recent years, contact sensitization in children has been increasingly recognized (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015). Recent reports point to a prevalence of allergic contact dermatitis of 13.3–23.3%, and some reports show an incidence of positive patch tests as high as 67% in children suspected of having an allergic contact dermatitis (Johansen et al. 2015; Waard-van der Spek et al. 2013; Beattie et al. 2007; Belloni Fortina et al. 2015, 2016). Data on adolescents are very similar to adults with respect to prevalence and causal agents (Johansen et al. 2015; Belloni Fortina et al. 2015). Children up to 12 years of age show some particularities (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015). In this group age, the most frequently encountered sensitizations vary between Europe and North America, but include: nickel sulphate, cobalt chloride, potassium dichromate, neomycin sulphate, *Myroxylon pereirae*, PPD, Kathon CG, fragrance mix, lanolin alcohols, colophony, compositae mix, propylene glycol, turpentine, bufexamac, bacitracin, budesonide, tixocortol-21-pivalate, carba mix, cocamidopropyl betaine, disperse blue 124/106, formaldehyde, quaternium 15 (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015) (Table 2).

Patch tests are considered safe in children and are recommended when allergic contact dermatitis is suspected or needs to be excluded (Johansen et al. 2015; Fisher et al. 2008; Kostner et al. 2017; Waard-van der Spek et al. 2013; Nosbaum et al. 2009; Tan et al. 2014; Lim et al. 2017; Skoet et al. 2003; Swietlik and Reeder 2016; Ramirez et al. 2017; Braunberger et al. 2016; Bennike et al. 2019; Tennstedt 2009; Beattie et al. 2007; Fonacier 2015; Lazzarini et al. 2013; Le Coz and Sasseville 2009; Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015). The technique is the same as in adults; however, it needs to account for a few factors:

- Children move and have greater mobility, requiring stronger adhesive to maintain the patch tests in place (Johansen et al. 2015).
- Smaller back may require a reduction of the baseline series (Johansen et al. 2015).
- Some allergens included in the adult baseline series have little relevance of exposure in children (e.g., epoxy resin) and may not need to be tested regularly in children under 12 (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015).
- There is a concern that testing with some allergens, especially if they have little relevance of exposure, can induce sensitization or cause a too intense positive reaction (e.g., PPD) (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015; Belloni Fortina et al. 2016; Spornraft-Ragaller et al. 2011, 2012). With regard to PPD, some authors suggest reducing the concentration to as low as 0.05% to compensate for the extreme

Table 2 Recommended allergens to be tested in children according to Refs. (Waard-van der Spek et al. 2015; Jacob et al. 2014)

Recommended allergens to be tested as standard series in children proposed by EAACI	
Nickel sulphate	
Thiuram mix	
Colophony	
Mercaprobenzothiazole	
Fragrance mix I	
Fragrance mix II	
Mercapto mix	
Kathon CG	
Sesquiterpene lactone mix	
Additional allergens to be tested according to clinical history	
Allergen	**Relevant exposure history**
p-Tert-butylphenol formaldehyde resin	Rubber containing shoe allergens, bras, sports gear
Potassium dichromate	Shoe allergens
Wool alcohols	Skin care products or cosmetics
p-Phenylenediamine (PPD)	Henna tattoos, hair dye
Disperse blue 124/106	Clothing dyes
Tixocortol pivalate	Topical corticosteroids
Budesonide	Topical corticosteroids
Bufexamac	Bufexamac
Neomycin	Neomycin
Dibromodicyanobutane (methyldibromo glutaronitrile)	Skin care products or cosmetics
Compositae mix	Plants
Lyral	Skin care products or cosmetics

patch test reactivity to this allergen in children (Johansen et al. 2015; Spornraft-Ragaller et al. 2011, 2012).

Considering all these facts, some authors suggest that children should be tested with a reduced baseline series, adding specific allergens when there is relevant exposure story (Table 2) (Belloni Fortina et al. 2015; Worm et al. 2007; Jacob et al. 2014, 2017; Waard-van der Spek et al. 2015).

6.2 Elderly

There is no evidence nor any studies that suggest that patch testing in the elderly may be harmful or is unreliable.

6.3 Patients with Generalized Dermatitis or Dermatitis on the Patch Testing Area

A commonly encountered clinical situation is a patient with active, often severe, dermatitis on the sites of application of the patch tests (Owen et al. 2018). This scenario is usually an indication to postpone testing to a future date, as patch testing on actively inflamed skin may lead to both false-positive and false-negative reactions (Owen et al. 2018). In addition, the patient may experience immense discomfort from the adhesives used (pruritus and pain), increased heat and sweat, and exposure to potentially irritating reagents being tested (Owen et al. 2018).

This can affect the evaluation of patients with common skin diseases, like acne, lichen planus, pityriasis, atopic dermatitis, and others which frequently affect the upper back. The existence of an active dermatitis on the sites of application of the patch tests is a reason to postpone the tests (Johansen et al. 2015). Whenever possible, the dermatitis should be treated, and the tests performed at a later date.

The existence of an active dermatitis on the sites of application of the patch tests is a reason to postpone the tests (Johansen et al. 2015). Of all, atopic dermatitis deserves special mention.

Atopic dermatitis is a chronic relapsing inflammatory skin disease, and two main questions are still debated when patch testing these patients: (1) do atopic dermatitis patients have altered prevalence or increased risk for contact sensitization, and (2) are patch tests results influenced by atopic dermatitis (Hamann et al. 2017).

With respect to the first point, there are arguments to support both cases. In favour of a decreased risk of contact sensitization is the fact that atopic dermatitis is primarily a Th2-driven disease and contact dermatitis is Th1-driven (Rundle et al. 2017). In addition, some experimental studies have found an increased elicitation threshold in patients with atopic dermatitis (Hamann et al. 2017). On the other hand, some suggest there is an increased risk of contact sensitization because the skin of patients with atopic dermatitis has a nearly twofold increased skin absorption of chemicals, including irritants and contact allergens (Hamann et al. 2017). This is especially significant because these patients are exposed daily to innumerous substances, in creams and lotions, as part of their regular skin care routine and recommended treatment plans (Hamann et al. 2017).

Epidemiologic studies on the prevalence of contact sensitization have shown mixed results (Belloni Fortina et al. 2016; Hamann et al. 2017; Rundle et al. 2017; Mortz et al. 2015). A recent meta-analysis showed no significant association between atopic dermatitis and contact sensitization, with atopic dermatitis individuals having similar rates of contact sensitization as those of individuals without atopic dermatitis (Hamann et al. 2017). Even if the prevalence of contact dermatitis is the same as in the general population, it is still a high prevalence and clinicians should consider patch testing in this population (Hamann et al. 2017). Special attention should be paid to the agents who are in frequent contact with topical corticosteroids, antiseptics, antibiotics, fragrances and preservatives (Rundle et al. 2017).

Pertaining to the influence of atopic dermatitis on patch tests result, many studies show that clinically relevant sensitizations can be uncovered by patch testing these patients (Johansen et al. 2015; Belloni Fortina et al. 2016; Hamann et al. 2017; Rundle et al. 2017). However, *the reading and interpretation of the results must be prudent*. Patients with atopic dermatitis have a hyper-reactive skin, with a lower irritancy threshold, which may lead to higher rates of irritant or false-positive reactions (most commonly with metals, fragrances, formaldehyde, and lanolin) (Johansen et al. 2015; Owen et al. 2018). This raises concerns, as even the unaffected skin of patients with atopic dermatitis has been shown to have barrier dysfunction and potentially be more predisposed to develop irritation reactions (Rundle et al. 2017). Paradoxically, in this altered skin, positive reactions may display weaker reactions and be misdiagnosed as an irritant reaction (i.e., false-negative) (Owen et al. 2018). In light of all these and other factors, a consensus report was published on how to perform patch tests on patients with atopic dermatitis (Chen et al. 2016).

In summary, atopic dermatitis in not a contraindication for patch testing, in fact, these patients should absolutely be tested (Johansen et al. 2015; Owen et al. 2018; Hamann et al. 2017). If complete clearing of the patch test area cannot be achieved, then the patch test should still be performed, because relevant sensitizations can still be uncovered. Whenever possible, after the patient improves and the patch testing area clears, the tests should be repeated to confirm the results. However, reading and interpretation of the results should be performed by skilled experienced physicians.

6.4 Tattoos, Scars and Vitiligo on the Patch Test Area

Patch tests should always be performed in as healthy a skin as possible (Johansen et al. 2015). Therefore, physicians should avoid placing the strips on scars and tattoos, which may alter skin reactivity and/or conceal the reaction (Johansen et al. 2015).

There is some evidence that allergic contact dermatitis can cause vitiligo, with vitiligo areas appearing at the site of positive patch tests (e.g., testing with PPD) (Lee et al. 2014; Jappe et al. 2005; Kwok et al. 2011). This is also supported by the improvement seen with the corresponding allergen avoidance (Lee et al. 2014; Jappe et al. 2005; Kwok et al. 2011). However, there is no data on patch test reactivity performed of skin with vitiligo. The general recommendation of avoiding altered skin should be followed, but it is not an absolute contraindication.

6.5 Immunosuppression, Secondary to Disease

There are many highly prevalent diseases that cause various degrees of immunosuppression or immune dysfunction: HIV, diabetes, auto-immune diseases and primary immune deficiencies. However, very little data exist on their impact on patch testing.

Concerning HIV, a few reports show these patients can have relevant positive patch test results, even in severely immunocompromised patients with AIDS (Curr

and Nixon 2006; Muñoz-Pérez et al. 1999; Bellegrandi et al. 1999; Smith et al. 1997; Viraben et al. 1994). However, the frequency of contact dermatitis and whether the infection impacts patch tests results is not known. A single report of 26 HIV patients with dermatitis and/or itching showed positive tests in 31% and the finding was clinically relevant in 19% (Bellegrandi et al. 1999).

Diabetic patients have been reported to have contact dermatitis, particularly related to their medical devices (Herman et al. 2018; Passanisi et al. 2018; Peeters et al. 2017; Jolanki et al. 2001). But, like HIV, the prevalence is not known, nor the impact of diabetes on patch tests results. A single report – which analysed 13,315 patients patch-tested between 1985 and 2003 – found that 229 (1.7%) had type 1 diabetes and 60 (26%) of the 229 had positive patch results (Engkilde et al. 2006). The same report found an inverse correlation between type 1 diabetes and contact dermatitis (Engkilde et al. 2006). Another report suggests that DPP-4 inhibitors may increase the risk of contact dermatitis (Tasic et al. 2011). However, more information is needed. Currently, there is no recommendation that these patients need to be systematically tested, unless there is a suspicion of contact dermatitis.

Auto-immune diseases, type I diabetes and contact dermatitis follow a Th1 profile and it is not known if this impacts skin reactivity or disease risk. Patients with autoimmune diseases can develop contact dermatitis (Dermendzhiev et al. 2018; Niedziela and Bluvshteyn-Walker 2012; Trindade et al. 2004; Kosboth et al. 2007). One report, in a small sample, found that patients with discoid lupus had a higher frequency of contact dermatitis than healthy controls (Güner et al. 2013).

There are no studies regarding primary immune deficiency patients.

Transplant patients usually have an immunosuppression induced by drugs, which will be discussed ahead.

In all these situations, more studies are needed. Currently, no formal contraindications exist for patch testing these patients and, if suspected, contact dermatitis should always be tested.

6.6 Immunosuppression, Secondary to Drugs

There are many different classes of drugs that modulate the response of the immune system. Given that many of the patients referred for patch testing have some sort of dermatitis, it is not unusual for them to be taking an immunosuppressing drug. The relative impact of each on patch testing is a matter of current debate, complicated by the lack of placebo-controlled studies (Johansen et al. 2015).

- Anti-histamines and Cromoglycate – These drugs do not influence the results of the patch tests and can be used whilst performing them (Johansen et al. 2015). Anti-histamines may provide symptom relief to some patients with positive reactions.
- Topical corticosteroids – They only affect patch testing if they are applied to the patch testing area (Johansen et al. 2015). Small studies have demonstrated this (Johansen et al. 2015; Smeenk 1975; Sukanto et al. 1981; Green 1996). They modulate the positivity of these tests in several ways: immunosuppressive effect,

vasoconstrictor effect and epidermal rebound phenomena (Johansen et al. 2015). According to current practice, not applying topical corticosteroids for 7 days prior to testing is considered adequate, although there are no controlled studies concerning this (Johansen et al. 2015).

- Systemic corticosteroids – Systemic corticosteroids have been shown to suppress patch test reactivity. Earlier studies in the 50s, 60s and 70s strongly indicated it, but lacked procedural consistency (Sulzberger et al. 1952; O'Quinn and Isbell 1969; Feuerman and Levy 1972; Condie and Adams 1973). In recent years, a multicentre study demonstrated that prednisone (20 mg/day) reduced the number and intensity of the reaction of positive patch tests compared to placebo (Anveden et al. 2004). This effect seemed to be avoided if the dose was of only 10 mg/day of prednisone (Olupona and Scheinman 2008). Other corticosteroids are less studied, but a study with betamethasone (2mg/day, equivalent to 16.7 mg of prednisolone) for 6 months revealed a reduction on positive reactions of 42.8% (Verma et al. 2016a). This is a higher rate than the one was observed with the 20 mg/day of prednisone, suggesting that a specific corticosteroid may impact patch tests in more ways than that which can be determined by simple dose equivalency with prednisone.
- Other immunosuppressants (cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, dupilumab, rituximab, infliximab, adalimumab, etanercept, and others) – like corticosteroids, these drugs have the capacity to inhibit the immune system and, possibly, the reaction responsible for eliciting a positive result (Patel et al. 2018). Some are used and effectively treat allergic contact dermatitis (Patel et al. 2018). However, very little is known of the actual effect these drugs have on patch tests. Some data show positive results can still be found in patients taking these drugs, but the rate of false negatives is not known (Wee et al. 2010; Rosmarin et al. 2009; Pigatto et al. 2008; Verma et al. 2016b; Puza and Atwater 2018). While it is best to patch test when patients are off immunosuppressants, immunosuppressive therapies should not be an absolute contraindication to patch testing.
- Cancer and chemotherapy – Skin conditions are very frequent in cancer patients (Phillips et al. 2018). In a study where 412 cancer patients with skin complaints were evaluated by dermatologists, 645 diagnoses were reached (Phillips et al. 2018). Across all diagnoses, the specific conditions of herpes zoster (4%) and contact dermatitis (3%) occurred most frequently (Phillips et al. 2018). Despite this indication of the frequency of contact dermatitis in cancer patients, there are no studies on the effect of active chemotherapy on patch tests results.

In summary, anti-histamines and cromoglycate can be taken and have no effect on patch testing. Topical corticosteroids, if being applied to the patch testing area, should be suspended for 7 days prior to testing. If a patient is taking systemic immunosuppressants (corticosteroids, cyclosporine, etc.), whenever possible, they should suspend them and wait for a period of five half-lives of the specific drug before patch testing. If it is imperative to continue the treatment, it is recommended to reduce its dose to the minimum possible dose and proceed with patch testing. There is the risk of false-negative reactions. However, many positive relevant reactions can still be found. Whenever possible, after the patient weans off the medication, the tests should be repeated.

6.7 Patients Under Immunomodulatory Drugs or Treatments

Some treatments are also known to modulate the immune system, without inducing immunosuppression:

- Retinoids – They can be used to treat certain forms of eczema, like hand eczema (Johansen et al. 2015; Kostner et al. 2017). However, there are no reports assessing their effect on the positivity of patch tests (Johansen et al. 2015). Topical retinoids are known to be irritant and it is strongly advised that patients refrain from applying topical retinoids to the patch test area (Fullerton and Serup 1997; Greenspan et al. 2003). There are no data on systemic retinoids.
- UV radiation – Ultra-violet radiation has a known immunomodulatory effect on the skin (Johansen et al. 2015). It induces a reduction in epidermal Langerhans cells numbers; UV-B temporarily reduces the ability to elicit an allergic reaction; and UV-A, in combination with psoralen, causes a reduction of patch test reactions (Johansen et al. 2015).
- Patients are advised not to have a suntan or use a sunbed 2–4 weeks before patch testing (Fonacier 2015).
- Omalizumab – There are no reports which suggest that patch test reactivity is altered by omalizumab.
- Allergen immunotherapy – Some reports suggest that subcutaneous immunotherapy can induce contact allergy to aluminium in the form of granulomas (Verma et al. 2016a; Patel et al. 2018; Wee et al. 2010; Rosmarin et al. 2009; Pigatto et al. 2008; Verma et al. 2016b; Puza and Atwater 2018; Phillips et al. 2018; Fullerton and Serup 1997; Greenspan et al. 2003; Vogelbruch et al. 2000; García-Patos et al. 1995; Castelain et al. 1988). However, this fact failed to be demonstrated in a larger study (Netterlid et al. 2013). No studies exist to indicate that patch test reactivity is altered during immunotherapy.

6.8 Pregnancy or Lactation

Patch testing during pregnancy or lactation is not known to be harmful, but most physicians postpone testing as a general precaution (Johansen et al. 2015). There is no reason to suspect patch testing will have any deleterious effect on the pregnancy or baby (Johansen et al. 2015). However, in most cases, there is no urgent need for immediate testing and testing can be postponed a few months.

7 Applying the Recommendations to Clinical Practice

All patients have unique characteristics. Taking into account all the previous aspects is necessary in order to arrive at a correct diagnosis. Figure 4 offers a summary of all the steps:

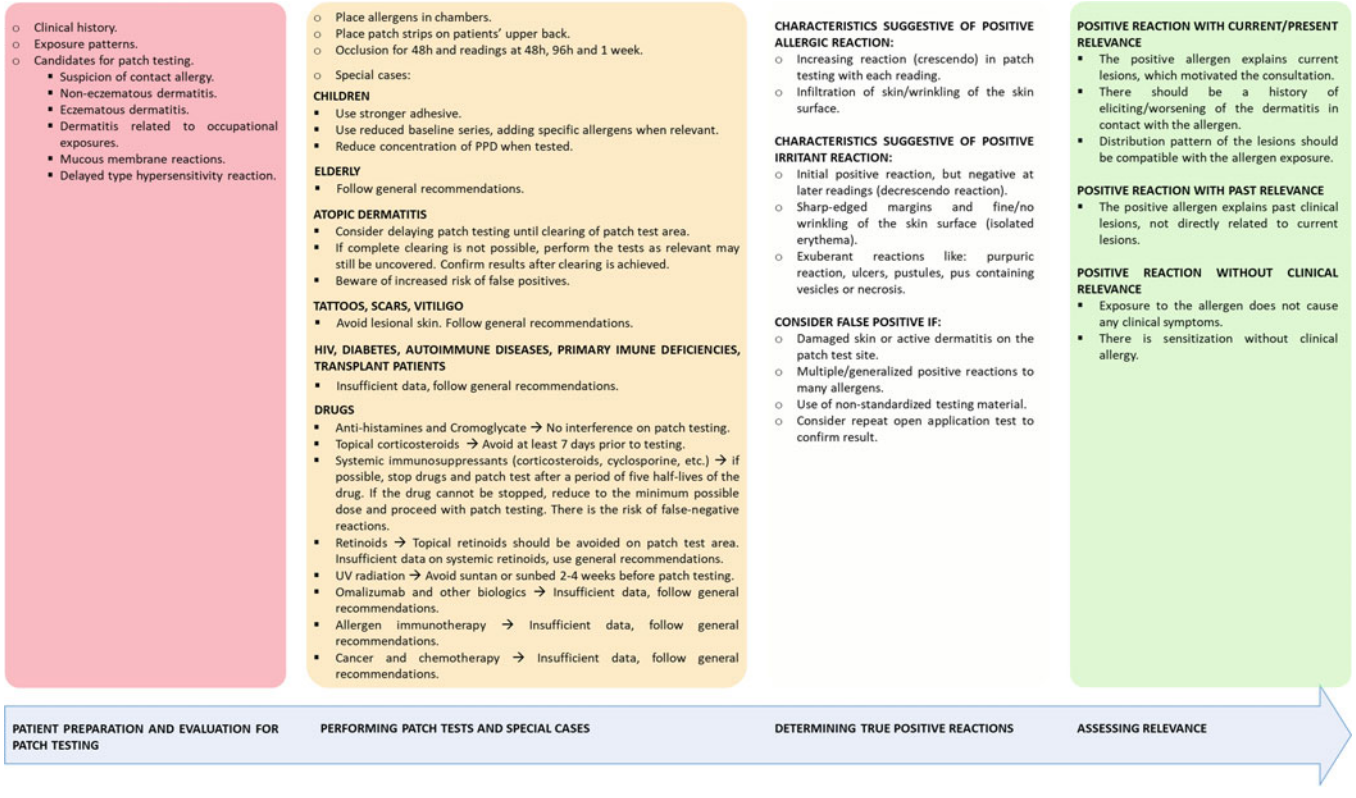

Fig. 4 Steps to patch testing

8 Conclusion

For the moment, patch tests remain the gold standard for the diagnosis of allergic contact dermatitis. Knowing how to perform them and the particularities of specific cases is essential to correctly interpret the results. A correct evaluation and diagnosis will significantly impact the natural history of the disease and significantly improve the quality of life of the patient.

References

Anveden I, Lindberg M, Andersen KE, Bruze M, Isaksson M, Liden C et al (2004) Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel. Contact Dermatitis. 50(5):298–303

Beattie PE, Green C, Lowe G, Lewis-Jones MS (2007) Which children should we patch test? Clin Exp Dermatol. 32(1):6–11

Bellegrandi S, Rosso R, Mattiacci G, Ferrara R, D'Offizi G, Aiuti F et al (1999) Contact dermatitis in subjects infected with HIV type 1. J Am Acad Dermatol. 40(5 Pt 1):777–779

Belloni Fortina A, Cooper SM, Spiewak R, Fontana E, Schnuch A, Uter W (2015) Patch test results in children and adolescents across Europe. Analysis of the ESSCA Network 2002-2010. Pediatr Allergy Immunol. 26(5):446–455

Belloni Fortina A, Fontana E, Peserico A (2016) Contact sensitization in children: a retrospective study of 2,614 children from a single center. Pediatr Dermatol. 33(4):399–404

Bennike NH, Heisterberg MS, White IR, Mahler V, Silvestre-Salvador JF, Giménez-Arnau A et al (2019) Quality of life and disease severity in dermatitis patients with fragrance allergy – a cross-sectional European Questionnaire Study. Contact Dermatitis 81(2):89–96

Braunberger T, Lynn D, Reimer C, Doctor M, Hill MK, Mounessa J et al (2016) Disease severity and quality of life measurements in contact dermatitis: a systematic review 2005-2015. Dermatitis 27(6):362–371

Castelain PY, Castelain M, Vervloet D, Garbe L, Mallet B (1988) Sensitization to aluminium by aluminium-precipitated dust and pollen extracts. Contact Dermatitis. 19(1):58–60

Chen JK, Jacob SE, Nedorost ST, Hanifin JM, Simpson EL, Boguniewicz M et al (2016) A pragmatic approach to patch testing atopic dermatitis patients: clinical recommendations based on expert consensus opinion. Dermatitis. 27(4):186–192

Condie MW, Adams RM (1973) Influence of oral prednisone on patch-test reactions to Rhus antigen. Arch Dermatol 107:540–543

Curr N, Nixon R (2006) Allergic contact dermatitis to basic red 46 occurring in an HIV-positive patient. Australas J Dermatol. 47(3):195–197

Dermendzhiev S, Ivanovska M, Dermendzhiev T (2018) Allergic contact dermatitis, angioneurotic edema and conjunctivitis in a patient with autoimmune thrombocytopenia – a clinical case. Open Access Maced J Med Sci. 6(11):2142–2146

Engkilde K, Menné T, Johansen JD (2006) Inverse relationship between allergic contact dermatitis and type 1 diabetes mellitus: a retrospective clinic-based study. Diabetologia. 49(4):644–647

Feuerman E, Levy A (1972) A study of the effect of prednisone and an antihistamine on patch test reactions. Br J Dermatol 86:68–71

Fisher AA, Rietschel RL, Fowler JF, Fisher AA (2008) Fisher's contact dermatitis. BC Decker Inc, Hamilton

Fonacier L (2015) A practical guide to patch testing. J Allergy Clin Immunol Pract. 3(5):669–675

Fullerton A, Serup J (1997) Characterization of irritant patch test reactions to topical D vitamins and all-trans retinoic acid in comparison with sodium lauryl sulphate. Evaluation by clinical scoring and multiparametric non-invasive measuring techniques. Br J Dermatol. 137(2):234–240

García-Patos V, Pujol RM, Alomar A, Cisteró A, Curell R, Fernández-Figueras MT et al (1995) Persistent subcutaneous nodules in patients hyposensitized with aluminum-containing allergen extracts. Arch Dermatol. 131(12):1421–1424

Green C (1996) The effect of topically applied corticosteroid on irritant and allergic patch test reactions. Contact Dermatitis 35:331–333

Greenspan A, Loesche C, Vendetti N, Georgeian K, Gilbert R, Poncet M et al (2003) Cumulative irritation comparison of adapalene gel and solution with 2 tazarotene gels and 3 tretinoin formulations. Cutis. 72(1):76–81

Güner E, Kalkan G, Meral E, Baykır M (2013) The triggering role of allergic contact dermatitis in discoid lupus erythematosus. Cutan Ocul Toxicol. 32(3):194–199

Hamann CR, Hamann D, Egeberg A, Johansen JD, Silverberg J, Thyssen JP (2017) Association between atopic dermatitis and contact sensitization: a systematic review and meta-analysis. J Am Acad Dermatol. 77(1):70–78

Herman A, de Montjoye L, Tromme I, Goossens A, Baeck M (2018) Allergic contact dermatitis caused by medical devices for diabetes patients: a review. Contact Dermatitis. 79(6):331–335

Jacob SE, Admani S, Herro EM (2014) Invited commentary: recommendation for a north american pediatric patch test series. Curr Allergy Asthma Rep. 14(6):444

Jacob SE, Lipp MB, Suh E, Goldenberg A (2017) Practice patterns of dermatologists in the pediatric contact dermatitis registry. Pediatr Dermatol. 34(4):408–412

Jappe U, Geier J, Hausen BM (2005) Contact vitiligo following a strong patch test reaction to triglycidyl-p-aminophenol in an aircraft industry worker: case report and review of the literature. Contact Dermatitis. 53(2):89–92

Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M et al (2015) European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. Contact Dermatitis. 73(4):195–221

Jolanki R, Kanerva L, Estlander T, Henriks-Eckerman ML, Suhonen R (2001) Allergic contact dermatitis from phenoxyethoxy ethylacrylates in optical fiber coating, and glue in an insulin pump set. Contact Dermatitis. 45(1):36–37

Kosboth M, Chin-Loy A, Lyons R, Wesson SK, Reeves WH (2007) Malar rash caused by metal allergy in a patient with systemic lupus erythematosus. Nat Clin Pract Rheumatol. 3(4):240–245

Kostner L, Anzengruber F, Guillod C, Recher M, Schmid-Grendelmeier P, Navarini AA (2017) Allergic contact dermatitis. Immunol Allergy Clin North Am. 37(1):141–152

Kwok C, Wilkinson M, Sommer S (2011) A rare case of acquired leukoderma following patch testing with an acrylate series. Contact Dermatitis. 64(5):292–294

Lazzarini R, Duarte I, Ferreira AL (2013) Patch tests. An Bras Dermatol. 88(6):879–888

Le Coz CJ, Sasseville D (2009) Interpretation and relevance of patch testing: false-positive and false-negative test reactions, compound allergy, cross-sensitivity. Ann Dermatol Venereol. 136 (8-9):610–616

Lee JH, Ahn BJ, Noh M, Lee AY (2014) Patch test reactions in patients with the additional diagnosis of vitiligo. Int J Dermatol. 53(2):187–191

Lim HW, Collins SAB, Resneck JS Jr, Bolognia JL, Hodge JA, Rohrer TA et al (2017) The burden of skin disease in the United States. J Am Acad Dermatol 76(5):958–972.e952

Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C (2015) Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy. 70(7):836–845

Muñoz-Pérez MA, García-Bravo B, Rodriguez-Pichardo A, Camacho F (1999) Coexistence of allergic contact dermatitis and granuloma annulare in an HIV-1-infected patient: a casual association? Am J Contact Dermat. 10(2):100–101

Netterlid E, Hindsén M, Siemund I, Björk J, Werner S, Jacobsson H et al (2013) Does allergen-specific immunotherapy induce contact allergy to aluminium? Acta Derm Venereol. 93 (1):50–56

Niedziela M, Bluvshteyn-Walker S (2012) Autoimmune thyroid disease and allergic contact dermatitis: two immune-related pathologies in the same patient. J Pediatr Endocrinol Metab. 25(1-2):31–32

Nosbaum A, Vocanson M, Rozieres A, Hennino A, Nicolas JF (2009) Allergic and irritant contact dermatitis. Eur J Dermatol. 19(4):325–332

O'Quinn SE, Isbell KH (1969) Influence of oral prednisone on eczematous patch test reactions. Arch Dermatol 99:380–389

Olupona T, Scheinman P (2008) Successful patch testing despite concomitant low-dose prednisone use. Dermatitis. 19(2):117–118

Owen JL, Vakharia PP, Silverberg JI (2018) The role and diagnosis of allergic contact dermatitis in patients with atopic dermatitis. Am J Clin Dermatol. 19(3):293–302

Passanisi S, Lombardo F, Barbalace A, Caminiti L, Panasiti I, Crisafulli G et al (2018) Allergic contact dermatitis and diabetes medical devices: 2 clinical cases. Contact Dermatitis 79 (2):115–117

Patel A, Burns E, Burkemper NM (2018) Methotrexate use in allergic contact dermatitis: a retrospective study. Contact Dermatitis. 78(3):194–198

Peeters C, Herman A, Goossens A, Bruze M, Mowitz M, Baeck M (2017) Allergic contact dermatitis caused by 2-ethyl cyanoacrylate contained in glucose sensor sets in two diabetic adults. Contact Dermatitis. 77(6):426–429

Phillips GS, Freites-Martinez A, Hsu M, Skripnik Lucas A, Barrios DM, Ciccolini K et al (2018) Inflammatory dermatoses, infections, and drug eruptions are the most common skin conditions in hospitalized cancer patients. J Am Acad Dermatol. 78(6):1102–1109

Pigatto P, Cesarani A, Barozzi S, Guzzi G (2008) Positive response to nickel and azathioprine treatment. J Eur Acad Dermatol Venereol. 22(7):891

Puza CJ, Atwater AR (2018) Positive patch test reaction in a patient taking dupilumab. Dermatitis. 29(2):89

Ramirez F, Chren MM, Botto N (2017) A review of the impact of patch testing on quality of life in allergic contact dermatitis. J Am Acad Dermatol. 76(5):1000–1004

Rosmarin D, Gottlieb AB, Asarch A, Scheinman PL (2009) Patch-testing while on systemic immunosuppressants. Dermatitis. 20(5):265–270

Rundle CW, Bergman D, Goldenberg A, Jacob SE (2017) Contact dermatitis considerations in atopic dermatitis. Clin Dermatol. 35(4):367–374

Skoet R, Zachariae R, Agner T (2003) Contact dermatitis and quality of life: a structured review of the literature. Br J Dermatol. 149(3):452–456

Smeenk G (1975) Influence of local triamcinolone acetonide on patch test reactions to nickel sulphate. Dermatologica 150:116–121

Smith KJ, Skelton HG, Nelson A, Wagner KF, Hackley BE Jr (1997) Preservation of allergic contact dermatitis to poison ivy (urushiol) in late HIV disease. The implications and relevance to immunotherapy with contact allergens. Dermatology. 195(2):145–149

Spornraft-Ragaller P, Schnuch A, Uter W (2011) Extreme patch test reactivity to p-phenylenediamine but not to other allergens in children. Contact Dermatitis. 65(4):220–226

Spornraft-Ragaller P, Kämmerer E, Gillitzer C, Schmitt J (2012) Severe allergic reactions to para-phenylenediamine in children and adolescents: should the patch test concentration of PPD be changed? J Dtsch Dermatol Ges. 10(4):258–264

Sukanto H, Nater JP, Bleumink E (1981) Influence of topically applied corticosteroids on patch test reactions. Contact Dermatitis 7:180–185

Sulzberger MB, Witten VH, Zimmerman EH (1952) The effects of oral cortisone acetate on patch test reactions to eczematogenous contact allergens. Acta Derm Venereol Suppl (Stockh) 29:343–352

Swietlik J, Reeder M (2016) Current Quality-of-Life Tools Available for Use in Contact Dermatitis. Dermatitis. 27(4):176–185

Tan CH, Rasool S, Johnston GA (2014) Contact dermatitis: allergic and irritant. Clin Dermatol. 32 (1):116–124

Tasic T, Bäumer W, Schmiedl A, Schwichtenhövel F, Pabst R, Raap U et al (2011) Dipeptidyl peptidase IV (DPP4) deficiency increases Th1-driven allergic contact dermatitis. Clin Exp Allergy. 41(8):1098–1107

Tennstedt D (2009) Patch tests: indications or when testing should be performed. Ann Dermatol Venereol. 136(8-9):579–583

Trindade MA, Alchorne AO, da Costa EB, Enokihara MM (2004) Eyelid discoid lupus erythematosus and contact dermatitis: a case report. J Eur Acad Dermatol Venereol. 18 (5):577–579

Verma KK, Mahesh R, Bhari N, Pandey RM (2016a) Effect of betamethasone on patch test reactivity in patients with parthenium dermatitis. Contact Dermatitis. 75(3):193–194

Verma KK, Bhari N, Sethuraman G (2016b) Azathioprine does not influence patch test reactivity in Parthenium dermatitis. Contact Dermatitis. 74(1):64–65

Viraben R, Aquilina C, Cambon L, Bazex J (1994) Allergic contact dermatitis in HIV-positive patients. Contact Dermatitis. 31(5):326–327

Vogelbruch M, Nuss B, Körner M, Kapp A, Kiehl P, Bohm W (2000) Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. Allergy. 55(9):883–887

Waard-van der Spek FB, Andersen KE, Darsow U, Mortz CG, Orton D, Worm M et al (2013) Allergic contact dermatitis in children: which factors are relevant? (Review of the literature). Pediatr Allergy Immunol. 24(4):321–329

Waard-van der Spek FB, Darsow U, Mortz CG, Orton D, Worm M, Muraro A et al (2015) EAACI position paper for practical patch testing in allergic contact dermatitis in children. Pediatr Allergy Immunol. 26(7):598–606

Wee JS, White JM, McFadden JP, White IR (2010) Patch testing in patients treated with systemic immunosuppression and cytokine inhibitors. Contact Dermatitis. 62(3):165–169

Worm M, Aberer W, Agathos M, Becker D, Brasch J, Fuchs T et al (2007) Patch testing in children--recommendations of the German Contact Dermatitis Research Group (DKG). J Dtsch Dermatol Ges. 5(2):107–109

Part V

Specific Mechanisms

B Cell Functions in the Development of Type I Allergy and Induction of Immune Tolerance

Lisa Naomi Pointner, Fatima Ferreira, and Lorenz Aglas

Contents

Abstract

B cells are key players in the mechanisms underlying allergic sensitization, allergic reactions, and tolerance to allergens. Allergen-specific immune responses are initiated when peptide:MHCII complexes on dendritic cells are recognized by antigen-specific receptors on T cells followed by interactions between

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costimulatory molecules on the surfaces of B and T cells. In the presence of IL-4, such T-B cell interactions result in clonal expansion and isotype class-switching to IgE in B cells, which will further differentiate into either memory B cells or PCs. Allergic reactions are then triggered upon cross-linking of IgE-FcεRI complexes on basophils and mast cells, leading to cell degranulation and the release of pro-inflammatory mediators.

Mechanisms underlying effective allergen-specific immunotherapy (AIT) involve the induction of Tregs and the secretion of blocking IgG4 antibodies, which together mediate the onset and maintenance of immune tolerance towards non-hazardous environmental antigens. However, the importance of regulatory B cells (Breg) for tolerance induction during AIT has gained more attention lately. Studies in grass pollen- and house dust mite-allergic patients undergoing SCIT reported increased frequencies of IL-10+ Breg cells and a positive correlation between their number and the improvement of clinical symptoms. Thus, Breg are emerging as biomarkers for monitoring tolerance to allergens under natural exposure conditions and during AIT. Further research on the role of other anti-inflammatory cytokines secreted by Breg will help to understand their role in disease development and tolerance induction.

Keywords

Adaptive immunity · AIT · Antibody · B cells · Breg

1 Introduction

B cells play an essential role in type I allergy. In this chapter will be described how B cells contribute to the development of allergic sensitization, to the effector phase via the secretion of high-affinity IgE antibodies but also how they participate in immune tolerance during allergen exposure (Fig. 1).

2 The Contribution of B Cells in the Development of Allergic Sensitization

The development of type I allergies or immediate hypersensitivity reactions are characterized by two phases (van Ree et al. 2014). First, an asymptomatic phase, called *sensitization*, occurs upon first encounter with a specific allergenic source. Subsequent exposures to the same allergen can then trigger the *effector phase*, which corresponds to the manifestation of the disease.

The sensitization process is orchestrated by the interplay of various immune cells resulting in the induction of effector type 2 T helper cells (Th2) and an enhanced production of Immunoglobulin E (IgE), the hallmarks of the allergic sensitization. During this phase, antigen-presenting cells (APC), mainly dendritic cells (DCs), take up and process allergens. Activated DCs then migrate to the draining lymph nodes to present antigenic peptides in complex with major histocompatibility class II

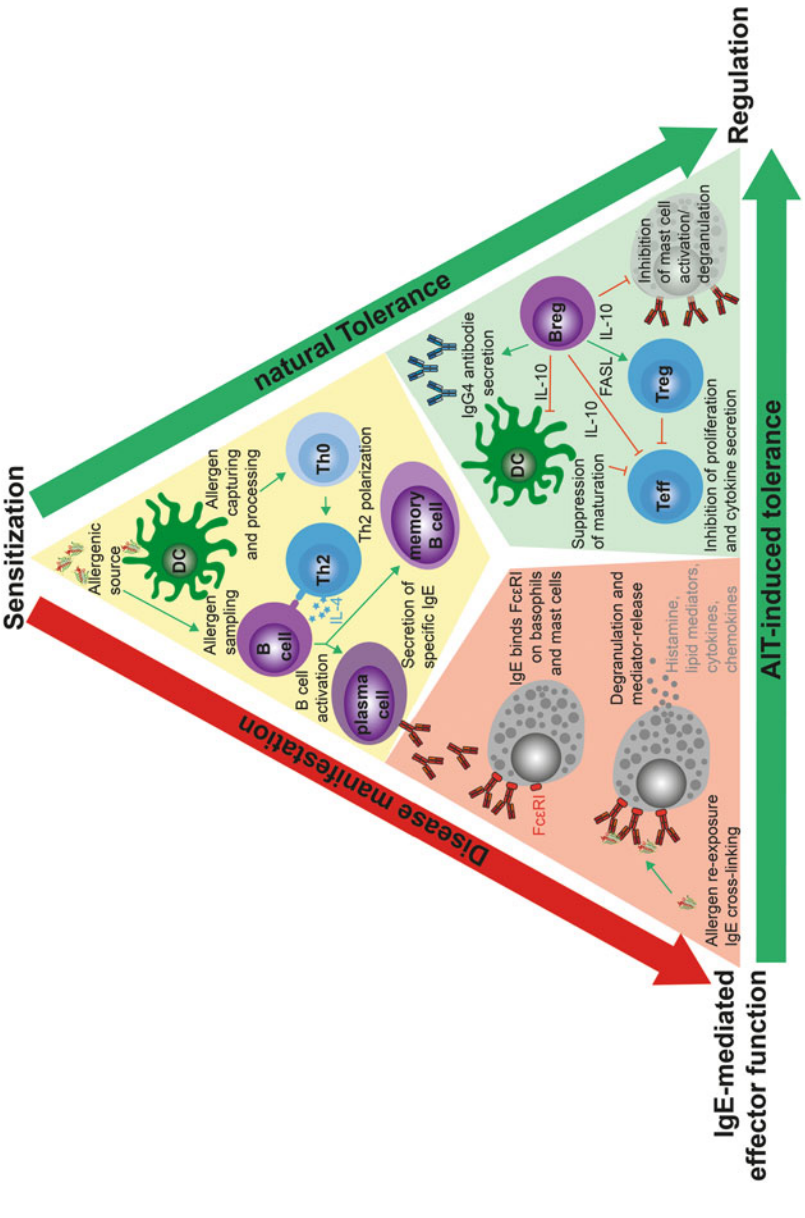

Fig. 1 The B cell function triad in type I allergy. Summary scheme showing the interconnected and versatile role of B cells in three different aspects of type I allergy. During allergic sensitization (in yellow), allergens are taken up and processed by dendritic cells (DC) and B cells. DC present allergenic peptides to

(MHCII) molecules to allergen-specific naïve CD4+ T cells. In the presence of an efficient co-stimulation and the appropriate local microenvironment, provided by the cytokine IL-4, they differentiate into Th2 cells that express characteristic cytokines including IL-4, IL-5, and IL-13 (van Ree et al. 2014). Th2 cells then circulate in the blood or reside in specialized T cell zones of peripheral lymphoid organs (spleen and lymph nodes) where they become specialized follicular T helper cells (Tfh) waiting to encounter their specific antigen.

During sensitization, allergens are also recognized by B cells, which are lymphocytes expressing cell surface antigen-specific immunoglobulins (Ig), also called B-cell antigen receptors (BCR) (LeBien and Tedder 2008). During their development in the bone marrow, B cells undergo a structured rearrangement of their immunoglobulin gene segments in order to generate a huge repertoire of BCR recognizing over a billion different antigenic epitopes (Gould and Wu 2018). Fully developed B cells express the isotype IgM and IgD on the cell surface and migrate into lymphoid follicles of peripheral lymphoid tissues for antigen surveillance (Pieper et al. 2013; LeBien and Tedder 2008).

The binding of the specific antigen to the BCR of a naïve immature B cell triggers the activation of specific intracellular signaling pathways, internalization of the antigen-BCR complex, and the subsequent presentation of antigenic peptides in the MHCII groove at the cell surface. The antigen-activated B cell is concomitantly guided towards T cell zones in order to facilitate the meeting with the cognate Tfh cell (Cyster and Allen 2019). The communication between both cells involves a cell-to-cell contact via the interaction of the peptide:MHCII complex and the antigen-specific T cell receptor as well as through the interaction of the costimulatory molecules CD40 and CD40 ligand (CD40L) and OX40L and OX40 on the B cell and T cell surfaces, respectively (Akiba et al. 1999). In addition, a *soluble factor*, IL-4, provided by the Th2-like Tfh cells drives the switching to IgE. IL-4 acts via the type I IL-4 receptor and triggers the activation of the STAT6 signaling pathway (Dullaers et al. 2012; van Ree et al. 2014). In consequence, these signals result in clonal expansion and isotype class-switching into IgE-expressing B cells, which will

Fig. 1 (continued) allergen-specific naïve T cells (Th0) and induce their polarization into type 2 effector T cells (Th2). Allergen-loaded B cells interact with cognate Th2 cells, which triggers their activation and differentiation into IgE-secreting plasma cells (PC) or memory B cells. Allergen-specific IgE binds to the high-affinity receptors FcεRI on mast cells and basophils in tissues and blood circulation, respectively. During allergen challenge (in red), the cross-linking of IgE-FcεRI complexes triggers cell degranulation and release of pro-inflammatory mediators such as histamine, lipid mediators, cytokines, and chemokines and leads to manifestation of allergic symptoms. The concomitant upregulation of FcεRI, interleukin 4 (IL-4) and CD40 ligand (CD40L) leads to an enhanced and sustained allergic immune response. Regulatory B cells (Breg) are key players in natural- and allergen-specific immunotherapy (AIT)-induced immune tolerance (in green). Breg cells secrete allergen-specific IgG4 antibodies that compete with IgEs for allergen binding. Through the secretion of IL-10, Breg cells display a pleiotropic immunoregulatory function. IL-10 can block the function of effector T cells (Teff) either directly or indirectly; on the one hand via the induction of regulatory T cells (Treg), and on the other hand by the inhibition of antigen-presenting cells. Finally, IL-10 can inhibit degranulation and activation of mast cells

differentiate into either plasma or memory B cells (Janeway et al. 2001). The mechanisms underlying this choice are still under investigation; however, studies have reported that the isotype of the BCR can influence the differentiation path, in which the IgE BCR promotes a spontaneous preferential differentiation into plasma cells (PCs) (Cyster and Allen 2019).

The defined state of a sensitized individual is then when the secreted allergen-specific IgEs have primed mast cells in tissues and basophils in the blood circulation by binding to their high-affinity receptors, FCεRI.

2.1 Plasma Cells in Type I Allergy

The differentiation of B cells into PCs can occur in two ways, depending on the duration of allergen exposure. After a short contact with the allergen, activated B cells can differentiate into short-lived PCs that produce low-affinity IgE antibodies (Roth et al. 2014). Mouse studies have shown that under certain conditions, the production of IgEs of low affinity can be sufficient to induce allergic reactions and occurs in extra follicular areas of the draining lymph nodes (Jimenez-Saiz et al. 2017; Wu and Zarrin 2014). However, in case of a persisting antigen exposure, the sustained B cell activation gives rise to follicles followed by the formation of germinal centers (GCs), which are sites of intense B cell proliferation, selection, maturation, and death in secondary lymphoid tissues. In GCs, B cells initially continue to proliferate as plasmablasts and then undergo important maturation steps leading to high-affinity IgE-secreting PCs and memory B cells (Tedder; Medina et al. 2002; Oracki et al. 2010; Klein and Dalla-Favera 2008). In fact, the huge variety of antigen specificity is determined by the two variable domains of the heavy and light chains of the immunoglobulin whereas the function is determined by the isotype of the constant (C) region of the heavy chains; C epsilon (Cε) being the heavy chain in IgE (Pieper et al. 2013). Three major modifications occur at the genetic level of differentiating B cells, which aim to further diversification of their BCR:

- Firstly, point mutations, termed *somatic hyper-mutations,* mediated by cytidine deaminase (AID), occur in the variable regions of the expressed immunoglobulin gene in order to increase the affinity of the antibody to its respective antigen (Geha et al. 2003).
- Secondly, in a process called *affinity maturation*, B cells expressing a BCR with high affinity are selected for proliferation and survival by competing with follicular dendritic cells for antigen presentation to Tfh cells (Gould and Wu 2018). Mutations that improve Ig's affinity facilitate the efficient activation of the B cell, whereas cells bearing lower affinity Igs undergo apoptosis. The GCs are therefore a site of both, high B cell death and proliferation (Janeway et al. 2001; Vinuesa et al. 2010).
- Thirdly, selected B cells undergo *class-switch recombination,* also driven by AID, in order to change the isotype of the expressed Ig while retaining antigen's

specificity. In regard to IgE responses, the synergistic effect of CD40L-mediated co-stimulation and IL4 triggers the genetic rearrangement in the genomic locus of the heavy chain to replace the constant C region of IgM (Cμ) by the constant region of IgG (Cγ) and subsequently of IgE (Cε); the IgE gene being located downstream of the IgG gene (Geha et al. 2003).

The final differentiation process is controlled by different TFs (e.g., the B cell specific activating protein and the positive regulator domain I-binding factor 1) and associated with phenotypic changes (Roth et al. 2014; Dullaers et al. 2012). Even though PCs still respond to differentiation and survival signals provided by T cells, such as IL6 and CD40L, they become unable to express MHCII, making them incapable of presenting antigens to T cells (Saunders et al. 2019). Once their differentiation is completed, PCs can home into different immune compartments. PCs that reside in secondary lymphoid organs behave as short-lived PCs. In contrast, PCs that migrate through the circulation back to the bone marrow and the lamina propria of inflamed tissues survive in niches as long-lived resident cells, thus, representing a form of IgE memory (Moutsoglou and Dreskin 2016; Roth et al. 2014).

IgE-secreting PCs are key players of type I allergic reactions due to their capacity to secrete large amounts of high-affinity and isotype switched IgE antibodies (IgE proteins represent 10–20% of all synthetized proteins in a PC) (Medina et al. 2002).

2.2 Memory B Cells in Type I Allergy

The humoral immune memory is mostly characterized by the generation of memory B cells, which are quiescent, antigen-experienced, long-lived B cells originating from GCs and persisting long after antigen challenge in order to act in the surveillance for antigen in the circulation and mucosal tissues. Under basal conditions, memory B cells express surface Ig antibodies but secrete them at low rate. Upon antigen re-exposure, they can mount a rapid and high-affinity secondary humoral immune response that is more efficient than the primary response (Saunders et al. 2019; He et al. 2017).

Despite the importance of IgE in the pathogenesis of type I allergies, the mechanisms underlying the generation of IgE memory are still unclear and intensively studied. Most studies support the existence of a memory for IgE-mediated allergic responses in mice and humans and claim that this memory is attributed to IgG1+ memory B cells that can, upon activation, differentiate into IgE-secreting plasma cells by de novo class-switching to IgE (Talay et al. 2012; He et al. 2013). In fact, isotype class-switching towards IgE seems to be a sequential procedure in which a B cell undergoes a successive isotype switch from IgM to IgE via one or more intermediate isotypes (IgG1 and IgG4). Since, after a primary response, IgG precursor cells are selected after somatic hyper-mutations and persist for weeks in the GCs, the sequential de novo switching generates IgE antibodies of high affinity (Gould and Wu 2018; He et al. 2013).

Alternatively, IgE class-switching can occur directly from an IgM precursor cell resulting in a low IgE affinity and B cell apoptosis during selection in the GC, which was observed in IgG1-deficient mice that upon repeated immunizations developed IgE-secreting PCs derived directly from IgM precursor cells. The cells failed to produce high-affinity IgEs although the levels were comparable to those of wild type mice, suggesting that IgG1 cells are essential for the generation of high-affinity IgE influenced by Th2 conditions (Erazo et al. 2007).

The existence of IgE memory B cells is still a matter of debate. Although IgE+ memory B cells have been reported in human, their functionality and cell fate remain unclear (Talay et al. 2012; Gould and Wu 2018). In mice, IgE memory B cells are very rare and the reason might be the transiency of GCs containing IgE-expressing B cells that quickly disappear during the primary response. Indeed, IgE BCRs are expressed at low levels compared to IgG BCRs, which reduces the ability of these cells to capture and present antigens and, thus, might explain the poor competition ability of IgE B cells within GCs (Cyster and Allen 2019).

3 The Contribution of B Cells in the Effector Phase of Type I Allergy

3.1 B Cell-Derived IgE

In the absence of disease, IgE is present in very low concentrations in the serum (the lowest of all five isotypes), has a short half-life and, because of its highly active and rather invasive biological nature, the expression of IgE is tightly regulated (Wu and Zarrin 2014). IgE antibodies normally serve to protect the host from parasitic infections such as helminths as well as to neutralize venoms and toxins, preventing tissue damages of the host. Individuals mounting a protective IgE response have elevated serum IgE levels but they remain below IgG levels indicating a well-regulated IgE synthesis. In contrast, when the IgE response is inappropriately initiated in response to allergen exposure, these antibodies become deleterious in the pathogenesis of allergic disorders.

3.2 IgE Binding to FcεRI: Mediator Release Function

During the sensitization phase, IgE antibodies secreted by PCs enter the circulation and, due to their small size (190 kDa), diffuse easily into periphery such as blood circulation and mucosal tissues. There, IgE molecules bind via their constant region to the high-affinity receptor, FcεRI, on the cell surface of circulating basophils and tissue-resident mast cells. Such sensitized immune cells react sensitively to allergens even when the concentration of circulating IgE is low (Dullaers et al. 2012).

Upon re-exposure, the specific allergen binds to the variable regions of adjacent cell-bound IgE molecules resulting in physical cross-linking of IgE-FcεRI complexes. This interaction triggers activation of downstream signaling pathways

leading to cell degranulation and release of pro-inflammatory mediators. The early release of pre-synthesized mediators (e.g., histamine, serine proteases, carboxypeptidase A, and proteoglycans) is responsible for the immediate phase reaction of the allergic immune response that develops within minutes. Four to eight hours thereafter, newly sensitized lipid mediators such as arachidonic acid products (e.g., leukotrienes and prostaglandin), as well as cytokines and chemokines (e.g., IL-4, IL-5) are released in the delayed phase reaction that is accompanied by the recruitment of additional inflammatory cells (such as eosinophils). The resulting effects are inflammation, vasodilation, increased permeability, smooth muscle contraction, and further tissue damages (van Ree et al. 2014).

The manifestations of IgE responses are very variable regarding the magnitude, the localization, and the type of clinical symptoms (e.g., sneezing, itching, coughing, eczema). They usually develop at the entry sites as local reaction (the skin, in the mucosal tissues of the airways, and in the gut) whereas a strong IgE response associated with a massive mast cell degranulation can cause a potentially lethal systemic reaction, called anaphylaxis (Gould and Sutton 2008).

3.2.1 Amplification of the IgE Response

Once initiated, the IgE response can be further amplified at the site of inflammation by the recruitment and activation of other immune cells expressing FcεRI such as basophils, mast cells, and eosinophils. The binding of allergens to the related IgE-FcεRI complex on these cells enhances the expression of FcεRI on the cell surface resulting in a positive feedback-loop that increases the sensitivity to the allergen. Moreover, it induces the expression of CD40L and the secretion of IL-4. Therefore, like Th2 cells, these cells can drive class-switching of B cells to IgE, thus, enhancing the allergic response (Gould and Sutton 2008).

3.2.2 IgE Binding to CD23: FAP and Epitope Spreading

IgE also binds to the low-affinity receptor, FcεRII (or CD23), which is expressed on antigen-activated B cells as well as other immune cells (dendritic cells, epithelial cells, and eosinophils) (Dullaers et al. 2012). Binding of allergens to the IgE-CD23 complex improves the antigen-presenting capacity of B cells by ameliorating their aptitude of allergen internalization and presentation to T cells, hence maintaining the activation of the immune system (Gould and Sutton 2008; Acharya et al. 2010). Indeed, this process called CD23-mediated *"facilitated antigen presentation" (FAP)* is known to be as efficient as the antigen presentation by dendritic cells via FcγR, and much more effective than BCR-mediated internalization by B cells (Wypych et al. 2018)

Activated B cells expressing CD23 can bind other pre-existing circulating IgE via their constant region and thus, present unrelated allergens to cognate T cells regardless of the specificity of the B cell's own BCR. This phenomenon, called *epitope spreading,* leads to an enhanced allergic sensitization as well as to the simultaneously development of allergic reactions towards several allergens (Gould and Sutton 2008).

3.2.3 IgE Binding to CD23: Allergen Transport into Mucosal Tissues

An additional role for CD23 is the transport of free and allergen-bound IgE across the epithelial barrier into the underlying mucosa (Acharya et al. 2010). In a process, called transcytosis, IgE secreted into the gut lumen was found to bind food-derived allergens, which were further delivered to immune cells from the mucosal gastrointestinal tract, to trigger food allergic reactions (Gould and Sutton 2008).

3.3 B Cell-Derived IgG in Type I Allergy

As previously mentioned, an IgE response is usually associated with IgG production; IgG1 and IgG4 production in humans, and with IgG1 production in mice. These IgG antibodies are playing a significant role in allergy. However, in contrast to IgE, they are involved in protection and regulation of type I allergic reactions by contributing to immune tolerance, which will be discussed in detail below.

4 B Cells in Natural and Allergen-Specific Immunotherapy (AIT)-Induced Tolerance

Many advances have been achieved in the field of allergy research over the last centuries such as the successful implementation of biomarkers (either cellular, humoral or functional) for the interpretation of clinical outcomes and treatment efficacy, the development of hypoallergenic vaccine candidates, and the characterization of hundreds of allergenic molecules and sources. Still, up to now AIT represents the only treatment option for allergic diseases providing a long-term if not permanent relief of symptoms. The underlying cellular mechanism enabling an effective AIT depends on the onset and maintenance of immune tolerance towards non-hazardous environmental antigens mainly via inducing Treg cells and the secretion of allergen-specific IgG4 blocking antibodies. At present, limited information is available concerning the role of regulatory B cells (Breg) in induction of immune tolerance in course of AIT but gains more attention by the day. Here, we describe the involvement of B cells in allergen tolerance and in AIT with special focus on Breg, an immunosuppressive subset of B cells.

4.1 Altered Antibody Secretion Profile Induced by AIT

The production of antibodies is a crucial function of plasma cells, hence inevitably associated with the induction of allergen tolerance by AIT mostly characterized by a 10- to 100-fold increased secretion of serological, allergen-specific IgG blocking antibodies (Jutel et al. 2005; Reisinger et al. 2005). A successful AIT is usually accompanied by a decreased IgE/IgG4 ratio. Besides this common feature, AIT-induced changes in allergen-specific IgE levels seem to vary greatly among studies. Depending on treatment duration, many studies report an early increase in

allergen-specific IgE levels followed by a later decline (Shamji et al. 2019b; Huber et al. 2018; Vizzardelli et al. 2018). The increase in the concentrations of specific IgG1 and IgG4 antibodies mainly results in a competition with IgE for the allergen and, consequently, in a decreased degranulation and activity of mast cells and basophils. Besides the competitive function of IgG4, it has other remarkable features rendering it an anti-inflammatory antibody such as a low binding affinity to Fcγ receptors on immune cells and an incapability to induce complement activation (van der Neut Kolfschoten et al. 2007). However, the question how antibody subclass levels are correlating with clinical outcome, as determined by provocation tests or the scoring of symptoms, remains a matter of discussion. An indicator and broadly accepted biomarker for treatment efficacy is the blocking capacity of serum-derived antibodies able to inhibit IgE-facilitated allergen binding (Kouser et al. 2017; Shamji and Durham 2017). In addition to serological blocking effects, recently, nasal fluids of SCIT-treated grass pollen allergic patients were found to possess an increased IgG-associated inhibitory activity compared to untreated patients. The magnitude of this local blocking activity even exceeded by 27% the serological inhibitory capacity (Shamji et al. 2019b). Accordingly, the nasal Phl p 1- and Phl p 5-specific IgG4 levels were increased in the SCIT group. A not negligible aspect when summarizing AIT-induced alterations of the humoral antigen-specific immune response is the potential of de novo sensitizations induced as a side effect of extract-based vaccines serving as source for multiple other allergenic proteins (e.g., minor allergens), which can induce allergen-specific IgE within the patients.

4.2 Allergen-Specific Breg Cells

When discussing the role of B cells in allergen tolerance, either induced by AIT or pre-existing in a non-allergic/healthy subject, allergen-specific Breg cells seem to exert an extraordinary function. By secreting anti-inflammatory cytokines (mainly IL-10) and the direct as well as indirect suppression of effector T cells, Breg cells are able to skew the inflammatory allergic immune response towards an immunosuppressive, tolerant response. Although several review articles discussing the role of Breg cells in allergic diseases are available, studies addressing these aspects are rather limited and urgently needed.

4.2.1 Phenotype of Breg Cells

By definition, Breg cells are classified either upon their functional properties or by their phenotype, based on the expression of distinct cell surface molecules and signal transduction-associated proteins such as CD19, CD62L, MHC-II, Fas ligand, T cell immunoglobulin and mucin domain, and programmed death ligand 1 (van de Veen 2017). Functional-based classification mainly refers to the secretion of immune-modulatory cytokines such as IL-10, TGF-β, and IL-35 (Layhadi et al. 2019; Shamji et al. 2019a). An involvement of Breg cells was described for autoimmune and infectious diseases, as well as for malignancies and organ transplantations (Wortel and Heidt 2017), where their main function, in general, is to suppress effector CD4+

and CD8+ T cells and, in parallel, to promote the induction of immune-regulatory Tregs. In allergy research, Breg cells were mostly investigated in the context of allergies to bee venom, foods, grass pollen, and house dust mite (Berthelot et al. 2013; Boonpiyathad et al. 2017, 2019; Noh et al. 2010). Allergen tolerance was primarily described to be associated with IL-10-producing Bregs of either the B regulatory 1 (Br1) or B10 subset (Noh et al. 2010; Shamji et al. 2019b; van de Veen 2017). Therefore the focus herein will be on these two subtypes. In human, IL-10-secreting Br1 cells were identified to be CD19+ CD25hi CD71hi CD73−, whereas B10 cells have a CD19+ CD24hi, CD27+ cell phenotype (Wortel and Heidt 2017; Berthelot et al. 2013; Iwata et al. 2011; van de Veen et al. 2013). The general abundance of Br1-like cells in human is relatively low and they encompass approximately 0.6% of peripheral blood B cells, although this number can increase up to 5% since, especially, CD24hi CD27+ cells were found to occasionally differentiate into Br1 cells (Berthelot et al. 2013). However, until now, no Breg-specific transcription factor has been identified.

4.2.2 Function of Breg Cells

With regard to allergic diseases, five major functions can be attributed to Breg cells in mediating allergen tolerance, which are (1) the cytokine-mediated independent or (2) the direct suppression of effector T cells (including T follicular helper cells), (3) the suppression of dendritic cell maturation, (4) the induction of Treg cells, as well as (5) the secretion of anti-inflammatory antibodies (Lin et al. 2019; Achour et al. 2017; Palomares et al. 2017; Samitas et al. 2010). Most of these functions can be allocated to the immunosuppressive activity of the cytokine IL-10, a key regulator of inflammatory immune responses able to restrict and terminate the responsiveness of effector T cells. Via induction of a signaling cascade that involves the associated IL-10 receptor and the transcription factor STAT3, T cell proliferation and cytokine secretion are downregulated (Schulke 2018; Saraiva and O'Garra 2010; van de Veen et al. 2013). Breg-secreted IL-10 also affects other critical effector cells involved in the acute and late-phase allergic reactions. Mast cell degranulation and cytokine release induced by cross-linking of antigen by FcεRI-bound IgE were inhibited by IL-10-secreting Breg both, in vitro and in vivo conditions (Kim et al. 2015). In addition to the IL-10 secretion, which decreases the activity of tyrosine kinases in mast cells by activating the JAK/STAT3 pathway, a direct cell-to-cell contact through CD40/CD40L interaction was required to facilitate this suppressive function. Noteworthy, the direct cell-to-cell contact further enhanced the secretion of IL-10 by Breg. This study also demonstrated the suppression of IgE-mediated anaphylactic reactions by Breg cells in an IL-10-dependent manner (Kim et al. 2015). Furthermore, IL-10 prevents antigen-presenting cells such as DCs from maturation resulting in a diminished signal transduction to Th cells and thus, an intensification of the suppressive effect on effector T cells (Schulke 2018). In general, the most important function of IL-10 is to initiate a crucial regulatory feedback-loop for mediation of anti-inflammatory responses via differentiation of naïve T cells into Treg cells. B10 and other IL-10-producing Breg cells can induce the differentiation of IL-10-secreting type 1 regulatory T cells (Tr1) and Foxp3+

Treg cells (Pennati et al. 2016; Mielle et al. 2018). Besides the undeniable crucial role of IL-10 secreted by Breg cells, it should be stated that Breg cells secreting other anti-inflammatory cytokines such as IL-35, TGF-β, TSP-1, and IDO exist as well (van de Veen 2017). However, their involvement in allergic diseases has not been fully investigated yet.

In contrast to the IL-10-mediated indirect suppression of effector T cells, by expressing Fas ligand Breg cells have the potential to induce apoptosis in effector T cells, thus mitigating allergic Th2 response by direct cell contact (Tian et al. 2001; Lundy and Klinker 2014). Finally, the secretion of anti-inflammatory IgG4 blocking antibodies by Breg cells able to compete with IgE for the allergen is an exceptionally important aspect in mediating allergen tolerance. Noteworthy, human IL-10-secreting Br1 cells were found to represent the main source for the production of phospholipase A_2-specific IgG4 antibodies in bee venom-tolerant subjects (van de Veen et al. 2013).

4.2.3 The Role of IL-10-Producing Breg in Natural Tolerance

When discussing the role of Breg cells in the context of allergic diseases and the onset and maintenance of natural tolerance, the comparison between tolerant subjects and allergic patients becomes evident. Noh et al. investigated the frequency of allergen-specific Br1 cells in milk-allergic and milk-tolerant subjects, which were selected by double-blind, placebo-controlled food challenges (Noh et al. 2010). The study showed that the abundance of Br1 cells increased upon allergen stimulation in the milk-tolerant group (around 9%) and decreased in the allergic group (10%), implying a superordinate regulatory role of Br1 in the maintenance of tolerance in healthy individuals. In parallel, the level of non-IL-10-producing Breg undergoing apoptosis increased upon allergen stimulation in the milk allergy group, whereas remained unaltered in the tolerant group, indicating the presence of at least a second functional-active Breg subset relevant for allergen tolerance that is not secreting IL-10. Noteworthy, in this study the frequency of IL-10-producing Breg cells exceeded the number of IL-10-secreting T cells (Noh et al. 2010). In a study comparing bee venom-allergic patients with tolerant beekeepers, the authors observed that allergen-specific IgG4 was mainly produced by Br1 cells, secreting high levels of IL-10, and subsequently resulted in the suppression of CD4+ T cell proliferation. This suppressive effect could be reversed by blockage of the IL-10 receptor, implying an essential role for IL-10 in the suppression of effector T cells. Beekeepers, possessing natural tolerance towards bee venom, showed an increased IL-10 and IgG4 expression by Br1 cells, whereas in allergic patients the frequency of IL-10+ B cells was in general very low (van de Veen et al. 2013).

4.2.4 Induction of IL-10-Producing Breg During AIT

For allergic patients, who are suffering from symptoms resulting from the exposure to an allergen that is not tolerated by their immune system, the most meaningful therapeutic action would be the reconstitution of allergen tolerance by AIT. Therefore, the contribution of Breg in the induction of allergen tolerance during AIT, and the question to what extent the thereby induced state of tolerance would reflect

natural tolerance need to be further assessed and discussed. In this respect, van de Veen et al. investigated the induction of circulating allergen-specific IL-10+ Breg in bee venom-allergic patients during AIT. The authors observed a steady increase in the frequency of allergen-specific IL-10+ and IgG4+ B cells, which were presumably Br1 cells, in both, treatment-induced tolerant (from 1.8–2.9% to 5.5–13.9%) and naturally tolerant subjects (non-allergic beekeepers), when compared to the untreated group (van de Veen et al. 2013). Although the IgE/IgG4 ratio in patients' sera was significantly reduced upon AIT (100-fold), mainly because of the increase of IgG4, still a highly significant difference remained between the IgE/IgG4 ratio of patients undergoing AIT compared to tolerant beekeepers (tenfold), which can mostly be ascribed to the higher IgE baseline levels that remained unaltered during the patients' therapy. In a follow-up study by Boonpiyatha et al. a striking similarity regarding the allergen-specific B cell response, including IL-10+ Br1 cells, IgG4+ memory cells and plasmablasts, was observed between AIT patients before or after treatment and beekeepers before or during beekeeping season, respectively (Boonpiyathad et al. 2017). In summary, although in both groups a high similarity was achieved, AIT-induced allergen-specific tolerance seems not to completely restore the immunological conditions observed in natural tolerance. Whether high dose exposure to bee venom, as it is the case in non-allergic beekeepers, can be interpreted as natural "inherited" tolerance rather than an altered variant of immunotherapy is also a matter of debate.

In a recent study, increased frequencies of two distinct populations of IL-10+ Breg cells were observed by monitoring the allergic immune response in and out of pollen season in grass pollen allergic patients undergoing SCIT. In contrast, untreated patients had a significantly lower number of Breg that did not change in and out of season (Shamji et al. 2019b). In another study, a correlation between Breg number and the improvement of clinical symptoms was also observed during grass pollen AIT (Zissler et al. 2018). These findings strongly support a beneficial regulatory effect of treatment-induced Breg in grass pollen allergic patients.

In the context of another respiratory allergy, the frequency of IL-10+ Breg was significantly increased in house dust mite-allergic patients who responded well to the treatment, as shown by the treatment-induced improvement of clinical symptoms, compared to non-responders (Boonpiyathad et al. 2019). Noteworthy, the induction of allergen-specific B10 during AIT and the associated improvement of symptoms in asthmatic, house dust mite-allergic patients were observed to be significantly enhanced by the concomitant daily administration of oral probiotics (Liu et al. 2016). Taken together, Breg cells could potentially be regarded as biomarkers for monitoring treatment efficacy in respiratory allergies.

4.2.5 The New Breg-Treg Paradigm in AIT

The present paradigm indicates that tolerogenic antigen-specific Breg cells are being induced early during AIT (early treatment/up-dosing phase) and functionally active prior to the onset of allergen-specific Treg cells. In course of the proceeding AIT (late-treatment/tolerance-mounting phase), allergen tolerance is maintained by Treg

cells, which seem to completely take over this function from Breg cells (Zissler et al. 2018; Berthelot et al. 2013).

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References

Acharya M, Borland G, Edkins AL, Maclellan LM, Matheson J, Ozanne BW, Cushley W (2010) CD23/FcepsilonRII: molecular multi-tasking. Clin Exp Immunol 162:12–23

Achour A, Simon Q, Mohr A, Seite JF, Youinou P, Bendaoud B, Ghedira I, Pers JO, Jamin C (2017) Human regulatory B cells control the TFH cell response. J Allergy Clin Immunol 140:215–222

Akiba H, Oshima H, Takeda K, Atsuta M, Nakano H, Nakajima A, Nohara C, Yagita H, Okumura K (1999) CD28-independent costimulation of T cells by OX40 ligand and CD70 on activated B cells. J Immunol 162:7058–7066

Berthelot JM, Jamin C, Amrouche K, Le Goff B, Maugars Y, Youinou P (2013) Regulatory B cells play a key role in immune system balance. Joint Bone Spine 80:18–22

Boonpiyathad T, Meyer N, Moniuszko M, Sokolowska M, Eljaszewicz A, Wirz OF, Tomasiak-Lozowska MM, Bodzenta-Lukaszyk A, Ruxrungtham K, van de Veen W (2017) High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers. Allergy 72:407–415

Boonpiyathad T, van de Veen W, Wirz O, Sokolowska M, Ruckert B, Tan G, Sangasapaviliya A, Pradubpongsa P, Fuengthong R, Thantiworasit P, Sirivichayakul S, Ruxrungtham K, Akdis CA, Akdis M (2019) Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy. J Allergy Clin Immunol 143:1077–86 e10

Cyster JG, Allen CDC (2019) B cell responses: cell interaction dynamics and decisions. Cell 177:524–540

Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN (2012) The who, where, and when of IgE in allergic airway disease. J Allergy Clin Immunol 129:635–645

Erazo A, Kutchukhidze N, Leung M, Christ AP, Urban JF Jr, Curotto de Lafaille MA, Lafaille JJ (2007) Unique maturation program of the IgE response in vivo. Immunity 26:191–203

Geha RS, Jabara HH, Brodeur SR (2003) The regulation of immunoglobulin E class-switch recombination. Nat Rev Immunol 3:721–732

Gould HJ, Sutton BJ (2008) IgE in allergy and asthma today. Nat Rev Immunol 8:205–217

Gould HJ, Wu YB (2018) IgE repertoire and immunological memory: compartmental regulation and antibody function. Int Immunol 30:403–412

He JS, Meyer-Hermann M, Xiangying D, Zuan LY, Jones LA, Ramakrishna L, de Vries VC, Dolpady J, Aina H, Joseph S, Narayanan S, Subramaniam S, Puthia M, Wong G, Xiong H, Poidinger M, Urban JF, Lafaille JJ, Curotto de Lafaille MA (2013) The distinctive germinal center phase of IgE+ B lymphocytes limits their contribution to the classical memory response. J Exp Med 210:2755–2771

He JS, Subramaniam S, Narang V, Srinivasan K, Saunders SP, Carbajo D, Wen-Shan T, Hidayah Hamadee N, Lum J, Lee A, Chen J, Poidinger M, Zolezzi F, Lafaille JJ, Curotto de Lafaille MA (2017) IgG1 memory B cells keep the memory of IgE responses. Nat Commun 8:641

Huber S, Lang R, Steiner M, Aglas L, Ferreira F, Wallner M, Hawranek T, Gadermaier G (2018) Does clinical outcome of birch pollen immunotherapy relate to induction of blocking antibodies preventing IgE from allergen binding? A pilot study monitoring responses during first year of AIT. Clin Transl Allergy 8:39

Iwata Y, Matsushita T, Horikawa M, Dilillo DJ, Yanaba K, Venturi GM, Szabolcs PM, Bernstein SH, Magro CM, Williams AD, Hall RP, Clair EWS, Tedder TF (2011) Characterization of a rare

IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. Blood 117:530–541

Janeway CA Jr, Travers P, Walport M, Shlomchik MJ (2001) B-cell activation by armed helper T cells. In: Immunobiology: the immune system in health and disease, 5th edn. Garland Science, New York

Jimenez-Saiz R, Chu DK, Mandur TS, Walker TD, Gordon ME, Chaudhary R, Koenig J, Saliba S, Galipeau HJ, Utley A, King IL, Lee K, Ettinger R, Waserman S, Kolbeck R, Jordana M (2017) Lifelong memory responses perpetuate humoral TH2 immunity and anaphylaxis in food allergy. J Allergy Clin Immunol 140:1604–1615.e5

Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O (2005) Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 116:608–613

Kim HS, Kim AR, Kim DK, Kim HW, Park YH, Jang GH, Kim B, Park YM, You JS, Kim HS, Beaven MA, Kim YM, Choi WS (2015) Interleukin-10-producing CD5+ B cells inhibit mast cells during immunoglobulin E-mediated allergic responses. Sci Signal 8:ra28

Klein U, Dalla-Favera R (2008) Germinal centres: role in B-cell physiology and malignancy. Nat Rev Immunol 8:22–33

Kouser L, Kappen J, Walton RP, Shamji MH (2017) Update on biomarkers to monitor clinical efficacy response during and post treatment in allergen immunotherapy. Curr Treat Options Allergy 4:43–53

Layhadi JA, Eguiluz-Gracia I, Shamji MH (2019) Role of IL-35 in sublingual allergen immunotherapy. Curr Opin Allergy Clin Immunol 19:12–17

LeBien TW, Tedder TF (2008) B lymphocytes: how they develop and function. Blood 112:1570–1580

Lin X, Wang X, Xiao F, Ma K, Liu L, Wang X, Xu D, Wang F, Shi X, Liu D, Zhao Y, Lu L (2019) IL-10-producing regulatory B cells restrain the T follicular helper cell response in primary Sjogren's syndrome. Cell Mol Immunol 16:921–931

Liu J, Chen FH, Qiu SQ, Yang LT, Zhang HP, Liu JQ, Geng XR, Yang G, Liu ZQ, Li J, Liu ZG, Li HB, Yang PC (2016) Probiotics enhance the effect of allergy immunotherapy on regulating antigen specific B cell activity in asthma patients. Am J Transl Res 8:5256–5270

Lundy SK, Klinker MW (2014) Characterization and activity of Fas ligand producing CD5(+) B cells. Methods Mol Biol 1190:81–102

Medina F, Segundo C, Campos-Caro A, Gonzalez-Garcia I, Brieva JA (2002) The heterogeneity shown by human plasma cells from tonsil, blood, and bone marrow reveals graded stages of increasing maturity, but local profiles of adhesion molecule expression. Blood 99:2154–2161

Mielle J, Audo R, Hahne M, Macia L, Combe B, Morel J, Daien C (2018) IL-10 producing B cells ability to induce regulatory T cells is maintained in rheumatoid arthritis. Front Immunol 9:961

Moutsoglou DM, Dreskin SC (2016) B cells establish, but do not maintain, long-lived murine anti-peanut IgE(a). Clin Exp Allergy 46:640–653

Noh J, Lee JH, Noh G, Bang SY, Kim HS, Choi WS, Cho S, Lee SS (2010) Characterisation of allergen-specific responses of IL-10-producing regulatory B cells (Br1) in cow milk allergy. Cell Immunol 264:143–149

Oracki SA, Walker JA, Hibbs ML, Corcoran LM, Tarlinton DM (2010) Plasma cell development and survival. Immunol Rev 237:140–159

Palomares O, Akdis M, Martin-Fontecha M, Akdis CA (2017) Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells. Immunol Rev 278:219–236

Pennati A, Ng S, Wu Y, Murphy JR, Deng J, Rangaraju S, Asress S, Blanchfield JL, Evavold B, Galipeau J (2016) Regulatory B cells induce formation of IL-10-expressing T cells in mice with autoimmune neuroinflammation. J Neurosci 36:12598–12610

Pieper K, Grimbacher B, Eibel H (2013) B-cell biology and development. J Allergy Clin Immunol 131:959–971

Reisinger J, Horak F, Pauli G, van Hage M, Cromwell O, Konig F, Valenta R, Niederberger V (2005) Allergen-specific nasal IgG antibodies induced by vaccination with genetically modified

allergens are associated with reduced nasal allergen sensitivity. J Allergy Clin Immunol 116:347–354
Roth K, Oehme L, Zehentmeier S, Zhang Y, Niesner R, Hauser AE (2014) Tracking plasma cell differentiation and survival. Cytometry A 85:15–24
Samitas K, Lotvall J, Bossios A (2010) B cells: from early development to regulating allergic diseases. Arch Immunol Ther Exp 58:209–225
Saraiva M, O'Garra A (2010) The regulation of IL-10 production by immune cells. Nat Rev Immunol 10:170–181
Saunders SP, Ma EGM, Aranda CJ, Curotto de Lafaille MA (2019) Non-classical B cell memory of allergic IgE responses. Front Immunol 10:715
Schulke S (2018) Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. Front Immunol 9:455
Shamji MH, Durham SR (2017) Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol 140:1485–1498
Shamji MH, Layhadi JA, Achkova D, Kouser L, Perera-Webb A, Couto-Francisco NC, Parkin RV, Matsuoka T, Scadding G, Ashton-Rickardt PG, Durham SR (2019a) Role of IL-35 in sublingual allergen immunotherapy. J Allergy Clin Immunol 143:1131–1142 e4
Shamji MH, Kappen J, Abubakar-Waziri H, Zhang J, Steveling E, Watchman S, Kouser L, Eifan A, Switzer A, Varricchi G, Marone G, Couto-Francisco NC, Calderon M, Durham SR (2019b) Nasal allergen-neutralizing IgG4 antibodies block IgE-mediated responses: novel biomarker of subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol 143:1067–1076
Talay O, Yan D, Brightbill HD, Straney EE, Zhou M, Ladi E, Lee WP, Egen JG, Austin CD, Xu M, Wu LC (2012) IgE(+) memory B cells and plasma cells generated through a germinal-center pathway. Nat Immunol 13:396–404
Tian J, Zekzer D, Hanssen L, Lu Y, Olcott A, Kaufman DL (2001) Lipopolysaccharide-activated B cells down-regulate Th1 immunity and prevent autoimmune diabetes in nonobese diabetic mice. J Immunol 167:1081–1089
van de Veen W (2017) The role of regulatory B cells in allergen immunotherapy. Curr Opin Allergy Clin Immunol 17:447–452
van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, Ruckert B, Akdis CA, Akdis M (2013) IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol 131:1204–1212
van der Neut Kolfschoten M, Schuurman J, Losen M, Bleeker WK, Martinez-Martinez P, Vermeulen E, den Bleker TH, Wiegman L, Vink T, Aarden LA, De Baets MH, van de Winkel JG, Aalberse RC, Parren PW (2007) Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. Science 317:1554–1557
van Ree R, Hummelshoj L, Plantinga M, Poulsen LK, Swindle E (2014) Allergic sensitization: host-immune factors. Clin Transl Allergy 4:12
Vinuesa CG, Linterman MA, Goodnow CC, Randall KL (2010) T cells and follicular dendritic cells in germinal center B-cell formation and selection. Immunol Rev 237:72–89
Vizzardelli C, Gindl M, Roos S, Mobs C, Nagl B, Zimmann F, Sexl V, Kenner L, Neunkirchner A, Zlabinger GJ, Pickl WF, Pfutzner W, Bohle B (2018) Blocking antibodies induced by allergen-specific immunotherapy ameliorate allergic airway disease in a human/mouse chimeric model. Allergy 73:851–861
Wortel CM, Heidt S (2017) Regulatory B cells: phenotype, function and role in transplantation. Transpl Immunol 41:1–9
Wu LC, Zarrin AA (2014) The production and regulation of IgE by the immune system. Nat Rev Immunol 14:247–259
Wypych TP et al (2018) Role of B cells in TH cell responses in a mouse model of asthma. J Allergy Clin Immunol 141(4):1395–1410
Zissler UM, Jakwerth CA, Guerth FM, Pechtold L, Aguilar-Pimentel JA, Dietz K, Suttner K, Piontek G, Haller B, Hajdu Z, Schiemann M, Schmidt-Weber CB, Chaker AM (2018) Early IL-10 producing B-cells and coinciding Th/Tr17 shifts during three year grass-pollen AIT. EBioMedicine 36:475–488

Diversity of T Helper and Regulatory T Cells and Their Contribution to the Pathogenesis of Allergic Diseases

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Contents

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Abstract

T helper (Th) and regulatory T (Treg) cells represent important effectors of adaptive immunity. They mediate communication between the immune system and tissue sites and thereby coordinate effective defense against environmental threats or maintain tolerance, respectively. Since the discovery of two prototypic T helper cells, Th1 and Th2, additional phenotypic and functional distinct subsets have been described ranging from Th17, Th22, Th9, and T follicular helper cells. The same holds true for regulatory T cells that represent a family with functionally distinct subsets characterized by co-expression of the transcription factors T-bet, Gata3, or RORγt. Here, we summarize the current knowledge on differentiation and function of T helper and regulatory T cell subsets and discuss their lineage stability versus plasticity towards other subsets. In addition, we highlight the direct and indirect contribution of each subset to the pathology of allergies and indicate novel therapies for specific targeting the effector functions of T helper and regulatory T cells.

Keywords

Allergy · Plasticity · Regulatory T cells (Treg) · T helper cells (Th cells)

New technologies analyzing single cells on the molecular level coupled to modern bioinformatics nowadays revealed a plethora of T cell flavors and cell states. Importantly, such analysis confirmed a very early observation by Mosmann and Coffman who found already in 1986 two different CD4+ T cell populations that have been instrumental for our understanding of allergic inflammation, T helper (Th) 1 and Th2 cells. Today it has become clear that the dichotomy between Th1 and Th2 cells must be extended to other T cell subsets such as Th17, Th22, follicular helper T cells (Tfh), and regulatory T cells (Tregs) and is mirrored within the innate lymphoid cell compartment (LINK TO INNATE CHAPTER). Furthermore, plasticity and imprinting of phenotypes on the epigenetic level complicates a precise standardization of all T cell states across tissues and potential cell fates. Nevertheless, grouping according to phenotypes is still useful to reveal conserved T cell functions and links to disease endotypes not only for scientific purposes but also for treatment regimens of patients sharing certain disease phenotypes. This chapter

provides an overview on currently known adaptive T helper (Th) cell populations and regulatory T (Treg) cells, their differentiation, general function and plasticity as well as their direct or indirect involvement in allergic inflammation.

1 Th2 Cells: The Prototype of an Adaptive T Cell Driving Allergic Inflammation

The term allergy is inevitably associated with one T cell subtype – the Th2 cell. It was first described together with Th1 cells in 1986 by Mosmann et al. (1986) and defined as IL-4, IL-5, and IL-13 producing T cell. Only a few years later, CD8+ T cells have been discovered that could be subdivided accordingly into a type 1/type 2 subset (Kaech and Cui 2012). On the innate branch of the immune system, Th2 cells find their counterpart in type 2 innate lymphoid cells (ILC2) with similar functional features, but without recognition of MHC-displayed antigens and different developmental cues (Ishizuka et al. 2016).

1.1 Differentiation of Th2 Cells

The generation of Th2 cells from naïve precursors critically relies on the cytokine IL-4 (Fig. 1). Binding of IL-4 to its receptor on naïve T cells induces the phosphorylation of STAT6 that in turn enhances the expression of the master transcription factor Gata3 (O'Shea and Paul 2010). Deletion of Gata3 in CD4+ T cells inhibits the capacity of these cells to differentiate into Th2 cells (Zhu et al. 2004) and in addition reduces their proliferative capacity (Zhu et al. 2004). Gata3 orchestrates type 2 differentiation by binding to in total 623 genes. Among those, Gata3 binds to the IL-4 enhancer leading to increased IL-4 secretion and further STAT6 mediated transcription of Gata3. This opens a positive feedback loop and ensures maintained de novo generation of Th2 cells (Agarwal et al. 2000). This feedback loop is further supported by the T cell growth factor IL-2 that leads to translocation of phosphorylated STAT5 into the nucleus and consecutive induction of IL-4 and IL-4 receptor gene expression (Liao et al. 2008). IL-2 thereby enhances the autocrine and paracrine responsiveness of developing Th2 cells to IL-4 and supports the maintenance of the Th2 pool. Th2 cells also secrete IL-5 and IL-13 that are not involved in the differentiation process, but are exclusively regulated by Gata3 (Yamashita et al. 2002). Whereas Gata3 is with no doubt the master regulator of type 2 differentiation, other factors have been identified that support type 2 development. Here, Dec-2, Tcf-1, Gfi-1 or Ikaros either induce positive regulators or inhibit differentiation programs into other subsets (e.g., Thomas et al. 2010). Unexpectedly, Th2 cells also developed in IL-4Ra/IL-4 deficient mice after, e.g., prolonged allergen exposure or Leishmania major infection (Grunewald et al. 2001) highlighting the existence of IL-4 independent Th2 differentiation pathways. Here, the Notch pathway with Rbpj, Notch 1, and Notch 2 has been proven to be sufficient for the induction of Gata3 and Th2 cell development in absence of IL-4 (Amsen et al. 2009).

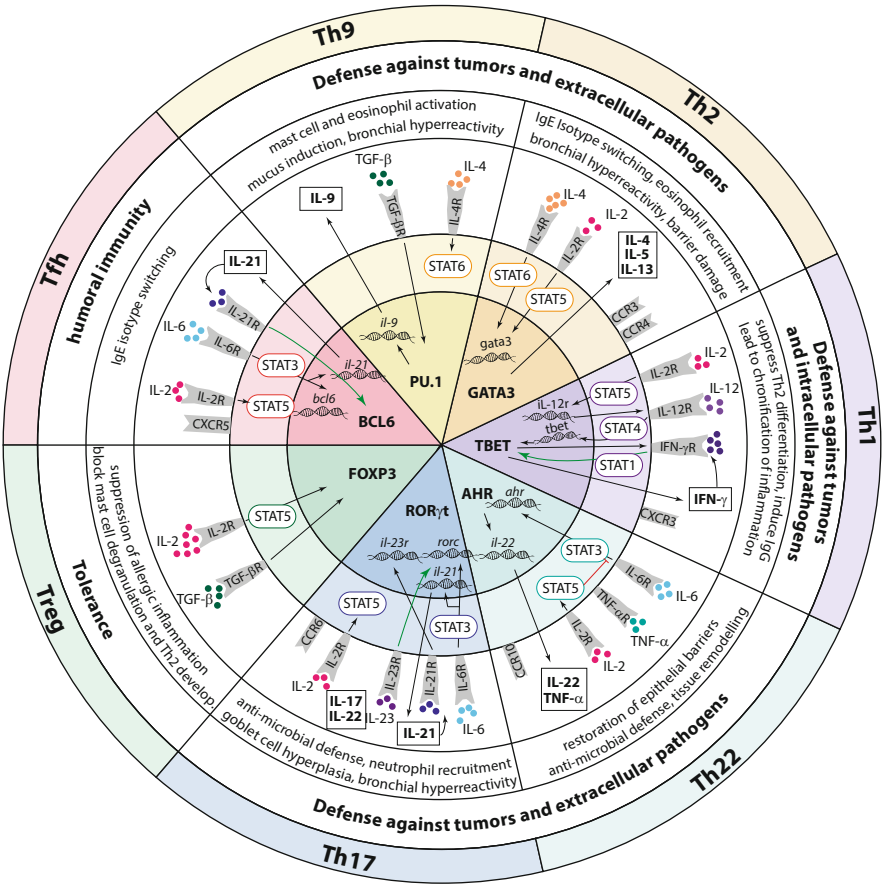

Fig. 1 Overview on CD4+ T cell subsets, their differentiation, phenotype and function. Distinct CD4+ T cell subsets fulfill (first ring) specific tasks in the human immune system (second ring) and during allergic inflammation (third ring). They are equipped with a specific repertoire of cytokine and chemokine receptors (fourth ring) and secrete subset-specific cytokines. Signals from cytokine receptors are transmitted from the cytoplasm (fifth ring) into the nucleus via STAT proteins. Here, they induce the expression of subset-specific transcription factors (sixth ring) that in turn initiate the differentiation program towards the indicated subset. Inhibitory and stabilizing/activating interactions are highlighted with red or green lines, respectively. Th: T helper cell; Treg: regulatory T cell; Tfh: follicular T helper cell; IL: interleukin; parts of the figures were obtained from vecteezy.com

Despite the already existing profound knowledge on Th2 cell development, this finding points to a probably redundant system of naïve T cell differentiation even in the absence of signature factors. However, we are just at the start to understand this complex system.

1.2 Function of Th2 Cells During Allergic Inflammation

The cytokines of Th2 cells, IL-4, IL-5, IL-13, and IL-31 are critical mediators of allergic inflammation. Both, IL-4 and IL-13 cause the proliferation and differentiation of B cells to plasma cells that preferentially secrete IgE antibodies. Furthermore, both induce mucin hypersecretion in the airway, which ultimately leads to airway obstruction. In epithelial cells, both cytokines lead to the reduction of filaggrin expression and decreased levels of anti-microbial peptides and thereby to a sustained damaged epithelial barrier in the skin that consequently results in a dysbiosis and colonization with *Staphylococcus aureus* (Eyerich et al. 2009a) (LINK TO AE CHAPTER). IL-5, on contrary, enhances secretion of IgA antibodies by plasma cells and is the most important factor for eosinophil maturation, survival, and their recruitment into tissues. With the release of their preformed granules, eosinophils contribute to the allergic symptoms by mediating tissue toxicity, oxidative stress, and activation of mast cells and basophils (Wynn 2015). In addition to these effector functions, IL-4 and IL-13 can also promote the type-2 differentiation of other cells such as macrophages (M1/M2, ref) and epithelial cells (E1/E2) (Zissler et al. 2016).

1.3 Heterogeneity of Th2 Cells Is Reflected by Their Diverse Function

The prototypic Th2 cell produces IL-4 and IL-13; however, during the last years it appeared that this prototype comes in different flavors, e.g. with co-production of IL-5, IL-17, and IFN-γ (Fig. 2). Consequently, these different phenotypes have different functions during inflammation. High-level IL-5 producing Th2 cells has been identified in allergic asthma and depletion of this subset was accompanied by reduction of eosinophils in the lungs of mice and improved airway hyperresponsiveness (Upadhyaya et al. 2011).

In steroid resistant airway inflammation, another Th2 subset that co-produced IL-4 and IL-17 has been identified (Raymond et al. 2011). These IL-4 + IL-17+ T cells were more pathogenic than classical IL-4+ Th2 or IL-17+ Th17 cells and lead to mixed and augmented infiltration of eosinophils, neutrophils, macrophages, and lymphocytes into the lung. IL-4 + IL-17+ double-positive T cells have been also described in human skin inflammation where IL-4 inhibits the anti-microbial defense of IL-17 and thereby might contribute to the microbial dysbiosis of atopic eczema skin (Eyerich et al. 2009a). Finally, interferons induced by systemic viral infections are able to reprogram committed Th2 cells into IL-4 and IFN-γ coproducing T cells that can be essential to prevent viral persistence and associated immunopathology (Hegazy et al. 2010).

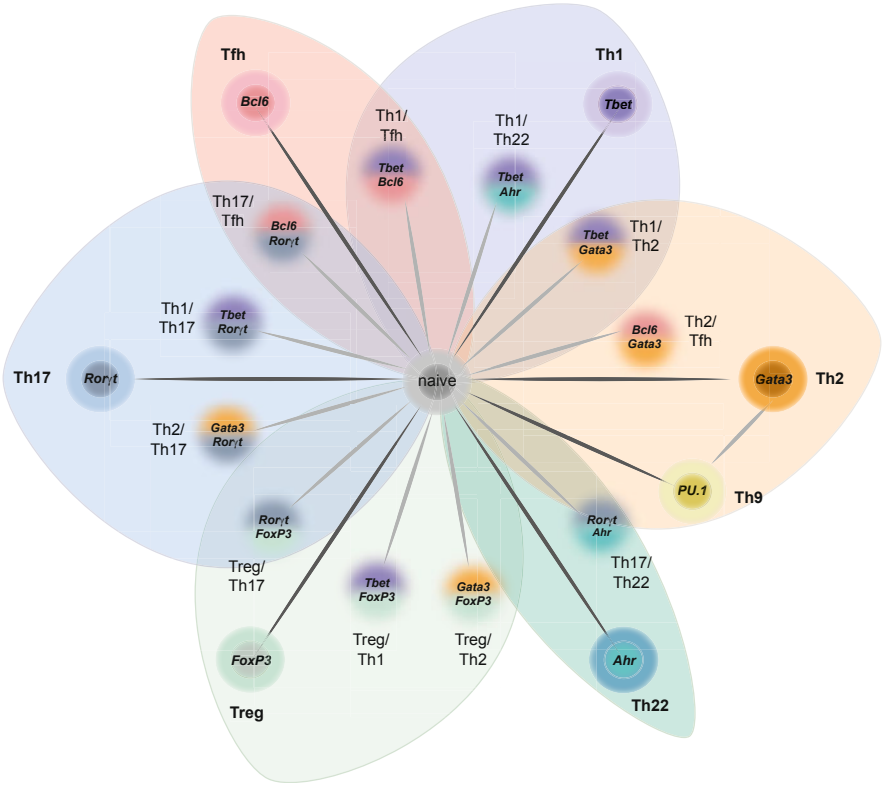

Fig. 2 Functional diversity of the main CD4+ T cell subsets towards other subsets. Naïve T cells differentiate into seven main subsets, Th1, Th2, Th9, Th22, Th17, Tfh, and Treg (dark gray line). These subsets are either terminally differentiated and their phenotype is quite stable (phenotypes in outer ring) or present with a functional diversity and phenotypic features (cytokine and transcription factor expression) of other subsets. These phenotypic diverse subsets develop either from naïve T cells in presence of cytokines or microorganisms and often in a tissue- and disease-specific context or by conversion of already differentiated T cells

1.4 Therapeutic Targeting of Type 2 Cells in Allergic Diseases

The importance of type 2 cytokines in allergic inflammation is impressively demonstrated in recent studies in which the IL-4 receptor alpha chain and thus the efficacy of IL-4 and IL-13 is blocked with a monoclonal antibody (dupilumab). This new therapy is already approved for moderate to severe atopic eczema, while recent studies are investigating efficacy in asthma and eosinophilic esophagitis. For the first time, this biological achieved a 75% improvement in the symptoms of atopic dermatitis in approximately 50% of the study patients – a breakthrough in this difficult-to-treat disease (Simpson et al. 2016). Furthermore, Mepolizumab and Reslizumab (both targeting IL-5) and Benralizumab (targeting the IL-5 receptor) are approved for treatment of asthma. Neutralization of the central mediator of itch,

IL-31, reduced pruritus in two phase two studies II of atopic eczema patients, but did only moderately improve disease severity. Other cytokines such as IL-13 (Tralokinumab, Lebrikizumab), TSLP (Tezepelumab), or IL-33 (REGN3500, ANB020) and the surface marker of a Th2 subset, CrTh2 (Fevipiprant), are currently evaluated in clinical trials (Eyerich et al. 2019; Wollenberg et al. 2019).

In conclusion, the Th2 cell is the prototypic adaptive immune cell involved in allergic inflammation. By secretion of cytokines, Th2 cells have many effector functions in diverse organs leading to barrier disruption, infiltration of immune cells with consecutive tissue inflammation, and instruction of B cells to secrete IgE. Targeting the effector cytokines of Th2 cells has revolutionized the treatment of atopic eczema and will hopefully continue its triumphal therapeutic path in other allergic diseases (LINK TO AE CHAPTER).

2 Th9 Cells: The Sibling of Th2 Cells

IL-9 has long been considered a Th2 cytokine until 2008 a T cell population that produced IL-9 independently of IL-4, IL-5, or IL-13 was described. According to its lead cytokine, this T cell subset was called Th9 (Veldhoen et al. 2008). Only a little later, the CD8+ T cell counterpart was described (Visekruna et al. 2013). In addition to IL-9, Th9 cells also secrete IL-3 and IL-21 (Kaplan et al. 2015) (Fig. 1). In fact, there is a close connection between Th2 and Th9 cells, since Th2 cells can differentiate into Th9 cells by administering TGF-β, which is why both populations belong to the class of type 2 cells (Veldhoen et al. 2008). Moreover, the tight functional associations between IL-9 and other type 2 cytokine secreting cells are further mirrored in ILC2s which are under some conditions even the dominant IL-9 producing cell type (Wilhelm et al. 2011).

2.1 Differentiation of Th9 Cells

In contrast to other T cell subsets, no specific transcription factor has been identified for Th9 cells so far and it seems that the differentiation of this subset depends more on a combination of factors that interact during the developmental process. The most critical cytokine in generation of Th9 cells is TGF-β combined with the signaling cascades induced by IL-2/STAT5 and IL-4/STAT6. As both STAT5 and STAT6 mediate Th2 development, the main function of TGF-β is to block this differentiation path. In addition, TGF-β induces a bunch of transcription factors such as Smad2, Smad3, Smad4, and PU.1 that all bind to the promoter of IL-9 and enhance its expression. PU.1, furthermore, builds a complex at the IL-9 promoter with the histone acetyltransferase Gcn5 leading to enhanced transcriptional activity and probably maintained IL-9 expression (Goswami and Kaplan 2012). STAT5 also directly binds the IL-9 promoter and supports PU.1 function, whereas IL-4 and STAT6 block Foxp3 induction by TGF-β and thereby the development of Tregs. Just recently, Foxo1, a transcription factor regulating cellular fitness and growth (Newton

et al. 2018), has been shown to be involved in Th9 development by enhancing IL-9 expression (Malik et al. 2017).

2.2 Functions of Th9 Cells During Allergic Inflammation

Owing to their close relationship, Th9 and Th2 cells share many functional features. Naturally, Th9 cells are important for defense against helminths and immunity against tumors. Here, IL-9 induces activation of mast cells and goblet cell hyperplasia with consecutive increased mucus production and worm expulsion (Licona-Limon et al. 2013). IL-9, furthermore, increases the response of mast cells against tumor cells (Purwar et al. 2012). Further anti-tumor activity of Th9 cells is mainly dependent on IL-3 and IL-21 that enhance the survival of antigen presenting dendritic cells in the tumor environment and the cytotoxic activity of NK cells, respectively (Park et al. 2014; Vegran et al. 2014). These beneficial functions, however, can turn pathologic if they are not properly controlled and lead to auto-inflammation. As IL-9 is able to activate mast cells and eosinophils and induces mucus production and bronchial hyperresponsiveness (Kaplan et al. 2015), Th9 cells are prone to influence the pathogenesis of allergic diseases. So far, Th9 cells have been described in asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, allergic contact dermatitis, and food allergy. Higher numbers or Th9 cells have been detected in blood of allergic asthma and atopic eczema patients as well as in patients sensitized to house dust mite (Jia et al. 2017). Furthermore, IL-9+ cells are increased during the pollen season in nasal mucosa and reduced after immunotherapy (Nouri-Aria et al. 2005) highlighting their responsiveness to therapeutic regimens. Beyond the description of presence of Th9 cells in disease, the transfer of Th9 cells in mouse studies confirmed their involvement in asthma pathogenesis (Yao et al. 2011). Interestingly, transfer of the CD8+ T cell counterpart, the Tc9 cells, was without effect. Only a co-transfer of a sub-pathogenic number of Th2 cells led to the development of asthmatic symptoms (Visekruna et al. 2013) indicating a close interaction of Tc9 (and presumably Th9 cells) with Th2 cells leading to the aggravation of allergic symptoms.

2.3 Targeting of Th9 Cells in Allergic Diseases

So far, no therapy targeting IL-9 or Th9 cells has been approved. A humanized monoclonal antibody targeting IL-9 (MEDI-528) has been tested in a Phase IIa trial in 36 patients with mild asthma, but did not show improvement of lung function. Co-administration of MEDI-528 with the current treatment did also fail to show efficacy (Oh et al. 2013). However, in a small study with nine mild to moderate asthma patients with exercise induced bronchoconstriction (EIB), MEDI-528 had a positive effect on EIB (Parker et al. 2011). With respect to the high heterogeneity of asthma patients, the small clinical trial cohorts investigated so far and the promising

results from mouse models, the treatment with MEDI-528 might be effective in a subgroup of patients and needs further investigation in the future.

In conclusion, Th9 cells and IL-9 are increased in allergies arguing for a pathogenic role of these cells. The identification of functional differences between Th9 and Th2 cells as well as the identification of disease endotypes that might respond to targeting of IL-9 needs clarification.

3 Th1 Cells: Anti-type 2 or Pro-inflammatory?

Th1 cells are characterized by the secretion of their lead cytokine IFN-γ and the expression of T-bet as master transcription factor (Fig. 1). Whereas their general function is to detect intracellular pathogens and to kill infected as well as tumor cells, their role in allergy is controversial – it ranges from anti-allergic by inhibiting Th2 development to aggravating by the induction of apoptosis recruitment of immune cells to the inflamed peripheral tissue.

3.1 Differentiation of Th1 Cells

Development of Th1 cells critically depends on IL-12 and IFN-γ. IL-2 induces via STAT5 the expression of IL-12 receptor beta (IL-12Rb) that renders naïve T cells responsive to IL-12. IL-12 in turn activates STAT4 and leads to expression of the master transcription factor of Th1 cells, T-bet. T-bet then enhances the expression of IL-12Rβ and IFN-γ that in turn stabilizes T-bet expression via STAT1 (Schulz et al. 2009). Therefore, Th1 differentiation depends on two feedback loops that sustain the phenotype – the IL-12/STAT4/T-bet and the IFN-γ/STAT1/T-bet loop. Interestingly, Th1 differentiation can also happen independently of IL-12 and IFN-γ in vivo during infection with some bacteria, viruses, or parasites indicating that products of microorganisms might be sufficient to induce efficient Th1 mediated inflammation (Szabo et al. 2003). According to IL-4-independent Th2 differentiation, the Notch pathway is also involved in IL-12-independent Th1 development. Here, Toll-like receptor ligands such as LPS or CpG-containing DNA interact with dendritic cells and upregulate Delta-like ligands that bind to Notch on naïve T cells and activate the Th1 differentiation process efficiently in environments that lack or only have limited amounts of IL-12 (Amsen et al. 2009).

3.2 Functions of Th1 Cells During Allergic Inflammation

The role of Th1 cells in allergic diseases is controversial and ranging from anti-type 2 to pro-inflammatory. On the one side, it is well established that once the Th1 differentiation program is initiated differentiation towards Th2 is inhibited by the action of T-bet (Djuretic et al. 2007). In addition, IFN-γ, by activation of STAT1, inhibits de novo differentiation of Th2 cells, proliferation of Th2 effector cells and

eosinophil recruitment into the lung. Furthermore, IFN-γ inhibits class switching to IgE and induces IgG antibodies instead that might neutralize allergens and facilitate Fcγ receptor mediated endocytosis (Sehra et al. 2003). Interestingly, IFN-γ producing T cells are increasing after 3 years of allergen-specific immunotherapy, which may be related to the restored balance of Th1/Th2 cells (Zissler et al. 2018). On the other side, one finds an increased IFN-γ production in severe asthma and atopic dermatitis especially in chronic lesions (Eyerich and Novak 2013). By its capacity to induce apoptosis in target cells, e.g. mucus producing cells, T cells, or eosinophils, IFN-γ might be beneficial during allergic inflammation. However, apoptosis is a pathogenic event during allergic contact dermatitis and definitely leads to aggravation of tissue pathology. Through its differential effects on immune and epithelial cells (Zissler et al. 2016), IFN-γ contributes to the increased recruitment of effector cells into the tissue and their activation, which not only aggravates an allergic reaction, but can also lead to a chronic course.

3.3 Treatment of Allergic Diseases with Recombinant IFN-γ

As Th1 cells are, except in allergic contact dermatitis, underrepresented in allergic inflammation, targeting of IFN-γ is not of use. However, due to the potential beneficial effects of IFN-γ, administration of this cytokine has been considered as therapeutic option. Indeed, several clinical trials have been performed with atopic eczema patients treated with recombinant IFN-γ showing improvement of skin lesions and also allergic comorbidities such as asthma, allergic rhinitis, and ocular symptoms with relatively little side effects (Brar and Leung 2016). The observation of Czarnowicki et al. (2015) that skin homing T cells of young children produce lower levels of IFN-γ compared to adults combined with a high variance in lesional IFN-γ levels in adult patients indicates that recombinant IFN-γ therapy should be only considered in a personalized and endotype-based approach.

In conclusion, Th1 cells counteract Th2 mediated pathology and enhancing their activity during acute allergic reactions in clearly type 2 mediated pathogenesis might be beneficial, however, associated with inflammatory side effects.

4 Th17 Cells: Aggravating, But Only in Certain Disease Endotypes

The existence of Th17 cells was first described in 2005 and not only led to the questioning of the previously valid T cell division into Th1 and Th2, but also paved the way for the discovery of further T cell subtypes. Th17 cells are characterized by expression of the master transcription factor RORγt and secretion of IL-17A, IL-17F, IL-21, and IL-22. (Fig. 1) On the innate arm of the immune system IL-17 family members as well as IL-22 are constantly expressed by ILC3s residing predominantly in the lamina propria of the gut. The main function of Th17 and

ILC3 cells is defense against extracellular bacteria and fungi at epithelial barrier organs.

4.1 Differentiation of Th17 Cells

Differentiation of Th17 cells critically relies on the presence of IL-6 that induces STAT3 and in turn activates expression of RORyt and consecutively production of IL-17 (Zhou et al. 2007). The contribution of TGF-β has been controversially discussed. As TGF-β is able to inhibit expression of IL-4 and IFN-γ by negatively regulating T-bet and Gata3 expression, it was identified as important factor during the differentiation process of Th17 cells (Harrington et al. 2005). While two reports noted that TGF-β might be dispensable for the development of human Th17 cells (Acosta-Rodriguez et al. 2007; Wilson et al. 2007), others have identified a delicate balance between TGF-β and IL-6 that decides about the fate of naïve T cells to develop either into Th17 cells or Tregs. Here, high levels of TGF-β combined with low levels of IL-6 favor Treg differentiation whereas vice versa high levels of IL-6 prevent expression of Foxp3 and thereby favor Th17 differentiation (Yang et al. 2008). The controversial role of TGF-β has been at least in part solved by work of Ghoreschi et al. that described phenotypic and functionally different subsets of Th17 cells, pathogenic (IFN-γ+) and non-pathogenic (IL-10+) T cells, that develop in absence or presence of TGF-β, respectively (Ghoreschi et al. 2010). IL-6 furthermore induces IL-21 expression via STAT3 that leads to an autocrine upregulation of IL-23 receptor expression and responsiveness of developing Th17 cells to IL-23. Both IL-21 and IL-23 are dispensable for the differentiation process, but however, foster the development of the pathogenic phenotype with an enhanced secretion of IFN-γ via STAT3 (Lee et al. 2009). IL-1β represents another part of the Th17 differentiation cocktail as it induces RORγt and IL-17 even independent of IL-6 or IL-23 and as it counteracts the inhibitory role of IL-2 on RORγt and IL-23 receptor expression (Acosta-Rodriguez et al. 2007; Kryczek et al. 2007).

4.2 Function of Th17 Cells During Allergic Inflammation

The primary function of Th17 cells is to protect epithelial barriers from invading bacterial and fungal pathogens. Here, type 17 cytokines induce a bunch of antimicrobial peptides, pro-inflammatory cytokines, and chemokines in epithelial cells that either directly kill pathogens or recruit immune cells such as neutrophils to the site of invasion to assist in clearance of invaders (Stockinger and Omenetti 2017). However, Th17 are not much famous because of their protective, but because of their detrimental role in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (Stockinger and Omenetti 2017). Evidence that IL-17 producing T cells play a role in the allergic diseases is found in studies of asthma, allergic rhinitis, allergic contact dermatitis, food allergy, and atopic dermatitis. However, IL-17 is not present in all patients, but seems to be associated with

endotypes characterized by an increase in neutrophilic granulocytes and is associated with a more severe phenotype (Al-Ramli et al. 2009). Next to the recruitment of neutrophils, IL-17 acts on airway smooth muscle cells and induces their contraction as well as migration (Al-Alwan et al. 2012; Kudo et al. 2012). Thereby, IL-17 is involved in the development of airway hyperresponsiveness and increased mucus production mediated by goblet cell hyperplasia and tissue remodeling and prone to impact on the pathogenesis of asthma (Oda et al. 2005). By its ability to strengthen the epithelial defense against microorganisms, IL-17 is always found in places with an increased risk of pathological colonization such as gut, lung, or skin. However, in the case of an intrinsically disturbed barrier, as observed in atopic eczema, presence of Th17 cells appears to be counterproductive and aggravating through the increased recruitment of neutrophils and the subsequent tissue inflammation. In addition, the per se beneficial function of IL-17 in anti-microbial defense is dramatically reduced in a type 2 mediated environment as IL-4, IL-5, and IL-13 counteract the induction of anti-microbial peptides in epithelial cells allowing the establishment of epithelial dysbiosis (Eyerich et al. 2009a).

4.3 Targeting of Th17 Cells in Allergic Diseases

Targeting the development and effector functions of Th17 cells has a longstanding history in the field of tissue inflammation and autoimmunity, however, not in the field of allergy. TNF-α inhibitors such as Etanercept and Infliximab have been used off-label to treat atopic eczema patients and were either not effective or showed contradictory results (Jacobi et al. 2005). In asthma, TNF-α inhibitors are no longer followed due to a high risk of developing side effects (Eyerich et al. 2019). Ustekinumab, an antibody targeting the IL-12p40 subunit and thereby affecting IL-12 and IL-23, has been used to treat atopic eczema with no effect (Khattri et al. 2017). Clinical trials to block IL-17 or the IL-17 receptor have so far shown no promising effects in the context of asthma therapy (Busse et al. 2013; Kirsten et al. 2013). However, these studies have not focused on IL-17+ asthma patients and it remains to be seen how this specific subgroup of patients might benefit from the inhibition of IL-17.

In conclusion, the contribution of Th17 cells to allergic diseases seems to be rather pro-inflammatory/aggravating than protective, but in general their part in the complex network of allergic inflammation has to be critically evaluated in a disease- and tissue-specific manner.

5 Th22 Cells: Contributors to the Chronic Phase of Allergic Inflammation

Th22 cells joined the T helper family in 2009 (Duhen et al. 2009; Eyerich et al. 2009b) and are together with Th17 cells referred to as type 3T cells. Th22 cells are characterized by secretion of their name-giving cytokine IL-22 and co-produce

TNF-α but no other subtype specific cytokines such as IL-4, IFN-γ, or IL-17 (Eyerich et al. 2009b) (Fig. 1).

5.1 Differentiation of Th22 Cells

Whereas some factors important for differentiation of Th22 cells are known, the detailed mechanisms and master transcription factor/s are not well understood so far. Especially the developmental processes that dissect IL-22 producing Th17 cells from Th22 cells are yet unknown.

Th22 cell develop in a micromilieu containing IL-6 and TNF-α. IL-6 activates STAT3 that in turn initiates the transcriptional profile of Th22 cells. Interestingly, addition of IL-1β to the cocktail leads to development of IL-22 producing Th17 cells. Addition of TGF-β completely abrogates Th22 development (Duhen et al. 2009). While the differentiation conditions are known, there is still some speculation about the master transcription factor of Th22 cells (Trifari et al. 2009). So far, the aryl hydrocarbon receptor (Ahr) represents the only identified transcription factor, however, it only plays a major role in the regulation of IL-22 production, thus in the maintenance of the phenotype, but does not regulate the de novo differentiation of Th22 cells from naïve T cells (Effner et al. 2017). Also the plasticity of Th22 towards other subsets, e.g. Th17 or Th1 cells as well as the fact that the existence of Th22 cells in mice has been not proven beyond doubt hampers the detailed understanding on their developmental paths.

5.2 Functions of Th22 Cells During Allergic Inflammation

Since mouse models with a specific knockout of Th22 cells do not exist, the function of these cells must be evaluated according to the effects of their lead cytokine IL-22. Since the IL-22 receptor is expressed exclusively on epithelial cells, IL-22 is a cytokine that plays an important role in the immune system's instruction of tissue cells. IL-22 stimulates the proliferation and migration of epithelial cells while preventing their differentiation and reducing their sensitivity to apoptosis (Wolk et al. 2004). In addition, IL-22 stimulates the production of anti-microbial peptides and stimulates the defense of pathogens at the interfaces of the organism. Taken together, these effects cause regeneration and preservation of the epithelial barrier (Eyerich et al. 2009b). Models of asthma, inflammatory bowel disease, pancreatitis, hepatitis, and bacterial infection hence have demonstrated a protective effect of IL-22 during inflammation (Sabat et al. 2014). However, if this per se positive function is dysregulated, it may contribute to the pathogenesis of various diseases, such as psoriasis that – due to massively dividing keratinocytes – can be regarded as an overactive wound healing reaction. Since no specificity for classical aerosol- or food-derived allergens has been identified for Th22 cells so far, this T cell subset probably might play a more indirect pathologic role in the field of allergy. In allergic rhinitis and atopic eczema, expression of IL-22 in tissue correlates with elevated

serum IgE levels (Farfariello et al. 2011). Interestingly, IL-22+ T cells are present in high numbers in chronic lesions of atopic eczema, which, with a marked thickening of the epidermis (acanthosis), often resemble those of psoriasis. While type 2 cytokines such as IL-4 and IL-13 inhibit Filaggrin expression and thereby induce a damage to the skin barrier, recruitment of IL-22+ T cells may be a compensatory effect to fight against microorganisms such as *Staphylococcus aureus* that now have the possibility to colonize deeper areas of the skin. IL-22 attempts to counteract this colonization by inducing anti-microbial peptides, which, however, are less potent in a type 2 dominated microenvironment (Eyerich et al. 2009a). In addition, IL-22 enhances keratinocyte proliferation and tries to restore the barrier, however, due to reduced Filaggrin expression barrier integrity is disrupted which cannot be restored by IL-22. Thus, a vicious circle of inefficient pathogen defense and the construction of a further disturbed epithelial barrier is built up. Th22 cells have been also identified in human asthma and here, IL-22 counteracts the pro-inflammatory functions of IFN-γ (Pennino et al. 2013). Whereas this points towards an anti-inflammatory role, the fact that depleting IL-22 in human atopic eczema patients with an IL-22-specific antibody (Fezakinumab) has beneficial effects, however, points to a more inflammation-enhancing involvement of Th22 cells during allergic inflammation (Brunner et al. 2019).

5.3 Therapeutic Targeting of Th22 Cells in Allergic Diseases

As no Th22-specific marker has been identified so far, IL-22 represents the only possibility to target the function of Th22 cells. Here, one study has been performed in 60 moderate-to-severe atopic eczema patients that received Fezakinumab, an IL-22 blocking antibody, over a period of 20 weeks. Especially severely affected patients (SCORAD >50) with high lesional baseline IL-22 expression significantly improved under therapy (Brunner et al. 2019). However, additional studies are needed to validate the effectiveness in other cohorts and to identify the subset of patients that might be responsive.

In conclusion, Th22 cells represent a distinct T helper lineage characterized by IL-22 secretion that is primarily involved in maintaining epithelial barriers. In allergic inflammation, IL-22 has been described as a pro- or anti-inflammatory cytokine highlighting that IL-22 function has to be considered with respect to the local and disease-specific environment.

6 Follicular T Helper (Tfh) Cells: Drivers of Antibody Production

Tfh cells represent a subpopulation of T cells that is found in the germinal centers of secondary lymphoid organs. Here, they stimulate B cells to proliferate and differentiate into antibody-producing plasmablasts. Tfh cells are characterized by the secretion of IL-21, the master transcription factor Bcl-6 and the expression of CXCR5,

PD-1, Icos, CD40L, Btla-4, Sap and CD84 on their cell surface (Vinuesa et al. 2016) (Fig. 1). Interestingly, there is also a circulating counterpart in the blood, which also expresses CXCR5 and can stimulate B cells to produce antibodies and it is assumed that these cells represent resting memory Tfh cells (Locci et al. 2013). Circulating Tfh cells can be classified into a Th1-like, Th2-like, and Th17-like phenotype based on their produced cytokines and transcription factors.

6.1 Differentiation of Tfh Cells

Tfh cells differentiate as all T cells in secondary lymphoid organs, but in contrast, stay there as educated effector T cells to instruct B cells. The process of differentiation can be subdivided in three phases. During the priming phase presentation of high doses of antigens or high-affinity T cell receptors (TCRs) on naïve T cells favors Tfh development in the T cell zone of lymph nodes (Tubo et al. 2013). IL-6 acting via STAT3 induces the expression of the master regulator Bcl-6 as well as IL-21. Together, IL-6 and IL-21 sustain Bcl6 expression and maintain the Tfh phenotype (Nurieva et al. 2008). In addition, CXCR5 is expressed at the cell surface whereas CCR7 is downregulated licensing Tfh cells from the primary stage to migrate to the T-B-cell border (Hardtke et al. 2005). In the second stage, T cells closely interact with B cells via their TCR and the newly induced surface molecules Icos, CD40L and Sap which stabilizes Bcl6 expression and allows entry into the B cell follicle where the differentiation process is finished (Choi et al. 2011).

6.2 Functions of Tfh Cells During Allergic Inflammation

The primary function of Tfh cells is to help naïve B cells to produce IgM and IgG antibodies. Therefore, Tfh cells are an important part of humoral defense against pathogens. If, however, germinal center responses are not terminated after pathogen clearance, autoimmune responses might occur. Tfh cells have been described in the pathogenesis of lupus and inhibition of IL-21 function by specific antibodies could improve auto-inflammation in a lupus mouse model (Choi et al. 2017). The evidence on the contribution of Tfh cells and especially the involvement of IL-21 in the pathogenesis of allergic diseases is still quite poor and in some cases contradictory. Th2-like Tfh cells preferentially induce IgE antibodies and an increase of circulating Th2-like Tfh cells has been demonstrated in patients with allergic rhinitis or food allergy (De Bruyne et al. 2015; Kamekura et al. 2015), but still the exact functional role of Tfh cells in allergic events and the potential of anti-IL-21 therapy remains to be clarified.

So far, Tfh cells cannot be specifically targeted.

7 T Helper Lineage Stability Versus Plasticity or Multiple Functional Identities

The discovery of Th17 cells challenged the Th1/Th2 paradigm and the fact that their lead cytokine could be co-produced with cytokines of other T cell subsets such as IFN-γ, IL-4, and IL-10 highlighted that our view on T cell phenotypes might be over simplified. Nowadays plasticity is a well-recognized, but often not fully understood process in T cell development and function. In general, three kinds of plasticity have to be distinguished – the first during a meta-stable phase of T cell development, the second where polarized T cell subsets exhibit a phenotypic plasticity towards another subset under certain environmental circumstances, and third the complete reprogramming of a fully differentiated T cell into another subset. All these kinds of plasticity are regulated by a variety of factors such as cytokines, TCR and cytosolic signaling, metabolism and finally can be manifested on epigenetic level. As T cell plasticity alone could fill a book chapter, we would like to refer to some brilliant reviews in the field and just extract the common notion of T helper cell plasticity (DuPage and Bluestone 2016; Sallusto 2016; Sallusto et al. 2018) (Fig. 2).

Cytokines are probably the most important factor to induce plasticity in T helper cells. IL-4, for instance, has the capacity to induce Gata3 and subsequent IL-4 expression in Th1 cells (Fig. 2). Vice versa, IL-12, the differentiation factor for Th1 cells, induces T-bet and IFN-γ production in Th2 or Th17 cells (Hegazy et al. 2010). Polarized Tfh cells can be pushed towards a Th1, Th2, or Th17 phenotype in presence of IL-12, IL-4 or IL-6, respectively, whereas the cytokines driving Tfh differentiation IL-21 and IL-6 are able to induce IL-21 expression in Th1, Th2, and Th17 cells (Lu et al. 2011). TGF-β has been shown to reprogram polarized Th2 cells towards the Th9 phenotype and also induces Foxp3 expression in Th17 cells (see below) (Veldhoen et al. 2008).

In addition to cytokines, microorganisms can alter the phenotype of polarized and developing T helper cells. *Mycobacterium tuberculosis* or *Candida albicans* fosters the development of T cells that co-produce IFN-γ and IL-17, whereas *Staphylococcus aureus* induces IL-17 and IL-10 double-positive cells (Zielinski et al. 2012). IL-17 and IL-4 double-positive T cells have been described in allergic asthma and atopic dermatitis (Eyerich et al. 2009a; Wang et al. 2010) which highlight their potential contribution to disease pathology.

The remaining question is, however, if T helper cell plasticity is the exception or the rule. There is growing evidence that plasticity is highest early in the differentiation process and nearly lost in terminally differentiated T helper cells (Messi et al. 2003). The fact that plasticity allows flexible responses to invading pathogens in different tissue environments and that plasticity of Th1 cells towards IL-4 or IL-10 secreting cells may reduce detrimental tissue damage argues for a more general principle than for an exception. However, understanding this plasticity will be the challenge for the next years in T cell research.

8 Foxp3+ Regulatory T Cells (Tregs): Mediators of Tolerance

The existence of a T cell subpopulation with regulatory function has long been suspected but only after the identification of the master transcription factor Foxp3 a role in immune regulation could unambiguously be demonstrated by gene knockout in mice resulting in a "scurfy" phenotype and severe autoimmune syndromes in various tissues (Fontenot et al. 2003; Hori et al. 2003). Deficiency or mutations in the *Foxp3* gene have also been observed in humans and cause the so-called IPEX (*Immune dysregulation Polyendocrinopathy Enteropathy X-linked)* syndrome (Bennett et al. 2001). Both in mice and humans, elevated levels of IgE and Th2 cells could be readily detected in the absence of Foxp3+ Tregs leading to the idea that Foxp3+ Tregs play also a key role in preventing Th2-mediated diseases including allergy (Lahl et al. 2009).

8.1 Treg Origin and Oral Tolerance

Initially, thymic differentiation was considered as the main site of Foxp3+ Treg origin (tTregs) and it is estimated that around 80% of Tregs in lymphoid organs such as spleen and lymph nodes are thymus-derived (Shevach 2018). Noteworthy, in recent years it became evident that mucosal sites such as the gastrointestinal tract can equally favor the differentiation of peripherally-induced Tregs (pTregs). While tTregs have been selected on cognate recognition of self-antigens to prevent autoimmune reactivity in the periphery pTregs are supposed to provide immune tolerance to harmless foreign antigens including allergens (Curotto de Lafaille et al. 2008). In the intestinal tract this phenomenon has been referred to as oral tolerance. Indeed the highest frequencies of Foxp3+ Tregs in mice can be found at this site (Atarashi et al. 2011) but this does not exclude that similar mechanisms are in place at other barrier organs such as the skin or lung.

The most dramatic role of oral tolerance could be deduced from the LEAP study. In this study, it was investigated whether children at high risk developing food allergy to peanuts benefit from an early-on allergen avoidance regimen – which was the main guideline at the time for such high-risk children. Contrary to the expectations, children consuming a defined amount of peanut during their first years of life showed a greatly reduced probability to get sensitized to peanut allergens at 5 years of age when compared to the peanut-avoidance group (Du Toit et al. 2015). Thus, enforcing oral tolerance in early childhood presumably through the induction of antigen-specific Tregs might be one way to reduce the risk of developing sustained food allergy later in life. Importantly, murine studies have shown recently that intestinal Treg induction in response to microbial colonization requires to happen in a critical time window in childhood in order to prevent future exacerbated inflammation in the intestinal tract (Al Nabhani et al. 2019). This observation fits well with the observation that children grown up on rural farms with exposure to farm dust are protected from allergic disorders later in life (Stein et al. 2016).

Foxp3+ Tregs can also be detected in the peripheral blood of humans and the development of new techniques has enabled to even assess the frequency of antigen-specific Tregs. Surprisingly, most Tregs in peripheral blood lymphocytes of healthy persons are directed against particle-associated antigens of typical lung-penetrating allergens such as pollen (Bacher et al. 2016). Therefore, it has been suggested that in allergic persons a deviation of the TCR repertoire of differentiating Th2 cells must have occurred and Treg-mediated control of allergen-reactive T cells is no longer in place.

8.2 Differentiation of Tregs

High levels of IL-2 together with TGF-β are necessary and sufficient to drive the differentiation of Tregs from naïve T cells. IL-2 derived from conventional T cells promotes the phosphorylation of STAT5 which in turn directly regulates Foxp3 expression (Burchill et al. 2007). Furthermore, IL-2 binding to the high-affinity IL-2 receptor (CD25) together with a constant TCR stimulus has a key role in the maintenance and function of mature Tregs (Levine et al. 2014; Vahl et al. 2014). TGF-β in turn is known to favor Treg differentiation in combination with IL-2 while it can also drive Th17 differentiation in the presence of IL-6 (Korn et al. 2008). In fact a small cell population (Tr17) of FOXP3 and IL-17 co-expressing cells was described that occur early on in allergen-specific immunotherapy (Zissler et al. 2018) that may represent cells that are in transition from Th17 into Tregs. Treg themselves do not secrete IL-2 but rely at least partially on an inactive TGF-β form that needs to be cleaved by integrin αvβ8 on the surface of Tregs (Worthington et al. 2015). Peripherally-induced Tregs rely on classical antigen presentation by bona-fide antigen presenting cells such as CD103+ DCs (in the gut) or F4/80+ tissue macrophages (in the lung) both secreting high levels of TGF-β and retinoic acid, an important vitamin A metabolite known to increase pTreg differentiation and maintenance (Hall et al. 2011). Given the prominent role of IL-2, current trials are underway investigating the potential of a low dose IL-2 therapy to boost Treg function (Bonnet et al. 2016).

As discussed above Foxp3 is the main transcription factor responsible for the imprinting of a tolerogenic function on developing T helper cells. Foxp3 in conjunction with additional transcription factors directly regulate a number of genes known to contribute to the tolerogenic function of Tregs (Gavin et al. 2007; Samstein et al. 2012). Due to the importance of the *Foxp3* gene locus also non-coding regulatory elements next to the *Foxp3* promoter region (CNS1-3; "conserved non-coding sequence") have been investigated (Zheng et al. 2010). Interestingly, Foxp3 binds to CNS2 which needs to be maintained completely demethylated in mature Tregs in order to ensure Treg lineage stability; therefore, this region initially has been termed TSDR (Treg-specific demethylated region) (Polansky et al. 2008). In vitro differentiation of Tregs often fails to achieve complete demethylation of CNS2 impeding Treg-mediated immune therapies in various contexts (Floess et al. 2007). The CNS1 region – while being dispensable for thymic Treg differentiation – has been found to

be critical for the differentiation of peripherally-induced Tregs in vivo (Josefowicz et al. 2012).

In the intestinal tract, peripheral Treg differentiation relies to a large extent on the colonization by commensal microbes with a prominent role for the genus *Clostridium* (Atarashi et al. 2013). Importantly, colonization with mixtures of *Clostridium* clusters was sufficient to limit a Th2 immune response after injection of a prototypical Th2-differentiating adjuvants (Atarashi et al. 2011). Mechanistically, fermentation products such as short chain fatty acids (SCFA) are able to directly boost Treg accumulation in a GPR43-dependent manner (Furusawa et al. 2013; Smith et al. 2013). SCFA and here especially butyrate are thought to act via inhibition of HDACs (histone deacetylases) to enable proper histone acetylation at the *Foxp3* promoter region as well as CNS1 and CNS3 regions (Furusawa et al. 2013; Smith et al. 2013).

8.3 General Functional Mechanisms of Tregs

Murine models including those for lung- and food allergy have shown clear evidence for an immune regulation by Foxp3+ Tregs through a variety of mechanisms but it is not always clear whether these mechanisms are also active in patients with allergic diseases. Among the best-understood mechanisms are the release of inhibitory cytokines IL-10, IL-35, and TGF-β or cytolytic molecules (granzyme A and B) and the down modulation of antigen presenting cell function via CTLA-4 or LAG-3. Additionally, deprivation of homeostatic cytokines for T cell activation (IL-2) via high CD25 expression and degradation of nucleotides via CD39 and CD73 expression on the surface of Tregs contribute to the overall regulatory capacity of Tregs. Very often it is however not always possible to reveal the precise mechanism how Tregs exert their function and various pathways may cooperate. Along the same line, whether only antigen-specific Foxp3+ Tregs are active during on-going inflammatory conditions or whether non-specific Tregs present in the same organ fulfill bystander suppressive functions possibly related to other aims such as preserving tissue function and integrity remains to be thoroughly investigated.

8.4 Functional Mechanisms of Tregs in Allergic Diseases

All of the above mechanisms can be attributed to Treg-mediated tolerance to allergens or to the regulation of the severity of the allergic reaction. Most prominently, Treg-derived IL-10 has been shown to have a critical and non-redundant role in the regulation of allergic airway inflammation (Rubtsov et al. 2008). Nevertheless, Tregs might also induce IL-10 production by local CD4+ T cells and potentially even other subpopulations (Kearley et al. 2005). IL-10 is a very potent immunosuppressive cytokine and is able to regulate a number of key players involved in the allergic reaction such as Th2 cells, dendritic cells, mast cells, and eosinophils. TGF-β in turn has been shown to be required for the protective role of Tregs in the context of

oral allergen exposure (Mucida et al. 2005). However, beyond such generic mechanism about Treg-mediated immune regulation, more sophisticated ways of immune regulation have been described. This includes both regulation of innate and adaptive immune effector cells.

In terms of innate immune effector cells, direct interaction between Tregs and mucosal mast cells via OX40-OX40L interaction is able to block mast cell degranulation and release of preformed granules (Gri et al. 2008). This interaction also reduces IL-4 release by mast cells after crosslinking of FcεRI-bound IgE and thereby the amplification of Th2 cells and the IgE response – two critical parameters for food allergy. Treg-mediated control of mast cells might therefore be one important control point where Tregs regulate innate immune cells with a critical effect on adaptive immunity and allergic disease. Besides mast cells, Tregs have been shown to regulate the expansion and cytokine production of murine innate lymphoid cells type 2 (ILC2s) both in vitro and in vivo (Noval Rivas et al. 2016; Rigas et al. 2017). Reciprocally, ILC2-derived IL-4 may limit the induction of pTregs at least in food allergy prone mice with a mutation in the *il4r* gene (Noval Rivas et al. 2016). Finally, Tregs generally are able to down modulate the expression of CD80/CD86 on DCs via CTLA-4, LAG-3, and LFA-1 and thereby prevent the priming of differentiating Th2 cells (Liang et al. 2008; Onishi et al. 2008).

Besides these innate cellular targets, Tregs are able to control adaptive and therefore rather antigen-specific T cell immune responses. In animal studies adoptive transfer of Tregs prior to allergen challenge of sensitized mice has been shown to result in reduced airway hyperresponsiveness and inflammation (Kearley et al. 2005). Along the same line, depletion of CD25+ T cells prior to delivery of house dust mite led to elevated levels of IgE and eosinophils (Lewkowich et al. 2005). Furthermore, antigen-specific Tregs induced via oral administration of the allergen have been shown to be necessary and sufficient to prevent development of a Th2-dominated allergic response (Mucida et al. 2005). In a follow-up study it has been shown that peripherally-induced Tregs are required to prevent the allergen-specific sensitization but not IL-5 production and associated tissue eosinophilia frequently observed under chronic allergic conditions (Curotto de Lafaille et al. 2008). Thus, allergen-specific Tregs are most likely constantly induced from naïve T cells in the periphery of non-allergic individuals and are required to prevent de novo sensitization. Whether such Tregs need to acquire additional features to efficiently function as allergy-preventing cells remains to be discovered.

8.5 Regulation of Treg Function by Transcription Factors of Other T Helper Lineages

Even though Foxp3 has been identified as the key transcription factor for Treg stability and function, several studies in recent years have highlighted a role of master transcription associated with other T helper lineages including T-bet, RORγt, and Gata3. Expression of these transcription factors varies according to anatomical

location and is often restricted to non-lymphoid tissues. This implies a role of Tregs beyond immune regulation in normal tissue function and repair.

8.6 T-bet Expressing Tregs

Co-expression of master transcription factors from other T helper lineages has been first observed for T-bet in Foxp3+ Tregs. Mechanistically, exposure of Treg cells to IFN-γ leads to co-expression of T-bet and Foxp3 and these T-bet+ Tregs were particularly potent in the suppression of Th1-dominated immune responses (Koch et al. 2012). One explanation for this potency may be the concomitant upregulation of the chemokine receptor CXCR3 enabling T-bet+ Tregs to migrate along the same gradient as Th1 cells and to locally suppress Th1 cells and CD8 T cells very efficiently (Koch et al. 2009). However, while such T-bet+ Tregs become stable even under non-permissive conditions and become essential to control Th1-driven pathology, the T-bet expression in Tregs itself becomes needless with time (Levine et al. 2017). In line with this observation, mice lacking T-bet in Tregs do not develop autoimmune features (Yu et al. 2015). Additionally, Notch signaling within Tregs is involved in the fine-tuning of such T cells at the border of Th1 to Treg cells (Charbonnier et al. 2015). In summary, T-bet expression may be important to imprint the initial identity of this Treg subset but becomes redundant once the function has been successfully imprinted. Whether T-bet-expressing Tregs exert a specific function in non-lymphoid tissues or during allergic disorders remains currently unknown.

8.7 RORγt Expressing Tregs

As Tregs and Th17 cells share the need for a TGF-β signal for their differentiation from naïve T cells both populations have been extensively compared. Indeed, it has been observed that T cells expressing Foxp3 and RORγt exist both in vitro and in vivo and that both transcription factors physically interact with each other (Lochner et al. 2008; Zhou et al. 2008). Initially, it was considered that RORγt +Foxp3+ cells constitute an intermediate or transient cell state of differentiating T cells that will diverge into Th17 and Treg cells according to respective cytokine environments (Zhou et al. 2008). Indeed, plasticity among Th17 cells and Tregs has been described in both directions during rheumatoid arthritis (Komatsu et al. 2014) and resolution of inflammation (Gagliani et al. 2015). Noteworthy, RORγt+ Tregs can be found at high frequencies within the intestinal lamina propria and appear at least under steady conditions relatively stable (Yang et al. 2015). Several lines of evidence including the absence of thymic Treg markers Helios and Neuropilin-1 indicate that RORγt+ Tregs differentiate locally from naïve T cells and are not of thymic origin (Ohnmacht et al. 2015). As these cells depend on the presence of commensal microbes it has been proposed that RORγt+ Tregs differentiate locally and especially the gut-associated lymphoid tissues (GALT) are required to actively tolerate the intestinal microbiota (Ohnmacht et al. 2015). Indeed, RORγt+ Tregs play

a key role to prevent hyperactivation of the immune system in response to commensal microbes in a variety of intestinal inflammation models (Ohnmacht et al. 2015; Xu et al. 2018). By contrast, tolerance to food antigens is mostly achieved by the induction of another Treg subset lacking both Helios and RORγt expression (Kim et al. 2016). Given that germfree mice (and sometimes even mice with a dysbiotic microbiota) have (1) a general type 2 immune bias at steady state (Cahenzli et al. 2013), (2) are prone to develop more severe allergic reactions (Stefka et al. 2014), and (3) often fail to induce oral tolerance to dietary antigens (Kim et al. 2016) RORγt + Tregs may be a central player in the host-microbiome axis to regulate or prevent allergic disorders.

There has been a strong interest to understand why RORγt+ Tregs do not start to produce the same cytokines as Th17 cells. Apparently, these Tregs rely on the presence of a transcriptional regulator called Blimp1 to suppress IL-17 production (Ogawa et al. 2018). Given that microbial dysbiosis is considered as one of the main risk factors to develop food allergies, insufficient induction of RORγt+ Tregs by dysbiotic microbiomes has been considered as one potential mechanism how intestinal Th2 cells escape from Treg-mediated control: First, RORγt+ Tregs are able to control intestinal Th2-mediated immune responses (Ohnmacht et al. 2015). In humans, patients with the Hyper-IgE syndrome due to heterozygous dominant-negative STAT3 mutations show a severe deficiency in CCR6+ Tregs most likely reflecting RORγt+ Tregs (Kluger et al. 2014). Second, transfer of fecal maters from children with food allergy to mice raised under germfree conditions induces a more severe allergic and anaphylactic reaction upon allergen challenge (Feehley et al. 2019) and this is correlated with a reduced induction of RORγt+ Tregs in both mice and humans (Abdel-Gadir et al. 2019). However, RORγt+ Tregs have also been shown to become pathogenic during house dust mite-induced allergic airway inflammation in mice with enhanced IL4R signaling because under these conditions such cells start to secrete IL-17 cytokines in the lungs and contribute to allergic exacerbation (Massoud et al. 2016). Overall, RORγt+ Tregs can be considered now as one central player acting as a critical link between the commensal flora and immune dysregulation including allergies (Ohnmacht 2016).

8.8 Gata3 Expressing Tregs

An initial in vitro study revealed that overexpression of Gata3 prevents the subsequent upregulation of Foxp3 in differentiating T cells (Mantel et al. 2007). In experimental and clinical trials anti-IL4 was therefore investigated as pro-tolerogenic adjuvant in the context of allergen-vaccination (Chaker et al. 2016; Russkamp et al. 2019). After this observation it was noted, however, that Tregs within non-lymphoid tissues such as skin or gut surprisingly harbor a substantial fraction of Gata3+ Tregs (Schiering et al. 2014). In contrast to RORγt+ Tregs, Gata3+ Tregs develop in the absence of commensal microbes (Ohnmacht et al. 2015). Signaling of the alarmin IL-33 and also the cytokines IL-4 and IL-2 in Tregs have been shown to induce Gata3 expression in Tregs and it has been suggested that

Gata3 is necessary to maintain a stable Treg phenotype to allow for Treg accumulation under strong inflammatory conditions (Delacher et al. 2017; Schiering et al. 2014). Indeed, ablation of Gata3 alone or in combination with T-bet selectively in Tregs leads to autoimmune features in mice (Yu et al. 2015). Importantly, enhanced IL-4R signaling in Tregs in combination with food allergy models can lead to the production of type 2 cytokines by Gata3+ Tregs making this Treg subpopulation a potential target for immune therapy (Noval Rivas et al. 2015). Indeed, neutralization of IL-4 in vivo can prevent to some degree the accumulation of Gata3+ Tregs during allergen immune therapy (AIT) (Russkamp et al. 2019), but the relevant contribution of Gata3+ Tregs to the production of type 2 cytokines during the inflammatory conditions of different allergies beyond IL-4 receptor mutations remains to be explored. Currently, it is still unclear whether the developmental origin of Gata3+ Tregs coincides with the TCR specificity: Whereas thymic Tregs presumably have been selected on the basis of cognate self-antigens and might further acquire Gata3 expression within tissues, Treg differentiation starting from naïve T cells upon recognition of allergens in the periphery should have a non-overlapping TCR repertoire.

This concept is further highlighted by the fact that Gata3 expression under non-allergic conditions seems to be one hallmark (among others) of a general tissue Treg fingerprint (Delacher et al. 2017). Type 2 immunity has been implicated in physiological tissue function and repair processes (Gause et al. 2013) and it is tempting to speculate that Gata3+ tissue Tregs fulfill a related function under non-allergic conditions, e.g. by regulating epithelial stem cell function within hair follicles, or providing help to regeneration of muscle and lung epithelial cells after pathogen-induced injury (Ali et al. 2017). During allergic inflammation, tissue damage occurs frequently and Gata3+ Tregs may ensure unwanted T cell reactivity against neo self-epitopes in the inflamed tissue. Thus, targeting Gata3+ Tregs themselves may come at a high risk to interfere with normal tissue function particularly under tissue stress conditions. However, the production of cytokines by Gata3+ Tregs is clearly able to contribute to aggravation of allergies at least in murine models. This necessitates uncovering the molecular mechanisms how Gata3+ Tregs in tissues prevent the production of type 2 cytokines at steady state and conversely, which genetic pathways or environmental conditions interfere with this regulation.

8.9 Other Treg-Associated Co-factors Necessary to Regulate Th2 Immunity

A number of genetic elements or gene products have been found necessary to prevent spontaneous differentiation of Th2 cells. Early on it was noticed that Foxp3 exerts its regulation by co-opting a network of pre-existing transcriptional regulators that are also used by other T helper lineages. For instance, IRF4 deletion in Tregs results in the unregulated differentiation of Th2 cells and plasma cells (Zheng et al. 2009). Another important effector molecule comes from the observation that patients with the Wiskott-Aldrich syndrome (WAS) suffer frequently from

severe food allergy. Interestingly, mice lacking WASP expression in Tregs do recapitulate this observation as frequent sensitization to common food antigens and uncontrolled Th2 responses after induction of food allergy can be observed in such mice (Lexmond et al. 2016). In addition the already mentioned deficiency of CNS1 with the accompanied deficiency in pTreg differentiation results in a spontaneous, age-dependent Th2-dominated inflammation at mucosal sites (Josefowicz et al. 2012). This phenomenon might reflect the inadequate response to microbial colonization due to deficiency of RORγt+ Tregs. A similar scenario has been recently found in the absence of the transcriptional regulator Rbpj because Treg-specific ablation results equally in accumulating Th2 cells and high IgE levels with time (Delacher et al. 2019). Additionally, functional impairment of Tregs to control DC function has also been shown to result in Th2-driven inflammation: For instance, the protein kinase CK2 has been shown to enable Tregs to suppress IRF4+ PD-L2+ DCs required for the differentiation of pulmonary Th2 cells in vivo (Ulges et al. 2015). Conversely, deletion of a critical signaling molecule called TRAF6 in DCs has been shown to impair the de novo generation of Tregs in the intestinal tract in turn inducing a strong Th2-dominated inflammation in such mice (Han et al. 2013). Finally, also the deletion of known effector mechanisms from Tregs such as CTLA-4 can result in the systemic accumulation of Th2 cells and high IgE levels (Wing et al. 2008).

All of the above-described examples do not yet reflect a role of these mechanisms directly in allergic disorders as some of these inflammatory responses are probably rather driven by autoimmune reactivity. Nevertheless, environmental parameters with an impact on the regulation of such key regulation nodes in Tregs or rare single nucleotide polymorphisms (SNPs) in these genes of allergic patients could favor and/or enhance the risk to develop allergic disorders.

9 Conclusion and Outlook

The last two decades in T cell research did not only challenge the outdated Th1/Th2 paradigm, but also revealed a plethora of new T cell subsets that now offer huge possibilities to better understand the sometimes very heterogeneous phenotypes during allergic inflammation. Besides the fact that we need to understand more about the contribution of each single subset to different disease entities, it will be of outermost importance to not only reduce the function of a T cell subset to secreted cytokines, but also develop a more comprehensive approach evaluating the role of these cells under certain disease- and tissue-specific environments, understand their interaction with resident epithelial cells and their interplay with innate counterparts. This should give insights into T cell functions ultimately on a single level that can be therapeutically targeted to prevent pathology in one specific organ or disease endotypes. This will help to estimate the risk of side effects in treatment of allergic diseases and will be the basis for stratified, T cell-targeted therapeutic regimens in the future.

References

Abdel-Gadir A et al (2019) Microbiota therapy acts via a regulatory T cell MyD88/RORgammat pathway to suppress food allergy. Nat Med 25:1164–1174. https://doi.org/10.1038/s41591-019-0461-z

Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F (2007) Interleukins 1 beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 8:942–949. https://doi.org/10.1038/ni1496

Agarwal S, Avni O, Rao A (2000) Cell-type-restricted binding of the transcription factor NFAT to a distal IL-4 enhancer in vivo. Immunity 12:643–652

Al Nabhani Z et al (2019) A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. Immunity 50:1276–1288.e1275. https://doi.org/10.1016/j.immuni.2019.02.014

Al-Alwan LA et al (2012) Autocrine-regulated airway smooth muscle cell migration is dependent on IL-17-induced growth-related oncogenes. J Allergy Clin Immunol 130:977–985.e6. https://doi.org/10.1016/j.jaci.2012.04.042

Ali N et al (2017) Regulatory T cells in skin facilitate epithelial stem cell differentiation. Cell 169:1119–1129.e1111. https://doi.org/10.1016/j.cell.2017.05.002

Al-Ramli W, Prefontaine D, Chouiali F, Martin JG, Olivenstein R, Lemiere C, Hamid Q (2009) T (H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. J Allergy Clin Immunol 123:1185–1187. https://doi.org/10.1016/j.jaci.2009.02.024

Amsen D, Antov A, Flavell RA (2009) The different faces of Notch in T-helper-cell differentiation. Nat Rev Immunol 9:116–124. https://doi.org/10.1038/nri2488

Atarashi K et al (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331:337–341. https://doi.org/10.1126/science.1198469

Atarashi K et al (2013) Treg induction by a rationally selected mixture of clostridia strains from the human microbiota. Nature 500:232–236. https://doi.org/10.1038/nature12331

Bacher P et al (2016) Regulatory T cell specificity directs tolerance versus allergy against aeroantigens in humans. Cell 167:1067–1078.e1016. https://doi.org/10.1016/j.cell.2016.09.050

Bennett CL et al (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27:20–21. https://doi.org/10.1038/83713

Bonnet B et al (2016) Low-dose IL-2 induces regulatory T cell-mediated control of experimental food allergy. J Immunol 197:188–198. https://doi.org/10.4049/jimmunol.1501271

Brar K, Leung DY (2016) Recent considerations in the use of recombinant interferon gamma for biological therapy of atopic dermatitis. Expert Opin Biol Ther 16:507–514. https://doi.org/10.1517/14712598.2016.1135898

Brunner PM et al (2019) Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J Allergy Clin Immunol 143:142–154. https://doi.org/10.1016/j.jaci.2018.07.028

Burchill MA, Yang J, Vogtenhuber C, Blazar BR, Farrar MA (2007) IL-2 receptor beta-dependent STAT5 activation is required for the development of Foxp3+ regulatory T cells. J Immunol 178:280–290. https://doi.org/10.4049/jimmunol.178.1.280

Busse WW, Holgate ST, Kerwin EM, Chon Y, Feng JY, Lin JH, Lin SL (2013) A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of Brodalumab (AMG 827) in subjects with moderate to severe asthma. J Allergy Clin Immunol 131:Ab230. https://doi.org/10.1016/j.jaci.2012.12.1486

Cahenzli J, Koller Y, Wyss M, Geuking MB, McCoy KD (2013) Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. Cell Host Microbe 14:559–570. https://doi.org/10.1016/j.chom.2013.10.004

Chaker AM et al (2016) Short-term subcutaneous grass pollen immunotherapy under the umbrella of anti-IL-4: a randomized controlled trial. J Allergy Clin Immunol 137:452–461.e459. https://doi.org/10.1016/j.jaci.2015.08.046

Charbonnier LM, Wang S, Georgiev P, Sefik E, Chatila TA (2015) Control of peripheral tolerance by regulatory T cell-intrinsic Notch signaling. Nat Immunol 16:1162–1173. https://doi.org/10.1038/ni.3288

Choi YS et al (2011) ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6. Immunity 34:932–946. https://doi.org/10.1016/j.immuni.2011.03.023

Choi JY et al (2017) Disruption of pathogenic cellular networks by IL-21 blockade leads to disease amelioration in murine lupus. J Immunol 198:2578–2588. https://doi.org/10.4049/jimmunol.1601687

Curotto de Lafaille MA, Kutchukhidze N, Shen S, Ding Y, Yee H, Lafaille JJ (2008) Adaptive Foxp3+ regulatory T cell-dependent and -independent control of allergic inflammation. Immunity 29:114–126. https://doi.org/10.1016/j.immuni.2008.05.010

Czarnowicki T et al (2015) Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) TH2/TH1 cell imbalance, whereas adults acquire CLA(+) TH22/TC22 cell subsets. J Allergy Clin Immunol 136:941–951.e943. https://doi.org/10.1016/j.jaci.2015.05.049

De Bruyne R et al (2015) Raised immunoglobulin A and circulating T follicular helper cells are linked to the development of food allergy in paediatric liver transplant patients. Clin Exp Allergy 45:1060–1070. https://doi.org/10.1111/cea.12514

Delacher M et al (2017) Genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues. Nat Immunol 18:1160–1172. https://doi.org/10.1038/ni.3799

Delacher M et al (2019) Rbpj expression in regulatory T cells is critical for restraining TH2 responses. Nat Commun 10:1621. https://doi.org/10.1038/s41467-019-09276-w

Djuretic IM, Levanon D, Negreanu V, Groner Y, Rao A, Ansel KM (2007) Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells. Nat Immunol 8:145–153. https://doi.org/10.1038/ni1424

Du Toit G et al (2015) Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 372:803–813. https://doi.org/10.1056/NEJMoa1414850

Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F (2009) Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat Immunol 10:857–863. https://doi.org/10.1038/ni.1767

DuPage M, Bluestone JA (2016) Harnessing the plasticity of CD4(+) T cells to treat immune-mediated disease. Nat Rev Immunol 16:149–163. https://doi.org/10.1038/nri.2015.18

Effner R et al (2017) Cytochrome P450s in human immune cells regulate IL-22 and c-kit via an AHR feedback loop. Sci Rep 7:44005. https://doi.org/10.1038/srep44005

Eyerich K, Novak N (2013) Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. Allergy 68:974–982. https://doi.org/10.1111/all.12184

Eyerich K et al (2009a) IL-17 in atopic eczema: linking allergen-specific adaptive and microbial-triggered innate immune response. J Allergy Clin Immunol 123:59–66. https://doi.org/10.1016/j.jaci.2008.10.031

Eyerich S et al (2009b) Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 119:3573–3585. https://doi.org/10.1172/JCI40202

Eyerich S, Metz M, Bossios A, Eyerich K (2019) New biological treatments for asthma and skin allergies Allergy. https://doi.org/10.1111/all.14027

Farfariello V et al (2011) IL-22 mRNA in peripheral blood mononuclear cells from allergic rhinitic and asthmatic pediatric patients. Pediatr Allergy Immunol 22:419–423. https://doi.org/10.1111/j.1399-3038.2010.01116.x

Feehley T et al (2019) Healthy infants harbor intestinal bacteria that protect against food allergy. Nat Med 25:448–453. https://doi.org/10.1038/s41591-018-0324-z

Floess S et al (2007) Epigenetic control of the foxp3 locus in regulatory T cells. PLoS Biol 5:e38. https://doi.org/10.1371/journal.pbio.0050038

Fontenot JD, Gavin MA, Rudensky AY (2003) Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol 4:330–336. https://doi.org/10.1038/ni904

Furusawa Y et al (2013) Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 504:446–450. https://doi.org/10.1038/nature12721
Gagliani N et al (2015) Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. Nature 523:221–225. https://doi.org/10.1038/nature14452
Gause WC, Wynn TA, Allen JE (2013) Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. Nat Rev Immunol 13:607–614. https://doi.org/10.1038/nri3476
Gavin MA, Rasmussen JP, Fontenot JD, Vasta V, Manganiello VC, Beavo JA, Rudensky AY (2007) Foxp3-dependent programme of regulatory T-cell differentiation. Nature 445:771–775. https://doi.org/10.1038/nature05543
Ghoreschi K et al (2010) Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature 467:967–971. https://doi.org/10.1038/nature09447
Goswami R, Kaplan MH (2012) Gcn5 is required for PU.1-dependent IL-9 induction in Th9 cells. J Immunol 189:3026–3033. https://doi.org/10.4049/jimmunol.1201496
Gri G et al (2008) CD4+CD25+ regulatory T cells suppress mast cell degranulation and allergic responses through OX40-OX40L interaction. Immunity 29:771–781. https://doi.org/10.1016/j.immuni.2008.08.018
Grunewald SM et al (2001) Upon prolonged allergen exposure IL-4 and IL-4Ralpha knockout mice produce specific IgE leading to anaphylaxis. Int Arch Allergy Immunol 125:322–328. https://doi.org/10.1159/000053833
Hall JA, Grainger JR, Spencer SP, Belkaid Y (2011) The role of retinoic acid in tolerance and immunity. Immunity 35:13–22. https://doi.org/10.1016/j.immuni.2011.07.002
Han D et al (2013) Dendritic cell expression of the signaling molecule TRAF6 is critical for gut microbiota-dependent immune tolerance. Immunity 38:1211–1222. https://doi.org/10.1016/j.immuni.2013.05.012
Hardtke S, Ohl L, Forster R (2005) Balanced expression of CXCR5 and CCR7 on follicular T helper cells determines their transient positioning to lymph node follicles and is essential for efficient B-cell help. Blood 106:1924–1931. https://doi.org/10.1182/blood-2004-11-4494
Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT (2005) Interleukin 17-producing CD4(+) effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 6:1123–1132. https://doi.org/10.1038/ni1254
Hegazy AN et al (2010) Interferons direct Th2 cell reprogramming to generate a stable GATA-3(+) T-bet(+) cell subset with combined Th2 and Th1 cell functions. Immunity 32:116–128. https://doi.org/10.1016/j.immuni.2009.12.004
Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. Science 299:1057–1061. https://doi.org/10.1126/science.1079490
Ishizuka IE, Constantinides MG, Gudjonson H, Bendelac A (2016) The innate lymphoid cell precursor. Annu Rev Immunol 34:299–316. https://doi.org/10.1146/annurev-immunol-041015-055549
Jacobi A, Antoni C, Manger B, Schuler G, Hertl M (2005) Infliximab in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol 52:522–526. https://doi.org/10.1016/j.jaad.2004.11.022
Jia L et al (2017) Detection of IL-9 producing T cells in the PBMCs of allergic asthmatic patients. BMC Immunol 18:38. https://doi.org/10.1186/s12865-017-0220-1
Josefowicz SZ et al (2012) Extrathymically generated regulatory T cells control mucosal TH2 inflammation. Nature 482:395–399. https://doi.org/10.1038/nature10772
Kaech SM, Cui W (2012) Transcriptional control of effector and memory CD8+ T cell differentiation. Nat Rev Immunol 12:749–761. https://doi.org/10.1038/nri3307
Kamekura R et al (2015) Alteration of circulating type 2 follicular helper T cells and regulatory B cells underlies the comorbid association of allergic rhinitis with bronchial asthma. Clin Immunol 158:204–211. https://doi.org/10.1016/j.clim.2015.02.016
Kaplan MH, Hufford MM, Olson MR (2015) The development and in vivo function of T helper 9 cells. Nat Rev Immunol 15:295–307. https://doi.org/10.1038/nri3824

Kearley J, Barker JE, Robinson DS, Lloyd CM (2005) Resolution of airway inflammation and hyperreactivity after in vivo transfer of CD4+CD25+ regulatory T cells is interleukin 10 dependent. J Exp Med 202:1539–1547. https://doi.org/10.1084/jem.20051166

Khattri S et al (2017) Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. Exp Dermatol 26:28–35. https://doi.org/10.1111/exd.13112

Kim KS et al (2016) Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. Science. https://doi.org/10.1126/science.aac5560

Kirsten A et al (2013) The anti-IL-17A antibody secukinumab does not attenuate ozone-induced airway neutrophilia in healthy volunteers. Eur Respir J 41:239–241. https://doi.org/10.1183/09031936.00123612

Kluger MA et al (2014) Stat3 programs Th17-specific regulatory T cells to control GN. J Am Soc Nephrol 25:1291–1302. https://doi.org/10.1681/ASN.2013080904

Koch MA, Tucker-Heard G, Perdue NR, Killebrew JR, Urdahl KB, Campbell DJ (2009) The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nat Immunol 10:595–602. https://doi.org/10.1038/ni.1731

Koch MA, Thomas KR, Perdue NR, Smigiel KS, Srivastava S, Campbell DJ (2012) T-bet(+) Treg cells undergo abortive Th1 cell differentiation due to impaired expression of IL-12 receptor beta2. Immunity 37:501–510. https://doi.org/10.1016/j.immuni.2012.05.031

Komatsu N et al (2014) Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. Nat Med 20:62–68. https://doi.org/10.1038/nm.3432

Korn T et al (2008) IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. Proc Natl Acad Sci U S A 105:18460–18465. https://doi.org/10.1073/pnas.0809850105

Kryczek I, Wei S, Vatan LH, Escara-Wilke J, Szeliga W, Keller ET, Zou W (2007) Cutting edge: opposite effects of IL-1 and IL-2 on the regulation of IL-17(+) T cell pool IL-1 subverts IL-2-mediated suppression. J Immunol 179:1423–1426. https://doi.org/10.4049/jimmunol.179.3.1423

Kudo M et al (2012) IL-17A produced by alpha beta T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. Nat Med 18:547–554. https://doi.org/10.1038/nm.2684

Lahl K et al (2009) Nonfunctional regulatory T cells and defective control of Th2 cytokine production in natural scurfy mutant mice. J Immunol 183:5662–5672. https://doi.org/10.4049/jimmunol.0803762

Lee YK, Turner H, Maynard CL, Oliver JR, Chen DQ, Elson CO, Weaver CT (2009) Late developmental plasticity in the T helper 17 lineage. Immunity 30:92–107. https://doi.org/10.1016/j.immuni.2008.11.005

Levine AG, Arvey A, Jin W, Rudensky AY (2014) Continuous requirement for the TCR in regulatory T cell function. Nat Immunol 15:1070–1078. https://doi.org/10.1038/ni.3004

Levine AG et al (2017) Stability and function of regulatory T cells expressing the transcription factor T-bet. Nature 546:421–425. https://doi.org/10.1038/nature22360

Lewkowich IP et al (2005) CD4+CD25+ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function. J Exp Med 202:1549–1561. https://doi.org/10.1084/jem.20051506

Lexmond WS et al (2016) FOXP3+ Tregs require WASP to restrain Th2-mediated food allergy. J Clin Invest 126:4030–4044. https://doi.org/10.1172/JCI85129

Liang S, Ristich V, Arase H, Dausset J, Carosella ED, Horuzsko A (2008) Modulation of dendritic cell differentiation by HLA-G and ILT4 requires the IL-6--STAT3 signaling pathway. Proc Natl Acad Sci U S A 105:8357–8362. https://doi.org/10.1073/pnas.0803341105

Liao W et al (2008) Priming for T helper type 2 differentiation by interleukin 2-mediated induction of interleukin 4 receptor alpha-chain expression. Nat Immunol 9:1288–1296. https://doi.org/10.1038/ni.1656

Licona-Limon P et al (2013) Th9 cells drive host immunity against gastrointestinal worm infection. Immunity 39:744–757. https://doi.org/10.1016/j.immuni.2013.07.020

Locci M et al (2013) Human circulating PD-1+CXCR3-CXCR5+ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. Immunity 39:758–769. https://doi.org/10.1016/j.immuni.2013.08.031

Lochner M et al (2008) In vivo equilibrium of proinflammatory IL-17+ and regulatory IL-10+ Foxp3+ RORgamma t+ T cells. J Exp Med 205:1381–1393. https://doi.org/10.1084/jem.20080034

Lu KT et al (2011) Functional and epigenetic studies reveal multistep differentiation and plasticity of in vitro-generated and in vivo-derived follicular T helper cells. Immunity 35:622–632. https://doi.org/10.1016/j.immuni.2011.07.015

Malik S et al (2017) Transcription factor Foxo1 is essential for IL-9 induction in T helper cells. Nat Commun 8:815. https://doi.org/10.1038/s41467-017-00674-6

Mantel PY et al (2007) GATA3-driven Th2 responses inhibit TGF-beta1-induced FOXP3 expression and the formation of regulatory T cells. PLoS Biol 5:e329. https://doi.org/10.1371/journal.pbio.0050329

Massoud AH, Charbonnier LM, Lopez D, Pellegrini M, Phipatanakul W, Chatila TA (2016) An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to TH17-like cells. Nat Med 22:1013–1022. https://doi.org/10.1038/nm.4147

Messi M, Giacchetto I, Nagata K, Lanzavecchia A, Natoli G, Sallusto F (2003) Memory and flexibility of cytokine gene expression as separable properties of human T(H)1 and T(H)2 lymphocytes. Nat Immunol 4:78–86. https://doi.org/10.1038/ni872

Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136:2348–2357

Mucida D, Kutchukhidze N, Erazo A, Russo M, Lafaille JJ, Curotto de Lafaille MA (2005) Oral tolerance in the absence of naturally occurring Tregs. J Clin Invest 115:1923–1933. https://doi.org/10.1172/JCI24487

Newton RH et al (2018) Maintenance of CD4 T cell fitness through regulation of Foxo1. Nat Immunol 19:838–848. https://doi.org/10.1038/s41590-018-0157-4

Nouri-Aria KT, Pilette C, Jacobson MR, Watanabe H, Durham SR (2005) IL-9 and c-kit+ mast cells in allergic rhinitis during seasonal allergen exposure: effect of immunotherapy. J Allergy Clin Immunol 116:73–79. https://doi.org/10.1016/j.jaci.2005.03.011

Noval Rivas M et al (2015) Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. Immunity 42:512–523. https://doi.org/10.1016/j.immuni.2015.02.004

Noval Rivas M, Burton OT, Oettgen HC, Chatila T (2016) IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function. J Allergy Clin Immunol 138:801–811.e809. https://doi.org/10.1016/j.jaci.2016.02.030

Nurieva RI et al (2008) Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. Immunity 29:138–149. https://doi.org/10.1016/j.immuni.2008.05.009

O'Shea JJ, Paul WE (2010) Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. Science 327:1098–1102. https://doi.org/10.1126/science.1178334

Oda N, Canelos PB, Essayan DM, Plunkett BA, Myers AC, Huang SK (2005) Interleukin-17F induces pulmonary neutrophilia and amplifies antigen-induced allergic response. Am J Respir Crit Care Med 171:12–18. https://doi.org/10.1164/rccm.200406-778OC

Ogawa C et al (2018) Blimp-1 functions as a molecular switch to prevent inflammatory activity in Foxp3(+)RORgammat(+) regulatory T cells. Cell Rep 25:19–28.e15. https://doi.org/10.1016/j.celrep.2018.09.016

Oh CK, Leigh R, McLaurin KK, Kim K, Hultquist M, Molfino NA (2013) A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma. Respir Res 14:93. https://doi.org/10.1186/1465-9921-14-93

Ohnmacht C (2016) Microbiota, regulatory T cell subsets, and allergic disorders. Allergo J Int 25:114–123. https://doi.org/10.1007/s40629-016-0118-0

Ohnmacht C et al (2015) MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORgammat(+) T cells. Science 349:989–993. https://doi.org/10.1126/science.aac4263

Onishi Y, Fehervari Z, Yamaguchi T, Sakaguchi S (2008) Foxp3+ natural regulatory T cells preferentially form aggregates on dendritic cells in vitro and actively inhibit their maturation. Proc Natl Acad Sci U S A 105:10113–10118. https://doi.org/10.1073/pnas.0711106105

Park J et al (2014) Murine Th9 cells promote the survival of myeloid dendritic cells in cancer immunotherapy. Cancer Immunol Immunother 63:835–845. https://doi.org/10.1007/s00262-014-1557-4

Parker JM et al (2011) Safety profile and clinical activity of multiple subcutaneous doses of MEDI-528, a humanized anti-interleukin-9 monoclonal antibody, in two randomized phase 2a studies in subjects with asthma. BMC Pulm Med 11:14. https://doi.org/10.1186/1471-2466-11-14

Pennino D et al (2013) IL-22 suppresses IFN-gamma-mediated lung inflammation in asthmatic patients. J Allergy Clin Immunol 131:562–570. https://doi.org/10.1016/j.jaci.2012.09.036

Polansky JK et al (2008) DNA methylation controls Foxp3 gene expression. Eur J Immunol 38:1654–1663. https://doi.org/10.1002/eji.200838105

Purwar R et al (2012) Robust tumor immunity to melanoma mediated by interleukin-9-producing T cells. Nat Med 18:1248–1253. https://doi.org/10.1038/nm.2856

Raymond M, Van VQ, Wakahara K, Rubio M, Sarfati M (2011) Lung dendritic cells induce T(H)17 cells that produce T(H)2 cytokines, express GATA-3, and promote airway inflammation. J Allergy Clin Immunol 128:192–201.e196. https://doi.org/10.1016/j.jaci.2011.04.029

Rigas D et al (2017) Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction. J Allergy Clin Immunol 139:1468–1477.e1462. https://doi.org/10.1016/j.jaci.2016.08.034

Rubtsov YP et al (2008) Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. Immunity 28:546–558. https://doi.org/10.1016/j.immuni.2008.02.017

Russkamp D et al (2019) IL-4 receptor alpha blockade prevents sensitization and alters acute and long-lasting effects of allergen-specific immunotherapy of murine allergic asthma. Allergy 74:1549–1560. https://doi.org/10.1111/all.13759

Sabat R, Ouyang WJ, Wolk K (2014) Therapeutic opportunities of the IL-22-IL-22R1 system. Nat Rev Drug Discov 13:21–38. https://doi.org/10.1038/nrd4176

Sallusto F (2016) Heterogeneity of human CD4(+) T cells against microbes. Annu Rev Immunol 34:317–334. https://doi.org/10.1146/annurev-immunol-032414-112056

Sallusto F, Cassotta A, Hoces D, Foglierini M, Lanzavecchia A (2018) Do memory CD4 T cells keep their cell-type programming: plasticity versus fate commitment? T-cell heterogeneity, plasticity, and selection in humans. Cold Spring Harb Perspect Biol 10. https://doi.org/10.1101/cshperspect.a029421

Samstein RM et al (2012) Foxp3 exploits a pre-existent enhancer landscape for regulatory T cell lineage specification. Cell 151:153–166. https://doi.org/10.1016/j.cell.2012.06.053

Schiering C et al (2014) The alarmin IL-33 promotes regulatory T-cell function in the intestine. Nature 513:564–568. https://doi.org/10.1038/nature13577

Schulz EG, Mariani L, Radbruch A, Hofer T (2009) Sequential polarization and imprinting of type 1 T helper lymphocytes by interferon-gamma and interleukin-12. Immunity 30:673–683. https://doi.org/10.1016/j.immuni.2009.03.013

Sehra S et al (2003) Airway IgG counteracts specific and bystander allergen-triggered pulmonary inflammation by a mechanism dependent on Fc gamma R and IFN-gamma. J Immunol 171:2080–2089. https://doi.org/10.4049/jimmunol.171.4.2080

Shevach EM (2018) Foxp3(+) T regulatory cells: still many unanswered questions-a perspective after 20 years of study. Front Immunol 9:1048. https://doi.org/10.3389/fimmu.2018.01048

Simpson EL et al (2016) Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis. N Engl J Med 375:2335–2348. https://doi.org/10.1056/NEJMoa1610020

Smith PM et al (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341:569–573. https://doi.org/10.1126/science.1241165
Stefka AT et al (2014) Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A. https://doi.org/10.1073/pnas.1412008111
Stein MM et al (2016) Innate immunity and asthma risk in amish and hutterite farm children. N Engl J Med 375:411–421. https://doi.org/10.1056/NEJMoa1508749
Stockinger B, Omenetti S (2017) The dichotomous nature of T helper 17 cells. Nat Rev Immunol 17:535–544. https://doi.org/10.1038/nri.2017.50
Szabo SJ, Sullivan BM, Peng SL, Glimcher LH (2003) Molecular mechanisms regulating Th1 immune responses. Annu Rev Immunol 21:713–758. https://doi.org/10.1146/annurev.immunol.21.120601.140942
Thomas RM, Chen C, Chunder N, Ma L, Taylor J, Pearce EJ, Wells AD (2010) Ikaros silences T-bet expression and interferon-gamma production during T helper 2 differentiation. J Biol Chem 285:2545–2553. https://doi.org/10.1074/jbc.M109.038794
Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H (2009) Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T-H-17, T(H)1 and T(H)2 cells. Nat Immunol 10:864–873. https://doi.org/10.1038/ni.1770
Tubo NJ et al (2013) Single naive CD4+ T cells from a diverse repertoire produce different effector cell types during infection. Cell 153:785–796. https://doi.org/10.1016/j.cell.2013.04.007
Ulges A et al (2015) Protein kinase CK2 enables regulatory T cells to suppress excessive TH2 responses in vivo. Nat Immunol 16:267–275. https://doi.org/10.1038/ni.3083
Upadhyaya B, Yin Y, Hill BJ, Douek DC, Prussin C (2011) Hierarchical IL-5 expression defines a subpopulation of highly differentiated human Th2 cells. J Immunol 187:3111–3120. https://doi.org/10.4049/jimmunol.1101283
Vahl JC et al (2014) Continuous T cell receptor signals maintain a functional regulatory T cell pool. Immunity 41:722–736. https://doi.org/10.1016/j.immuni.2014.10.012
Vegran F et al (2014) The transcription factor IRF1 dictates the IL-21-dependent anticancer functions of TH9 cells. Nat Immunol 15:758–766. https://doi.org/10.1038/ni.2925
Veldhoen M et al (2008) Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. Nat Immunol 9:1341–1346. https://doi.org/10.1038/ni.1659
Vinuesa CG, Linterman MA, Yu D, MacLennan IC (2016) Follicular helper T cells. Annu Rev Immunol 34:335–368. https://doi.org/10.1146/annurev-immunol-041015-055605
Visekruna A et al (2013) Tc9 cells, a new subset of CD8(+) T cells, support Th2-mediated airway inflammation. Eur J Immunol 43:606–618. https://doi.org/10.1002/eji.201242825
Wang YH et al (2010) A novel subset of CD4(+) T(H)2 memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. J Exp Med 207:2479–2491. https://doi.org/10.1084/jem.20101376
Wilhelm C et al (2011) An IL-9 fate reporter demonstrates the induction of an innate IL-9 response in lung inflammation. Nat Immunol 12:1071–1077. https://doi.org/10.1038/ni.2133
Wilson NJ et al (2007) Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol 8:950–957. https://doi.org/10.1038/ni1497
Wing K et al (2008) CTLA-4 control over Foxp3+ regulatory T cell function. Science 322:271–275. https://doi.org/10.1126/science.1160062
Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R (2004) IL-22 increases the innate immunity of tissues. Immunity 21:241–254. https://doi.org/10.1016/j.immuni.2004.07.007
Wollenberg A et al (2019) Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. J Allergy Clin Immunol 143:135–141. https://doi.org/10.1016/j.jaci.2018.05.029
Worthington JJ, Kelly A, Smedley C, Bauche D, Campbell S, Marie JC, Travis MA (2015) Integrin alphavbeta8-mediated TGF-beta activation by effector regulatory T cells is essential for suppression of T-cell-mediated inflammation. Immunity 42:903–915. https://doi.org/10.1016/j.immuni.2015.04.012

Wynn TA (2015) Type 2 cytokines: mechanisms and therapeutic strategies. Nat Rev Immunol 15:271–282. https://doi.org/10.1038/nri3831

Xu M et al (2018) c-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. Nature 554:373–377. https://doi.org/10.1038/nature25500

Yamashita M, Ukai-Tadenuma M, Kimura M, Omori M, Inami M, Taniguchi M, Nakayama T (2002) Identification of a conserved GATA3 response element upstream proximal from the interleukin-13 gene locus. J Biol Chem 277:42399–42408. https://doi.org/10.1074/jbc.M205876200

Yang XO et al (2008) Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. Immunity 29:44–56. https://doi.org/10.1016/j.immuni.2008.05.007

Yang BH et al (2015) Foxp3 T cells expressing RORgammat represent a stable regulatory T-cell effector lineage with enhanced suppressive capacity during intestinal inflammation. Mucosal Immunol. https://doi.org/10.1038/mi.2015.74

Yao W, Tepper RS, Kaplan MH (2011) Predisposition to the development of IL-9-secreting T cells in atopic infants. J Allergy Clin Immunol 128:1357–1360.e1355. https://doi.org/10.1016/j.jaci.2011.06.019

Yu F, Sharma S, Edwards J, Feigenbaum L, Zhu J (2015) Dynamic expression of transcription factors T-bet and GATA-3 by regulatory T cells maintains immunotolerance. Nat Immunol 16:197–206. https://doi.org/10.1038/ni.3053

Zheng Y et al (2009) Regulatory T-cell suppressor program co-opts transcription factor IRF4 to control T(H)2 responses. Nature 458:351–356. https://doi.org/10.1038/nature07674

Zheng Y, Josefowicz S, Chaudhry A, Peng XP, Forbush K, Rudensky AY (2010) Role of conserved non-coding DNA elements in the Foxp3 gene in regulatory T-cell fate. Nature 463:808–812. https://doi.org/10.1038/nature08750

Zhou LA et al (2007) IL-6 programs TH-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol 8:967–974. https://doi.org/10.1038/ni1488

Zhou L et al (2008) TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. Nature 453:236–240. https://doi.org/10.1038/nature06878

Zhu J et al (2004) Conditional deletion of Gata3 shows its essential function in T(H)1-T(H)2 responses. Nat Immunol 5:1157–1165. https://doi.org/10.1038/ni1128

Zielinski CE et al (2012) Pathogen-induced human TH17 cells produce IFN-gamma or IL-10 and are regulated by IL-1beta. Nature 484:514–518. https://doi.org/10.1038/nature10957

Zissler UM et al (2016) Interleukin-4 and interferon-gamma orchestrate an epithelial polarization in the airways. Mucosal Immunol 9:917–926. https://doi.org/10.1038/mi.2015.110

Zissler UM et al (2018) Early IL-10 producing B-cells and coinciding Th/Tr17 shifts during three year grass-pollen AIT. EBioMedicine 36:475–488. https://doi.org/10.1016/j.ebiom.2018.09.016

Innate Immune Mechanisms in Contact Dermatitis

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Contents

Abstract

Allergies are highly prevalent hypersensitivity responses to usually harmless substances. They are mediated by the immune system which causes pathologic responses such as type I (rhinoconjunctivitis, allergic asthma, atopy) or type IV hypersensitivity (allergic contact dermatitis). The different types of allergy are mediated by effector and memory T cells and, in the case of type I hypersensitivity, B cells. A prerequisite for the activation of these cells of the adaptive immune system is the activation of the innate immune system. The resulting inflammation is essential not only for the initiation but also for the elicitation and maintenance of allergies. Great progress has been made in the elucidation of the cellular and molecular pathomechanisms underlying allergen-induced inflammation. It is now recognized that the innate immune system in concert with tissue stress and

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damage responses orchestrates inflammation. This should enable the development of novel mechanism-based anti-inflammatory treatment strategies as well as of animal-free in vitro assays for the identification and potency classification of contact allergens.

Keywords

Allergy · Contact dermatitis · Inflammation · Innate immune response · Skin · Stress response

Abbreviations

ACD	Allergic contact dermatitis
ASC	Apoptotic speck protein
CHS	Contact hypersensitivity
DAMPs	Damage-associated molecular patterns
DNFB	2,4-Dinitrofluorobenzene
FITC	Fluorescein isothiocyanate
ICD	Irritant contact dermatitis
ILC	Innate lymphoid cell
Keap1	Kelch-like ECH-associated protein 1
ko	Knockout
MAMPs	Microbe-associated molecular patterns
NLRP	NOD-like receptor protein
Nrf2	Nuclear factor erythroid 2-related factor 2
PAMPs	Pathogen-associated molecular patterns
RAG	Recombination activating gene
ROS	Reactive oxygen species
TLR	Toll-like receptor
TNCB	2,4,6-Trinitrochlorobenzene
Trm	Tissue-resident memory T cell

1 Introduction

Allergic contact dermatitis (ACD) is an inflammatory skin disease caused by low molecular weight organic chemicals and metal ions. The eczematous lesions are caused by contact allergen-specific T cells in concert with cells of the innate immune system and skin cells (Nassau and Fonacier 2020). The prevalence of contact dermatitis is high. 20–27% of the general population are sensitized to at least one contact allergen of the European Standard Series (Diepgen et al. 2016; Alinaghi et al. 2019). As an occupation-related skin disease it is of great importance, not least due to the difficulty to treat chronic ACD. Nickel is still the most important contact allergen worldwide and it affects many occupations (Ahlström et al. 2019). Irritant contact dermatitis (ICD) is induced by chemicals which damage the skin barrier such

as detergents (Bains et al. 2019). It also involves an inflammatory response with participation of the innate immune system but without activation of the adaptive immune system. Both forms of contact dermatitis disturb the barrier function of the skin. This is an important pathogenic factor not only due to alteration of the permeability of the skin but also due to the activation of innate immune signalling (Jakasa et al. 2018).

ACD is a prevailing problem with new contact allergens emerging every year (Johansen and Werfel 2019). This indicates that the methods for hazard identification and risk assessment such as the Local Lymph Node Assay and its in vitro alternatives (Ezendam et al. 2016) are not perfect. One problem is the use of single substances for testing. Some potential contact allergens are weakly immunogenic and therefore show up as negative in the current tests. However in mixtures as found in finished products weak allergens can become highly immunogenic due to augmentation effects (Pedersen et al. 2004; Bonefeld et al. 2011). The presence of other immunogenic substances such as other weak contact allergens or irritants may lead to additive or synergistic pro-inflammatory effects (Martin 2014; Bonefeld et al. 2017). Therefore testing of mixtures and formulations should be considered in future testing strategies. Such measures should improve the prevention of ACD.

Atopic diseases such as rhinoconjunctivitis, allergic asthma or food allergy are often driven by IgE-mediated hypersensitivities. IgE reacts mostly to protein allergens but sometimes also to carbohydrates. Atopic diseases are on the rise and currently affect 20% of the population. Allergy and ACD are eventually mediated by the adaptive immune system, i.e. T- and B cells or T cells, respectively. For their initiation and maintenance both forms of hypersensitivity require the innate immune system. Here we discuss mechanisms of innate immune responses in allergies with a focus on ACD. Furthermore, we discuss the critical contribution of stress responses to inflammation and provide an outlook regarding potential new treatment strategies based on the mechanisms of inflammation in allergy.

2 Innate Immune Mechanisms and Tissue Stress Responses

Inflammation is required for the initiation of adaptive immune responses. Inflammation opens the constitutive break on the immune system, a prerequisite for the initiation of T- and B cell responses. A key element of inflammation is the activation of the innate immune system. Moreover, tissue stress and damage responses contribute significantly to inflammation. Innate immunity relies largely on the triggering of pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I like receptors (RLRs) and C-type lectin receptors (CLRs) and on the cGAS-STING pathway. Ligands for these receptors are derived from pathogen- or microbe-associated molecular patterns (PAMPs, MAMPs) or from endogenous cellular sources or from the extracellular matrix (damage-associated molecular patterns, DAMPs). In addition, danger signals such as reactive oxygen species (ROS) or extracellular ATP often resulting from tissue stress and damage contribute to inflammation. There are different types of inflammation which

are important for the polarization of T cell responses (Annunziato et al. 2015; Rankin and Artis 2018). Type 1 inflammation is characterized by IL-12 that drives the polarization of T cell responses towards IFN-γ producing innate lymphoid cells 1 (ILC1) and CD4+ Th1 and CD8+ Tc2 cells. Type 2 inflammation involves IL-25, IL-33 and TSLP and IL-4, IL-5 and IL-13 producing ILC2 and Th2 and Tc2 cells. Type 3 inflammation is driven by IL-23 and involves IL-17 and IL-22 production by ILC3 and Th17 and Tc17 cells. This simplified classification does not describe exclusive patterns. Mixed patterns can also be found.

In order to induce a contact allergen-specific T cell response, an inflammatory response must be induced by contact allergens in the skin. Many studies have been performed in the contact hypersensitivity (CHS) model, the mouse model for contact dermatitis (Martin 2013; Gaspari et al. 2016), addressing cellular and molecular mechanisms and exploring potential novel mechanism-based treatment strategies. The effector T cell responses to experimental contact allergens such as 2,4,6,-trinitrochlorobenzene (TNCB) or 2,4,-dinitrofluorobenzene (DNFB) are predominantly Tc1 responses with an involvement of Tc17 cells. For fluorescein isothiocyanate (FITC) type 1 or type 2 responses can be induced depending on the protocol. Regulation of CHS is mediated by regulatory T cells (Treg) and by NKT cells (Vocanson et al. 2009; Martin et al. 2010; Goubier et al. 2013).

Much progress has been made in our understanding of the mechanisms underlying innate immune responses in ACD (Kaplan et al. 2012; Honda et al. 2013; Martin 2015; Brys et al. 2019). The emerging picture highlights the central importance of the innate immune response and the resulting inflammation not only in the sensitization but also in the elicitation phase of ACD.

3 Innate Immune Cells in ACD

The skin contains various types of resident immune cells (Ho and Kupper 2019). Among these are dermal mast cells. Their participation in CHS has been shown recently by the use of new mouse models that allow specific permanent or conditional mast cell removal (Dudeck et al. 2011). These studies have shown the induction of type 1 inflammation with a rapid activation of mast cells by contact allergens such as DNFB or FITC and their subsequent release of histamine. As a consequence there is blood vessel dilatation and an influx of neutrophils. In contrast to human ACD where sensitization is clinically inapparent, sensitization of mice for CHS results in an inflammatory response that manifests as a slight, mast-cell dependent ear swelling reaction peaking at around 6 h after contact allergen application. Neutrophil recruitment may be further supported by the secretion of the neutrophil-attracting chemokines CXCL1 and CXCL2 by mast cells and monocytes (De Filippo et al. 2013).

Mast cell-derived TNF-α contributes to the expansion, migration and the T cell priming efficiency of DCs cells as shown by mast cell-specific TNF depletion (Suto et al. 2006; Dudeck et al. 2015). DNFB-induced CHS was significantly reduced in mice lacking mast cell-derived TNF. Interestingly, DCs engulf and take up

exocytosed mast cell granules. This promotes their maturation and lymph node migration. The basis for this seems to be due to the release of the granule content after uptake. This releases mediators, among them mast cell-derived TNF-α (Dudeck et al. 2019).

Mast cells can also have a regulatory role in CHS (Gimenez-Rivera et al. 2016). Repeated application of the contact allergen oxazolone in a chronic CHS model showed increased ear swelling responses in mast cell deficient C57BL/6-KitW-sh/W-sh (Sash) and also in mast cell-depleted (MCPT5-Cre + iDTR+) mice compared to wildtype mice. This correlated with an accumulation of tissue-resident antigen-specific CD8+ T cells producing pro-inflammatory cytokines such as IFN-γ and IL-17 in the repeatedly challenged skin sites that was significantly higher than the accumulation observed in wildtype mice. Local mast cell reconstitution prevented this effect. It was further shown that mast cells control the recruitment of CD8+ T cells into the skin and most likely also their development in the draining lymph nodes. As one potential mechanism it was proposed that mast cell proteases degrade IL-15 which is required for Trm maintenance and which was elevated in the challenged skin. In contrast, TGF-β and IL-7 which are also required for Trm were not elevated.

A pathogenic role for neutrophils in CHS has been demonstrated. Neutrophils rapidly infiltrate contact allergen challenged skin. Depletion of neutrophils by antibodies before sensitization or before challenge abrogated CHS responses and neutrophil-deficient mice also had reduced CHS (Weber et al. 2015). Interestingly, the challenge dose of the hapten correlates with the number of infiltrating neutrophils and this, in turn, determines the number of infiltrating T cells and the severity of ear swelling (Engeman et al. 2004). In this study, increased levels of neutrophil-attracting chemokine CXCL1 was detected when the challenge dose of DNFB was increased. This finding is explained by the fact that the higher challenge dose causes stronger skin inflammation in general.

Recently, it was reported that neutrophil cathepsin G plays a role in the bias towards CD8+ effector T cells in CHS (Kish et al. 2019). CD4+ Th1/Th17 cells are usually not induced. In this study, cathepsin G released from neutrophils reduced IL-12 produced by DCs and thereby prevented the generation of Th1/Th17 cells. The lack of cathepsin G resulted in increase in IL-12 levels and the induction of both hapten-reactive CD8+ effector cells and CD4+ IFN-γ producing T cells.

Innate lymphoid cells (ILCs) are a heterogeneous group of cells that are found in lymphoid and non-lymphoid tissues (Vivier et al. 2018). They can be differentiated into different subsets according to their phenotype and function. Currently, there are five major subsets: ILC1, ILC2 and ILC3 which functionally resemble Th1, Th2 and Th17 cells, respectively, LTi (lymphoid tissue inducer) cells and NK (natural killer) cells. ILCs are mostly tissue-resident and enriched especially in barrier tissues such as the skin. They are sentinels that maintain tissue homeostasis and serve to prime and boost adaptive immune responses (Vivier et al. 2018). Their role in allergic diseases such as asthma has been recognized (Morita et al. 2016; Kortekaas Krohn et al. 2018). In atopy, ILC2s are activated by skin derived IL-25, IL-33 and TSLP. They promote the allergic response by production of IL-4, IL-5 and IL-13. IL-17A

and IL-22 producing ILC3s have been associated with psoriasis and they may play an effector role in ACD.

A role for ILCs in ACD has been shown. Kim and colleagues described lineage-negative IL-10 producing ILCs that express CD45, CD127 and Sca-1 (Kim et al. 2016). These so-called ILC10 were increased in the axillary and inguinal lymph nodes and ear skin in oxazolone-induced CHS. It was speculated that ILC10 have a regulatory role in CHS. Another study using antibody-mediated ILC depletion or mice deficient for ILC2 revealed a regulatory role in CHS. When CHS to TNCB was induced in mice depleted of ILCs after sensitization or deficient for ILC2s the ear swelling response was increased (Rafei-Shamsabadi et al. 2019). There was an early increase of Eomes+ NK cells expressing IFN-γ and TNF-α in the ear skin peaking at 24 h after hapten challenge, the peak of inflammation, and a delayed increase of IL-5 and IL-13 producing ILC2 at 48–72 h, the resolution phase of CHS. These data indicate a clear pro-inflammatory role of NK cells and a regulatory role of ILC2 in Tc1/Th1 driven CHS. A role for IL-10 producing ILC was not observed. Up to now the role of ILC1s in ACD has not been formally demonstrated but it is likely that they are involved in the initiation of the immune response to contact allergens (Kim 2015). Interestingly, in FITC-induced CHS which is Th2-driven, ILC2 have a regulatory role. It remains to be shown how these cells are activated in CHS but it is likely that the innate immune system is responsible.

The role of NK cells has been studied in the CHS model. NK cell depletion of WT mice does not alter CHS. However, NK cells can mediate CHS in the absence of T cells and B cells as shown in RAG2−/− mice (O'Leary et al. 2006; Paust et al. 2010). This CHS is abrogated in RAG2−/− x IL-2Rγ knockout mice which lack T- and B-cells and also NK cells. Surprisingly, NK cell-mediated CHS is antigen-specific with a memory-like response which can be elicited months after sensitization. Peng et al. reported that the cell type which is responsible for this hapten-specific memory-like CHS response are liver-resident CD49 + DX5- NK cells (Peng et al. 2013). These NK cells seem to become primed by hapten-bearing APCs in the liver. The priming occurs very rapidly, and ear swelling can be observed as fast as 30 min after challenge (Majewska-Szczepanik et al. 2013) with a small increase of NK cell numbers in the challenged ear skin of wildtype and RAG−/− mice (O'Leary et al. 2006). Peng et al. detected only very few CD49 + DX5- NK cells in the skin. CXCR6 expression by liver-resident NK cells is required, most likely for their persistence in the liver where CXCL16, the ligand for CXCR6 is produced (Paust et al. 2010). Moreover, the absence of CHS after transfer of liver mononuclear cells from IFN-αR knockout or IFN-γ or IL-12 knockout mice suggests that the liver NK cells are dependent on IFN-α signalling and require IFN-γ or IL-12 or must produce it. It was shown that the formation of hapten-specific NK cell memory requires the NLRP3 inflammasome in macrophages (van den Boorn et al. 2016).

A study using the pro-hapten monobenzone, that is selectively metabolized to the full hapten in melanocytes by tyrosinase revealed that a CHS response was induced in wildtype mice that was NK cell-dependent and antigen specific and was mediated by liver-resident CD49b + NK1.1+ NK memory cells which expressed LY49 C-I and CD18 (van den Boorn et al. 2016). Monobenzone sensitization of wildtype mice

and challenge 4 weeks later resulted in CHS. It was demonstrated that monobenzone induced the migration of tissue-resident monocytes to the draining lymph nodes where they primed NK cells. This required ASC, NLRP3 and IL-18 in the monocytes. Activation of the NLRP3 inflammasome was independent of P2X7R. The NK memory cells were cytotoxic to the melanocytes and caused vitiligo-like skin depigmentation in RAG2 ko mice after repeated application. CHS induced by oxazolone was mediated by T cells. NK cells were dispensable for CHS induction.

Interestingly, it was noted that the NK cell-mediated and conventional, T-cell mediated CHS are different in several aspects including histology (Rouzaire et al. 2012). Up to now the mechanism for the induction of CHS by memory-like NK cells as well as the basis for the antigen specificity in T cell–independent CHS remains unclear.

4 Pattern Recognition Receptors and Danger Signals in ACD

The PRRs TLR2 and TLR4 are often involved in allergic and autoimmune reactions. As cell surface TLRs they are predestined to monitor changes in the extracellular environment by detection of PAMPs and DAMPs. Contact allergens cause tissue stress and damage. This includes the degradation of hyaluronic acid (Esser et al. 2012), biglycan (Esser et al. 2018) or release of HMGB1 (Galbiati et al. 2014). These DAMPs play a role in TLR2/4-mediated inflammation. In this context, further danger signals such as ROS and ATP are involved in the orchestration of the skin inflammation in CHS. ROS and contact allergens themselves by covalent modification of Keap1 trigger the antioxidant phase 2 response. Keap1 is a cytosolic sensor for oxidative and electrophilic stress. Specific cysteine residues can be oxidized or modified by contact allergens and also by drugs. This results in the release and nuclear translocation of the transcription factor Nrf2 which then activates genes for the antioxidant response (Mussotter et al. 2018; Helou et al. 2019a). Experiments in Nrf2 knockout (ko) mice have shown that the level of oxidative stress determines the sensitization threshold. Nrf2 ko mice can be sensitized to fragrance allergens which are weak allergens that fail to sensitize wildtype mice (El Ali et al. 2013). Furthermore, Nrf2 regulates the accumulation of neutrophils in the skin (Helou et al. 2019b, p. 201). It was shown that neutrophil recruitment is significantly enhanced in Nrf2 deficient mice. This was due to increased oxidative stress associated with increased production of neutrophil-attracting chemokines CCL2, CCL4 and CCL11. Interestingly, CD36 expression on macrophages and neutrophil efferocytosis were also decreased. These findings show an important role for the regulation of oxidative stress by Nrf2 with regard to the neutrophil involvement in the innate inflammatory response in CHS.

The NLRP3 inflammasome is also crucially involved in ACD. Mice deficient for the adaptor protein ASC or the PRR NLRP3 have a dramatically reduced CHS response (Sutterwala et al. 2006). It was shown that contact allergens such as TNCB induced a rapid release of ATP from cells in the skin (Weber et al. 2010). ATP triggers P2X7R which is important for the activation of the inflammasome. Mice

lacking P2X7R fail to develop CHS. The inflammasome via activation of caspase-1 processes pro-IL-1β and pro-IL-18 to the mature and bioactive cytokines. The pro-forms are produced, e.g., after TLR2/4 activation. The role of IL-1β was demonstrated by blocking experiments. Injection of the IL-1R antagonist Anakinra before sensitization abrogated CHS (Weber et al. 2010).

The innate immune response triggered by contact allergens involves the same mechanisms as triggered by infectious agents. The coupled activation of TLRs and the NLRP3 inflammasome is a prototypic innate immune response pattern in type 1 inflammation in general, seen both in infectious and sterile immune responses such as autoimmunity, inflammatory diseases of the skin and other organs and adverse reactions to drugs such as acetaminophen (Woolbright and Jaeschke 2017) or abacavir (Toksoy et al. 2017). Which TLRs and which cell types are involved depends on the inflamed tissue. PAMPs and DAMPs trigger this response. Additional pro-inflammatory factors are danger signals generated in response to cellular stress such as ROS, extracellular ATP, etc. These contribute to the activation of the "TLR/inflammasome module".

It turns out that for different contact allergens there are variations of these mechanisms. This may be small variations of the common theme, e.g., the participation of other cell types, other TLRs, other inflammasomes, etc. due to a different spectrum of danger signals and DAMPs generated or released from stressed cells or from the extracellular matrix. There may also be greater differences such as a bias towards type 2 inflammation or mixed type 1/type 2/type 3 inflammation. In fact, recent profiling studies show allergen-specific patterns of gene expression (Dhingra et al. 2014; Leonard and Guttman-Yassky 2019).

5 Stress Responses in ACD

It is becoming clear how important tissue stress and damage are as promoters of inflammation. Production/release of danger signals from stressed and damaged cells is not the only consequence. Many DAMPs are released in response to cellular stress, and cellular stress responses can activate pro-inflammatory signalling. The Keap1/Nrf2-dependent antioxidant phase 2 response is triggered by ROS and electrophilic chemicals such as contact allergens. Another stress response is triggered by un- or misfolded protein in the endoplasmic reticulum or in mitochondria. This so-called unfolded protein response (UPR) plays a role in many diseases where protein homeostasis is disturbed and modulation of the UPR holds great potential for therapies (Hetz et al. 2019; Gonzalez-Teuber et al. 2019). Examples are neurodegenerative diseases such as Parkinson's or Alzheimer's and autoimmune diseases such as diabetes, and the role of the UPR in immune responses has been recognized (Janssens et al. 2014). It is possible that the UPR also plays a role in contact dermatitis due to the generation of misfolded proteins due to protein oxidation by ROS or covalent modification or complex formation by contact allergens. Recently, it was demonstrated that the contact sensitizer DNFB activates the UPR in THP-1 cells and primary human monocyte-derived DCs. DNFB-induced rapid ROS

production which was required for the activation of the PERK-eIF2a-ATF4 branch of the UPR (Luís et al. 2014). Pre-treatment with the antioxidant N-acetylcysteine abrogated the UPR activation. DNFB also induced transcriptional upregulation of the genes for IL-8, CD86 and IL-1β in a biphasic manner. HMOX1 upregulation was explained by an interaction of ATF4 with Nrf2 which is important in the regulation of HMOX1 expression. Furthermore DNFB modulated autophagy-related genes via ATF4. These findings show a role of the UPR in the activation of DCs and a cross-talk with other pathways involved in the regulation of cellular homeostasis such as the antioxidant phase 2 response and autophagy.

It is increasingly clear that inflammation involves both the innate immune system and cellular stress responses. Cross-talk between innate immune responses and tissue stress and damage responses is seen at different levels including the regulation of innate inflammatory responses via NF-kB or the NLRP3 inflammasome.

6 Innate Immunity and ILCs in Type 1 Allergy

Type 1 allergies (immediate type) such as rhinoconjunctivitis, allergic asthma, food allergy and atopy affect about 20% of adults in Germany (Bergmann et al. 2016). They are mediated by Th2 cells and the prominent effector cytokines are IL-4, IL-5, IL-9 and IL-13 which promote IgE production by B cells and attraction of eosinophils. As in contact dermatitis the activation of the innate immune system precedes the adaptive immune response. The role of PRRs and other components of the innate immune system in allergy is highlighted in great detail in a recent review (Maeda et al. 2019). The overall findings so far indicate a contribution of essentially all molecular pathways of innate immunity either in the initiation, progression or modulation/regulation of and protection from different types of allergic diseases (Maeda et al. 2019; Pivniouk et al. 2019).

The type of inflammation is different in type I compared to type IV allergies. Type I allergy is associated with the early production of IL-25, IL-33 and TSLP by epithelial cells. IL-33 and TSLP can synergistically activate ILC2s and promote their secretion of IL-5 and IL-13. They also act on DCs to promote their activation and DC2 polarization. This precedes DC migration to the lymph nodes where epitopes of the allergen are presented to T cells. OX40L is induced on the DCs which also produce IL-4. The resulting T cell response is polarized to a Th2 phenotype.

7 Therapeutic Options

The knowledge about the mechanisms of inflammation in allergy holds great potential for therapies. More specific anti-inflammatory therapies beyond topical immunosuppressive therapy with, e.g., corticosteroids or tacrolimus can be envisioned for the treatment of ACD. Ideally topical therapies should be developed in order to use the advantage of the skin as target organ. This may help to avoid or reduce unwanted systemic effects. In the CHS model it has been shown that

pharmacological inhibition of the innate immune response is efficient in presenting sensitization and elicitation of the ear swelling response to TNCB (Weber et al. 2010; Esser et al. 2012). Injection of hyaluronidases, P2X7R antagonist KN-62, the IL-1R antagonist Anakinra prevented subsequent sensitization with TNCB. Anakinra also prevents elicitation in sensitized mice (our unpublished data). Topical antioxidant application was also efficient. Further strategies to be explored include blocking of TLRs (Joosten et al. 2016) and inhibition of the inflammasome (Swanson et al. 2019), e.g., by using glyburide, an inhibitor of the NLRP3 inflammasome which is used in the treatment of diabetes. Blocking the UPR also holds great potential (Hetz et al. 2019). The fact that these mechanisms are operating not only in the sensitization phase but also in the elicitation phase makes them attractive candidates for the treatment of established ACD. Their role in chronic ACD has not been studied, yet, in part due to the lack of appropriate preclinical mouse models. Combination therapies may be most efficient. By targeting several mechanisms simultaneously they may prevent compensatory upregulation and allow for reduction of the dose of the respective drugs helping to minimize side effects.

8 Conclusion

The progress made in the understanding of the pathomechanisms of type I allergies is paralleled by the development of novel therapeutic approaches (Simon 2018). Nowadays biologics are in the clinic that target effector cytokines. Antibodies to the target cytokine, to its receptor or neutralizing soluble receptors are being used. In addition small molecule drugs are used to interfere with signalling pathways such as JAK/STAT (Tan et al. 2016; Kaufman and Alexis 2018; Eyerich et al. 2019). An optimistic vision for future treatment strategies is the use of combinations of anti-inflammatory drugs and biologics that should not only neutralize the effector cytokines but also interfere with the generation, maintenance and tissue residency of the pathogenic T cells. The exciting research on mechanisms of resolution of inflammation may provide supporting therapeutic pro-resolution strategies (Fullerton and Gilroy 2016). In addition enforcing immune regulation, e.g., by shifting the balance towards Treg and by the potential conversion of effector T cells into Treg (Guo et al. 2019; Akamatsu et al. 2019) should promote the re-establishment of tolerance.

References

Ahlström MG, Thyssen JP, Wennervaldt M et al (2019) Nickel allergy and allergic contact dermatitis: a clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis 81:227–241. https://doi.org/10.1111/cod.13327

Akamatsu M, Mikami N, Ohkura N et al (2019) Conversion of antigen-specific effector/memory T cells into Foxp3-expressing Treg cells by inhibition of CDK8/19. Sci Immunol 4:eaaw2707. https://doi.org/10.1126/sciimmunol.aaw2707

Alinaghi F, Bennike NH, Egeberg A et al (2019) Prevalence of contact allergy in the general population: a systematic review and meta-analysis. Contact Dermatitis 80:77–85. https://doi.org/10.1111/cod.13119

Annunziato F, Romagnani C, Romagnani S (2015) The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol 135:626–635. https://doi.org/10.1016/j.jaci.2014.11.001

Bains SN, Nash P, Fonacier L (2019) Irritant contact dermatitis. Clinic Rev Allerg Immunol 56:99–109. https://doi.org/10.1007/s12016-018-8713-0

Bergmann K-C, Heinrich J, Niemann H (2016) Current status of allergy prevalence in Germany: position paper of the Environmental Medicine Commission of the Robert Koch Institute. Allergo J Int 25:6–10. https://doi.org/10.1007/s40629-016-0092-6

Bonefeld CM, Nielsen MM, Rubin IMC et al (2011) Enhanced sensitization and elicitation responses caused by mixtures of common fragrance allergens. Contact Dermatitis 65:336–342. https://doi.org/10.1111/j.1600-0536.2011.01945.x

Bonefeld CM, Geisler C, Gimenéz-Arnau E et al (2017) Immunological, chemical and clinical aspects of exposure to mixtures of contact allergens. Contact Derm 77:133–142. https://doi.org/10.1111/cod.12847

Brys AK, Rodriguez-Homs LG, Suwanpradid J et al (2019) Shifting paradigms in allergic contact dermatitis: the role of innate immunity. J Investig Dermatol. https://doi.org/10.1016/j.jid.2019.03.1133

De Filippo K, Dudeck A, Hasenberg M et al (2013) Mast cell and macrophage chemokines CXCL1/CXCL2 control the early stage of neutrophil recruitment during tissue inflammation. Blood 121:4930–4937. https://doi.org/10.1182/blood-2013-02-486217

Dhingra N, Shemer A, Correa da Rosa J et al (2014) Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. J Allergy Clin Immunol 134:362–372. https://doi.org/10.1016/j.jaci.2014.03.009

Diepgen T, Ofenloch RF, Bruze M et al (2016) Prevalence of contact allergy in the general population in different European regions. Br J Dermatol 174:319–329. https://doi.org/10.1111/bjd.14167

Dudeck A, Dudeck J, Scholten J et al (2011) Mast cells are key promoters of contact allergy that mediate the adjuvant effects of Haptens. Immunity 34:973–984. https://doi.org/10.1016/j.immuni.2011.03.028

Dudeck J, Ghouse SM, Lehmann CHK et al (2015) Mast-cell-derived TNF amplifies CD8(+) dendritic cell functionality and CD8(+) T cell priming. Cell Rep 13:399–411. https://doi.org/10.1016/j.celrep.2015.08.078

Dudeck J, Froebel J, Kotrba J et al (2019) Engulfment of mast cell secretory granules on skin inflammation boosts dendritic cell migration and priming efficiency. J Allergy Clin Immunol 143:1849–1864.e4. https://doi.org/10.1016/j.jaci.2018.08.052

El Ali Z, Gerbeix C, Hemon P et al (2013) Allergic skin inflammation induced by chemical sensitizers is controlled by the transcription factor Nrf2. Toxicol Sci 134:39–48. https://doi.org/10.1093/toxsci/kft084

Engeman T, Gorbachev AV, Kish DD, Fairchild RL (2004) The intensity of neutrophil infiltration controls the number of antigen-primed CD8 T cells recruited into cutaneous antigen challenge sites. J Leukoc Biol 76:941–949. https://doi.org/10.1189/jlb.0304193

Esser PR, Wolfle U, Durr C et al (2012) Contact sensitizers induce skin inflammation via ROS production and hyaluronic acid degradation. PLoS One 7:e41340. https://doi.org/10.1371/journal.pone.0041340

Esser PR, Zech A, Idzko M, Martin SF (2018) Lack of biglycan reduces contact hypersensitivity in mice. Contact Derm 79:326–328. https://doi.org/10.1111/cod.13082

Eyerich S, Metz M, Bossios A, Eyerich K (2019) New biological treatments for asthma and skin allergies. Allergy. https://doi.org/10.1111/all.14027

Ezendam J, Braakhuis HM, Vandebriel RJ (2016) State of the art in non-animal approaches for skin sensitization testing: from individual test methods towards testing strategies. Arch Toxicol 90:2861–2883. https://doi.org/10.1007/s00204-016-1842-4

Fullerton JN, Gilroy DW (2016) Resolution of inflammation: a new therapeutic frontier. Nat Rev Drug Discov 15:551–567. https://doi.org/10.1038/nrd.2016.39

Galbiati V, Papale A, Galli CL et al (2014) Role of ROS and HMGB1 in contact allergen-induced IL-18 production in human keratinocytes. J Invest Dermatol 134:2719–2727. https://doi.org/10.1038/jid.2014.203

Gaspari AA, Katz SI, Martin SF (2016) Contact hypersensitivity. Curr Protoc Immunol 113:4.2.1–4.2.7. https://doi.org/10.1002/0471142735.im0402s113

Gimenez-Rivera V-A, Siebenhaar F, Zimmermann C et al (2016) Mast cells limit the exacerbation of chronic allergic contact dermatitis in response to repeated allergen exposure. J Immunol 197:4240–4246. https://doi.org/10.4049/jimmunol.1600236

Gonzalez-Teuber V, Albert-Gasco H, Auyeung VC et al (2019) Small molecules to improve ER proteostasis in disease. Trends Pharmacol Sci 40:684–695. https://doi.org/10.1016/j.tips.2019.07.003

Goubier A, Vocanson M, Macari C et al (2013) Invariant NKT cells suppress CD8+ T-cell-mediated allergic contact dermatitis independently of regulatory CD4+ T cells. J Invest Dermatol 133:980–987

Guo Z, Wang G, Lv Y et al (2019) Inhibition of Cdk8/Cdk19 activity promotes Treg cell differentiation and suppresses autoimmune diseases. Front Immunol 10. https://doi.org/10.3389/fimmu.2019.01988

Helou DG, Martin SF, Pallardy M et al (2019a) Nrf2 involvement in chemical-induced skin innate immunity. Front Immunol 10. https://doi.org/10.3389/fimmu.2019.01004

Helou DG, Noël B, Gaudin F et al (2019b) Cutting edge: Nrf2 regulates neutrophil recruitment and accumulation in skin during contact hypersensitivity. J Immunol 202:2189–2194. https://doi.org/10.4049/jimmunol.1801065

Hetz C, Axten JM, Patterson JB (2019) Pharmacological targeting of the unfolded protein response for disease intervention. Nat Chem Biol 15:764–775. https://doi.org/10.1038/s41589-019-0326-2

Ho AW, Kupper TS (2019) T cells and the skin: from protective immunity to inflammatory skin disorders. Nat Rev Immunol 19:490–502. https://doi.org/10.1038/s41577-019-0162-3

Honda T, Egawa G, Grabbe S, Kabashima K (2013) Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. J Invest Dermatol 133:303–315. https://doi.org/10.1038/jid.2012.284

Jakasa I, Thyssen JP, Kezic S (2018) The role of skin barrier in occupational contact dermatitis. Exp Dermatol 27:909–914. https://doi.org/10.1111/exd.13704

Janssens S, Pulendran B, Lambrecht BN (2014) Emerging functions of the unfolded protein response in immunity. Nat Immunol 15:910–919. https://doi.org/10.1038/ni.2991

Johansen JD, Werfel T (2019) Highlights in allergic contact dermatitis 2018/2019. Curr Opin Allergy Clin Immunol 19:334–340. https://doi.org/10.1097/ACI.0000000000000552

Joosten LAB, Abdollahi-Roodsaz S, Dinarello CA et al (2016) Toll-like receptors and chronic inflammation in rheumatic diseases: new developments. Nat Rev Rheumatol 12:344–357. https://doi.org/10.1038/nrrheum.2016.61

Kaplan DH, Igyártó BZ, Gaspari AA (2012) Early immune events in the induction of allergic contact dermatitis. Nat Rev Immunol 12:114–124. https://doi.org/10.1038/nri3150

Kaufman BP, Alexis AF (2018) Biologics and small molecule agents in allergic and immunologic skin diseases. Curr Allergy Asthma Rep 18:55. https://doi.org/10.1007/s11882-018-0804-8

Kim BS (2015) Innate lymphoid cells in the skin. J Invest Dermatol 135:673–678. https://doi.org/10.1038/jid.2014.401

Kim HS, Jang J-H, Lee MB et al (2016) A novel IL-10-producing innate lymphoid cells (ILC10) in a contact hypersensitivity mouse model. BMB Rep 49:293–296. https://doi.org/10.5483/bmbrep.2016.49.5.023

Kish DD, Min S, Dvorina N et al (2019) Neutrophil cathepsin G regulates dendritic cell production of IL-12 during development of CD4 T cell responses to antigens in the skin. J Immunol 202:1045–1056. https://doi.org/10.4049/jimmunol.1800841

Kortekaas Krohn I, Shikhagaie MM, Golebski K et al (2018) Emerging roles of innate lymphoid cells in inflammatory diseases: clinical implications. Allergy 73:837–850. https://doi.org/10.1111/all.13340

Leonard A, Guttman-Yassky E (2019) The unique molecular signatures of contact dermatitis and implications for treatment. Clin Rev Allergy Immunol 56:1–8. https://doi.org/10.1007/s12016-018-8685-0

Luís A, Martins JD, Silva A et al (2014) Oxidative stress-dependent activation of the eIF2α–ATF4 unfolded protein response branch by skin sensitizer 1-fluoro-2,4-dinitrobenzene modulates dendritic-like cell maturation and inflammatory status in a biphasic manner [corrected]. Free Radic Biol Med 77:217–229. https://doi.org/10.1016/j.freeradbiomed.2014.09.008

Maeda K, Caldez MJ, Akira S (2019) Innate immunity in allergy. Allergy 74:1660–1674. https://doi.org/10.1111/all.13788

Majewska-Szczepanik M, Paust S, von Andrian UH et al (2013) Natural killer cell-mediated contact sensitivity develops rapidly and depends on interferon-α, interferon-γ and interleukin-12. Immunology 140:98–110. https://doi.org/10.1111/imm.12120

Martin SF (2013) Induction of contact hypersensitivity in the mouse model. Methods Mol Biol 961:325–335. https://doi.org/10.1007/978-1-62703-227-8_21

Martin SF (2014) Adaptation in the innate immune system and heterologous innate immunity. Cell Mol Life Sci 71:4115–4130. https://doi.org/10.1007/s00018-014-1676-2

Martin SF (2015) New concepts in cutaneous allergy. Contact Derm 72:2–10. https://doi.org/10.1111/cod.12311

Martin SF, Esser PR, Schmucker S et al (2010) T-cell recognition of chemicals, protein allergens and drugs: towards the development of in vitro assays. Cell Mol Life Sci 67:4171–4184. https://doi.org/10.1007/s00018-010-0495-3

Morita H, Moro K, Koyasu S (2016) Innate lymphoid cells in allergic and nonallergic inflammation. J Allergy Clin Immunol 138:1253–1264. https://doi.org/10.1016/j.jaci.2016.09.011

Mussotter F, Potratz S, Budczies J et al (2018) A multi-omics analysis reveals metabolic reprogramming in THP-1 cells upon treatment with the contact allergen DNCB. Toxicol Appl Pharmacol 340:21–29. https://doi.org/10.1016/j.taap.2017.12.016

Nassau S, Fonacier L (2020) Allergic contact dermatitis. Med Clin N Am 104:61–76. https://doi.org/10.1016/j.mcna.2019.08.012

O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH (2006) T cell- and B cell-independent adaptive immunity mediated by natural killer cells. Nat Immunol 7:507–516. https://doi.org/10.1038/ni1332

Paust S, Gill HS, Wang B-Z et al (2010) Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. Nat Immunol 11:1127–1135. https://doi.org/10.1038/ni.1953

Pedersen LK, Johansen JD, Held E, Agner T (2004) Augmentation of skin response by exposure to a combination of allergens and irritants – a review. Contact Derm 50:265–273. https://doi.org/10.1111/j.0105-1873.2004.00342.x

Peng H, Jiang X, Chen Y et al (2013) Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. J Clin Invest 123:1444–1456. https://doi.org/10.1172/JCI66381

Pivniouk V, Gimenes Junior JA, Honeker L, Vercelli D (2019) The role of innate immunity in asthma development and protection: lessons from the environment. Clin Exp Allergy. https://doi.org/10.1111/cea.13508

Rafei-Shamsabadi DA, Klose CSN, Halim TYF et al (2019) Context dependent role of type 2 innate lymphoid cells in allergic skin inflammation. Front Immunol 10:2591. https://doi.org/10.3389/fimmu.2019.02591

Rankin LC, Artis D (2018) Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. Cell 173:554–567. https://doi.org/10.1016/j.cell.2018.03.013

Rouzaire P, Luci C, Blasco E et al (2012) Natural killer cells and T cells induce different types of skin reactions during recall responses to haptens. Eur J Immunol 42:80–88. https://doi.org/10.1002/eji.201141820

Simon D (2018) Recent advances in clinical allergy and immunology. Int Arch Allergy Immunol 177:324–333. https://doi.org/10.1159/000494931

Suto H, Nakae S, Kakurai M et al (2006) Mast cell-associated TNF promotes dendritic cell migration. J Immunol 176:4102–4112. https://doi.org/10.4049/jimmunol.176.7.4102

Sutterwala FS, Ogura Y, Szczepanik M et al (2006) Critical role for NALP3/CIAS1/cryopyrin in innate and adaptive immunity through its regulation of caspase-1. Immunity 24:317–327. https://doi.org/10.1016/j.immuni.2006.02.004

Swanson KV, Deng M, Ting JP-Y (2019) The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol 19:477–489. https://doi.org/10.1038/s41577-019-0165-0

Tan H-TT, Sugita K, Akdis CA (2016) Novel biologicals for the treatment of allergic diseases and asthma. Curr Allergy Asthma Rep 16:70. https://doi.org/10.1007/s11882-016-0650-5

Toksoy A, Sennefelder H, Adam C et al (2017) Potent NLRP3 inflammasome activation by the HIV reverse transcriptase inhibitor Abacavir. J Biol Chem 292:2805–2814. https://doi.org/10.1074/jbc.M116.749473

van den Boorn JG, Jakobs C, Hagen C et al (2016) Inflammasome-dependent induction of adaptive NK cell memory. Immunity 44:1406–1421. https://doi.org/10.1016/j.immuni.2016.05.008

Vivier E, Artis D, Colonna M et al (2018) Innate lymphoid cells: 10 years on. Cell 174:1054–1066. https://doi.org/10.1016/j.cell.2018.07.017

Vocanson M, Hennino A, Rozières A et al (2009) Effector and regulatory mechanisms in allergic contact dermatitis. Allergy 64:1699–1714. https://doi.org/10.1111/j.1398-9995.2009.02082.x

Weber FC, Esser PR, Muller T et al (2010) Lack of the purinergic receptor P2X(7) results in resistance to contact hypersensitivity. J Exp Med 207:2609–2619. https://doi.org/10.1084/jem.20092489

Weber FC, Németh T, Csepregi JZ et al (2015) Neutrophils are required for both the sensitization and elicitation phase of contact hypersensitivity. J Exp Med 212:15–22. https://doi.org/10.1084/jem.20130062

Woolbright BL, Jaeschke H (2017) Role of the inflammasome in acetaminophen-induced liver injury and acute liver failure. J Hepatol 66:836–848. https://doi.org/10.1016/j.jhep.2016.11.017

Part VI

Risk Factors

Genetics of Asthma and Allergic Diseases

Sadia Haider, Angela Simpson, and Adnan Custovic

Contents

Abstract

Asthma genes have been identified through a range of approaches, from candidate gene association studies and family-based genome-wide linkage analyses to genome-wide association studies (GWAS). The first GWAS of asthma, reported in 2007, identified multiple markers on chromosome 17q21 as associates of the childhood-onset asthma. This remains the best replicated asthma locus to date. However, notwithstanding undeniable successes, genetic studies have produced relatively heterogeneous results with limited replication, and despite considerable promise, genetics of asthma and allergy has, so far, had limited impact on patient care, our understanding of disease mechanisms, and development of novel therapeutic targets. The paucity of precise replication in genetic studies of asthma

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is partly explained by the existence of numerous gene–environment interactions. Another important issue which is often overlooked is that of time of the assessment of the primary outcome(s) and the relevant environmental exposures. Most large GWASs use the broadest possible definition of asthma to increase the sample size, but the unwanted consequence of this is increased phenotypic heterogeneity, which dilutes effect sizes. One way of addressing this is to precisely define disease subtypes (e.g. by applying novel mathematical approaches to rich phenotypic data) and use these latent subtypes in genetic studies.

Keywords

Allergic diseases · Asthma · Birth cohorts · Gene-environment interactions · GWAS · Longitudinal data · Machine learning · Phenotypes

Asthma is a complex multifactorial disorder caused by a variety of different mechanisms which result in multiple clinical phenotypes (Pavord et al. 2018; Saglani and Custovic 2019). Although asthma does not show classical Mendelian inheritance (Jenkins et al. 1997), it has a strong genetic component, and a familial aggregation has been described in numerous studies. Twin studies have confirmed higher concordance of asthma in monozygotic than in dizygotic twins and estimated the heritability to be in the region of 60–70% (Duffy et al. 1990). The evidence to date suggests that the genetic component of asthma likely derives from numerous genes with small to moderate effects (Ober and Yao 2011).

1 Genetics of Asthma: From Candidate Genes to Genome-Wide Association Studies

"Asthma genes" have been identified through a range of approaches, from candidate gene association studies (Simpson et al. 2012) and family-based genome-wide linkage analyses (Daniels et al. 1996) to genome-wide association studies (GWAS) (Moffatt et al. 2007, 2010; Demenais et al. 2018). Results of the first genome-wide linkage study for asthma were published in 1996 (Daniels et al. 1996), suggesting six potential loci, one of which (chromosome 11q13) has been reported previously in a candidate gene association study (Lympany et al. 1992). The first lung-specific asthma candidate gene (*ADAM33*) was identified by positional cloning in 2002 (Van Eerdewegh et al. 2002), and the first GWAS of asthma was reported in 2007 (Moffatt et al. 2007), identifying multiple markers on chromosome 17q21 as associates of the childhood-onset asthma. Since then, a number of other loci were identified using these techniques, including (but not limited to) *GPRA* (Laitinen et al. 2004), *HLA-G* (Nicolae et al. 2005), *PHF11* (Zhang et al. 2003), *DPP10* (Allen et al. 2003), *CYFIP2* (Noguchi et al. 2005), etc. Genome-wide association studies have identified many risk alleles and loci (some of which have been replicated in worldwide populations (Kim and Ober 2019)), including novel candidate genes

such as *CH13L1* (Ober et al. 2008) and *DENND1B* (Sleiman et al. 2010). Overall, the evidence suggests that there may be multiple genes underlying the linkage peaks (e.g. in the region 5q31–33 lie *ADRB2*, *IL4*, *IL13*, *SPINK5*, *CD14*, *LTC4S*, *CYFIP2* and *TIM1,* and 17q21 locus includes genes *ORMDL3, GSDMB, CDHR3, GSDMA* and *GSDML* (Kim and Ober 2019; Zhang et al. 2019; Das et al. 2017; Ober 2016)). Each of these has relatively small effect or may be associated with different asthma endotypes. A comprehensive review which summarised the results of 42 GWASs to date of asthma, different asthma phenotypes and asthma-related traits has been published recently (Kim and Ober 2019) and provides an excellent summary of the many risk alleles and loci which were replicated in different populations. The most widely replicated asthma locus in GWASs is 17q12–21, followed by 6p21 (HLA region), 2q12 (*IL1RL1/IL18R1*), 5q22 (*TSLP*) and 9p24 (*IL33*) (Kim and Ober 2019). However, it is important to highlight the under-representation of ethnically diverse populations in most GWASs (Kim and Ober 2019). To mitigate against this, large consortia have been formed, which combine the results of multiple ethnically diverse GWASs in order to increase the overall power to identify asthma-susceptibility loci. Examples include the GABRIEL (Moffatt et al. 2010), EVE (Torgerson et al. 2011) and TAGC (Demenais et al. 2018) consortia, and the value of diverse, multi-ethnic participants in large-scale genomic studies has recently been shown in the Population Architecture using Genomics and Epidemiology (PAGE) study (Wojcik et al. 2019). The largest GWAS to date in asthma was performed by the Trans-National Asthma Genetic Consortium (TAGC) in 23,948 cases and 118,538 controls, revealing 18 loci that reached genome-wide significance (Demenais et al. 2018).

2 Genetics of Asthma and Allergic Diseases: Inconsistent Findings

However, despite undeniable successes, it is of note that genetic studies have produced relatively heterogeneous results with limited replication (Ober and Yao 2011; Ober and Hoffjan 2006). Furthermore, a "precise replication", namely the identical association of the specific single nucleotide polymorphism (SNP) with the same phenotype, is rare (Hirschhorn et al. 2002). In asthma literature, the whole gene, rather than a specific (SNP) is often used as a unit of replication, and the finding of any association between the genetic variant of interest with any asthma-related phenotype is sometimes considered as evidence of replication (even if the association is in the opposite direction in different populations (Ober and Hoffjan 2006)). Even for the best replicated asthma genes (e.g. those on chromosome 17q21), there is at least one negative finding, the risk alleles/SNPs are occasionally not consistent, and the effect size is relatively small (with odds ratios often in the region of 1.1–1.2) (Ober and Hoffjan 2006). Finally, only a relatively small proportion of the estimated heritability of asthma (and other atopic phenotypes such as IgE (Granada et al. 2012) and eczema (Paternoster et al. 2012)) has been explained. For example, although the estimated heritability for total IgE is ~60% (Strachan et al. 2001), a relatively large study of its

genetic determinants explained less than 1% of the variance (Maier et al. 2006). Similarly, two meta-analyses of GWASs for lung function identified several novel genome-wide significant loci (Hancock et al. 2010; Repapi et al. 2010), but these accounted for only 3% of the variation in lung function, with most of the variance remaining unexplained (Weiss 2010; Artigas et al. 2011). Overall, despite considerable promise, genetic studies of asthma and allergic diseases have so far had limited impact on our understanding of disease mechanisms and development of novel therapeutic targets, or on patient care.

One part of the explanation for the paucity of precise replication of genetic studies of asthma discussed in this chapter is the existence of numerous gene–environment interactions (Custovic et al. 2012; Ober and Vercelli 2011). Another important consideration is the heterogeneity of asthma (including considerable differences in the response to treatment, severity, age of onset and factors triggering symptoms), which has long been recognised and is a subject of a considerable debate. This culminated in the notion that asthma is not a single disease underpinned by similar pathophysiological mechanisms and genetic architecture leading to different clinical manifestations ("phenotypes"), but rather an "umbrella" diagnosis for a complex conglomerate of several different diseases ("endotypes") (Anderson 2008; Lotvall et al. 2011), each caused by both distinct and overlapping mechanisms and with different genetic associates, but with similar symptoms and clinical presentation (Custovic et al. 2019). One of the consequences of the use of an aggregated definition (such as "doctor-diagnosed asthma") in genetic studies is that important signals may be diluted by phenotypic heterogeneity (Custovic et al. 2015, 2019).

3 Gene–Environment Interactions

Asthma and allergic diseases are rarely purely genetically or environmentally driven and usually develop through complex interactions whereby environmental factors modulate the risk in genetically susceptible individuals (Ober and Yao 2011; Custovic et al. 2012; Vercelli and Martinez 2006). The concept that the same environmental exposure may have different effects among individuals with different genetic predisposition has been tested in studies which assessed the interaction between genes and the susceptibility to environmental factors (reviewed in Custovic et al. 2012). One of the most replicated gene–environment interactions which we will use as an exemplar is the relationship between endotoxin (lipopolysaccharide or LPS) and polymorphism in *CD14* gene (Simpson et al. 2006). Endotoxin is a component of the exterior cell wall of gram-negative bacteria, and in the broad context of the "hygiene hypothesis" (Schaub et al. 2006; von Mutius 2007), exposure to endotoxin and other microbial products which are sensed by "danger signal" innate immunity receptors (e.g. the toll-like receptors, TLRs) serves to mould and calibrate the maturation of immune competence that is typically developmentally compromised during early life (Stein et al. 2016; von Mutius and Vercelli 2010). However, similar to many other environmental factors, contradictory findings have been reported on the relationship between endotoxin exposure and atopic

phenotypes, with endotoxin in some studies conferring a protective effect (Braun-Fahrlander et al. 2002; Gereda et al. 2000), an increase in risk (Nicolaou et al. 2006), or having no effect (Bottcher et al. 2003). Endotoxin (LPS) is recognised by a cascade of receptors and accessory proteins, which include LPS binding protein, CD14 and the Toll-like receptor 4 (TLR4)–MD-2 complex (Park and Lee 2013). An association between a functional variant in the promoter region of the *CD14* gene (−159C/T, rs2569190) (Baldini et al. 1999) with allergic phenotypes has been reported in several populations (reviewed in Simpson and Martinez 2010). Initial studies from Tucson reported that T allele was protective (Baldini et al. 1999), but subsequent studies in Germany found no association (Kabesch et al. 2004), and a study among Hutterites reported the opposite finding (i.e. that the T allele confers increased risk (Ober et al. 2000)). Given that CD14 is a part of the pattern recognition receptor complex for endotoxin, we tested the hypothesis that the effect of endotoxin exposure on allergic sensitisation may differ in individuals with different variants in *CD14* SNP rs2569190 (−159C/T) (Simpson et al. 2006). The results have indicated that high endotoxin exposure is protective, but only in children who are C-allele homozygotes (Simpson et al. 2006). In contrast, there was no association between endotoxin exposure and sensitisation among T-allele homozygotes. These findings may explain the disparities in genetic association studies of this SNP and atopic phenotypes in different settings around the world (Simpson and Martinez 2010). For example, if this genetic variant is studied in isolation, in populations exposed to low level of endotoxin (such as Tucson), the T allele would confer protection (Baldini et al. 1999), while in those with high endotoxin exposure (such as a farming community of Hutterites) (Ober et al. 2000), the same allele (T) would confer the increase in risk. Finally, in populations with a range of exposures, there would be no clear association between genotype and outcome (Kabesch et al. 2004). Similar results which confirmed interaction between this polymorphism in *CD14* and endotoxin exposure have been reported in several independent populations (Eder et al. 2005; Williams et al. 2006; Zambelli-Weiner et al. 2005).

A further example of the opposite effect of environmental exposure(s) among individuals with different genetic predisposition is the finding that the association between early-life day-care attendance and development of asthma during childhood may depend on a variant in *TLR2* gene (Custovic et al. 2011). Day-care (likely a marker of high exposure to microbial agents) was found to be protective among T-allele carriers for *TLR2* SNP rs4696480, whilst among AA homozygotes day-care attendance appeared to increase the risk. Thus, the relevance of the *TLR2* gene was uncovered only when the relevant environmental exposure (day-care attendance) was identified and taken into account. Day-care appeared protective in the analysis in the whole population (Nicolaou et al. 2008), but the apparent protective effect is a consequence of a much larger number of children with the T allele in the population, who outnumbered AA homozygotes by a factor of almost 4:1, thereby concealing the fact that in a subgroup (AA homozygotes), day-care attendance actually increased the risk of disease (Custovic et al. 2011). These two examples indicate that if genotypes which interact with environmental exposures are studied in isolation, irrespective of the size of the population studied, associations can be missed.

Context dependency in terms of interactions with environmental exposure has also been shown for genes with an important and consistent main effect. For example, as outlined above, chromosome 17q21 locus is recognised as a major genetic risk locus for childhood-onset asthma (Moffatt et al. 2007; Stein et al. 2018; Hernandez-Pacheco et al. 2019) (in particular among children experiencing virus-induced wheezing in early infancy (Caliskan et al. 2013)). However, recent studies have shown that genetic polymorphism in *ORMDL3* which confers the risk of asthma (GG genotype in SNP rs8076131) is amenable to environmental protection through exposure to farm animal sheds and presence of older siblings, whilst no protective effect of these exposures was observed for the insusceptible genotype (rs8076131 AA/GA) (Loss et al. 2016). Similarly, 17q21 variants have been shown to interact with the environmental tobacco smoke (ETS) exposure (Marinho et al. 2012; Blekic et al. 2013) and early-life pet ownership (Blekic et al. 2013). These findings suggest that stratified prevention strategies informed by individual genetic predisposition may be possible.

Another example of the susceptibility genotype which may interact with environmental exposures is filaggrin (*FLG)*. *FLG* loss-of-function mutations cause impaired skin barrier and are associated with atopic dermatitis (AD) (Sandilands et al. 2007), and a range of other allergic conditions (Marenholz et al. 2006; Weidinger et al. 2008; Henderson et al. 2008a) and allergic sensitisation (Henderson et al. 2008a). However, certain environmental exposures may modify this association. For example, cat exposure in early life was found to increase the risk of AD in children with *FLG* loss-of-function mutations, with no effect cat ownership among those without *FLG* mutations (Bisgaard et al. 2008). In a study on peanut allergy, we have shown that early-life *environmental* exposure to peanut allergens measured in dust samples from homes increases the risk of peanut sensitisation and peanut allergy in children who carry *FLG* mutations, with no significant effect of exposure in children without *FLG* mutations (Brough et al. 2014). Our subsequent study has shown that *FLG* loss-of-function mutations also modify the impact of exposure to inhalant allergen such as house dust mite (HDM) and cat on the development of allergen-specific sensitisation, in that the impact of Der p 1 and Fel d 1 exposure on allergen-specific sensitisation was considerably higher among children with *FLG* loss-of-function mutations compared to those without (Simpson et al. 2020). In contrast to mite and cat exposure, the risk of sensitisation to any allergen was lower among children with *FLG* mutations who were exposed to dog in their home in infancy (Simpson et al. 2020). These findings may partly explain the differences in the effects of cat and dog ownership on allergic diseases and suggest that cat ownership may be a marker of high cat allergen exposure, while the protective effect of dog ownership (which extends to asthma and sensitisation to other allergens (Ownby et al. 2002)) may be mediated via changes in external or host microbiome (Sitarik et al. 2018). This study raises another important issue which is often overlooked in genetic studies of allergic diseases – that of time, and of a potentially crucial importance of longitudinal analyses. It confirmed previous observations that the association between early-life environmental exposures and allergic sensitisation changes with time (Ihuoma et al. 2018) and raised questions about the current

approach to replication in genetic and gene*environment studies, suggesting that the timing of the assessment of outcomes may have a critically important impact on the results (Simpson et al. 2020).

It is likely that the impact of many (if not most) environmental exposures which influence the risk of allergic diseases is modified by the genetic predisposition. For example, ETS exposure increases the risk of wheezing (Murray et al. 2004), accelerated decline of lung function and increased asthma severity and morbidity (Strachan and Cook 1998), as well as the reduced responsiveness to inhaled corticosteroids (ICS) (Chalmers et al. 2002). However, not all exposed individuals develop symptoms, suggesting that some may be more susceptible to the effects of tobacco smoke (possibly due to genetic variation). Interaction has been demonstrated between tobacco smoke exposure and several asthma candidate genes, such as glutathione S transferases (Panasevich et al. 2010; Palmer et al. 2006; Rogers et al. 2009), TNF-α (Wu et al. 2007) and the β_2-adrenoreceptor (*ADRB2*) (Wang et al. 2001), as well as other genomic loci (5q (Colilla et al. 2003), 1p, 9q (Colilla et al. 2003) and 1q43-q44, 4q34, 17p11, 5p15, 14q32 and 17q21 (Dizier et al. 2007; Meyers et al. 2005)). Similarly, variability in response to environmental HDM exposure in relation to HDM sensitisation has been attributed to the *IL4* gene promoter polymorphism C-590T (Liu et al. 2004). However, it should be noted that there are conflicting data on specific gene–environment interactions. For example, Reijmerink et al. found a significant effect modification by in utero ETS exposure of *ADAM33* polymorphisms on lung function and the development of AHR in children (Reijmerink et al. 2009), whereas Schedel et al. (Schedel et al. 2006) were unable to detect any interactions between passive smoke exposure (in utero or during childhood) and *ADAM33* variants.

4 Heterogeneity of Asthma and Allergic Diseases

The clinical presentation of wheezing and asthma varies widely over the life course, and the extent to which phenotypic variation signals differences in disease aetiology remains unclear. Most large GWASs use the broadest possible definition of asthma (e.g. parentally or patient-reported "doctor-diagnosed asthma"). As there is no universally accepted operational definition, this may lead to the under- or over-estimation of cases in genetic studies. For example, a study by Van Wonderen et al. (2010) found that the choice of "case" definition has a large impact on the estimate of asthma prevalence in early life. The authors identified 60 different "case" definitions for diagnosing childhood asthma in 122 published articles from cohort studies. They then chose four common definitions and applied them to a single cohort, to find that prevalence estimates varied considerably from 15.1% to 51.1%.

Another factor which may impact upon the power to detect associations is misclassification of controls. For example, we have recently shown that the choice of the definition a "control" has major implications for detecting an association between AD and *FLG* genotype (Nakamura et al. 2019). By using different definitions of controls ("strict" and "moderate") (Nakamura et al. 2019), we have

demonstrated that although the sample size was reduced by approximately one-fifth when moving from the moderate to strict definition (as fewer children fulfilled the more stringent criteria), the power to detect genetic association increased by ~50% from 0.58 to 0.85 by having a "purer" control as a comparator for AD cases. These findings confirm that bigger is not necessarily always better in genetic studies of common complex heterogenous phenotypes (Schoettler et al. 2019). Further consideration for defining cases and controls is the co-morbidity of allergic diseases. Twin studies have estimated pairwise genetic correlations of asthma, AD, and allergic rhinitis to be greater than 0.5, suggesting that there are specific risk variants for each disease, but also shared genetic risk variants between diseases (Ferreira et al. 2017). Consequently, if for example in genetic studies of asthma one includes in the control group non-asthmatic individuals who have other allergic diseases (e.g. allergic rhinitis or AD), genetic signals may be weakened. Ferreira has demonstrated that using a strict definition of controls, where individuals do not experience any allergic disease, has the potential to increase the power, confirming that tighter definition of both cases and controls could strengthen findings on the genetic architecture of diseases (Ferreira 2014). To account for this, we suggest that genetic studies of allergic diseases should investigate and publish the sensitivity of their findings based on different definitions of cases and controls.

5 Can Focus on Disease Subtypes Improve Genetic Studies?

Deep phenotyping has the potential to identify new risk loci. A recent comparatively small GWAS which used a specific subtype of early-onset childhood asthma with recurrent, severe exacerbations as an outcome identified a novel gene, Cadherin Related Family Member 3 (*CDHR3*) as an associate of this specific subtype, but not of doctor-diagnosed asthma (Bønnelykke et al. 2014). This important discovery was made in a considerably smaller sample size (1,173 cases and 2,522 controls), but using a much more precise asthma subtype than was available in large international consortia which did not detect this association. For example, the previously mentioned largest asthma GWAS to date (TAGC) had almost 40-fold higher sample size (Demenais et al. 2018), but reported no significant association between *CDHR3* and "asthma", likely due to phenotypic heterogeneity inherent in the definition of asthma. Mechanistic studies that followed have suggested that CDHR3 may be a receptor for Rhinovirus C, identifying this as a potential therapeutic target (Bochkov et al. 2015). A major implication of this study is that with careful phenotyping, smaller sample sizes may be adequately powered to identify larger effect sizes than those in large GWASs with "looser" outcome definitions.

6 Gene Discovery Using Phenotypes of Allergic Disease Derived by Data-Driven Techniques

As highlighted previously, an unwanted consequence of increasing sample size in large GWASs is increased phenotypic heterogeneity, which may dilute effect sizes. One way of addressing this is to derive subtypes of asthma and allergic diseases, which should ideally be homogenous. Whilst there are abundant studies using longitudinal data to characterise allergic diseases into data-driven phenotypes, a fertile yet under-investigated area of research is the investigation of genetic markers of these disease subtypes (Belgrave et al. 2017).

Over the past two decades, there has been a growth in the number of studies using data-driven classification techniques to identify subtypes of asthma. One such approach is latent trajectory modelling, in which repeated measurements of observed symptoms are modelled to identify more homogeneous sub-populations within the larger heterogeneous population (Oksel et al. 2018a, b; Prosperi et al. 2014). By incorporating the temporal evolution of observed symptoms across the life course, investigators have been able to capture the phenotypic heterogeneity of asthma based on the timing and persistence of symptoms in a hypothesis-neutral way, and to identify sub-groups with consistent patterns of disease that were not known a priori (reviewed in Oksel et al. 2018b; Deliu et al. 2017; Deliu et al. 2016; Howard et al. 2015). Latent modelling approaches have been extensively used to identify and validate longitudinal trajectories of childhood wheeze (Henderson et al. 2008b; Granell et al. 2016; Belgrave et al. 2013; Savenije et al. 2011), severe exacerbations (Deliu et al. 2019), atopy (Lee et al. 2017; Havstad et al. 2014; Garden et al. 2013; Lazic et al. 2013), asthma (Deliu et al. 2017; Howard et al. 2015; Weinmayr et al. 2013) and lung function (Belgrave et al. 2014a, 2018) and to evaluate their associations with environmental risk factors. Even though these studies have been instrumental in elucidating the heterogenous nature of allergic diseases, there has been a paucity of research into the genetic associations of such phenotypes. ALSPAC investigators explored associations between genes in the 17q21 locus and symptom-based longitudinal wheezing phenotypes derived by latent class analysis (Henderson et al. 2008b). Their findings suggested that SNPs near *ORMDL3*, *GSDML* and I*KZF3* were associated with persistent and intermediate-onset wheeze (characterised by onset before age 30 months), but not with early wheezing that resolved or with late-onset wheezing, indicating that the timing and pattern of symptoms in early life may have differential genetic associations (Granell et al. 2013). A further study related the same wheezing phenotypes to the genetic prediction scores based on 10–200,000 SNPs ranked according to their associations with physician-diagnosed asthma and found that the 46 highest ranked SNPs (which included SNPs in *ORMDL3/GSDMB*, *IL1RL1, IL18R1* and *IL33*) predicted persistent and intermediate-onset wheezing phenotypes more strongly than doctor-diagnosed asthma (Spycher et al. 2012). Furthermore, SNPs below the stringent genome-wide significance threshold were associated with bronchial hyper-responsiveness and atopy. Combining data from ALSPAC and PIAMA cohorts, Savenije et al. (2014) found that intermediate-onset and late-onset wheeze (both

highly associated with allergic sensitisation) were associated with several *IL1RL1* and *IL33* polymorphisms. The study suggested that allergic sensitisation, through the IL33-IL1RL1 pathway, may be a risk factor for the development of wheeze and subsequent asthma.

A recent study took this approach one step further by investigating the relationship between the polygenic risk score comprising 135 SNPs which were found to be associated with allergic diseases in a previous GWAS (Ferreira et al. 2017), and eight latent classes of allergic diseases which were derived using machine learning techniques applied on the longitudinal patterns of the development of eczema, wheeze and rhinitis (Belgrave et al. 2014b). The authors found strong evidence for differential genetic associations across the different developmental profiles of eczema, wheeze and rhinitis, with pooled polygenic risk score heterogeneity P-value of 3.3×10^{-14}. SNP rs61816761 (a protein truncating variant in *FLG* gene) and SNP rs921650 (within an intron of *GSDMB* on chromosome 17q21.1), which have previously been identified as having disease-specific effects (Ferreira et al. 2017), were differentially associated with distinct disease profiles. The *FLG* locus was associated with all profiles that included eczema, but the association was much stronger for the classes with co-morbid wheeze and rhinitis. In contrast, the *GSDMB* locus was associated with all profiles which included wheeze (including transient wheezing), but with no additional risk of co-morbid conditions. These studies suggest that the investigation of genetic associates of more holistic phenotypes which take into account temporality and co-occurrence of different symptoms may provide evidence of heterogenous aetiological pathways which are masked by the umbrella case definitions in genetic studies. Ultimately, the case is strengthening for reforming the taxonomy of atopic diseases away from traditional symptom-based diagnostic criteria to incorporate advances in data analysis techniques, as well as molecular and genetic medicine.

7 Integration of Data

There is a paucity of studies which have collected measurable data which dynamically influence the susceptibility to asthma, which would allow large-scale hypothesis-neutral GWAS using derived multinomial probabilistic phenotypes as an outcome. Gathering such data at a sufficient scale may be impractical due to the cost and complexity of externally validating findings of clinical importance in different populations. There may also be a risk of diluting genetic effects due to differences in exposure to environmental factors, which are difficult to control for, and variations in genetic backgrounds.

We propose that an integrated approach to understanding the mechanisms of asthma and allergic diseases (including genetics) through harnessing the power of different data sources may translate into a better understanding of causal mechanisms, more accurate diagnoses and more personalised treatment (Haider and Custovic 2019). The proliferation of new types of data, namely biomarkers from "omics" technologies and systems biology, coupled with advances in

computational power introduces new opportunities for the integration of different data sources to understand complex diseases more holistically (Canonica et al. 2018). More specifically, triangulation from different sources may help to elucidate the directionality of relationships between variables at a very individual level by modelling the complex interdependencies between multiple dimensions (e.g. genome, transcriptome, epigenome, microbiome and metabolome) thereby, moving away from associative to a more causal analysis. Pecak et al recently developed a catalogue of 190 potential asthma biomarkers from 73 studies covering 13 omics platforms (including genomics, epigenomics, transcriptomics, proteomics) (Pecak et al. 2018). They identified 10 candidate genes linked to asthma (for example, *IL3*, *IL13*, *GATA3*) that were present in at least two omics levels, thus demonstrating the potential for prioritising specific biomarker research and the development of targeted therapeutics.

8 Conclusions

The existence of numerous gene–environment interactions (many of which remain to be described (Vercelli and Martinez 2006)) and the use of aggregated phenotypes which are probably comprised of a number of different diseases with distinct pathophysiological mechanism make reproducible studies aiming to understand the mechanisms of allergic disorder difficult, if not impossible. Understanding the potential causes of heterogeneity in phenotyping may enable the identification of genetic associations in a more consistent way. We propose that one of the ways forward is to precisely define disease subtypes (for example, by applying novel mathematical approaches to rich phenotypic data) and use these latent subtypes in genetic association studies. Understanding of gene–environment interactions, which typically use simple binary definitions of outcomes, could also be enriched by taking a multinomial approach by exploring whether such interactions vary by disease subtype membership. The triangulating of genetic data with deep phenotyping, environmental and omics data may help to identify the underlying pathophysiology of allergic diseases more holistically and inform the development of personally tailored therapeutic targets, as well as the genotype-specific strategies for prevention (Custovic and Simpson 2004).

References

Allen M, Heinzmann A, Noguchi E et al (2003) Positional cloning of a novel gene influencing asthma from chromosome 2q14. Nat Genet 35(3):258–263

Anderson GP (2008) Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 372(9643):1107–1119

Artigas MS, Loth DW, Wain LV et al (2011) Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nat Genet 43(11):1082–1090

Baldini M, Lohman IC, Halonen M, Erickson RP, Holt PG, Martinez FD (1999) A polymorphism* in the 5′ flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E. Am J Respir Cell Mol Biol 20(5):976–983

Belgrave DC, Custovic A, Simpson A (2013) Characterizing wheeze phenotypes to identify endotypes of childhood asthma, and the implications for future management. Expert Rev Clin Immunol 9(10):921–936

Belgrave DC, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A (2014a) Trajectories of lung function during childhood. Am J Respir Crit Care Med 189(9):1101–1109

Belgrave DCM, Granell R, Simpson A et al (2014b) Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med 11(10):e1001748

Belgrave D, Henderson J, Simpson A, Buchan I, Bishop C, Custovic A (2017) Disaggregating asthma: big investigation versus big data. J Allergy Clin Immunol 139(2):400–407

Belgrave DCM, Granell R, Turner SW et al (2018) Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. Lancet Resp Med 6(7):526–534

Bisgaard H, Simpson A, Palmer CN et al (2008) Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. PLoS Med 5(6):e131

Blekic M, Kljaic Bukvic B, Aberle N et al (2013) 17q12-21 and asthma: interactions with early-life environmental exposures. Ann Allergy Asthma Immunol 110(5):347–353 e2

Bochkov YA, Watters K, Ashraf S et al (2015) Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc Natl Acad Sci U S A 112(17):5485–5490

Bønnelykke K, Sleiman P, Nielsen K et al (2014) A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet 46(1):51–55

Bottcher MF, Bjorksten B, Gustafson S, Voor T, Jenmalm MC (2003) Endotoxin levels in Estonian and Swedish house dust and atopy in infancy. Clin Exp Allergy 33(3):295–300

Braun-Fahrlander C, Riedler J, Herz U et al (2002) Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 347(12):869–877

Brough HA, Simpson A, Makinson K et al (2014) Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. J Allergy Clin Immunol 134 (4):867–875 e1

Caliskan M, Bochkov YA, Kreiner-Moller E et al (2013) Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. New Engl J Med 368(15):1398–1407

Canonica GW, Ferrando M, Baiardini I et al (2018) Asthma: personalized and precision medicine. Curr Opin Allergy Clin Immunol 18(1):51–58

Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC (2002) Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 57(3):226–230

Colilla S, Nicolae D, Pluzhnikov A et al (2003) Evidence for gene-environment interactions in a linkage study of asthma and smoking exposure. J Allergy Clin Immunol 111(4):840–846

Custovic A, Simpson A (2004) Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk. Thorax 59(10):825–827

Custovic A, Rothers J, Stern D et al (2011) Effect of day care attendance on sensitization and atopic wheezing differs by toll-like receptor 2 genotype in 2 population-based birth cohort studies. J Allergy Clin Immunol 127(2):390–397 e1-9

Custovic A, Marinho S, Simpson A (2012) Gene-environment interactions in the development of asthma and atopy. Expert Rev Respir Med 6(3):301–308

Custovic A, Ainsworth J, Arshad H et al (2015) The study team for early life asthma research (STELAR) consortium 'asthma e-lab': team science bringing data, methods and investigators together. Thorax 70(8):799–801

Custovic A, Henderson J, Simpson A (2019) Does understanding endotypes translate to better asthma management options for all? J Allergy Clin Immunol 144(1):25–33

Daniels SE, Bhattacharrya S, James A et al (1996) A genome-wide search for quantitative trait loci underlying asthma. Nature 383(6597):247–250

Das S, Miller M, Broide DH (2017) Chromosome 17q21 genes ORMDL3 and GSDMB in asthma and immune diseases. Adv Immunol 135:1–52

Deliu M, Sperrin M, Belgrave D, Custovic A (2016) Identification of asthma subtypes using clustering methodologies. Pulm Ther 2:19–41

Deliu M, Belgrave D, Sperrin M, Buchan I, Custovic A (2017) Asthma phenotypes in childhood. Expert Rev Clin Immunol 13(7):705–713

Deliu M, Fontanella S, Haider S et al (2019) Longitudinal trajectories of severe wheeze exacerbations from infancy to school age and their association with early-life risk factors and late asthma outcomes. Clin Exp Allergy 50(3):315–324

Demenais F, Margaritte-Jeannin P, Barnes KC et al (2018) Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. Nat Genet 50(1):42–53

Dizier MH, Bouzigon E, Guilloud-Bataille M et al (2007) Evidence for gene x smoking exposure interactions in a genome-wide linkage screen of asthma and bronchial hyper-responsiveness in EGEA families. Eur J Hum Genet 15(7):810–815

Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD (1990) Genetics of asthma and hay fever in Australian twins. Am Rev Respir Dis 142(6 Pt 1):1351–1358

Eder W, Klimecki W, Yu L et al (2005) Opposite effects of CD 14/−260 on serum IgE levels in children raised in different environments. J Allergy Clin Immunol 116(3):601–607

Ferreira MAR (2014) Improving the power to detect risk variants for allergic disease by defining case-control status based on both asthma and hay fever. Twin Res Hum Genet 17(6):505–511

Ferreira MA, Vonk JM, Baurecht H et al (2017) Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet 49(12):1752–1757

Garden F, Simpson J, Marks G (2013) Atopy phenotypes in the childhood asthma prevention study (CAPS) cohort and the relationship with allergic disease. Clin Exp Allergy 43(6):633–641

Gereda JE, Leung DY, Thatayatikom A et al (2000) Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. Lancet 355(9216):1680–1683

Granada M, Wilk JB, Tuzova M et al (2012) A genome-wide association study of plasma total IgE concentrations in the Framingham heart study. J Allergy Clin Immunol 129(3):840–845

Granell R, Henderson AJ, Timpson N et al (2013) Examination of the relationship between variation at 17q21 and childhood wheeze phenotypes. J Allergy Clin Immun 131(3):685–694

Granell R, Henderson AJ, Sterne JA (2016) Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: a population-based birth cohort. J Allergy Clin Immun 138(4):1060–1070.e11

Haider S, Custovic A (2019) Breaking down silos in asthma research: the case for an integrated approach. EMJ Innov 3(1):82–92

Hancock DB, Eijgelsheim M, Wilk JB et al (2010) Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet 42(1):45–52

Havstad S, Johnson CC, Kim H et al (2014) Atopic phenotypes identified with latent class analyses at age 2 years. J Allergy Clin Immun 134(3):722–727 e2

Henderson J, Northstone K, Lee SP et al (2008a) The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol 121 (4):872–877

Henderson J, Granell R, Heron J et al (2008b) Associations of wheezing phenotypes in the first six years of life with atopy, lung function and airway responsiveness in mid childhood. Thorax 63 (11):974–980

Hernandez-Pacheco N, Pino-Yanes M, Flores C (2019) Genomic predictors of asthma phenotypes and treatment response. Front Pediatr 7:6

Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K (2002) A comprehensive review of genetic association studies. Genet Med 4(2):45–61

Howard R, Rattray M, Prosperi M, Custovic A (2015) Distinguishing asthma phenotypes using machine learning approaches. Curr Allergy Asthma Rep 15(7):1–10

Ihuoma H, Belgrave DC, Murray CS, Foden P, Simpson A, Custovic A (2018) Cat ownership, cat allergen exposure, and trajectories of sensitization and asthma throughout childhood. J Allergy Clin Immunol 141(2):820–822 e7

Jenkins MA, Hopper JL, Giles GG (1997) Regressive logistic modeling of familial aggregation for asthma in 7,394 population-based nuclear families. Genet Epidemiol 14(3):317–332

Kabesch M, Hasemann K, Schickinger V et al (2004) A promoter polymorphism in the CD14 gene is associated with elevated levels of soluble CD14 but not with IgE or atopic diseases. Allergy 59(5):520–525

Kim KW, Ober C (2019) Lessons learned from GWAS of asthma. Allergy Asthma Immun 11 (2):170–187

Laitinen T, Polvi A, Rydman P et al (2004) Characterization of a common susceptibility locus for asthma-related traits. Science 304(5668):300–304

Lazic N, Roberts G, Custovic A et al (2013) Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. Allergy 68(6):764–770

Lee E, Lee SH, Kim Y-H et al (2017) Association of atopy phenotypes with new development of asthma and bronchial hyperresponsiveness in school-aged children. Ann Allergy Asthma Immunol 118(5):542–50 e1

Liu X, Beaty TH, Deindl P et al (2004) Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. J Allergy Clin Immunol 113(3):489–495

Loss GJ, Depner M, Hose AJ et al (2016) The early development of wheeze environmental determinants and genetic susceptibility at 17q21. Am J Respir Crit Care Med 193(8):889–897

Lotvall J, Akdis CA, Bacharier LB et al (2011) Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immun 127(2):355–360

Lympany P, Welsh K, MacCochrane G, Kemeny DM, Lee TH (1992) Genetic analysis using DNA polymorphism of the linkage between chromosome 11q13 and atopy and bronchial hyperresponsiveness to methacholine. J Allergy Clin Immunol 89(2):619–628

Maier LM, Howson JM, Walker N et al (2006) Association of IL13 with total IgE: evidence against an inverse association of atopy and diabetes. J Allergy Clin Immunol 117(6):1306–1313

Marenholz I, Nickel R, Ruschendorf F et al (2006) Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. J Allergy Clin Immunol 118(4):866–871

Marinho S, Custovic A, Marsden P, Smith JA, Simpson A (2012) 17q12-21 variants are associated with asthma and interact with active smoking in an adult population from the United Kingdom. Ann Allergy Asthma Immunol 108(6):402–411 e9

Meyers DA, Postma DS, Stine OC et al (2005) Genome screen for asthma and bronchial hyperresponsiveness: interactions with passive smoke exposure. J Allergy Clin Immunol 115 (6):1169–1175

Moffatt MF, Kabesch M, Liang L et al (2007) Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 448(7152):470–473

Moffatt MF, Gut IG, Demenais F et al (2010) A large-scale, consortium-based genomewide association study of asthma. N Engl J Med 363(13):1211–1221

Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A (2004) Tobacco smoke exposure, wheeze, and atopy. Pediatr Pulmonol 37(6):492–498

Nakamura T, Haider S, Colicino S et al (2019) Different definitions of atopic dermatitis: impact on prevalence estimates and associated risk factors. Br J Dermatol 181(6):1272–1279

Nicolae D, Cox NJ, Lester LA et al (2005) Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. Am J Hum Genet 76 (2):349–357

Nicolaou N, Yiallouros P, Pipis S, Ioannou P, Simpson A, Custovic A (2006) Domestic allergen and endotoxin exposure and allergic sensitization in Cyprus. Pediatr Allergy Immunol 17 (1):17–21

Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A (2008) Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. J Allergy Clin Immunol 122(3):500–6 e5
Noguchi E, Yokouchi Y, Zhang J et al (2005) Positional identification of an asthma susceptibility gene on human chromosome 5q33. Am J Respir Crit Care Med 172(2):183–188
Ober C (2016) Asthma genetics in the post-GWAS era. Ann Am Thorac Soc 13:S85–S90
Ober C, Hoffjan S (2006) Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun 7(2):95–100
Ober C, Vercelli D (2011) Gene-environment interactions in human disease: nuisance or opportunity? Trends Genet 27(3):107–115
Ober C, Yao TC (2011) The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev 242(1):10–30
Ober C, Tsalenko A, Parry R, Cox NJ (2000) A second-generation genomewide screen for asthma-susceptibility alleles in a founder population. Am J Hum Genet 67(5):1154–1162
Ober C, Tan Z, Sun Y et al (2008) Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. N Engl J Med 358(16):1682–1691
Oksel C, Granell R, Henderson J, Custovic A (2018a) Distinguishing wheezing phenotypes in childhood: a pooled analysis of five birth cohorts. Eur Respir J 52:868
Oksel C, Haider S, Fontanella S, Frainay C, Custovic A (2018b) Classification of pediatric asthma: from phenotype discovery to clinical practice. Front Pediatr 6:258
Ownby DR, Johnson CC, Peterson EL (2002) Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 288(8):963–972
Palmer CN, Doney AS, Lee SP et al (2006) Glutathione S-transferase M1 and P1 genotype, passive smoking, and peak expiratory flow in asthma. Pediatrics 118(2):710–716
Panasevich S, Lindgren C, Kere J et al (2010) Interaction between early maternal smoking and variants in TNF and GSTP1 in childhood wheezing. Clin Exp Allergy 40(3):458–467
Park BS, Lee JO (2013) Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med 45:e66
Paternoster L, Standl M, Chen CM et al (2012) Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. Nat Genet 44(2):187–192
Pavord ID, Beasley R, Agusti A et al (2018) After asthma: redefining airways diseases. Lancet 391 (10118):350–400
Pecak M, Korosec P, Kunej T (2018) Multiomics data triangulation for asthma candidate biomarkers and precision medicine. OMICS 22(6):392–409
Prosperi MC, Marinho S, Simpson A, Custovic A, Buchan IE (2014) Predicting phenotypes of asthma and eczema with machine learning. BMC Med Genet 7(Suppl 1):S7
Reijmerink NE, Kerkhof M, Koppelman GH et al (2009) Smoke exposure interacts with ADAM33 polymorphisms in the development of lung function and hyperresponsiveness. Allergy 64 (6):898–904
Repapi E, Sayers I, Wain LV et al (2010) Genome-wide association study identifies five loci associated with lung function. Nat Genet 42(1):36–44
Rogers AJ, Brasch-Andersen C, Ionita-Laza I et al (2009) The interaction of glutathione S-transferase M1-null variants with tobacco smoke exposure and the development of childhood asthma. Clin Exp Allergy 39(11):1721–1729
Saglani S, Custovic A (2019) Childhood asthma: advances using machine learning and mechanistic studies. Am J Respir Crit Care Med 199(4):414–422
Sandilands A, Terron-Kwiatkowski A, Hull PR et al (2007) Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet 39(5):650–654
Savenije OE, Granell R, Caudri D et al (2011) Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. J Allergy Clin Immun 127(6):1505–12 e14

Savenije OE, Mahachie John JM, Granell R et al (2014) Association of IL33-IL-1 receptor-like 1 (IL1RL1) pathway polymorphisms with wheezing phenotypes and asthma in childhood. J Allergy Clin Immunol 134(1):170–177
Schaub B, Lauener R, von Mutius E (2006) The many faces of the hygiene hypothesis. J Allergy Clin Immunol 117(5):969–977; quiz 78
Schedel M, Depner M, Schoen C et al (2006) The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. Respir Res 7:91
Schoettler N, Rodriguez E, Weidinger S, Ober C (2019) Advances in asthma and allergic disease genetics: is bigger always better? J Allergy Clin Immunol 144(6):1495–1506
Simpson A, Martinez FD (2010) The role of lipopolysaccharide in the development of atopy in humans. Clin Exp Allergy 40(2):209–223
Simpson A, John SL, Jury F et al (2006) Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. Am J Respir Crit Care Med 174(4):386–392
Simpson A, Custovic A, Tepper R et al (2012) Genetic variation in vascular endothelial growth factor-a and lung function. Am J Respir Crit Care Med 185(11):1197–1204
Simpson A, Brough HA, Haider S, Belgrave D, Murray CS, Custovic A (2020) Early-life inhalant allergen exposure, filaggrin genotype and the development of sensitization from infancy to adolescence. J Allergy Clin Immunol 145(3):993–1001
Sitarik AR, Havstad S, Levin AM et al (2018) Dog introduction alters the home dust microbiota. Indoor Air 28(4):539–547
Sleiman PM, Flory J, Imielinski M et al (2010) Variants of DENND1B associated with asthma in children. N Engl J Med 362(1):36–44
Spycher B, Henderson J, Granell R et al (2012) Genome-wide prediction of childhood asthma and related phenotypes in a longitudinal birth cohort. Eur Respir J 40:507
Stein MM, Hrusch CL, Gozdz J et al (2016) Innate immunity and asthma risk in amish and hutterite farm children. N Engl J Med 375(5):411–421
Stein MM, Thompson EE, Schoettler N et al (2018) A decade of research on the 17q12-21 asthma locus: piecing together the puzzle. J Allergy Clin Immunol 142(3):749–764 e3
Strachan DP, Cook DG (1998) Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 53(3):204–212
Strachan DP, Wong HJ, Spector TD (2001) Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. J Allergy Clin Immunol 108 (6):901–907
Torgerson DG, Ampleford EJ, Chiu GY et al (2011) Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet 43(9):887–892
Van Eerdewegh P, Little RD, Dupuis J et al (2002) Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 418(6896):426–430
Van Wonderen KE, Van Der Mark LB, Mohrs J, Bindels PJ, Van Aalderen WM, Ter Riet G (2010) Different definitions in childhood asthma: how dependable is the dependent variable? Eur Respir J 36(1):48–56
Vercelli D, Martinez FD (2006) The Faustian bargain of genetic association studies: bigger might not be better, or at least it might not be good enough. J Allergy Clin Immunol 117(6):1303–1305
von Mutius E (2007) Allergies, infections and the hygiene hypothesis--the epidemiological evidence. Immunobiology 212(6):433–439
von Mutius E, Vercelli D (2010) Farm living: effects on childhood asthma and allergy. Nat Rev Immunol 10(12):861–868
Wang Z, Chen C, Niu T et al (2001) Association of asthma with beta(2)-adrenergic receptor gene polymorphism and cigarette smoking. Am J Respir Crit Care Med 163(6):1404–1409
Weidinger S, O'Sullivan M, Illig T et al (2008) Filaggrin mutations, atopic eczema, hay fever, and asthma in children. J Allergy Clin Immunol 121(5):1203–1209
Weinmayr G, Keller F, Kleiner A et al (2013) Asthma phenotypes identified by latent class analysis in the ISAAC phase II Spain study. Clin Exp Allergy 43(2):223–232

Weiss ST (2010) Lung function and airway diseases. Nat Genet 42(1):14–16
Williams LK, McPhee RA, Ownby DR et al (2006) Gene-environment interactions with CD14 C-260T and their relationship to total serum IgE levels in adults. J Allergy Clin Immunol 118 (4):851–857
Wojcik GL, Graff M, Nishimura KK et al (2019) Genetic analyses of diverse populations improves discovery for complex traits. Nature 570(7762):514–518
Wu H, Romieu I, Sienra-Monge JJ et al (2007) Parental smoking modifies the relation between genetic variation in tumor necrosis factor-alpha (TNF) and childhood asthma. Environ Health Perspect 115(4):616–622
Zambelli-Weiner A, Ehrlich E, Stockton ML et al (2005) Evaluation of the CD14/−260 polymorphism and house dust endotoxin exposure in the Barbados Asthma Genetics Study. J Allergy Clin Immunol 115(6):1203–1209
Zhang Y, Leaves NI, Anderson GG et al (2003) Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. Nat Genet 34 (2):181–186
Zhang YM, Willis-Owen SAG, Spiegel S, Lloyd CM, Moffatt MF, Cookson WOCM (2019) The ORMDL3 asthma gene regulates ICAM1 and has multiple effects on cellular inflammation. Am J Resp Crit Care 199(4):478–488

Epigenetic Mechanisms in Allergy Development and Prevention

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Abstract

There has been a substantial increase in the incidence and the prevalence of allergic disorders in the recent decades, which seems to be related to rapid environmental and lifestyle changes, such as higher exposure to factors thought to exert pro-allergic effects but less contact with factors known to be associated with protection against the development of allergies. Pollution is the most remarkable example of the former, while less contact with microorganisms, lower proportion of unprocessed natural products in diet, and others resulting from urbanization and westernization of the lifestyle exemplify the latter. It is strongly believed that the effects of environmental factors on allergy susceptibility and development are mediated by epigenetic mechanisms, i.e. biologically relevant biochemical changes of the chromatin carrying transcriptionally-relevant information but not affecting the nucleotide sequence of the genome. Classical epigenetic mechanisms include DNA methylation and histone modifications, for instance acetylation or methylation. In addition, microRNA controls gene expression at the mRNA level. Such epigenetic mechanisms are involved in crucial regulatory processes in cells playing a pivotal role in allergies. Those include centrally managing cells, such as T lymphocytes, as well as specific structural and effector cells in the affected organs, responsible for the local clinical presentation of allergy, e.g. epithelial or airway smooth muscle cells in asthma. Considering that allergic disorders possess multiple clinical (phenotypes) and mechanistic (endotypes) forms, targeted, stratified treatment strategies based on detailed clinical and molecular diagnostics are required. Since conventional diagnostic or therapeutic approaches do not suffice, this gap could possibly be filled out by epigenetic approaches.

Keywords

Allergic rhinitis · Allergy · Asthma · Atopic dermatitis · Atopy · DNA methylation · Environment · Epigenetics · Histone acetylation · MicroRNA

Abbreviations

A. lwoffii	*Acinetobacter lwoffii*
AD	Atopic dermatitis
AHR	Airway hyperresponsiveness
APCs	Antigen-presenting cells
AR	Allergic rhinitis
BET	Bromo- and extraterminal
CB	Cord blood
DEPs	Diesel exhaust particles
DNMT	DNA methyltransferase
DUBs	Deubiquitinating enzymes
FOXP3 (*FOXP3*)	Forkhead box protein 3 (gene)

GATA3	GATA binding protein 3
HATs	Histone acetyltransferases
HDACis	HDAC inhibitors
HDACs	Histone deacetylases
HDMs	Histone demethylases
HMTs	Histone methyltransferases
HRVs	Human rhinoviruses
IFN-γ (*IFNG*)	Interferon-γ (gene)
IgE	Immunoglobulin E
IL	Interleukin
ILCs	Innate lymphoid cells
MAP	Mitogen-activated protein
MBD	Methyl-CpG binding protein
MeCP2	Methyl-CpG binding protein 2
miRNA	microRNA
NECs	Nasal epithelial cells
NO_2	Nitrogen dioxide
NOS1–3	Nitric oxide 1–3 synthase genes
PAHs	Polycyclic aromatic hydrocarbons
PBMCs	PB mononuclear cells
PKCζ	Protein kinase C, zeta
RISC	RNA-induced silencing complex
RORC2 (RORγT)	RAR related orphan receptor C, isoform 2
SAM	S-adenosyl-l-methionine
SCFAs	Short-chain fatty acids
SO_2	Sulfur dioxide
TBX21	T-box 21 (T-bet)
TET1 (*TET1*)	Tet (10–11 translocation) methylcytosine dioxygenase 1 (gene)
TFs	Transcription factors
Th	T helper
Tregs	Regulatory T cells

1 Epigenetic Mechanisms

1.1 Epigenetics

The term "epigenetics" was originally used to refer to the complex gene–environment interactions participating in higher organisms in processes related to the development, differentiation, and maturation of cells, tissues, and organs. Nowadays, it refers rather to functional, inheritable or acquired, modifiable, biologically relevant biochemical changes of the chromatin carrying the information but not affecting the nucleotide sequence of the genome (Handy et al. 2011). "Classical" epigenetic changes comprise DNA methylation and histone modifications (Harb et al. 2016; Kabesch et al. 2010). Actively participating in several other processes

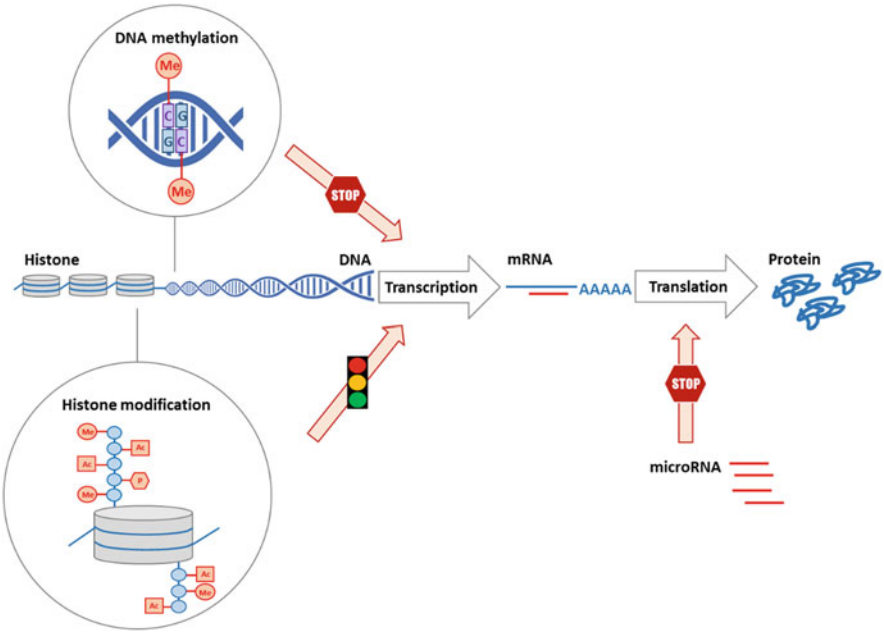

Fig. 1 Schematic representation of major epigenetic control mechanisms of gene expression, i.e. DNA methylation, histone modifications, and microRNA-mediated gene silencing. Methylation of a cytosine within the so-called CpG islands (5′-cytosine-phosphate-guanine-3′) located in a promoter region of a respective gene leads to downregulation of its transcription. Histone modifications exert varying effects on transcription, depending on their biochemical character. Silencing by microRNAs occurs at the mRNA level; microRNA binds to a target mRNA molecule, which blocks translation. *Me* methylation, *Ac* acetylation, *P* phosphorylation

as well, for example response to damage and DNA repair, classical epigenetic modifications are best known for their effects on the accessibility of certain genomic loci to transcription enzymes, regulating the expression of the respective genes, either in response to environmental impacts or as an important element of cellular homeostasis, activation or differentiation programs (Brook et al. 2015; Potaczek et al. 2017). In addition to classical epigenetic mechanisms, also some RNA molecules such as microRNAs (miRNAs) contribute to the post-transcriptional control of gene expression (Fig. 1) (Perry et al. 2015a; Piletič and Kunej 2016).

Environmental influences can be inherited between generations, most simply just by shared familial environment or other cultural influences. However, transmission of environmental experiences can also employ epigenetic mechanisms by two different types, i.e. transgenerational or intergenerational. Transgenerational inheritance occurs when the environmental factor directly affects the epigenetic patterns of germ cells of the parent or the fetus. The true intergenerational inheritance starts from the generation, whose germ cells have not been exposed to the relevant environmental factor (Mørkve Knudsen et al. 2018).

1.2 DNA Methylation

In mammals, DNA methylation is pivotal for a normal development and is related to multiple crucial processes such as aging, X-chromosome inactivation, genomic imprinting, repression of transposable elements, and carcinogenesis (Hackett and Surani 2013; Li and Zhang 2014). Biochemically, DNA methylation is a covalent transfer of a methyl group onto the C5 position of cytosine to form 5-methylcytosine. This typically occurs at cytosine nucleotides belonging to CpG dinucleotides, so-called CpG sites, i.e. DNA sequences where a cytosine nucleotide (C) is directly followed by a guanine nucleotide (G) (Jin et al. 2011; Moore et al. 2013). Several CpG sites sometimes cluster to form "CpG islands," which are typically located in regulatory elements influencing gene transcription, such as promoters or enhancers (Smith and Meissner 2013). The biochemical reaction of DNA methylation is catalyzed by a family of DNA methyltransferases (DNMTs) that represent enzymes transferring a methyl group from S-adenosyl-l-methionine (SAM) to the C5 position of the cytosine. DNMT1 targets hemimethylated dsDNA, which preserves the maintenance of DNA methylation patterns during DNA replication. DNMT3A and DNMT3B in turn target hemimethylated and unmethylated dsDNA thus creating de novo DNA methylation (Jurkowska and Jeltsch 2016; Moore et al. 2013; Smith and Meissner 2013).

Low DNA methylation levels in a promoter region are often, but not necessarily, associated with a higher transcriptional activity or at least a (higher) potential of the respective gene to become expressed, whereas high DNA methylation levels in the CpG island(s) of a promoter are usually associated with lower gene expression up to full gene silencing (Kabesch et al. 2010; Piletič and Kunej 2016). DNA methylation is thought to affect gene expression by influencing protein interactions with the affected gene sites. First, methylation of the CpG islands at the binding sites of specific transcription factors (TFs) is simply an obstacle for them to interact with the target DNA and thus hinder subsequent transcription. Second, there are indirect effects of the methylated CpGs mediated by the recruitment of proteins able to specifically bind methylated DNA such as methyl-CpG binding protein 2 (MeCP2) and other methyl-CpG binding domains (MBDs). These proteins secondarily recruit histone deacetylases (HDACs), histone methyltransferases (HMTs), and other biologically active molecules increasing chromatin compactness and hence are associated with gene repression (Della Ragione et al. 2016; Fasolino and Zhou 2017; Kim et al. 2009; Piletič and Kunej 2016).

1.3 Histone Modifications

There are several types of histone modifications, of which acetylation, methylation, phosphorylation, and ubiquitination have been most widely studied and found to be most important in the context of the regulation of chromatin structure and transcriptional activity. In addition to their contribution to epigenetic modulation of gene expression, histone modifications are also involved in other biological processes,

e.g. histone phosphorylation is best known for its role in DNA repair processes in response to cell damage (Bannister and Kouzarides 2011; Healy et al. 2012; Rossetto et al. 2012; Swygert and Peterson 2014).

Similarly to DNA methylation, posttranslational histone modifications do not change the nucleotide sequence of DNA but alter the availability of specific segments to the enzymatic machinery responsible for transcription. Biochemical reactions of histone modifications are generally catalyzed by specific enzymes that act mostly at amino acids such as lysines or arginines as well as serines, threonines, tyrosines and others positioned at the N-terminal tails of histone proteins (Morera et al. 2016; Swygert and Peterson 2014).

The acetylation status of the histones is controlled by two groups of enzymes exerting directly opposite effects, histone acetyltransferases (HATs) and HDACs. HATs catalyze the transfer of an acetyl group from acetyl-CoA to the terminal amino group of lysines in the histone tails. Addition of the negatively charged acetyl groups neutralizes a positive charge from the histones, which weakens the interaction between histones and negatively charged phosphate groups of the DNA. As a result, chromatin becomes less condense thereby increasing its accessibility to the transcriptional machinery. By contrast, removal of acetyl groups from histone tail lysine residues catalyzed by opposing HDACs reestablishes a positive charge on histones thus strengthening histone–DNA interaction. This leads to higher condensation of the chromatin associated with repression of gene expression. In conclusion, histone acetylation marks are generally permissive (Alaskhar Alhamwe et al. 2018; Angiolilli et al. 2017; Hull et al. 2016; Marmorstein and Zhou 2014).

In contrast, histone methylations maybe either transcriptionally permissive or repressive depending on the number of methyl groups added and the position of the targeted amino acid residues in the histone tail. Trimethylation at lysine 4 of histone H3 (H3K4me3) is related to transcriptional activation, whereas trimethylation at lysine 27 of the same histone (H3K27me3) is associated with transcriptional repression. Histone methylation is conducted by HMTs and histone demethylation by histone demethylases (HDMs). HMTs, being more specific than HATs and usually targeting a specific lysine residue, are capable of transferring up to three methyl groups from the cofactor SAM to a lysine or an arginine residue (Hyun et al. 2017; Kaniskan et al. 2018; Morera et al. 2016). Opposite to histone acetylations, histone methylations do not influence the electrostatic charge of histones but exert indirect effects through the effect on the recruitment and the binding of different regulatory proteins to chromatin instead.

Two types of enzymes with opposing modes of action control the histone phosphorylation status, i.e. phosphokinases adding phosphate groups and phosphatases removing them. The three best known functions of histone phosphorylations comprise chromatin condensation related to mitosis and meiosis, repair of DNA damage, and regulation of transcriptional activity. Histone phosphorylations establish a platform for the crosstalk between other histone marks, which ultimately leads to the altered chromatin status and its consequences (Bannister and Kouzarides 2011; Rossetto et al. 2012). Histone ubiquitination, another important histone modification, is conducted by histone ubiquitin ligases

and can be removed by ubiquitin-specific peptidases, so-called deubiquitinating enzymes (DUBs). While histone 2A monoubiquitination (H2Aub) is more frequently related to gene silencing, monoubiquitination of histone 2B (H2Bub) is rather associated with transcription activation. Similarly to histone phosphorylations, histone ubiquitinations also interact with other types of histone modifications (Cao and Yan 2012; Weake and Workman 2008; Zhang et al. 2017).

The epigenetic enzymes described above represent either "writers" that are the enzymes adding epigenetic marks to histone tails, such as HATs, HMTs, phosphokinases, and ubiquitin ligases, or "erasers" removing histone marks, including HDACs, HDMs, phosphatases, and DUBs. There is, however, a third group of the so-called "readers," comprising proteins containing bromodomains, chromodomains, or Tudor domains. These molecules can recognize the epigenetic marks created by writers as well as determine their functional effects. In addition, certain enzymes with primary activities different from epigenetic reading, for example some HATs, also possess bromodomains (Falkenberg and Johnstone 2014; Fujisawa and Filippakopoulos 2017).

1.4 MicroRNA

Some post-transcriptional control elements, such as miRNA molecules, also own epigenetic functions. They contribute to the epigenetic control of gene expression at various levels of the genome, for instance through their ability to target other epigenetic regulators, such as DNMTs or HDACs (Ha and Kim 2014; Kala et al. 2013).

miRNAs are about 22 nucleotides long noncoding RNA molecules. They demonstrate high abundancy in the genome; above 2,500 mature human miRNAs have been identified. In humans, mainly but not exclusively introns of both noncoding and coding transcripts encode canonical miRNA molecules. Transcription of miRNAs from genomic dsDNA occurs typically through RNA polymerase II. Subsequently, the immature transcripts undergo processing by two enzymes of the RNase III-type, namely Drosha and Dicer, operating in the cell nucleus or in the cytoplasm, respectively. Typically, only one strand of the mature miRNA becomes then incorporated into the RNA-induced silencing complex (RISC). Within RISC, miRNA is responsible for the specific recognition of and interaction with the respective target mRNA. RISC-bound mRNA molecules become degraded or their translation is suppressed in other ways, for instance by reducing the performance of the ribosomes. The level of complementarity between the miRNA and the targeted mRNA determines the magnitude of the silencing effect (Eulalio and Mano 2015; Piletič and Kunej 2016; Zhang et al. 2019).

The post-transcriptional regulation of gene expression by miRNAs was suggested to participate in buffering fluctuations in gene expression resulting from random intracellular modulations or from environmental influences as well as to contribute to the fine-tuning of transcriptional programs within bigger regulatory networks (Potaczek et al. 2017; Vidigal and Ventura 2015).

1.5 Epigenetic Crosstalk

Gene expression is ultimately governed by the cooperation of various epigenetic mechanisms that interact to induce or repress transcription (Moore et al. 2013; Tiffon 2018). This crosstalk involves all three major epigenetic mechanisms, including DNA methylation, histone modifications, and miRNA-associated silencing. Multiple relevant interactions have been reported. For instance, MBDs recognize methylated DNA and then recruit HDACs and HMTs, which remove acetyl and add methyl groups to the histone tail, respectively. Conversely, histone modifications can affect DNA methylation, too. For example, having recognized unmethylated histone H3 lysine 4, DNMT3-like factor stimulates de novo DNA methylation by recruiting DNMT3A and DNMT3B and enhancing their activity (Ben-Porath and Cedar 2001). Furthermore, DNA methylations and histone modifications regulate the expression not only of protein-encoding genes but also of genes encoding miRNAs. On the other hand, certain miRNA molecules control the expression of important protein regulators of the classical epigenetic mechanisms, such as DNMTs or HDACs (Moore et al. 2013; Sato et al. 2011).

2 Epigenetics and the Etiology of Allergic Disorders

2.1 Clinical Picture

Allergic diseases represent a wide spectrum of disorders caused by hypersensitivity, i.e. an inadequate reaction of the immune system to otherwise harmless environmental substances then called allergens. They can be roughly divided into (1) allergic conditions underlain by type I hypersensitivity where immunoglobulin E (IgE) plays a pivotal role and (2) those whose etiology is not associated with IgE. IgE-dependent allergic diseases include allergic asthma with the main manifestations occurring in the respiratory tract, allergic rhinitis (AR) or hay fever with the involvement of the upper airways, the extrinsic form of atopic dermatitis (AD) or eczema affecting skin, allergic conjunctivitis affecting eyes, and food allergy with the major local clinical symptoms appearing in the gastrointestinal tract (Gandhi et al. 2016; Potaczek et al. 2017). IgE-independent allergic disorders comprise contact dermatitis, intrinsic form of atopic dermatitis, non-allergic forms of asthma, and non-IgE-mediated food allergy. In fact, although it is still under debate and beyond the scope of this chapter, some of the latter diseases either do not have a real allergic background or their allergic mechanisms are not diagnostically covered by currently available methods, for instance local mucosal IgE or IgE to yet unknown allergens (Potaczek and Kabesch 2012). This heterogeneity is directly reflected by multiple described phenotypes, i.e. clinical presentations, of some allergic diseases, probably best known although still not fully characterized for asthma, AD, and AR. Furthermore, this heterogeneity gets even more complex when it comes to the characterization of the disease-underlying molecular mechanisms called endotypes (Czarnowicki et al. 2019; Miethe et al. 2018; Tomassen et al. 2016).

2.2 Mechanisms

Despite substantial mechanistic differences between particular allergic disorders and their various phenotypes, some core mechanisms involved in their etiopathogenesis have been described, at least among IgE-associated conditions. Those are underlain by (chronic) allergic inflammation with acute episodes leading to a clinical picture corresponding to the exacerbation of the respective allergic disease. Several types of cells are involved, including barrier cells such as epithelium, antigen-presenting cells (APCs), T cells, and B cells. Epithelial cells are not only a simple mechanical barrier between the organism and the environment and thus first-contact cells for environmental components including allergens but they also integrate innate and adaptive immune mechanisms. Their mediators secreted in response to contact with allergens contribute to the stimulation of APCs, e.g. dendritic cells, which themselves involve the whole adaptive immunity machinery by their activation of allergen-specific T cells (Gandhi et al. 2016; Lambrecht and Hammad 2015). The latter directly represent effector cells but, most importantly, they further orchestrate adaptive immune responses, e.g. by involvement of B cells responsible for synthesis of allergen-specific IgE molecules. T cells managing the adaptive immunity are $CD4^+$ T helper (Th) cells of different subpopulations. Depending on the set of cytokines they secrete, and thus the functional role they play, Th cells can be divided into Th1 (e.g., interferon-γ – IFN-γ), Th2, Th17 (interleukin-17 – IL-17), and regulatory T cells (Tregs; e.g., IL-10). Th2 cytokines include IL-4, IL-5, IL-13, and IL-9, the latter thought nowadays to be produced mostly by a separate subpopulation of the so-called Th9 cells (Garn 2018; Suarez-Alvarez et al. 2012). Th2 or better "type-2" (*see further*) cytokines play a crucial role in allergic or "type-2" inflammation. In brief, IL-4 induces differentiation of further Th2 cells and production of IgE by B cells, IL-13 activates mast cells, stimulates hyperplasia of goblet cells and mucus production as well as airway hyperresponsiveness (AHR), IL-5 activates eosinophils, while IL-9 contributes to proliferation of mast cells and mucus production (Potaczek et al. 2017). Direction of T cell differentiation is strictly regulated by the cytokine milieu, which determines the synthesis of the so-called master TFs preferentially expressed in one or the other T cell subpopulation. For example, in the presence of IL-4, naïve $CD4^+$ T cells express GATA binding protein 3 (GATA3), which determines their differentiation towards Th2 cells. Of importance, expression of master TFs and lineage-specific cytokines is strictly regulated by epigenetic mechanisms. Other master regulators include T-box 21 (TBX21, traditionally called "T-bet") for Th1 cells, RAR related orphan receptor C, isoform 2 (RORC2, traditionally called "RORγT") for Th17 cells, and forkhead box protein 3 (FOXP3) for Tregs (Pepper et al. 2017; Suarez-Alvarez et al. 2012). Th9 cells lack a single lineage-defining master regulator and their differentiation depends on the collective action of several TFs, which a kind of matches their specificity (Kaplan 2017). Th cytokines can be produced also by innate lymphoid cells (ILCs) that are innate immune cells belonging to the lymphoid linage but missing antigen specific receptors like in B or T cells. For example, ILC2s secrete Th2 cytokines, which are therefore referred to as "type-2" cytokines (Lambrecht and Hammad 2015).

2.3 Etiologic Model

There is no single locus explaining the genetic susceptibility to allergies. In other words, they have a polygenic character. Indeed, multiple susceptibility genes have been identified, some of which in a very consistent way. One remarkable example is chromosome 17q21 harboring *ORMDL3* and several other genes, which are associated with childhood asthma and have been replicated in multiple independent studies (Toncheva et al. 2015). Total serum IgE levels represent in turn a quantitative allergy-related trait the susceptibility loci for which have been identified in a replicated manner (Sharma et al. 2014). Still, in spite of this progress, it turned out to be impossible to explain the dramatic increase in the incidence and the prevalence of allergic disorders over the last several decades. One remarkable exemplification of this statement is the observation made in East Germany (the former German Democratic Republic). The incidence of allergic diseases in this region increased dramatically within only 20 years after the reunification of Germany, although the genetic profile of the population remained identical (Krämer et al. 2015). Thus, it became clear that other factors instead of genetics need to play a very important role here. Indeed, multiple epidemiologic studies robustly demonstrated strong associations of the explosion in allergies with westernization of the lifestyle and other rapid environmental changes. Those include both, an increase in "bad" factors, such as different kinds of pollution related to urbanization and industrialization, and a decrease in "good" factors, including living in natural environments and/or eating traditional diets (Fig. 2) (Garn and Renz 2007; Renz et al. 2011). Thus, on the epidemiological as well as molecular levels, allergies represent a kind of a prototypic example of gene–environment interactions-related disorders, the underlying mechanisms of which involve a variety of epigenetic mechanisms (Harb et al. 2016; Turner 2017).

An important feature characterizing the epigenetic effects of diverse environmental exposures is the existence of a time window, within which such factors exert their crucial effects on biological features. In the case of allergies these are the in utero and neonatal (first year of life) developmental periods. This "window of opportunity" would be the best time for the "good" factors to exert their major protective effects, while "bad" influences would increase the risk of disease development, the most within the "window of susceptibility" or "vulnerability" (Ho et al. 2012; Potaczek et al. 2017). Prenatal and neonatal periods can also become an ideal "window of intervention," for example with the so-called epigenetic diets, aiming to prevent or even revert (potential) adverse effects of "bad" factors (Fig. 2) (Li et al. 2019). However, this does not mean that environmental exposures or dietary interventions are unable to epigenetically affect mechanisms involved in the development of allergic disorders outside of those time ranges.

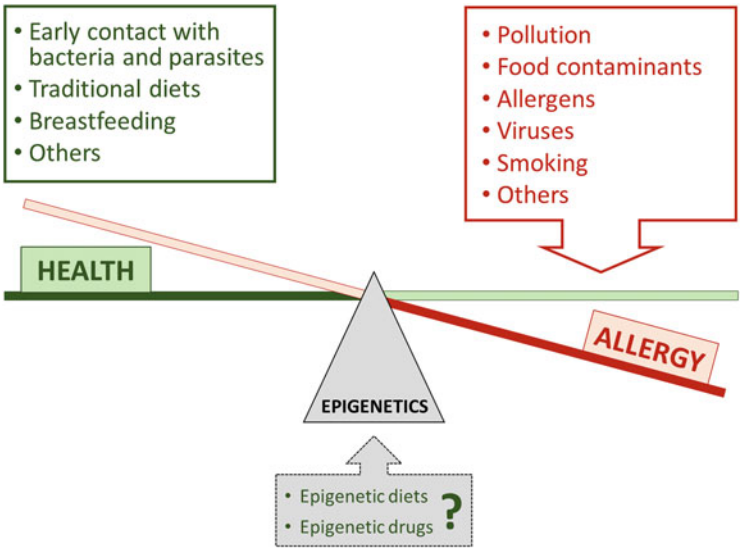

Fig. 2 The effects of the environment on the development of allergies mediated by molecular mechanisms involved in epigenetics. Unfavorable (upper left side) and favorable (upper right side) environmental factors influencing the balance between health and disease. Overall increase in unfavorable influences, accompanied by the decrease in beneficial factors, is related to environmental pollution and lifestyle changes both resulting from industrialization and urbanization. The imbalance fostering allergy development could possibly be counterbalanced by epigenetic interventions (lower right side)

2.4 "Bad" Environmental Influences

Although increasing hygiene and decreasing number of children within families limit the contact with some pathogens, at the same time, urbanization with public transport, kindergartens, large schools, and others all increase the chance for children to get infected by viruses, especially of the respiratory or gastrointestinal types. Hence, considering that epidemiologic studies have almost uniformly shown the association between early-life infections with airborne viruses such as respiratory syncytial virus or human rhinoviruses (HRVs) and the higher risk of asthma development, the above-mentioned civilization-related changes could indeed contribute to the increased asthma prevalence especially when combined with atopic predisposition (Holt et al. 2012; Potaczek et al. 2019). One possible mechanism explaining the association between respiratory tract virus infections and the development of asthma could be that airborne viruses, by trying to evade Th1/type-1 immune responses, somehow skew the balance towards Th2/type-2 immunity favoring in turn the development of allergies. Based on observations of epigenetic changes evoked by infections with some other non-respiratory viruses such as human papilloma virus (Cicchini et al. 2016) one could speculate that specifically airborne viruses may increase the risk of allergic asthma development through epigenetic mechanisms.

Indeed, the results of a recent study analyzing the effects of experimental HRVs infection of ex vivo cultured nasal epithelial cells (NECs) seem to confirm this hypothesis by showing in children with asthma specific modifications of DNA methylation accompanied by altered mRNA expression in genes involved in asthma pathogenesis and antiviral immune responses (Pech et al. 2018). Also other epigenetic mechanisms may contribute as suggested by the observation that HRVs infection in young children leads to changes in the airway secretory miRNome (Gutierrez et al. 2016). Furthermore, experimental ex vivo infection of bronchial epithelial cells obtained from asthmatics with influenza A virus has been shown to result in dysregulation of miRNAome subsequently affecting the expression of histone modifying enzyme HDAC4 (Moheimani et al. 2018).

Increasing air pollution levels resulting from industrialization and urbanization have been shown to be associated with strongly elevated risk of allergies, especially asthma. Recent studies have clearly demonstrated the involvement of epigenetic mechanisms, especially DNA methylation, in mediating negative health effects of air pollution (Jenerowicz et al. 2012; Ji et al. 2016; Zhang et al. 2018). For example, higher prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) has been demonstrated in cord blood (CB) leukocytes to correlate with increased DNA methylation at the promoter of the IFN-γ-encoding gene (*IFNG*) (Tang et al. 2012). Likewise, in Tregs isolated from peripheral blood mononuclear cells (PBMCs), greater PAH exposure has been associated with higher DNA methylation levels at the promoter of the FOXP3-encoding gene (*FOXP3*). Moreover, this effect was more prominent in asthmatic children compared to their non-asthmatic counterparts (Hew et al. 2015). Higher DNA methylation in the 5′ region of *FOXP3* has also been found in saliva samples in relation to diesel exhaust particles (DEPs) exposure, and the risk of asthma, persistent wheezing, or early transient wheezing was increased in children with higher levels of *FOXP3* DNA methylation (Brunst et al. 2013). Experimental lung exposure to allergens, DEPs, or both concomitantly had only minimal effects on the bronchial epithelial DNA methylome of the participating individuals, while a crossover exposure, i.e. allergen after DEPs or DEPs following allergen, 4 weeks after the initial exposure resulted in both cases in substantial epigenetic changes of potential biological relevance. This suggests that the initial insult can prime the bronchial epithelial DNA methylome for the second (Clifford et al. 2017). In another study, compared to filtered air inhalation, DEPs exposure was associated in asthmatic patients with altered levels of total blood cell miRNAs having plausible biological functions (Yamamoto et al. 2013). Exposure to particulate matter air pollution, especially to its fine fraction, correlated in children with DNA methylation of nitric oxide synthase genes (*NOS1–3*) in buccal brushings. Although DNA methylation at *NOS2* was also associated with current wheeze in the whole study group, no direct relationship between DNA methylation and asthma was observed; only some differential DNA methylation was observed for asthma medications or current wheezing in the asthmatic children subgroup (Breton et al. 2012). In a comparison of asthmatic and non-asthmatic siblings, lower NECs DNA methylation at the promoter of the tet (10–11 translocation) methylcytosine dioxygenase 1 (TET1) gene (*TET1*) was associated with the presence of the disease.

On the contrary, traffic-related air pollution exposure at participants' current homes increased DNA methylation at the *TET1* promoter (Somineni et al. 2016). TET1 is one of the so-called erasers, which are the enzymes actively removing DNA methylation (Huang et al. 2019). The biologic processes following allergen exposure in predisposed individuals seem to be at least partly mediated by epigenetic mechanisms (Nestor et al. 2014; North et al. 2018). Interestingly, it has been demonstrated that short-term exposure of oak pollen to high concentrations of nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) increases its fragility and disruption, leading this way to the subsequent release of pollen cytoplasmic granules into the atmosphere. This in turn increases the bioavailability of airborne pollen allergens to sensitized individuals, and thus potentially contributes to the higher prevalence of allergies observed these days (Ouyang et al. 2016).

Exposure to cigarette smoke is at the same time a widely recognized strong epigenetic modifier (Joehanes et al. 2016) and a well-defined risk factor of allergies, such as asthma (Vardavas et al. 2016) and AD (Wang et al. 2008). The influence of cigarette smoke on DNA methylation levels has been observed in different exposure settings including active smoking as well as passive prenatal or postnatal tobacco smoke exposure. Of importance, cigarette smoke-induced changes in DNA methylation are characterized by long persistence (Joubert et al. 2016).

2.5 "Good" Environmental Influences

It is meanwhile well accepted that, in order to function properly and thus guarantee health of the organism over the whole life span, the immune system, and especially its adaptive part, needs to be appropriately developed and trained early in life, i.e. within the "window of opportunity." In this regard, a bunch of very interesting epidemiologic studies comparing developing and developed countries have been conducted (McDade 2012). Those demonstrated cumulatively that living in developing countries is characterized by frequent early contacts with microorganisms such as bacteria or parasites often associated with infections and infection-related acute inflammatory processes. In this early-life education process, the adaptive immune system also learns to differentiate between harmful and harmless influences with mounting appropriate responses to the former and development of active tolerance to the latter. Later in life then, people in such countries typically possess the adaptive immune repertoire required to fulfill its protective function while harmless impacts are neglected. On the contrary, in the developed countries, sterile life conditions lead to a lack of microbial stimulation during fetal and neonatal periods, which leads to the suboptimal development of the immune system, and especially but not only its adaptive part. As a result, subjects living in the developed countries suffer more frequently from inflammatory conditions underlain by allergic, autoimmune, unnecessarily chronified acute inflammation, and otherwise inadequate response of the immune system (McDade 2012). This general mechanism has also its specific versions, such as the prototypic hygiene hypothesis in the field of allergy (Garn and Renz 2007).

Hygiene hypothesis can be very nicely exemplified by the observations made in small Alpine villages. It has been found that living in a traditional farming environment typical for such villages is associated with a (subsequent) substantial reduction in the risk of allergic diseases (von Mutius and Radon 2008). Several candidate factors underlying the protective effects of farming have been proposed, including the exposure to the so-called farm-dust, direct contact with farm animals, consumption of raw cow's milk, and others (von Mutius and Radon 2008). Interestingly, in most of the cases of these factors, at least part of the effect is thought to be triggered by the farm bacteria and, even more interestingly, those seem to be epigenetically mediated.

Several bacteria have been identified in the farming environment, such as *Staphylococcus sciuri* W620, *Lactococcus lactis* G121, *Acinetobacter lwoffii* (*A. lwoffii*) F78, and others. These microorganisms have been demonstrated to hamper allergic responses in mouse models and to favor Th1 immunity in vitro (Conrad et al. 2009; Debarry et al. 2007; Ege et al. 2012; Hagner et al. 2013). In addition, IFN-γ-dependent transmaternal protection against allergic asthma development has been demonstrated for maternal *A. lwoffii* exposure. This effect has been shown to be driven, at least in part, by histone acetylation at the *IFNG* promoter in $CD4^+$ T cells (Brand et al. 2011). Recently, it has been found that IL-6, a central innate immunity cytokine, plays a crucial and specific role in mediating the development of protective, anti-allergic effects of *A. lwoffii*. This, together with the observation that IL-6 might be generally important for skewing the adaptive immunity towards non-allergic, type-1 responses (Potaczek et al. 2018; Schleich et al. 2019), confirms the findings obtained in studies comparing inflammatory response patterns between developing and developed countries, already shortly discussed above (McDade 2012). In a very recent study (Krusche et al. 2019), PBMCs from asthmatic and healthy children were in turn cultured with or without stimulation with dust extracts from German and Finnish farms (Schuijs et al. 2015). Both, histone acetylation and mRNA levels of *DUSP1*, the negative regulator of mitogen-activated protein (MAP) kinase signaling, were lower in PBMC of asthmatic children. Stimulation with farm-dust extracts upregulated anti-inflammatory *DUSP1* expression and downregulated proinflammatory MAP kinases on mRNA and protein levels in various cell populations (Krusche et al. 2019). Finally, also our own gut microbiome can affect atopic sensitization and allergic inflammation, possibly through the effects of short-chain fatty acids (SCFAs) on the epigenetic regulation of Tregs (Smith et al. 2013; Vonk et al. 2019).

The consumption of raw cow's milk, another factor thought to mediate anti-allergic effects of farming although not only or not necessarily due to its microbial content (Brick et al. 2016; Van Neerven and Savelkoul 2019), is also decreasing in parallel to the decrease in farming. Independently of what are the exact substances responsible for the protective effects of unprocessed cow's milk, the epigenetic mechanism of DNA methylation has been shown to be involved, with the prominent example of *FOXP3* demethylation and subsequent activation of Treg cells (Lluis et al. 2014; Schaub et al. 2009). Moreover, recent studies in mouse models demonstrated that also histone acetylations (Abbring et al. 2019a, b) and miRNAs

(Kirchner et al. 2016) affecting or at least potentially affecting the expression of important allergy-related immune genes can contribute to the protective effects of raw cow's milk consumption.

2.6 Epigenetics and Allergy-Associated Genetic Variability

Although epigenetic modifications per se do not affect the genetic code, they can be "used" to mediate the effects of the genetic polymorphisms, which occurs also in the context of allergic disorders. For example, the association between one genetic variant upstream of the *MTRN1A* locus and asthma/AR comorbidity has been found to be mediated by differential *MTRN1A* DNA methylation (Sarnowski et al. 2016). Likewise, the polymorphism located in *RAD50*, within chromosome 5q31 harboring also the genes encoding three type 2 cytokines, IL-5, IL-13, and IL-4, has been shown to influence serum IgE levels through altered DNA methylation (Schieck et al. 2014).

3 Possible Practical Applications of Epigenetics in Allergies

3.1 Diagnostics

While disease phenotypes are identified by the complexity of clinical characteristics, molecular phenotypes additionally involve pathobiologic features and biomarker constellations. Moreover, endotypes are characterized by the identification of crucial underlying pathobiologic processes the inhibition of which results in significant improvement of the clinical features of the disease (Ray et al. 2015). Although a substantial progress has been achieved in the field of molecular diagnostics of allergic disorders and their different forms (Czarnowicki et al. 2019; Miethe et al. 2018; Tomassen et al. 2016), novel and more robust biomarkers need to be established to provide patients with the optimal diagnosis of their (molecular) phenotype/endotype accompanied by a stratified treatment. Based on the current status of knowledge, epigenetic markers may possess the potential to fill this diagnostic gap (Table 1).

Starting from histone modifications, in certain subgroups of a prospective birth cohort, placental histone acetylation levels at several allergy-related immune genes were able to partly predict the risk of sensitization to food allergens or aeroallergens later in childhood (Harb et al. 2019). A very elegant study comparatively analyzing epigenome-wide histone methylation (H3K4me2) profiles in naïve, Th1, and Th2 $CD4^+$ T cells obtained from asthmatics and non-asthmatics identified differential enrichment in 200 gene regions, 163 of which were Th2-specifc and 84 comprised binding sites for TFs involved in T cell differentiation (Seumois et al. 2014). Another very interesting study on $CD4^+$ T cells showed that DNA methylation patterns can be used to clearly distinguish between patients suffering from AR and healthy individuals. In addition, such DNA methylation-based stratification outperformed

Table 1 Selected studies showing the diagnostic potential of assessing the epigenetic marks in allergies

Epigenetic mark	Allergic disorder	Biological material; subjects (if not adults)	Major result	Publication
DNA methylation	Seasonal allergic rhinitis	$CD4^+$ T cells	Clear separation between patients and controls	Nestor et al. (2014)
DNA methylation	Asthma	Peripheral blood monocytes	Differential association with inflammatory phenotypes of asthma	Gunawardhana et al. (2014)
DNA methylation	Food sensitization	PBMCs corrected for cell heterogeneity; infants	Very good prediction of oral food challenge outcomes	Martino et al. (2015)
DNA methylation	Allergic rhinitis	Lymphocyte-enriched PBMCs	Good prediction of the symptom severity after controlled allergen exposure	North et al. (2018)
DNA methylation	Asthma, allergies	Nasal swabs; teenagers	Association with asthma, allergies, and their laboratory or clinical measures	Cardenas et al. (2019)
DNA methylation	Atopic dermatitis with eczema herpeticum	Whole blood	Indirect association with disease severity	Boorgula et al. (2019)
Histone methylation	Asthma	Naïve, Th1, and Th2 $CD4^+$ T cells	Differentiation between patients and controls	Seumois et al. (2014)
Histone acetylation	Allergic sensitization	Placenta; infants/children	Prediction of the risk of sensitization to food allergens or aeroallergens	Harb et al. (2019)
MicroRNA	Asthma	Serum; children	Prediction of the asthma exacerbations	Kho et al. (2018)
MicroRNA	Cow's milk allergy	PBMCs; children	Case–control differential expression	D'Argenio et al. (2018)
MicroRNA	Asthma	Plasma; children	Association with and good predictive profile for asthma and its severity	Karam and Abd Elrahman (2019)
MicroRNA	Asthma	Peripheral eosinophils, serum	Biomarker potential for asthma diagnosis and disease severity ranking	Rodrigo-Muñoz et al. (2019)

PBMCs peripheral blood mononuclear cells, *Th* T helper

mRNA-based separation. Further, due to higher stability of methylation signatures, establishing a reliable diagnosis was possible even outside the pollen season (Nestor et al. 2014). Moreover, DNA methylation at several loci such as *MUC4* in lymphocyte-enriched PBMCs demonstrated the potential to predict severity of the symptoms in grass pollen-exposed AR patients subjected to a controlled allergen challenge (North et al. 2018). Likewise, DNA methylation signatures analyzed in PBMCs corrected for cell population heterogeneity obtained from food-sensitized infants clearly outperformed skin prick testing and allergen-specific IgE in predicting the outcomes of the oral food challenge (Martino et al. 2015). DNA methylation analyzed in peripheral blood monocytes was able to differentiate between inflammatory asthma phenotypes (Gunawardhana et al. 2014), whereas whole blood DNA methylation levels indirectly associated with severity of AD with eczema herpeticum (Boorgula et al. 2019). Nasal DNA methylation variations have also been studied in the context of allergies (Zhang et al. 2018), showing that they have a potential to represent a sensitive biomarker for allergic asthma, airway inflammation, and other allergic phenotypes or their measures (Cardenas et al. 2019). Finally, also miRNAs, especially plasma/serum exosomal and free-circulating miRNAs, emerged as promising diagnostic tools for allergies (Tost 2018), as demonstrated by several very recent studies on asthma (Karam and Abd Elrahman 2019; Kho et al. 2018; Rodrigo-Muñoz et al. 2019) or cow's milk allergy (D'Argenio et al. 2018).

Even though the selection of the studies discussed above is subjective, it allows drawing some general conclusions. First, studies involving DNA methylation and, very recently, miRNAs outnumber those targeting histone modifications. Second, blood leukocyte types of varying sorting levels or DNA from nasal scrapings are the most common materials used for DNA methylation, most probably not only due to pathobiologic importance but also because of easy accessibility. For the same reasons, plasma or serum seems to be the most commonly used material for miRNA-related studies (Table 1).

3.2 Treatment

The proportions look rather different in case of anti-allergic interventions involving epigenetic mechanisms, with most of the studies either directly or indirectly targeting histone modifications here (Table 2).

Several studies tested broad-spectrum or specific HDAC inhibitors (HDACis), both in animal models and in ex vivo cultured human tissues. Treatment with a broad-spectrum HDACis, JNJ-26481585, restored the integrity of ex vivo cultured NECs isolated from AR patients. Besides, application of this HDACis to mice subjected to a house dust mite-based model of allergic asthma prevented them from developing bronchial hyperreactivity or allergic airway inflammation (Steelant et al. 2019). Beneficial effects of HDACis have also been observed in ovalbumin-based murine model of allergic asthma (Ren et al. 2016). Usage of trichostatin A, another broad-spectrum HDACis, was able to reduce the symptoms of AD-like

Table 2 Selected studies on the therapeutic or preventive potential of targeting the epigenetic signatures in allergies

Epigenetic mechanism	Study model, material	Type of intervention	Major result	Publication
DNA methylation	Murine OVA-model of allergic asthma; $CD4^+$ T cells	5-azacytidine, a DNA methylation inhibitor; in vivo	Inhibition of the increase in DNA methylation at the interferon-γ gene promoter by 5-azacytidine, with accompanying beneficial effects on the phenotype	Brand et al. (2012)
DNA methylation	Murine OVA-model of food (peanut) allergy, T cells	EPIT	DNA methylation patterns at the important T cell loci in the specific T cell compartments possibly explaining EPIT effects and sustainability	Mondoulet et al. (2019)
Histone acetylation	Murine model of AD, $CD4^+$ T cells	TSA, a broad-spectrum HDACis; in vivo	Reduction in the hallmarks of AD-like dermatitis; inhibition of IL-4 production by $CD4^+$ T cells	Kim et al. (2010)
Histone acetylation	Murine OVA-model of allergic asthma, $CD4^+$ T cells	Farm-derived gram-negative bacterium *Acinetobacter lwoffii* F78; in vivo, transmaternal effects	Protection against asthma in progeny due to prenatal bacterium administration mediated by preservation of histone H4 acetylation at the interferon-γ gene	Brand et al. (2011)
Histone acetylation	Asthma patients, ASMCs	PFI-1, I-BET and JQ-1, BET inhibitors; ex vivo	Reduction in IL-8 secretion	Clifford et al. (2015)
Histone acetylation	Asthma patients, ASMCs	JQ1/SGCBD01 and I-BET762, BET bromodomain mimics; ex vivo	Inhibition of FCS-/TGF-β-induced proliferation as well as IL-6 and IL-8 expression	Perry et al. (2015b)
Histone acetylation	Murine OVA-model of chronic allergic asthma, ASMCs	TSA-HCl and PCI-34051, selective HDACis; givinostat, a broad-spectrum HDACis; in vivo	Reduction in airway inflammation, airway remodeling, and airway hyperresponsiveness; reduction in synthesis of contractile proteins	Ren et al. (2016)

(continued)

Table 2 (continued)

Epigenetic mechanism	Study model, material	Type of intervention	Major result	Publication
Histone acetylation	Pregnant mothers, CB $CD4^+$ T cells	Prenatal fish oil exposure (maternal fish oil intake); in vivo	Differential H3 and/or H4 histone acetylation levels at important allergy-related immune genes	Harb et al. (2017)
Histone methylation	Murine house DM-model of allergic asthma	GSK-J4, a selective H3K27me3 demethylation inhibitor; in vivo	Amelioration of airway hyperresponsiveness, airway inflammation and remodeling	Yu et al. (2018)
Histone acetylation	Pregnant mothers, placenta	Maternal olive oil usage or maternal fish consumption; in vivo	Differential H3 and/or H4 histone acetylation levels at important allergy-related immune genes	Acevedo et al. (2019)
Histone acetylation	AR patients, primary NECs; murine model of house DM-induced allergic asthma	JNJ-26481585, a broad-spectrum HDACis; ex vivo/ in vivo	Restored integrity of NECs after treatment; reduced symptoms in treated mice	Steelant et al. (2019)
Histone acetylation	Murine model of food allergy, $CD4^+$ T cells, MLNs	Pretreatment with raw vs. shop milk; in vivo	Protective effects of raw milk accompanied by ultimately lower H3/H4 histone acetylation levels at Th2 genes	Abbring et al. (2019b)

OVA ovalbumin, *EPIT* epicutaneous immunotherapy, *AD* atopic dermatitis, *TSA* trichostatin A, *HDACis* histone deacetylase inhibitor, *IL* interleukin, *ASMCs* airway smooth muscle cells, *BET* bromo- and extraterminal, *FCS* fetal calf serum, *TGF-β* transforming growth factor β, *TSA-HCl* Tubastatin A HCl, *CB* cord blood, *DM* dust mite, *AR* allergic rhinitis, *NECs* nasal epithelial cells, *MLNs* mesenteric lymph nodes, *Th* T helper

dermatitis in mice, which was accompanied by the inhibition of IL-4 production by $CD4^+$ T cells (Kim et al. 2010). Ex vivo treatment of asthmatic and non-asthmatic airway smooth muscle cells with bromo- and extraterminal (BET) inhibitors (Clifford et al. 2015) or mimics (Perry et al. 2015b) led in either case to beneficial effects including reduced secretion of inflammatory cytokines. Histone acetylation has been targeted also indirectly, with the usage of prenatal diets or diet supplements known to possess protective capabilities against the development of allergic disorders. For example, prenatal treatment with fish oil was associated in CB $CD4^+$ T cells with histone acetylation changes at the promoter of the gene encoding protein kinase C, zeta (PKCζ) (Harb et al. 2017), thereby possibly explaining the previously observed association of anti-allergic effects of fish oil with CB T cell PKCζ expression (D'Vaz et al. 2012). Maternal fish consumption or olive oil usage

during pregnancy was associated with alterations of histone acetylation levels at the promoters of important allergy-related immune genes in placentas obtained from subgroups of a prospective birth cohort study (Acevedo et al. 2019). As already mentioned above, the anti-allergic effects of the cowshed bacterium *A. lwoffii* (Brand et al. 2011) or unprocessed cow's milk (Abbring et al. 2019b) have, at least partly, been attributed to their histone acetylation modifying effects. Regarding histone methylation, application of GSK-J4, a selective H3K27me3 demethylation inhibitor, reduced airway hyperresponsiveness, inflammation, and remodeling in a mouse model of allergic asthma (Yu et al. 2018). Increase in $CD4^+$ T cell DNA methylation at the *IFNG* promoter, otherwise observed in a murine model of allergic asthma, was in turn blocked by the DNA methylation inhibitor 5-azacytidine, which was accompanied by beneficial effects on the phenotype (Brand et al. 2012). Finally, it seems possible that the (long-lasting) effects of epicutaneous immunotherapy are underlain by alterations of DNA methylation patterns at important T cell loci (Mondoulet et al. 2019).

These and other, even more modern approaches such as epigenome editing using the CRISPR/dCas9 system represent promising new anti-allergic strategies (Alaskhar Alhamwe et al. 2018; Tost 2018), with further studies certainly required.

4 Concluding Remarks

Epigenetic mechanisms have been identified to significantly contribute to the etiopathogenesis, development, phenotypic heterogeneity, and clinical course of allergic disorders. They do this by mediating environmental influences and by participating in the physiology and pathophysiology of cells playing a major role in allergies. Those are especially T cells as systemic adaptive immunity "managers," and local cells in the affected organs such as airway epithelial or airway smooth muscle cells in the case of respiratory allergies. Therefore, epigenetic mechanisms represent a promising target for novel diagnostic methods and therapeutic approaches in the field of allergies.

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References

Abbring S, Ryan JT, Diks MAP, Hols G, Garssen J, van Esch BCAM (2019a) Suppression of food allergic symptoms by raw cow's milk in mice is retained after skimming but abolished after heating the milk-a promising contribution of alkaline phosphatase. Nutrients 11(7):1499. https://doi.org/10.3390/nu11071499

Abbring S, Wolf J, Ayechu-Muruzabal V, Diks MAP, Alhamwe BA, Alhamdan F et al (2019b) Raw cow's milk reduces allergic symptoms in a murine model for food allergy-a potential role for epigenetic modifications. Nutrients 11(8):1721. https://doi.org/10.3390/nu11081721

Acevedo N, Frumento P, Harb H, Alashkar Alhamwe B, Johansson C, Eick L et al (2019) Histone acetylation of immune regulatory genes in human placenta in association with maternal intake of olive oil and fish consumption. Int J Mol Sci 20(5):1060. https://doi.org/10.3390/ijms20051060

Alaskhar Alhamwe B, Khalaila R, Wolf J, von Bülow V, Harb H, Alhamdan F et al (2018) Histone modifications and their role in epigenetics of atopy and allergic diseases. Allergy Asthma Clin Immunol 14:39. https://doi.org/10.1186/s13223-018-0259-4

Angiolilli C, Baeten DL, Radstake TR, Reedquist KA (2017) The acetyl code in rheumatoid arthritis and other rheumatic diseases. Epigenomics 9(4):447–461. https://doi.org/10.2217/epi-2016-0136

Bannister AJ, Kouzarides T (2011) Regulation of chromatin by histone modifications. Cell Res 21 (3):381–395. https://doi.org/10.1038/cr.2011.22

Ben-Porath I, Cedar H (2001) Epigenetic crosstalk. Mol Cell 8(5):933–935. https://doi.org/10.1016/s1097-2765(01)00399-9

Boorgula MP, Taub MA, Rafaels N, Daya M, Campbell M, Chavan S et al (2019) Replicated methylation changes associated with eczema herpeticum and allergic response. Clin Epigenetics 11(1):122. https://doi.org/10.1186/s13148-019-0714-1

Brand S, Teich R, Dicke T, Harb H, Yildirim AÖ, Tost J et al (2011) Epigenetic regulation in murine offspring as a novel mechanism for transmaternal asthma protection induced by microbes. J Allergy Clin Immunol 128(3):618–25.e1-7. https://doi.org/10.1016/j.jaci.2011.04.035

Brand S, Kesper DA, Teich R, Kilic-Niebergall E, Pinkenburg O, Bothur E et al (2012) DNA methylation of TH1/TH2 cytokine genes affects sensitization and progress of experimental asthma. J Allergy Clin Immunol 129(6):1602–10.e6. https://doi.org/10.1016/j.jaci.2011.12.963

Breton CV, Salam MT, Wang X, Byun H-M, Siegmund KD, Gilliland FD (2012) Particulate matter, DNA methylation in nitric oxide synthase, and childhood respiratory disease. Environ Health Perspect 120(9):1320–1326. https://doi.org/10.1289/ehp.1104439

Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G et al (2016) ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk. J Allergy Clin Immunol 137(6):1699–1706.e13. https://doi.org/10.1016/j.jaci.2015.10.042

Brook PO, Perry MM, Adcock IM, Durham AL (2015) Epigenome-modifying tools in asthma. Epigenomics 7(6):1017–1032. https://doi.org/10.2217/epi.15.53

Brunst KJ, Leung Y-K, Ryan PH, Khurana Hershey GK, Levin L, Ji H et al (2013) Forkhead box protein 3 (FOXP3) hypermethylation is associated with diesel exhaust exposure and risk for childhood asthma. J Allergy Clin Immunol 131(2):592–594.e1-3. https://doi.org/10.1016/j.jaci.2012.10.042

Cao J, Yan Q (2012) Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer. Front Oncol 2:26. https://doi.org/10.3389/fonc.2012.00026

Cardenas A, Sordillo JE, Rifas-Shiman SL, Chung W, Liang L, Coull BA et al (2019) The nasal methylome as a biomarker of asthma and airway inflammation in children. Nat Commun 10 (1):3095. https://doi.org/10.1038/s41467-019-11058-3

Cicchini L, Westrich JA, Xu T, Vermeer DW, Berger JN, Clambey ET et al (2016) Suppression of antitumor immune responses by human papillomavirus through epigenetic downregulation of CXCL14. MBio 7(3):e00270. https://doi.org/10.1128/mBio.00270-16

Clifford RL, Patel JK, John AE, Tatler AL, Mazengarb L, Brightling CE, Knox AJ (2015) CXCL8 histone H3 acetylation is dysfunctional in airway smooth muscle in asthma: regulation by BET. Am J Physiol Lung Cell Mol Physiol 308(9):L962–L972. https://doi.org/10.1152/ajplung.00021.2015

Clifford RL, Jones MJ, MacIsaac JL, McEwen LM, Goodman SJ, Mostafavi S et al (2017) Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. J Allergy Clin Immunol 139(1):112–121. https://doi.org/10.1016/j.jaci.2016.03.046

Conrad ML, Ferstl R, Teich R, Brand S, Blümer N, Yildirim AO et al (2009) Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe Acinetobacter lwoffii F78. J Exp Med 206(13):2869–2877. https://doi.org/10.1084/jem.20090845

Czarnowicki T, He H, Krueger JG, Guttman-Yassky E (2019) Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 143(1):1–11. https://doi.org/10.1016/j.jaci.2018.10.032

D'Argenio V, Del Monaco V, Paparo L, de Palma FDE, Nocerino R, D'Alessio F et al (2018) Altered miR-193a-5p expression in children with cow's milk allergy. Allergy 73(2):379–386. https://doi.org/10.1111/all.13299

D'Vaz N, Ma Y, Dunstan JA, Lee-Pullen TF, Hii C, Meldrum S et al (2012) Neonatal protein kinase C zeta expression determines the neonatal T-cell cytokine phenotype and predicts the development and severity of infant allergic disease. Allergy 67(12):1511–1518. https://doi.org/10.1111/all.12027

Debarry J, Garn H, Hanuszkiewicz A, Dickgreber N, Blümer N, von Mutius E et al (2007) Acinetobacter lwoffii and Lactococcus lactis strains isolated from farm cowsheds possess strong allergy-protective properties. J Allergy Clin Immunol 119(6):1514–1521. https://doi.org/10.1016/j.jaci.2007.03.023

Della Ragione F, Vacca M, Fioriniello S, Pepe G, D'Esposito M (2016) MECP2, a multi-talented modulator of chromatin architecture. Brief Funct Genomics 15(6):420–431. https://doi.org/10.1093/bfgp/elw023

Ege MJ, Mayer M, Schwaiger K, Mattes J, Pershagen G, van Hage M et al (2012) Environmental bacteria and childhood asthma. Allergy 67(12):1565–1571. https://doi.org/10.1111/all.12028

Eulalio A, Mano M (2015) MicroRNA screening and the quest for biologically relevant targets. J Biomol Screen 20(8):1003–1017. https://doi.org/10.1177/1087057115578837

Falkenberg KJ, Johnstone RW (2014) Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov 13(9):673–691. https://doi.org/10.1038/nrd4360

Fasolino M, Zhou Z (2017) The crucial role of DNA methylation and MeCP2 in neuronal function. Genes 8(5):141. https://doi.org/10.3390/genes8050141

Fujisawa T, Filippakopoulos P (2017) Functions of bromodomain-containing proteins and their roles in homeostasis and cancer. Nat Rev Mol Cell Biol 18(4):246–262. https://doi.org/10.1038/nrm.2016.143

Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD (2016) Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov 15(1):35–50. https://doi.org/10.1038/nrd4624

Garn H (2018) Is 9 more than 2 also in allergic airway inflammation? J Allergy Clin Immunol 141(6):2024–2026. https://doi.org/10.1016/j.jaci.2018.04.002

Garn H, Renz H (2007) Epidemiological and immunological evidence for the hygiene hypothesis. Immunobiology 212(6):441–452. https://doi.org/10.1016/j.imbio.2007.03.006

Gunawardhana LP, Gibson PG, Simpson JL, Benton MC, Lea RA, Baines KJ (2014) Characteristic DNA methylation profiles in peripheral blood monocytes are associated with inflammatory phenotypes of asthma. Epigenetics 9(9):1302–1316. https://doi.org/10.4161/epi.33066

Gutierrez MJ, Gomez JL, Perez GF, Pancham K, Val S, Pillai DK et al (2016) Airway secretory microRNAome changes during rhinovirus infection in early childhood. PLoS One 11(9):e0162244. https://doi.org/10.1371/journal.pone.0162244

Ha M, Kim VN (2014) Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 15(8):509–524. https://doi.org/10.1038/nrm3838

Hackett JA, Surani MA (2013) DNA methylation dynamics during the mammalian life cycle. Philos Trans R Soc Lond Ser B Biol Sci 368(1609):20110328. https://doi.org/10.1098/rstb.2011.0328

Hagner S, Harb H, Zhao M, Stein K, Holst O, Ege MJ et al (2013) Farm-derived gram-positive bacterium Staphylococcus sciuri W620 prevents asthma phenotype in HDM- and OVA-exposed mice. Allergy 68(3):322–329. https://doi.org/10.1111/all.12094

Handy DE, Castro R, Loscalzo J (2011) Epigenetic modifications: basic mechanisms and role in cardiovascular disease. Circulation 123(19):2145–2156. https://doi.org/10.1161/CIRCULATIONAHA.110.956839

Harb H, Alashkar Alhamwe B, Garn H, Renz H, Potaczek DP (2016) Recent developments in epigenetics of pediatric asthma. Curr Opin Pediatr 28(6):754–763. https://doi.org/10.1097/MOP.0000000000000424

Harb H, Irvine J, Amarasekera M, Hii CS, Kesper DA, Ma Y et al (2017) The role of PKCζ in cord blood T-cell maturation towards Th1 cytokine profile and its epigenetic regulation by fish oil. Biosci Rep 37(2):BSR20160485. https://doi.org/10.1042/BSR20160485

Harb H, Alashkar Alhamwe B, Acevedo N, Frumento P, Johansson C, Eick L et al (2019) Epigenetic modifications in placenta are associated with the child's sensitization to allergens. Biomed Res Int 2019:1315257. https://doi.org/10.1155/2019/1315257

Healy S, Khan P, He S, Davie JR (2012) Histone H3 phosphorylation, immediate-early gene expression, and the nucleosomal response: a historical perspective. Biochem Cell Biol 90 (1):39–54. https://doi.org/10.1139/o11-092

Hew KM, Walker AI, Kohli A, Garcia M, Syed A, McDonald-Hyman C et al (2015) Childhood exposure to ambient polycyclic aromatic hydrocarbons is linked to epigenetic modifications and impaired systemic immunity in T cells. Clin Exp Allergy 45(1):238–248. https://doi.org/10.1111/cea.12377

Ho S-M, Johnson A, Tarapore P, Janakiram V, Zhang X, Leung Y-K (2012) Environmental epigenetics and its implication on disease risk and health outcomes. ILAR J 53 (3–4):289–305. https://doi.org/10.1093/ilar.53.3-4.289

Holt PG, Strickland DH, Sly PD (2012) Virus infection and allergy in the development of asthma: what is the connection? Curr Opin Allergy Clin Immunol 12(2):151–157. https://doi.org/10.1097/ACI.0b013e3283520166

Huang Y, Tian C, Li Q, Xu Q (2019) TET1 knockdown inhibits Porphyromonas gingivalis LPS/IFN-γ-induced M1 macrophage polarization through the NF-κB pathway in THP-1 cells. Int J Mol Sci 20(8):2023. https://doi.org/10.3390/ijms20082023

Hull EE, Montgomery MR, Leyva KJ (2016) HDAC inhibitors as epigenetic regulators of the immune system: impacts on cancer therapy and inflammatory diseases. Biomed Res Int 2016:8797206. https://doi.org/10.1155/2016/8797206

Hyun K, Jeon J, Park K, Kim J (2017) Writing, erasing and reading histone lysine methylations. Exp Mol Med 49(4):e324. https://doi.org/10.1038/emm.2017.11

Jenerowicz D, Silny W, Dańczak-Pazdrowska A, Polańska A, Osmola-Mańkowska A, Olek-Hrab K (2012) Environmental factors and allergic diseases. Ann Agric Environ Med 19(3):475–481

Ji H, Biagini Myers JM, Brandt EB, Brokamp C, Ryan PH, Khurana Hershey GK (2016) Air pollution, epigenetics, and asthma. Allergy Asthma Clin Immunol 12:51. https://doi.org/10.1186/s13223-016-0159-4

Jin B, Li Y, Robertson KD (2011) DNA methylation: superior or subordinate in the epigenetic hierarchy? Genes Cancer 2(6):607–617. https://doi.org/10.1177/1947601910393957

Joehanes R, Just AC, Marioni RE, Pilling LC, Reynolds LM, Mandaviya PR et al (2016) Epigenetic signatures of cigarette smoking. Circ Cardiovasc Genet 9(5):436–447. https://doi.org/10.1161/CIRCGENETICS.116.001506

Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C et al (2016) DNA methylation in newborns and maternal smoking in pregnancy: genome-wide consortium meta-analysis. Am J Hum Genet 98(4):680–696. https://doi.org/10.1016/j.ajhg.2016.02.019

Jurkowska RZ, Jeltsch A (2016) Mechanisms and biological roles of DNA methyltransferases and DNA methylation: from past achievements to future challenges. Adv Exp Med Biol 945:1–17. https://doi.org/10.1007/978-3-319-43624-1_1

Kabesch M, Michel S, Tost J (2010) Epigenetic mechanisms and the relationship to childhood asthma. Eur Respir J 36(4):950–961. https://doi.org/10.1183/09031936.00019310

Kala R, Peek GW, Hardy TM, Tollefsbol TO (2013) MicroRNAs: an emerging science in cancer epigenetics. J Clin Bioinform 3(1):6. https://doi.org/10.1186/2043-9113-3-6

Kaniskan HÜ, Martini ML, Jin J (2018) Inhibitors of protein methyltransferases and demethylases. Chem Rev 118(3):989–1068. https://doi.org/10.1021/acs.chemrev.6b00801

Kaplan MH (2017) The transcription factor network in Th9 cells. Semin Immunopathol 39 (1):11–20. https://doi.org/10.1007/s00281-016-0600-2

Karam RA, Abd Elrahman DM (2019) Differential expression of miR-155 and Let-7a in the plasma of childhood asthma: potential biomarkers for diagnosis and severity. Clin Biochem 68:30–36. https://doi.org/10.1016/j.clinbiochem.2019.04.007

Kho AT, McGeachie MJ, Moore KG, Sylvia JM, Weiss ST, Tantisira KG (2018) Circulating microRNAs and prediction of asthma exacerbation in childhood asthma. Respir Res 19(1):128. https://doi.org/10.1186/s12931-018-0828-6

Kim JK, Samaranayake M, Pradhan S (2009) Epigenetic mechanisms in mammals. Cell Mol Life Sci 66(4):596–612. https://doi.org/10.1007/s00018-008-8432-4

Kim T-H, Jung J-A, Kim G-D, Jang A-H, Cho J-J, Park YS, Park C-S (2010) The histone deacetylase inhibitor, trichostatin A, inhibits the development of 2,4-dinitrofluorobenzene-induced dermatitis in NC/Nga mice. Int Immunopharmacol 10(10):1310–1315. https://doi.org/10.1016/j.intimp.2010.08.004

Kirchner B, Pfaffl MW, Dumpler J, von Mutius E, Ege MJ (2016) microRNA in native and processed cow's milk and its implication for the farm milk effect on asthma. J Allergy Clin Immunol 137(6):1893–1895.e13. https://doi.org/10.1016/j.jaci.2015.10.028

Krämer U, Schmitz R, Ring J, Behrendt H (2015) What can reunification of East and West Germany tell us about the cause of the allergy epidemic? Clin Exp Allergy 45(1):94–107. https://doi.org/10.1111/cea.12458

Krusche J, Nowak E, Böck A, Hengst M, Roponen M, Kumbrink J et al (2019) DUSP1 plays a pivotal role in MAPK signaling in childhood asthma development and environment-mediated protection: abstracts LBOA1712. Allergy 74(S106):117–129. https://doi.org/10.1111/all.13958

Lambrecht BN, Hammad H (2015) The immunology of asthma. Nat Immunol 16(1):45–56. https://doi.org/10.1038/ni.3049

Li E, Zhang Y (2014) DNA methylation in mammals. Cold Spring Harb Perspect Biol 6(5): a019133. https://doi.org/10.1101/cshperspect.a019133

Li S, Chen M, Li Y, Tollefsbol TO (2019) Prenatal epigenetics diets play protective roles against environmental pollution. Clin Epigenetics 11(1):82. https://doi.org/10.1186/s13148-019-0659-4

Lluis A, Depner M, Gaugler B, Saas P, Casaca VI, Raedler D et al (2014) Increased regulatory T-cell numbers are associated with farm milk exposure and lower atopic sensitization and asthma in childhood. J Allergy Clin Immunol 133(2):551–559. https://doi.org/10.1016/j.jaci.2013.06.034

Marmorstein R, Zhou M-M (2014) Writers and readers of histone acetylation: structure, mechanism, and inhibition. Cold Spring Harb Perspect Biol 6(7):a018762. https://doi.org/10.1101/cshperspect.a018762

Martino D, Dang T, Sexton-Oates A, Prescott S, Tang MLK, Dharmage S et al (2015) Blood DNA methylation biomarkers predict clinical reactivity in food-sensitized infants. J Allergy Clin Immunol 135(5):1319–1328.e1-12. https://doi.org/10.1016/j.jaci.2014.12.1933

McDade TW (2012) Early environments and the ecology of inflammation. Proc Natl Acad Sci U S A 109(Suppl 2):17281–17288. https://doi.org/10.1073/pnas.1202244109

Miethe S, Guarino M, Alhamdan F, Simon H-U, Renz H, Dufour J-F et al (2018) Effects of obesity on asthma: Immunometabolic links. Pol Arch Intern Med 128(7–8):469–477. https://doi.org/10.20452/pamw.4304

Moheimani F, Koops J, Williams T, Reid AT, Hansbro PM, Wark PA, Knight DA (2018) Influenza A virus infection dysregulates the expression of microRNA-22 and its targets; CD147 and HDAC4, in epithelium of asthmatics. Respir Res 19(1):145. https://doi.org/10.1186/s12931-018-0851-7

Mondoulet L, Dioszeghy V, Busato F, Plaquet C, Dhelft V, Bethune K et al (2019) Gata3 hypermethylation and Foxp3 hypomethylation are associated with sustained protection and

bystander effect following epicutaneous immunotherapy in peanut-sensitized mice. Allergy 74 (1):152–164. https://doi.org/10.1111/all.13479

Moore LD, Le T, Fan G (2013) DNA methylation and its basic function. Neuropsychopharmacology 38(1):23–38. https://doi.org/10.1038/npp.2012.112

Morera L, Lübbert M, Jung M (2016) Targeting histone methyltransferases and demethylases in clinical trials for cancer therapy. Clin Epigenetics 8:57. https://doi.org/10.1186/s13148-016-0223-4

Mørkve Knudsen T, Rezwan FI, Jiang Y, Karmaus W, Svanes C, Holloway JW (2018) Transgenerational and intergenerational epigenetic inheritance in allergic diseases. J Allergy Clin Immunol 142(3):765–772. https://doi.org/10.1016/j.jaci.2018.07.007

Nestor CE, Barrenäs F, Wang H, Lentini A, Zhang H, Bruhn S et al (2014) DNA methylation changes separate allergic patients from healthy controls and may reflect altered CD4+ T-cell population structure. PLoS Genet 10(1):e1004059. https://doi.org/10.1371/journal.pgen.1004059

North ML, Jones MJ, MacIsaac JL, Morin AM, Steacy LM, Gregor A et al (2018) Blood and nasal epigenetics correlate with allergic rhinitis symptom development in the environmental exposure unit. Allergy 73(1):196–205. https://doi.org/10.1111/all.13263

Ouyang Y, Xu Z, Fan E, Li Y, Zhang L (2016) Effect of nitrogen dioxide and sulfur dioxide on viability and morphology of oak pollen. Int Forum Allergy Rhinol 6(1):95–100. https://doi.org/10.1002/alr.21632

Pech M, Weckmann M, König IR, Franke A, Heinsen F-A, Oliver B et al (2018) Rhinovirus infections change DNA methylation and mRNA expression in children with asthma. PLoS One 13(11):e0205275. https://doi.org/10.1371/journal.pone.0205275

Pepper AN, Renz H, Casale TB, Garn H (2017) Biologic therapy and novel molecular targets of severe asthma. J Allergy Clin Immunol Pract 5(4):909–916. https://doi.org/10.1016/j.jaip.2017.04.038

Perry MM, Adcock IM, Chung KF (2015a) Role of microRNAs in allergic asthma: present and future. Curr Opin Allergy Clin Immunol 15(2):156–162. https://doi.org/10.1097/ACI.0000000000000147

Perry MM, Durham AL, Austin PJ, Adcock IM, Chung KF (2015b) BET bromodomains regulate transforming growth factor-β-induced proliferation and cytokine release in asthmatic airway smooth muscle. J Biol Chem 290(14):9111–9121. https://doi.org/10.1074/jbc.M114.612671

Piletič K, Kunej T (2016) MicroRNA epigenetic signatures in human disease. Arch Toxicol 90 (10):2405–2419. https://doi.org/10.1007/s00204-016-1815-7

Potaczek DP, Kabesch M (2012) Current concepts of IgE regulation and impact of genetic determinants. Clin Exp Allergy 42(6):852–871. https://doi.org/10.1111/j.1365-2222.2011.03953.x

Potaczek DP, Harb H, Michel S, Alhamwe BA, Renz H, Tost J (2017) Epigenetics and allergy: from basic mechanisms to clinical applications. Epigenomics 9(4):539–571. https://doi.org/10.2217/epi-2016-0162

Potaczek DP, Harb H, Alashkar Alhamwe B, Kilic-Niebergall E, Kesper D, Garn H, Renz H (2018) Interleukin-6 is important for the development of Acinetobacter lwoffii-mediated protection against asthma. In: Allergy and immunology. European Respiratory Society, p PA1108. https://doi.org/10.1183/13993003.congress-2018.PA1108

Potaczek DP, Unger SD, Zhang N, Taka S, Michel S, Akdağ N et al (2019) Development and characterization of DNAzyme candidates demonstrating significant efficiency against human rhinoviruses. J Allergy Clin Immunol 143(4):1403–1415. https://doi.org/10.1016/j.jaci.2018.07.026

Ray A, Oriss TB, Wenzel SE (2015) Emerging molecular phenotypes of asthma. Am J Physiol Lung Cell Mol Physiol 308(2):L130–L140. https://doi.org/10.1152/ajplung.00070.2014

Ren Y, Su X, Kong L, Li M, Zhao X, Yu N, Kang J (2016) Therapeutic effects of histone deacetylase inhibitors in a murine asthma model. Inflamm Res 65(12):995–1008. https://doi.org/10.1007/s00011-016-0984-4

Renz H, Conrad M, Brand S, Teich R, Garn H, Pfefferle PI (2011) Allergic diseases, gene-environment interactions. Allergy 66(Suppl 95):10–12. https://doi.org/10.1111/j.1398-9995.2011.02622.x

Rodrigo-Muñoz JM, Cañas JA, Sastre B, Rego N, Greif G, Rial M et al (2019) Asthma diagnosis using integrated analysis of eosinophil microRNAs. Allergy 74(3):507–517. https://doi.org/10.1111/all.13570

Rossetto D, Avvakumov N, Côté J (2012) Histone phosphorylation: a chromatin modification involved in diverse nuclear events. Epigenetics 7(10):1098–1108. https://doi.org/10.4161/epi.21975

Sarnowski C, Laprise C, Malerba G, Moffatt MF, Dizier M-H, Morin A et al (2016) DNA methylation within melatonin receptor 1A (MTNR1A) mediates paternally transmitted genetic variant effect on asthma plus rhinitis. J Allergy Clin Immunol 138(3):748–753. https://doi.org/10.1016/j.jaci.2015.12.1341

Sato F, Tsuchiya S, Meltzer SJ, Shimizu K (2011) MicroRNAs and epigenetics. FEBS J 278(10):1598–1609. https://doi.org/10.1111/j.1742-4658.2011.08089.x

Schaub B, Liu J, Höppler S, Schleich I, Huehn J, Olek S et al (2009) Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol 123(4):774–782.e5. https://doi.org/10.1016/j.jaci.2009.01.056

Schieck M, Sharma V, Michel S, Toncheva AA, Worth L, Potaczek DP et al (2014) A polymorphism in the TH 2 locus control region is associated with changes in DNA methylation and gene expression. Allergy 69(9):1171–1180. https://doi.org/10.1111/all.12450

Schleich F, Bikov A, Mathioudakis AG, McDonnell M, Andersson C, Bonini M et al (2019) Research highlights from the 2018 European Respiratory Society International Congress: airway disease. ERJ Open Res 5(1):00225-2018. https://doi.org/10.1183/23120541.00225-2018

Schuijs MJ, Willart MA, Vergote K, Gras D, Deswarte K, Ege MJ et al (2015) Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. Science 349(6252):1106–1110. https://doi.org/10.1126/science.aac6623

Seumois G, Chavez L, Gerasimova A, Lienhard M, Omran N, Kalinke L et al (2014) Epigenomic analysis of primary human T cells reveals enhancers associated with TH2 memory cell differentiation and asthma susceptibility. Nat Immunol 15(8):777–788. https://doi.org/10.1038/ni.2937

Sharma V, Michel S, Gaertner V, Franke A, Vogelberg C, von Berg A et al (2014) Fine-mapping of IgE-associated loci 1q23, 5q31, and 12q13 using 1000 Genomes Project data. Allergy 69(8):1077–1084. https://doi.org/10.1111/all.12431

Smith ZD, Meissner A (2013) DNA methylation: roles in mammalian development. Nat Rev Genet 14(3):204–220. https://doi.org/10.1038/nrg3354

Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM et al (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341(6145):569–573. https://doi.org/10.1126/science.1241165

Somineni HK, Zhang X, Biagini Myers JM, Kovacic MB, Ulm A, Jurcak N et al (2016) Ten-eleven translocation 1 (TET1) methylation is associated with childhood asthma and traffic-related air pollution. J Allergy Clin Immunol 137(3):797–805.e5. https://doi.org/10.1016/j.jaci.2015.10.021

Steelant B, Wawrzyniak P, Martens K, Jonckheere A-C, Pugin B, Schrijvers R et al (2019) Blocking histone deacetylase activity as a novel target for epithelial barrier defects in patients with allergic rhinitis. J Allergy Clin Immunol 144(5):1242–1253. https://doi.org/10.1016/j.jaci.2019.04.027

Suarez-Alvarez B, Rodriguez RM, Fraga MF, López-Larrea C (2012) DNA methylation: a promising landscape for immune system-related diseases. Trends Genet 28(10):506–514. https://doi.org/10.1016/j.tig.2012.06.005

Swygert SG, Peterson CL (2014) Chromatin dynamics: interplay between remodeling enzymes and histone modifications. Biochim Biophys Acta 1839(8):728–736. https://doi.org/10.1016/j.bbagrm.2014.02.013

Tang W-Y, Levin L, Talaska G, Cheung YY, Herbstman J, Tang D et al (2012) Maternal exposure to polycyclic aromatic hydrocarbons and 5′-CpG methylation of interferon-γ in cord white blood cells. Environ Health Perspect 120(8):1195–1200. https://doi.org/10.1289/ehp.1103744

Tiffon C (2018) The impact of nutrition and environmental epigenetics on human health and disease. Int J Mol Sci 19(11):3425. https://doi.org/10.3390/ijms19113425

Tomassen P, Vandeplas G, van Zele T, Cardell L-O, Arebro J, Olze H et al (2016) Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 137(5):1449–1456.e4. https://doi.org/10.1016/j.jaci.2015.12.1324

Toncheva AA, Potaczek DP, Schedel M, Gersting SW, Michel S, Krajnov N et al (2015) Childhood asthma is associated with mutations and gene expression differences of ORMDL genes that can interact. Allergy 70(10):1288–1299. https://doi.org/10.1111/all.12652

Tost J (2018) A translational perspective on epigenetics in allergic diseases. J Allergy Clin Immunol 142(3):715–726. https://doi.org/10.1016/j.jaci.2018.07.009

Turner S (2017) Gene-environment interactions-what can these tell us about the relationship between asthma and allergy? Front Pediatr 5:118. https://doi.org/10.3389/fped.2017.00118

Van Neerven RJJ, Savelkoul HFJ (2019) The two faces of cow's milk and allergy: induction of cow's milk allergy vs prevention of asthma. Nutrients 11(8):1945. https://doi.org/10.3390/nu11081945

Vardavas CI, Hohmann C, Patelarou E, Martinez D, Henderson AJ, Granell R et al (2016) The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children. Eur Respir J 48(1):115–124. https://doi.org/10.1183/13993003.01016-2015

Vidigal JA, Ventura A (2015) The biological functions of miRNAs: lessons from in vivo studies. Trends Cell Biol 25(3):137–147. https://doi.org/10.1016/j.tcb.2014.11.004

von Mutius E, Radon K (2008) Living on a farm: impact on asthma induction and clinical course. Immunol Allergy Clin N Am 28(3):631–647., ix-x. https://doi.org/10.1016/j.iac.2008.03.010

Vonk MM, Blokhuis BRJ, Diks MAP, Wagenaar L, Smit JJ, Pieters RHH et al (2019) Butyrate enhances desensitization induced by oral immunotherapy in cow's milk allergic mice. Mediat Inflamm 2019:9062537. https://doi.org/10.1155/2019/9062537

Wang Y, Bai C, Li K, Adler KB, Wang X (2008) Role of airway epithelial cells in development of asthma and allergic rhinitis. Respir Med 102(7):949–955. https://doi.org/10.1016/j.rmed.2008.01.017

Weake VM, Workman JL (2008) Histone ubiquitination: triggering gene activity. Mol Cell 29(6):653–663. https://doi.org/10.1016/j.molcel.2008.02.014

Yamamoto M, Singh A, Sava F, Pui M, Tebbutt SJ, Carlsten C (2013) MicroRNA expression in response to controlled exposure to diesel exhaust: attenuation by the antioxidant N-acetylcysteine in a randomized crossover study. Environ Health Perspect 121(6):670–675. https://doi.org/10.1289/ehp.1205963

Yu Q, Yu X, Zhao W, Zhu M, Wang Z, Zhang J et al (2018) Inhibition of H3K27me3 demethylases attenuates asthma by reversing the shift in airway smooth muscle phenotype. Clin Exp Allergy 48(11):1439–1452. https://doi.org/10.1111/cea.13244

Zhang X, Li B, Rezaeian AH, Xu X, Chou P-C, Jin G et al (2017) H3 ubiquitination by NEDD4 regulates H3 acetylation and tumorigenesis. Nat Commun 8:14799. https://doi.org/10.1038/ncomms14799

Zhang X, Biagini Myers JM, Burleson JD, Ulm A, Bryan KS, Chen X et al (2018) Nasal DNA methylation is associated with childhood asthma. Epigenomics 10(5):629–641. https://doi.org/10.2217/epi-2017-0127

Zhang Z, Zhuang L, Lin C-P (2019) Roles of MicroRNAs in establishing and modulating stem cell potential. Int J Mol Sci 20(15):3643. https://doi.org/10.3390/ijms20153643

Indoor and Outdoor Pollution as Risk Factor for Allergic Diseases of the Skin and Lungs

Tamara Schikowski

Contents

Abstract

Air pollution is *worldwide a major public health problem* and affects large part of the population. Air pollution does not only harm the respiratory tract system but also the other organs of the body. The damage may result directly from the pollutants toxicity, because the pollutant enters into the organs through a direct route or indirectly through systemic inflammation. There is accumulating evidence suggesting that ambient air pollution not only affects the human lung and the cardiovascular system, but also has negative effects on allergic diseases. In this regard, it has been shown that exposure increases the risk of allergies and eczema in children and adults. However, the mechanism how ambient air pollution affects the skin is not well investigated up to now and needs further research.

Keywords

Air pollution · Allergies · Eczema · Health effects

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1 Introduction

Air pollution is the greatest preventable risk for health worldwide. The World Health Organization (WHO) estimates at least five million premature deaths annually due to air pollution worldwide (Mcglade and Landrigan 2019). Exposure to air pollution from either indoor or outdoor sources can increase the risk of morbidity and mortality (Burnett et al. 2018).

Exposure to indoor or outdoor air pollution can affect the human body immediately by causing symptoms such as coughing, tearing, and difficulties breathing, but it can also cause long-term harm with more severe health outcomes such as chronic obstructive pulmonary diseases (COPD) or cardiovascular diseases (Brook and Rajagopalan 2007). Pollutants can enter the body through the respiratory tract where they can cause systematic inflammation that can damage other organs beyond the lungs.

Air pollution exposure has gained attention as a risk factor for the development of allergies and eczema in children and adults in recent years. There is growing evidence that air pollution is associated with a variety of allergic diseases such as atopic eczema and allergic asthma in both, children and adults.

2 What Is Air Pollution?

2.1 Outdoor Air Pollution

Air pollution can be defined as any substance that changes the air quality and that can harm humans, animals, and plants. They exist in various forms and are a complex mixture of various substances. Depending on their characteristics, they can differ in composition, size, and conditions under which they are produced. Common pollutants are particulate matter (PM), and gases such as sulfur oxides (SO_x and SO_2), nitrogen oxides (NO_x and NO_2), reactive hydrocarbons and carbon monoxide (CO). They are the so-called primary pollutants which are directly released into the atmosphere. Secondary pollutants are formed in the atmosphere, largely from primary pollutants and ultraviolet radiation (UV). One of such secondary pollutants is ozone (O_3), which can be formed from nitrogen oxides and hydrocarbons in the atmosphere under UV exposure.

Particulate matter (PM) is the pollutant of greatest concern for human health. They are produced either by natural processes or by human activity such as fossil fuel combustion. The main sources of combustion derived PM are household heating and cooking, stationary combustion from industries, and mobile sources such as traffic or controlled burning of biomass and waste. They are classified by their size or aerodynamic diameter; PM ultrafine (aerodynamic diameter <0.1 μm: UFP), fine (<2.5 μm: $PM_{2.5}$), and coarse (<10 μm: PM_{10}). All $PM_{2.5}$ and $PM_{0.1}$ are included in PM_{10}. They can consist of a number of components including acids, organic chemicals, metals, and soil or dust particles.

2.2 Indoor Air Pollution

Indoor air quality is a mixture of outdoor pollutants and indoor contaminants. Outdoor pollutants can enter through infiltration and/or ventilation sources (mechanical and natural). These outdoor pollutants originate from traffic or industrial sources. Other sources of indoor air pollution are from activities inside the building such as burning of fossil fuels, burning of candles, emissions from building materials and paints, kind of heating and/or cooling systems as well as behavior of the occupants such as cigarette smoking and use of household products (Balmes 2019).

One major source of indoor pollution is from burning of wood, coal, or other biomass for either cooking or heating. This can lead to the emission of high levels of particulate matter and endotoxins. Another source are indoor allergens and microbes, which can have diverse sources with the most severe arising from growth of microorganisms or molds on walls that are wet or moist (Smith and Pillarisetti 2017).

3 Health Effects of Air Pollution

Air pollution is currently the largest single environmental health risk factor. The damage that can be caused by exposure to gases from ambient air pollution depends on their water solubility, their concentration as well as their ability to oxidize tissue. Furthermore, it depends on the susceptibility of the exposed person. Sulfur dioxide is highly water soluble and can cause damage to the upper airways and the skin. Nitrogen dioxide and ozone are both less soluble and can therefore penetrate deeper into the lung, whereas carbon oxide is highly soluble, non-irritating, and readily passes into the bloodstream (Schraufnagel et al. 2019). The toxicity of CO results from successfully competing with oxygen in binding to hemoglobin, which results in tissue hypoxia and the effects are usually acute: a 2-day increase of mean CO levels of 1 mg/m^3 was associated with a 1.2% increase in total deaths in a large European study (Samoli et al. 2007). Nitric oxide also attaches to hemoglobin and other iron-containing proteins, but it generally acts only at short distance from its contact point because of its binding affinity.

The damaging effect of PM depends on their size, composition, and structure. Large particles may affect the mucous membranes and the upper airways, which can cause irritation to the respiratory tract, coughing, and tearing. Fine particles ($PM_{2.5}$) easily find their way into lung alveoli, and ultrafine particles ($PM_{0.1}$) which pass through the alveolar-capillary membrane, are readily picked up by cells, and carried via the bloodstream and can affect virtually all cells in the body. The smaller the particles, the greater is their systemic toxicity.

Highly acidic particulate matter is more noxious and the toxic components are on the surface of the particle. This may be responsible for the tissue damage on contact. Toxic elements on the particle surface are arsenic, lead, or cadmium, or compounds such as sulfuric acid or polycyclic aromatic hydrocarbons, which are picked up during the combustion process and through inhalation carried deep into the lung. Since ultrafine particles have a larger surface they might also have more toxic

components on their surface. This is mostly the case from particles resulting from fossil fuel combustion, especially coal burning, which contains many heavy metal constituents and high levels of sulfur. If similar-sized particles do not contain as many toxic add-ons, they generally cause less harm (Thurston et al. 2017). PM, however, can also interact with airborne allergens as carriers to trigger or even induce allergic asthma reactions in sensitized subjects.

Air pollutants are also known to increase the frequency and intensity of symptoms in allergic patients (Health Effects Institute 2010; Bowatte et al. 2017; Carlsten et al. 2016); however, they may also promote airway sensitization to airborne allergens in predisposed persons (Amato et al. 2018). They can interact with pollen grains and plant-derived particles and can modify the morphology of antigen-carrying agents and alter their allergenic potential (Beck et al. 2013). In addition, by inducing airway inflammation, pollutants may overcome the mucosal barrier and therefore "prime" allergen-induced responses (Amato et al. 2018). Induction of airway mucosal damage and impaired mucociliary clearance can facilitate access of inhaled allergens to the cells of the immune system.

Exposure to indoor biological agents can also affect the upper and lower respiratory part and cause infections, immunological responses, and inflammation. In addition, they can cause allergic responses. Especially the exposure to fungi from indoor molds and damp environments can lead to hypersensitive disorders such as allergic bronchopulmonary aspergillosis, asthma symptoms, bronchial reactivity, and allergic fungal rhinosinusitis (Cincinelli and Martellini 2017).

Air pollution from outdoor and indoor sources may exert negative effects on allergies and human skin.

4 Epidemiological Evidence on Air Pollution and Allergic Diseases of the Respiratory Tract and the Skin

Numerous epidemiological studies indicate that air pollution can decrease lung function and trigger asthma exacerbation in children and adults leading to increased hospitalization and medication (Health Effects Institute 2010; Brandt et al. 2015). A large study from Canada could show that perinatal exposure to high levels of air pollution increases the risk of asthma in children (Sbihi et al. 2016). Results from the Southern California Children's Health Study show that exposure to higher NO_2 concentrations and living close to a freeway increase asthma prevalence in these children (Chen et al. 2015). Asthmatic children who lived in communities with higher levels of NO_2, PM_{10}, and $PM_{2.5}$ had increased chronic lower respiratory symptoms, phlegm, production, bronchitis, wheeze, and medication use (Chen et al. 2015). The results in adults are less clear, a meta-analysis of six cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE) that included 23,704 adults found that exposure to higher NO_2 increased the incidence of adult-onset asthma, although the results did not reach significance (Jacquemin et al. 2015).

However, within the population certain groups might be more susceptible to the damaging effect of air pollution than others. In particular, early life exposures to air

pollutants are hypothesized to be linked with adverse health outcomes later in life due to the harmful effects of exposure of the air pollutants on the developing lungs, the not developed immune system, and the immature metabolic pathways (Wright and Brunst 2013). Other studies indicated that high exposure to air pollutants in the first year of life increases the risk of aeroallergen sensitization by the age of four by 40–83% (Codispoti et al. 2015; Gruzieva et al. 2012). Children exposed to air pollution before the age of 1 also have an increased risk of developing food allergy by age eight, particularly those who are not sensitized at age four (Gruzieva et al. 2012).

There is a large body of evidence from epidemiological studies that show adverse effects of pollution on asthma especially asthma exacerbation, however very little is known on the effect on skin allergies and eczema.

Studies on the association between exposure to air pollution and prevalence of allergic diseases in children and adults have yielded mixed results (Naclerio et al. 2020). A recent systematic review by Krämer et al. found good evidence that "small-scale" exposure to traffic-related air pollution is associated with atopic eczema in children. They concluded that exposures from traffic-related pollutants, particularly from truck traffic, influenced the prevalence of atopic eczema, however, that the triggering factor was to a lesser extent NO_2, but more fine particulate matter and soot (Krämer and Behrendt 2019). Numerous studies have explored the adverse effects of PM on allergic diseases. For example, a study from Central Europe could show that long-term exposure to PM_{10} increased the risk of allergic rhinitis by up to 35% in children (Puklová et al. 2019). Positive associations between the prevalence of vernal keratoconjunctivitis and PM_{10}, as well as atopic keratoconjunctivitis and $PM_{2.5}$, were reported by a study from Japan (Miyazaki et al. 2019). In a cross-sectional study from France, the risk for skin rash after exposure to PM_{10} was increased by 3.2% (Larrieu et al. 2009). A birth cohort study from Germany found that exposure to traffic-related pollution ($PM_{2.5}$ absorbance and NO_2) was associated with the incidence and prevalence of respiratory allergies and eczema in children (Morgenstern et al. 2008).

Very few studies have investigated the effects of gaseous agents such as NO_2 and O_3. Exposure to NO_2 can irritate the mucous membrane of the lung, respiratory tract, and skin barrier and cause inflammation (Schlesinger and Lippmann 2020). Several studies reported adverse effects of NO_2 on atopic eczema and allergic diseases. A study from Korea reported a 7% rise in the risk of atopic eczema in schoolchildren per interquartile range (IQR) increase in the annual-average concentration of NO_2 (Min et al. 2020). Another study from China observed robust relationships between lifetime exposure to NO_2 and a series of allergic diseases including asthma, rhinitis, eczema, wheeze, and rhinitis for children ages 3–6 years (Norbäck et al. 2019).

Ground-level ozone may also trigger inflammatory response and other pathophysiologic changes in the skin. Several studies could show associations between exposure to ozone with various allergic diseases or symptoms (To et al. 2020; Kim et al. 2011). Exposure to ozone at birth was associated with the onset of asthma and allergic rhinitis during the 17-year follow-up in a Canadian study (To et al. 2020). A study from Korea reported that the preceding 5-year average concentration of ozone

was significantly associated with allergic rhinitis in industrial areas and rate of sensitization for schoolchildren (Kim et al. 2011). Higher annual outdoor concentrations of ozone were associated with increased total IgE levels in a French study (Rage et al. 2009).

So far only one study investigated the incidence of eczema in adults. A study in elderly German women indicated that long-term exposure to air pollutants was significantly associated with the incidence of eczema; however, the associations were stronger in nonatopic women. The odds for incidence of eczema symptoms was 1.45 (95% CI, 1.06–1.99). These associations were slightly more pronounced with nonatopic eczema 1.65 (95% CI of 1.15–2.34) for participants without hay fever or increased IgE levels (Huls et al. 2019).

While the majority of studies have focus on outdoor air pollution exposure and allergic diseases, only a small amount of studies has investigated the association between indoor exposure and allergic diseases. Inhalation is the major pathway for air pollutants to affect the human body; therefore, the majority of studies have investigated the relationship between asthma and indoor air quality (Kim et al. 2015). A study in France investigated exposure to $PM_{2.5}$ in school classrooms and found that differences between high versus low exposure in non-asthmatic children resulted in an increase in fractional exhaled nitric oxide (FeNO) ranging from 45% for indoor acetaldehyde to 62% for indoor $PM_{2.5}$ (Flamant-Hulin et al. 2009). However, most studies investigating indoor air pollution exposure and allergic diseases focus on the built environment and exposures emitting from renovations or newly built housing.

5 Conclusion

The association between air pollution and exacerbation of asthma is well established, whereas the evidence-base on studies on air pollution and allergies and eczema is still inconsistent. Air pollution exposure can exacerbate symptoms in children with existing atopic eczema. The pathological mechanisms might differ on how ambient air pollution exposure might affect people with pre-existing allergic diseases and healthy people, which require further investigation in the future.

References

Amato MD, Cecchi L, Annesi-Maesano I, Amato GD (2018) News on climate change, air pollution, and allergic triggers of asthma. J Investig Allergol Clin Immunol 28:91–97

Balmes JR (2019) Household air pollution from domestic combustion of solid fuels and health. J Allergy Clin Immunol 143:1979–1987

Beck I, Jochner S, Gilles S et al (2013) High environmental ozone levels lead to enhanced allergenicity of birch pollen. PLoS One 8:e80147

Bowatte G, Erbas B, Lodge CJ et al (2017) Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. Eur Respir J 50

Brandt EB, Myers JM, Ryan PH, Hershey GK (2015) Air pollution and allergic diseases. Curr Opin Pediatr 27:724–735

Brook RD, Rajagopalan S (2007) Air pollution and cardiovascular events. N Engl J Med 356:2104–2105. author reply 2105-2106

Burnett R, Chen H, Szyszkowicz M et al (2018) Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A 115:9592–9597

Carlsten C, Blomberg A, Pui M et al (2016) Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: a controlled human exposure study. Thorax 71:35–44

Chen Z, Salam MT, Eckel SP, Breton CV, Gilliland FD (2015) Chronic effects of air pollution on respiratory health in Southern California children: findings from the Southern California Children's Health Study. J Thorac Dis 7:46–58

Cincinelli A, Martellini T (2017) Indoor air quality and health. Int J Environ Res Public Health 14:1286

Codispoti CD, Lemasters GK, Levin L et al (2015) Traffic pollution is associated with early childhood aeroallergen sensitization. Ann Allergy Asthma Immunol 114:126–133

Flamant-Hulin M, Caillaud D, Sacco P, Pénard-Morand C, Annesi-Maesano I (2009) Air pollution and increased levels of fractional exhaled nitric oxide in children with no history of airway damage. J Toxic Environ Health A 73:272–283

Gruzieva O, Bellander T, Eneroth K et al (2012) Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. J Allergy Clin Immunol 129:240–246

Health Effects Institute (2010) Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. In: Special report 17. Health Effects Institute, Boston

Huls A, Abramson MJ, Sugiri D et al (2019) Nonatopic eczema in elderly women: effect of air pollution and genes. J Allergy Clin Immunol 143:378–385.e379

Jacquemin B, Siroux V, Sanchez M et al (2015) Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). Environ Health Perspect 123:613–621

Kim B-J, Kwon J-W, Seo J-H et al (2011) Association of ozone exposure with asthma, allergic rhinitis, and allergic sensitization. Ann Allergy Asthma Immunol 107:214–219.e211

Kim EH, Kim S, Lee JH et al (2015) Indoor air pollution aggravates symptoms of atopic dermatitis in children. PLoS One 10:e0119501

Krämer U, Behrendt H (2019) Air pollution and atopic eczema: systematic review of findings from environmental epidemiological studies. Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete 70:169–184

Larrieu S, Lefranc A, Gault G et al (2009) Are the short-term effects of air pollution restricted to cardiorespiratory diseases? Am J Epidemiol 169:1201–1208

Mcglade J, Landrigan PJ (2019) Five national academies call for global compact on air pollution and health. Lancet 394:23

Min K-D, Yi S-J, Kim H-C et al (2020) Association between exposure to traffic-related air pollution and pediatric allergic diseases based on modeled air pollution concentrations and traffic measures in Seoul, Korea: a comparative analysis. Environ Health 19:1–12

Miyazaki D, Fukagawa K, Fukushima A et al (2019) Air pollution significantly associated with severe ocular allergic inflammatory diseases. Sci Rep 9:1–9

Morgenstern V, Zutavern A, Cyrys J et al (2008) Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. Am J Respir Crit Care Med 177:1331–1337

Naclerio R, Ansotegui IJ, Bousquet J et al (2020) International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: impact of air pollution on patients with AR: current knowledge and future strategies. World Allergy Organ J 13:100106–100106

Norbäck D, Lu C, Zhang Y et al (2019) Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: synergistic effects between antibiotics use and PM10 and second hand smoke. Environ Int 125:252–260

Puklová V, Žejglicová K, Kratěnová J, Brabec M, Malý M (2019) Childhood respiratory allergies and symptoms in highly polluted area of Central Europe. Int J Environ Health Res 29:82–93
Rage E, Jacquemin B, Nadif R et al (2009) Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults. Allergy 64:40–46
Samoli E, Touloumi G, Schwartz J et al (2007) Short-term effects of carbon monoxide on mortality: an analysis within the APHEA project. Environ Health Perspect 115:1578–1583
Sbihi H, Tamburic L, Koehoorn M, Brauer M (2016) Perinatal air pollution exposure and development of asthma from birth to age 10 years. Eur Respir J 47:1062–1071
Schlesinger RB, Lippmann M (2020) Nitrogen oxides. Environmental toxicants: human exposures and their health effects, pp 721–781
Schraufnagel DE, Balmes JR, Cowl CT et al (2019) Air pollution and noncommunicable diseases: a review by the forum of international respiratory societies' environmental committee, part 1: the damaging effects of air pollution. Chest 155:409–416
Smith KR, Pillarisetti A (2017) Household air pollution from solid cookfuels and its effects on health. In: Mock CN, Nugent R, Kobusingye O, Smith KR (eds) Injury prevention and environmental health. The International Bank for Reconstruction and Development/The World Bank, Washington
Thurston GD, Kipen H, Annesi-Maesano I et al (2017) A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 49
To T, Zhu J, Stieb D et al (2020) Early life exposure to air pollution and incidence of childhood asthma, allergic rhinitis and eczema. Eur Respir J 55
Wright RJ, Brunst KJ (2013) Programming of respiratory health in childhood: influence of outdoor air pollution. Curr Opin Pediatr 25:232–239

Climate Effect, Globalization, and Ethics in Allergy

Clemens Heuson

Contents

Abstract

The prevalence of allergic diseases is increasing rapidly and has already reached an epidemic level. Two major drivers of this development are climate change and

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globalization, which both induce an increase in allergens. Concomitant climate change fosters the spreading of the latter on a global scale. The increase in allergens not only aggravates the symptoms and the degree of suffering for patients who already are allergic, but also gives rise to new cases of allergies. The distribution of allergies in society follows a steep socioeconomic gradient worldwide. According to well-established theories of justice such a distribution of the allergy burden is unfair. This fact adds a major ethical dimension and challenge to the allergy epidemic. This chapter draws on the key points of policies for allergy prevention and treatment. It shows how related programs and measures can be conceptualized and prioritized according to the principles of distributional justice.

Keywords

Climate change · Distributional justice · Ethics · Globalization · Policy · Pollen allergy

1 Motivation

The World Health Organization (WHO) rates the so-called noncommunicable diseases (short NCDs) as the biggest global medical challenge. These chronic diseases such as cancer, cardiovascular diseases, diabetes, respiratory and allergic diseases are globally the main cause for the loss of quality of life and premature death (GBD 2017). Especially allergies are on the rise and have already reached a prevalence rate which is epidemic (EAACI 2014). NCDs typically develop from the interaction of environmental risk factors and an individual's genetic and metabolic endowment. Climate change and globalization are two major risk factors for the spread of allergies. This chapter demonstrates how both climate change and globalization induce an increase in numbers of allergens and foster their distribution on a global scale. The symptoms of allergic patients are aggravated and there are many new incidents.

According to recent studies, the prevalence of allergic diseases is connected to socioeconomic factors, both across and within countries. Especially socially and economically weak parts of the population suffer from allergic diseases (Behrmann 2010). According to theories of justice, like the Rawlsian theory (Rawls 2003), this spread of allergies within the population is unfair. Therefore the handling of the allergy epidemic is connected to major ethical considerations and challenges. This chapter shows how key points of allergy mitigation policies, related programs, and measures can be conceptualized and prioritized according to the principles of distributional justice and such be handled in a more humane way.

2 Climate Change and Globalization as Major Drivers of the Allergy Prevalence

2.1 Prevalence Facts and Socioeconomic Impact

The twentieth century is characterized by enormous achievements in enhancing population health, especially with respect to life expectancy and infant mortality. However, recently this trend seems to have started to stagnate or even partly decline. Since the beginning of the twenty-first century, there is an increasing prevalence of NCDs (Behrmann 2010). Particularly, allergic diseases constitute a serious and large-scale health problem worldwide. Both in developed and in low to middle income countries, the rise in allergic sensitivities towards ordinary environmental substances has reached an epidemic level during the last decades (EAACI 2014). On a global scale, 10–40% of the population is affected (Pawankar et al. 2013). Allergies cover a broad range of severe to mild disorders such as life-threatening anaphylaxis, food allergies, asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, eosinophilic disorders, and drug and insect allergies (Pawankar 2014). Globally 300 million people suffer from asthma and about 200–250 million people suffer from food allergies. One tenth of the population suffers from drug allergies and 400 million from rhinitis (Pawankar et al. 2013). In Europe allergies are the most common NCD. There are 150 million European allergy sufferers and according to the current prediction half of the entire EU population will be affected by 2025 (EAACI 2016).

Alongside the substantial individual suffering due to the life-threatening or chronic course of the allergic condition and the impairment of the quality of life, allergies induce a high socioeconomic burden. On the one hand, they impose huge direct costs on health care systems, for instance in terms of pharmaceutical expenses, hospitalization, and other forms of treatment (Weiss et al. 2004). On the other hand, indirect costs due to the diminished productive capacity of allergy sufferers in school, studies, and work cause a considerable financial burden for societies (Zuberbier et al. 2014). Figure 1 gives an overview of these direct and indirect costs for selected countries.

2.2 General Classification of Risk Factors

The increasing prevalence of allergies together with the related suffering and costs urgently calls for efforts to identify the underlying causes, mechanisms, and risk factors in order to conceptualize and implement counter-measures in terms of prevention and therapy. The World Allergy Organization (Pawankar et al. 2013) provides a comprehensive overview of the state of research with respect to potential risk factors for allergic diseases which can be classified as follows:

The causes which lead to the development of allergies are complex – for an overview see Fig. 2. Allergies evolve through the interaction of risk factors rooted in the individual's genetic predisposition and environmental influences. In this context,

Country	Year costs calculated	Population (2010)	Disease	Direct costs*	Indirect costs**	Total costs estimated
Australia	2007	23 million	All allergies	A$ 1.1 billion	A$ 8.3 billion	A$ 9.4 billion
Finland	2005	5.3 million	All allergies	€468 million	€51.7 million	€519.7 million
South Korea	2005	50 million	Asthma Allergic rhinitis	- -	- -	US$ 1.78 billion US$ 266 million
Israel	2010	7.5 million	Asthma	-	-	US$ 250 million
Mexico	2007	103 million	Asthma	-	-	US$ 35 million
USA	2007 2005	310.2 million	Asthma Allergic rhinitis	US$ 14.7 billion US$ 11.2 billion	US$ 5 billion Up to US$ 9.7 billion	US$ 19.7 billion Up to $20.9 billion

Fig. 1 The Economic Burden of Allergy (World Allergy Organization 2011). * Expenditure on medications and health care provision. ** Cost to society from loss of work, social support, loss of taxation income, home modifications, lower productivity at work, etc.

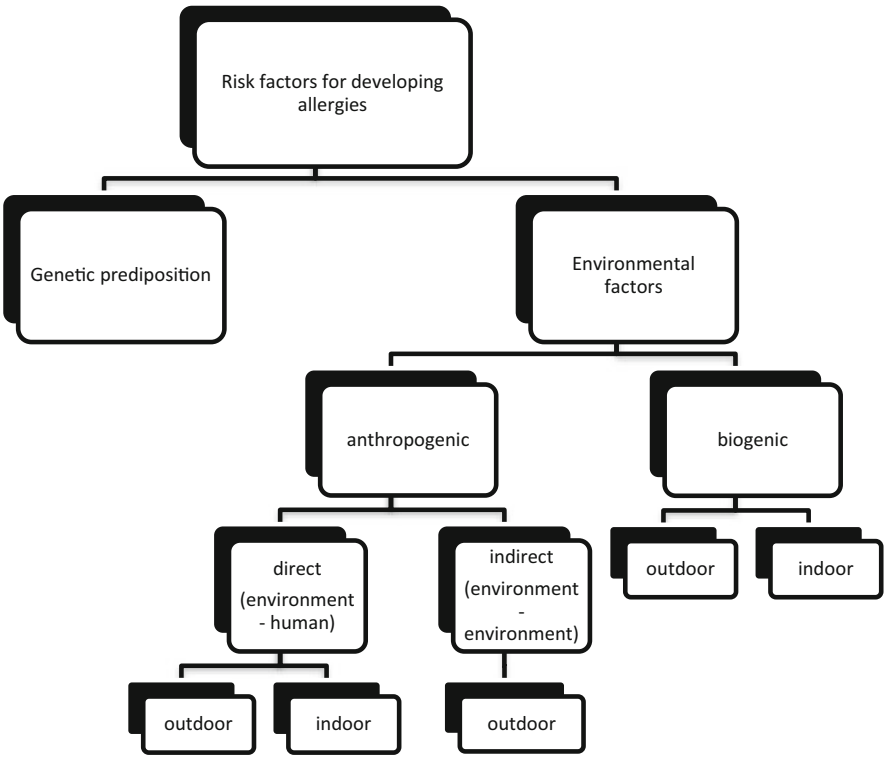

Fig. 2 Classification of risk factors for the development of allergies (Heuson and Traidl-Hoffmann 2018)

environmental influences need to be considered comprehensively as the unity of all exogenous factors humans are exposed to (Ring et al. 2012). Therefore, anthropogenic factors, of both physical and chemical nature (such as pollution), and biogenic factors (such as pollen or microbes), most notably in combination with specific lifestyles (including nutrition) and living environments, affect human health (Traidl-Hoffmann 2017).

2.2.1 Genetic Predisposition

Recent studies have shown that the functionality of the epithelial barrier of the skin, the respiratory tract, and the intestine plays a crucial role in an individual's susceptibility to allergies. This functionality may be seriously harmed by genetic mutations. For instance, the Filaggrin-null mutation is rated as the most frequent genetic disposition associated with atopic eczema. The instance of such mutations implies a considerably larger probability for allergenic environmental factors to cause a sensitization. Furthermore, the skin's natural protective film is impaired due to the lack of Filaggrin. Resulting changes in the microbial equilibrium cause further irritations of the skin barrier (Irvine et al. 2011).

2.2.2 Direct Anthropogenic Environmental Factors

Anthropogenic factors exert a direct influence on human health and this is also the case when it comes to the development of allergic diseases (environmental–human interaction) (D'Amato et al. 2016a). Figure 3 provides an overview of the most common factors, which are given by various forms of outdoor and indoor pollution.

Globally, the main sources of outdoor pollution are fuel combustion, emissions from vehicles, construction and agricultural operations, power plants and industries, primarily refineries. Primary pollutants such as CO, CO_2, NO_2, SO_2, and PAHs are directly emitted into the atmosphere, whereas O_3, a secondary pollutant, results from the reaction between UV radiation/sunlight, hydrocarbons, and NO_2. PM can either be emitted directly (primary PM) or be formed in the atmosphere from gaseous precursors, mainly SO_2, NO_x, ammonia, and non-methane VOCs (secondary PM) (Pawankar et al. 2013). These pollutants (either separately or mutually) cause or exacerbate the symptoms of major allergic diseases like asthma, allergic rhinitis, and respiratory allergy (EAACI 2014).

The sources of the leading risk factors for indoor pollution are environmental tobacco smoke (ETS), biomass (wood/coal) fuel, cleaning and washing products, and mold/dampness caused by humidity from cooking and heating on open fires or with inefficient stoves and poorly ventilated rooms. The emitted pollutants (see Fig. 3) can cause or aggravate allergic diseases and symptoms such as asthma, bronchial hyper-responsiveness, cough, irritations of nose, mouth and throat and may finally induce atopic sensitization (Weisse et al. 2012).

The basic mechanism of action of these direct anthropogenic risk factors can be described as follows. Environmental substances seem to achieve this via an interaction with the aryl hydrocarbon receptor, which responds to keratinocyte stimuli from the environment and mediates allergic symptoms such as atopic dermatitis (Hidaka et al. 2017).

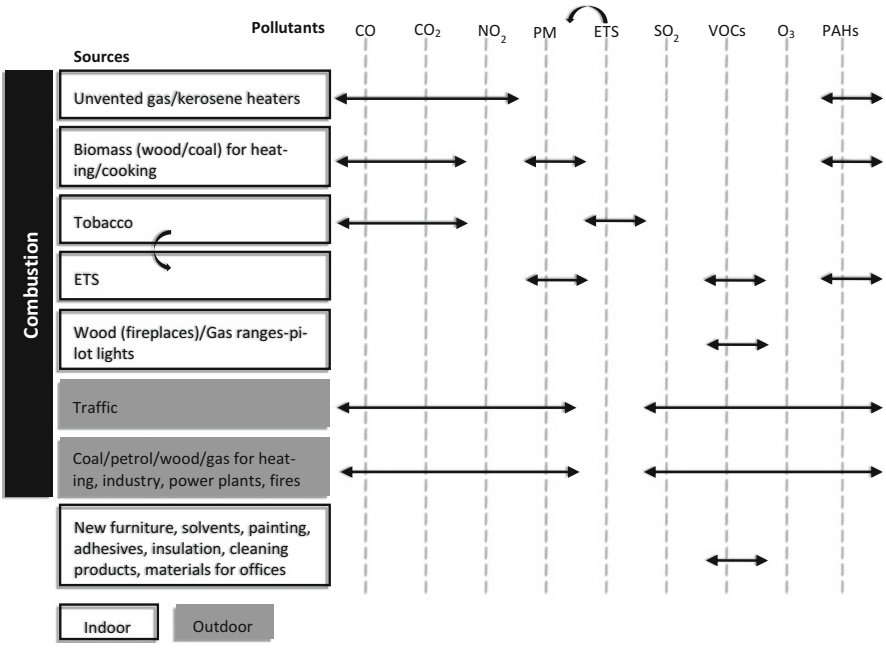

Fig. 3 Common anthropogenic direct risk factors and relative outdoor/indoor sources (Maio et al. 2013). Reused with permission from the World Allergy Organization. *CO* Carbon monoxide, CO_2 Carbon dioxide, NO_2 Nitrogen dioxide, *PM* Particulate matter, *ETS* Environmental tobacco smoke, SO_2 Sulfur dioxide, *VOCs* Volatile organic compounds, O_3: Ozone (secondary pollutant), *PAHs* Polycyclic aromatic hydrocarbons

2.2.3 Indirect Anthropogenic Environmental Factors

Additionally, the influence of anthropogenic environmental factors on the susceptibility to allergies can occur indirectly. Such environmental–environmental interactions appear to be a missing link in the comprehensive understanding of allergic diseases. This interaction is characterized by the influence of certain environmental factors amongst each other. It has been demonstrated both in vitro and in clinical studies that birch pollen from areas with a higher ozone load have a significantly increased allergenicity than those from areas with a comparatively lower concentration of ozone (Beck et al. 2013).

2.2.4 Biogenic Environmental Risk Factors

Biogenic factors, i.e. factors of organic origin, are usually involved in the development of allergic diseases. Figure 4 provides an overview of the major biogenic environmental risk factors.

In terms of inhaled biogenic allergens, it is important to distinguish between outdoor and indoor allergens. The majority of outdoor allergens arise seasonally such as pollen from grasses, trees, and weeds (Adkinson 2008). Typically, there is a positive correlation between the exposure to pollen and the severity of symptoms

Category			Primary site of exposure	Prevalence of exposure	Dispersal	Sensitization
Inhaled						
Out-doors	Pollen		Nose, eyes	+++	Windborne	Up to 30% worldwide
	Mold spores		Nose, eyes	+++	Windborne	Up to 10% worldwide
	Algae		Nose, eyes	+	Windborne	Rare
Indoors	Acarids	Dust mite	Nose, lungs	+++	Transient after disturbance	Temperate zones
		Storage mite	Nose, lungs	+		Farming
	Insects	Cockroach	Nose, lungs	++		Widespread
		Other	Nose, lungs	+		Locally common
	Mammals	Cats	Nose, lungs	++	Airborne for many hours	Common
		Dogs	Nose, lungs	++		Common
		Other	Nose, lungs	+		Dependent upon exposure
Non-inhaled						
Food	Peanuts, tree nuts, wheat, soy, egg, chicken, etc.		Oral and/or skin	+++	N/A	Sensitization variable; up to 4%; not clearly related to exposure
Bites, stings, etc.	Hymenoptera		Skin/circulation	+	N/A	
	Ticks		Skin	+	N/A	Locally important

Fig. 4 Major biogenic risk factors for allergic diseases (Pawankar et al. 2013)

(Gilles et al. 2011). Other significant causes of sensitization are mold allergens and fungal spores (Chew et al. 2000). Exposure to outdoor allergens is dependent on the concentration of aeroallergens, the time spent outdoors, and the capability to seal off indoor areas from outdoor allergens (Pawankar et al. 2013).

Major sources of indoor allergens include dust mite droppings, animal dander, cockroach droppings, and molds. With respect to asthma there also is a dose-response relationship between exposure to the above-mentioned allergens and sensitization (Platts-Mills et al. 1997).

Non-inhaled biogenic allergens mainly arise from food sources or insect bites and stings. In case of food allergies, the symptoms are primarily oral, gastrointestinal, or urticarial. Food allergens often occur regionally (Connett et al. 2012) and they can significantly contribute to the development of atopic dermatitis (Han et al. 2009). Insect venom is a potent allergen and repeated exposure bears the risk of both an IgE response and subsequent anaphylactic responses (Pawankar et al. 2013).

In conclusion, to a large extent the root causes leading to the epidemic increase in allergic diseases are still unknown (Ring et al. 2012). In the past, the genetic predisposition was seen as the only responsible factor for the development of allergic diseases. Yet the vast increase in the prevalence of allergies suggests that allergies are also an environmental disease (Traidl-Hoffmann 2017). Obviously, anthropogenic climate change and globalization (Castelain 2011) are two recent trends with enormous impact on our environment and on related (health-)conditions. The increase in both areas strongly overlaps with the spread of the allergic epidemic and hence we need to consider and analyze anthropogenic climate change and globalization themselves as risk factors for the development of allergies. Taking climate change and globalization into account would aid the understanding of the

sources of the allergic epidemic and is an essential prerequisite for creating effective counter-measures and strategies in terms of prevention and therapy. The following two sections demonstrate how climate change (Sect. 2.3) and globalization (Sect. 2.4) cross-sectionally influence the above-mentioned environmental risk factors for developing allergic diseases.

2.3 Anthropogenic Climate Change

2.3.1 Background

The climate system is subject to natural external factors and complex internal processes. Nevertheless, according to the current state of research, it is very likely that anthropogenic greenhouse gas (GHG) emissions are the main cause of global warming which has occurred since the middle of the twentieth century (IPCC 2014). Besides the well-known adverse ecological effects of climate change, the rise in temperature poses increased risks to human health, especially with respect to allergic diseases (see Sect. 2.3.2).

2.3.2 Impacts on Allergies

Climate change increases the prevalence of allergic diseases in a both direct and indirect manner (see Fig. 5). The largest effect is noticeable in pollen allergies and associated problems of respiratory health (Pawankar et al. 2013).

Direct Impacts

The major direct impact of climate change on allergic diseases is given by the increased occurrence of heat waves (Demain 2018). These prolonged periods of abnormally hot weather induce heat stress which, especially in combination with air pollution, promotes inflammation and lowers the airway hyper-reactivity threshold due to fluid loss and disrupted pulmonary perfusion. Consequently, during a heat

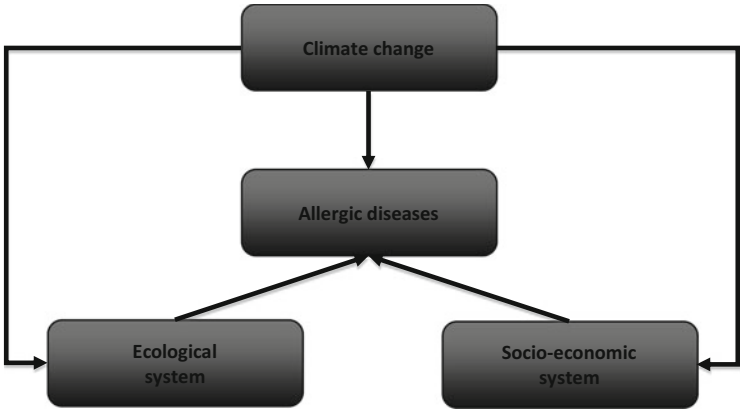

Fig. 5 Direct and indirect impacts of climate change with respect to allergic diseases

wave patients with chronic respiratory diseases, including asthma and related allergies, bear a higher mortality risk of 1.8–8.2% compared to average summer temperatures (Witt et al. 2015). According to recent projections, more intense heat waves in the future will induce further aggravation of respiratory allergies which will culminate in an increase in mortality (Costello et al. 2009).

Indirect Impacts (Ecological System)

The majority of the negative effects of climate change on allergic diseases are passed on via ecological pathways and most notably affect the respiratory system and respiratory related allergies (Beggs 2016). The major factors of climate change which impact on the development and worsening of allergies are the increasing global average temperature, sea level rise, extreme weather events, and with that changing crop production.

Increasing Global Average Temperature

Longer Pollen Season and Increased Pollen Concentration

The rise in global average temperature causes the expansion of vegetation periods. This prolongs the pollen season and increases the allergenic biomass. Consequently, allergy sufferers are exposed to higher pollen concentrations for longer periods of time and the level of suffering increases accordingly. Due to higher pollen exposure levels, the risk for previously healthy people to (re-)develop allergies increases as well. Empirical evidence has shown that there is a correlation between a rise in temperature and the total pollen concentration in Europe. This is especially noticeable for the allergenic birch and grass pollen (Smith et al. 2014). Particularly striking is the proportional increase in birch pollen concentrations in urban microclimates and hence one can assume that the ambient air pollution in terms of NO_x, CO_2, and VOCs can raise the pollen concentration in the environment (Ziello et al. 2012). This hypothesis is also consistent with experiments in climatic chambers (Zhao et al. 2017). However, recent studies show that the pollen concentrations in urban areas are subject to strong local and temporal variations, which necessitates tighter pollen monitoring networks within cities or even personal pollen exposure measurements (Werchan et al. 2017).

Rising Prevalence of Allergic Diseases Due to New Types of Pollen

Climate change promotes the growth of invasive plant species (so-called neophytes), which are mainly spread by anthropogenic processes. A prime example is given by ragweed which is originally endemic to the American continent and whose pollen is rated as a strong allergenic trigger. The smooth phenotype of ragweed seeds enhances the rapid spreading of the plant by wind. Anthropogenic activities, such as interregional trade in agricultural products, have further enabled the introduction and spread of ragweed in Europe (Rogers et al. 2006). The establishment of ragweed in new regions is further promoted by climate change, because longer periods of heat create new vegetation niches for non-native plants (Sikoparija et al. 2017). It is beyond dispute that the occurrence of ragweed causes new sensitizations and allergies (Burbach et al. 2009). In addition, other neophytes such as the Canadian goldenrod or the late goldenrod are suspected to cause pollen allergies. However,

because these plants are characterized by insect pollination rather than distribution of pollen by wind, their allergic potential is limited primarily to cut flowers indoors (BfN 2018).

Increasing Aggressiveness and Allergenicity of Pollen

Additionally, besides registering an increase in pollen due to anthropogenic climate change recent scientific studies have provided evidence for the fact that growing environmental pollution may enhance the allergenic potential of allergy-causing plants. Exposure experiments have shown that traffic-related pollutants strengthen the release of allergenic particles from pollen (Motta et al. 2006). But not only quantitative changes take place. Results from field and in vitro studies show a qualitative change in allergens too. NO_2 exposure leads to nitrosylation of the birch allergen (Zhao et al. 2016). Moreover, an exposition to particles induces nitration of allergenic proteins and moreover formation of new allergens (Zhao et al. 2017). The effect of environmental pollutants on allergenicity is by no means limited to pollen, but can also affect other airborne allergen carriers, such as mold fungi (Lang-Yona et al. 2016).

Furthermore, recent climate chamber experiments showed increased pollen allergenicity as a result of ozone pollution and this was especially striking for the ragweed pollen (Zhao et al. 2016). Yet also in field studies birch pollen from areas of high ozone pollution has a higher allergenicity than pollen from trees that thrive in areas with lower ozone levels (Beck et al. 2013). It is important to note that climate change fuels this pollutant-induced increase in allergenicity, as there is a positive correlation between temperature rise and ozone concentration. Finally, recent studies show that carbon dioxide in combination with drought stress promotes the allergenicity of ragweed pollen (Zhao et al. 2017). It is critical to note that not every pollutant necessarily increases the allergen content of pollen, especially under in vitro conditions (Rogerieux et al. 2007). This insight is strengthened by a field study, which was unable to prove a correlation between NO_2 and allergen content (Beck et al. 2013). However, it is now known that the allergenicity of pollen is determined not only by its allergen content but also by a variety of low-molecular-weight mediators (Gilles-Stein et al. 2016). These mediators are released from pollen in higher concentrations when they grow in an urban environment and under high NO_2 concentration (Beck et al. 2013). Even if not all effects of climate change lead to augmented pollen allergenicity, overall there is a clear trend.

Sea Level Rise

Since the beginning of the twentieth century, the global mean sea level has risen by approximately 0.2 m and a rise of approximately 0.08 m has occurred since 1993. According to current projections, it is very likely that by the end of the twenty-first century the sea level will have risen by one additional meter (Church et al. 2013). A higher sea level increases the indoor moisture in populated coastal areas. In the aftermath of Hurricane Katrina (New Orleans, USA) high fungal concentrations – both indoor and outdoor – were recorded (Barbeau et al. 2010). Wet housing conditions, especially when combined with increased temperatures and CO_2 levels, will encourage fungal growth and mold contamination which would have serious

adverse effects in terms of respiratory allergies (Katelaris and Beggs 2018). Allergic sensitization to fungi is an important risk factor for allergic asthma and fungal exposure has been linked to asthma exacerbations and hospital presentations involving a rise in asthma mortality (Tham et al. 2014). In addition to allergic rhinitis and asthma, fungal exposure has been associated with afflictions such as allergic broncho-pulmonary aspergillosis, hypersensitivity pneumonitis, allergic fungal sinusitis, and atopic dermatitis (Katelaris and Beggs 2018).

This sea level rise induced boost of respiratory allergies is aggravated by the fact that there has been a strong population growth in lower coastal areas over the past decades, implying that more and more people are exposed to damp housing conditions (Demain 2018). According to a meta-analysis of 33 epidemiologic studies, adverse respiratory health outcomes in occupants rise by 20–50% because of wet living conditions and related mold exposure (Fisk et al. 2007).

Extreme Weather Events

There is increasing evidence for severe asthma attacks during thunderstorms in high pollen seasons in various geographical zones, most notably in Europe and Australia (Lin et al. 2009). During the first 30 min of a thunderstorm the heavy rainfall ruptures pollen grains thus releasing respirable allergenic particles (USGCRP 2016). Furthermore, cold downdrafts transport these aeroallergens to the ground level where they spread due to strong electric fields caused by the thunderstorm and hence promote bronchial hyper-responsiveness (D'Amato et al. 2012). Consequently, pollen allergy sufferers who are exposed to the first phase of a thunderstorm are faced with high allergen levels and are at risk of severe asthmatic shocks and exacerbations of allergic symptoms (D'Amato et al. 2016b).

Food Allergies

Food allergies are on the rise. In industrialized countries, 4–8% of children and 3–4% of adults are affected (Burks 2015). Recent studies point out that IgE-mediated allergies to common food types result not only from sensitization through the gastrointestinal tract, but also from sensitization to homologous pollen allergens through the respiratory tract. The food allergies then arise due to the cross-reactivity with certain airborne allergens (Popescu 2015). For instance, the prevalence of plant food allergy in Europe is significantly influenced by sensitization to specific proteins in birch pollen, while in the Mediterranean area sensitization mainly occurs through profilins and non-specific lipid transfer proteins (Burney et al. 2014). This indicates that (re-)distribution of allergenic plants due to climate change will also probably induce altered patterns of food allergies (Katelaris and Beggs 2018). Additionally, recent experimental studies suggest that the allergenicity of some plant-based foods is enhanced at higher levels of CO_2 (Ziska et al. 2016). As a final comment aeroallergens have been shown to presumably play an important role in inducing pediatric eosinophilic esophagitis (Fahey et al. 2017).

Indirect Impacts (Socio-Economic System)

On top of the pathway of the ecological system, climate change transmits detrimental effects with respect to health and allergies via a socio-economic system (Haines and Ebi 2019). One major impact is that climate change impairs the food supply provided by the agricultural sector.

Altered climatic and environmental conditions diminish the yield of vegetables and legumes, which play a crucial role in sustaining health and preventing (non-communicable) diseases (Scheelbeek et al. 2018). This scarcity especially hits poor countries and parts of the population with lower incomes, which out of necessity consume cheaper and thus less healthy sources of food (Kinney 2008). Moreover, increasing CO_2 concentrations are suspected to be involved in lowering the nutritional quality (of proteins, B vitamins, and micronutrients) of major crops, such as rice or wheat. (Myers et al. 2014). The associated adverse effects on the general state of health foster the development and severity of allergic diseases.

Climate change also accelerates the impoverishment of poor countries due to the abovementioned production losses in the agricultural sector and damages caused by flooding or extreme weather events. As a result, fewer resources are available for investments in the public health system, implying an insufficient supply of measures for preventing and treating allergic diseases (Tanner and Horn-Phathanothai 2014). Finally, impoverishment causes migration and conflicts, both of which undermine a stable and resilient health condition of the people affected (Abel et al. 2019).

2.4 Globalization

2.4.1 Background

Globalization in simple terms refers to the rising flow of goods, people, services, labor, technology, and capital worldwide and the associated increase in interconnectedness of the various parts of the world. Major drivers of these accelerated exchanges are the creation and development of new information and communication technologies and of new means of transportation. Hence globalization is primarily an economic process of interaction and integration, accompanied by social, political, and cultural aspects (Guttal 2007). For obvious reasons and as explained below, globalization and associated changes have a major impact on human health, see Fig. 6.

Demographic Changes

Population growth plays an often neglected but crucial role in global change, especially with respect to its inherent contribution to the increase in GHG emissions and climate change. According to recent UN projections the world population is expected to rise to 9.3 billion by 2050. Therefore there is an urgent need for efficient climate change mitigation and adaptation strategies. These must include components to deal with related health problems (United Nations 2019). Besides climate change, population growth exerts massive pressure on regional environments. These pressures include soil exhaustion, water depletion, and the loss of various wild

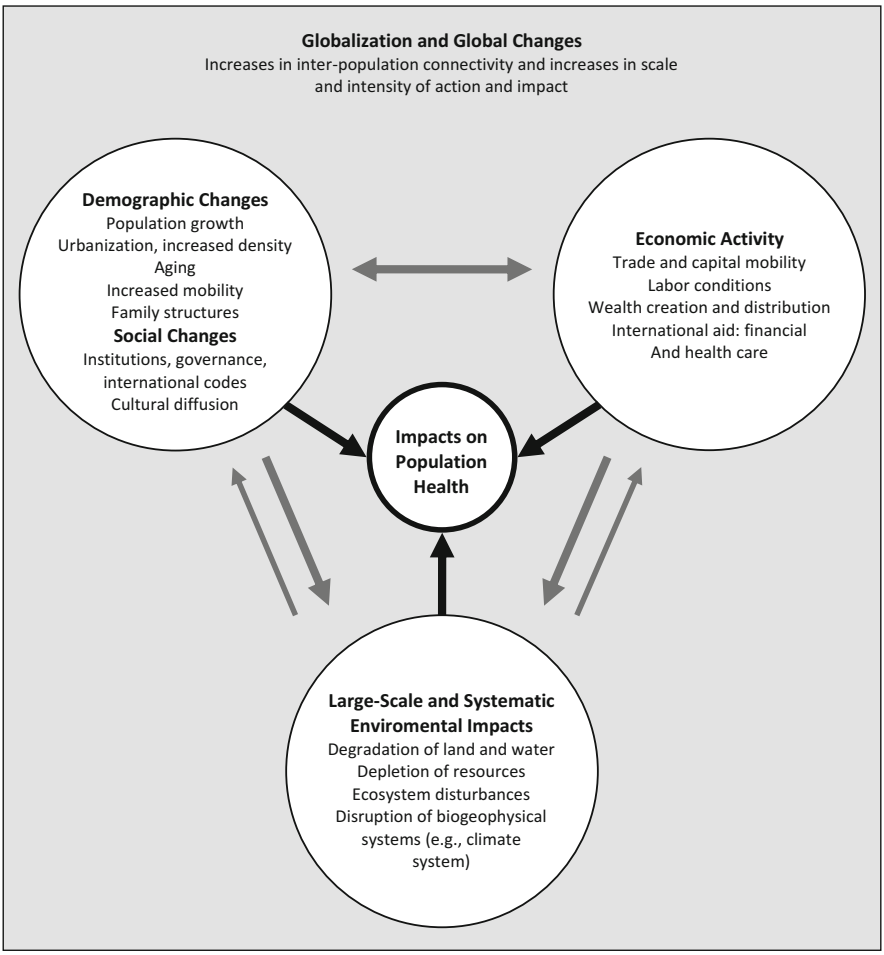

Fig. 6 Impacts of Globalization and associated changes on human health (McMichael 2013)

animal and plant food species. They harm the ecosystem and thus foster poverty and a decrease in human health.

Social Changes and Economic Activity

The social and economic dimension of globalization affects human health in various direct ways, such as the increased prevalence of both (new) infectious diseases and NCDs, rising resistances to antimicrobial agents, workplace-related health risks due to the deregulation of international labor markets or expansion of tobacco marketing (Labonté et al. 2011). Indirect health impacts are given by increasing inequalities in wealth, education, autonomy, and social inclusion (Marmot et al. 2008). Some aspects of globalization also benefit human health. For instance, the increased

availability of information, progress in international vaccination programs and systems to address infectious diseases as well as a greater capacity for long-distance responses to disasters. A prime example in this respect is given by the COVID-19 pandemic which has hit the EU in February 2020. Nevertheless, a sustainable improvement of conditions for human health requires linking environmental and sociocultural conditions and basic human biologic and psychological needs.

Environmental and Ecologic Changes

Primary prevention of health problems associated with global environmental and ecologic changes, such as degradation of land and water or depletion of natural resources, requires coordinated international policies and supplementary local policies and actions. This is for the reason that these problems, as in case of climate change, are rooted in individual actions on the local or regional level (e.g., GHG-emissions caused by economic activities of single agents), but then accumulate to adverse health impacts on a global scale (e.g., health problems related to global warming) (McMichael 2013).

2.4.2 Impact on Allergies

Globalization brings (potential) allergy sufferers increasingly into contact with products, food, plants, and animals from other cultures or countries (Castelain 2011). Allergic contact dermatitis, airborne allergies, animal dander, and food allergies are on the increase due to the global change and increased interconnectedness.

Allergic Contact Dermatitis

This type of allergy is mainly caused by toxic or allergenic substances that are processed in internationally traded commodities. For instance, 2006 marked the beginning of an epidemic with several hundred people suffering from eczema throughout Europe. All of these patients had purchased armchairs imported from China whose stuffing contained dimethyl fumarate (DMF). In China, DMF commonly serves as a cheap antifungal agent – despite its harmful effects on health and the environment. Due to its volatility, it causes acute contact dermatitis accompanied by biological signs of rhabdomyolysis (Lammintausta et al. 2010).

Another trigger of contact dermatitis can be nickel. Allergic sensitization may be caused by repeated skin contact with objects releasing nickel in critical quantities, such as fashion jewelry, belt buckles, or cell phones (Livideanu et al. 2007). Even though the EU has banned products whose release exceeds a critical nickel-threshold, imported nickel-containing commodities from overseas countries can reach the European market due to insufficient controls and thus constitute a serious source of allergic contact dermatitis (Thyssen et al. 2009).

Besides commercial products, specific types of plants may trigger allergic contact dermatitis. For instance, some plants from the anacardiaceae family (such as the cashew nut tree) contain “urushiol.” This highly allergenic substance can cause severe acute dermatitis by single contact. Relevant plants are common in the American wilderness, especially in the USA and Canada. However, globalization

bears the risk that these plants may invade Europe through contaminated cargo containing earth or vegetables or through illegal importation (Sasseville 2009).

Airborne Allergies

Plants causing airborne contact dermatitis may spread around the world as a result of two internationally interlinked economic activities. A famous example is given by *Parthenium hysterophorus* ("white grass"), a highly allergenic plant that cross-reacts with other asteraceae plants. Originating in Mexico, it made its way to the USA, Africa, Australia, and India via trade flows of contaminated cereals. Primarily in India, white grass has developed into a major trigger of contact allergy (Mahajan et al. 2004). Counter-measures to prevent the spread of toxic or harmful botanicals may cause additional allergic emergencies. For instance, many countries impose regulations prescribing shipped freight containers to be decontaminated with pesticides or other potentially deleterious gases. These fumigants have not only been detected in the air of shipping containers, but can also settle down and contaminate the transported commodities. With a half-life of up to several months, the contaminating substances persevere for a considerable amount of time. As a result, both dock workers and consumers are at risk to develop associated skin allergies or respiratory irritations (Castelain 2011).

Plants disseminating aeroallergens may themselves also spread around the globe due to processes of globalization. The prime example is ragweed, which was presumably transported from North America, its original habitat, to France in a load of animal feed. Due to the ragweed seeds' capability of sticking to tires, to the increase in traffic and the changing climatic conditions, it has been possible for ragweed to spread across Europe (Laaidi et al. 2003).

Finally, the increase of people travelling themselves can lead to the exposure to aeroallergens due to the different flowering seasons at the destination of travel.

(Domestic) Animals

One of the negative side effects of globalization consists in the expansion of the ruthless trade in exotic animals as pets. Amongst others, chinchillas (endemic to the Andes Mountains) presumably trigger asthma and rhinitis; gerbils (Mongolia) and jerboas (North America) may induce anaphylaxis by their bites (Curin and Hilger 2017). These animals need to be considered as dangerous and venomous. They are not adapted to our climate and are often abandoned by their overburdened or annoyed owners.

Food

Clearly, globalization has boosted the availability and consumption of (previously) exotic food, i.e. vegetables and fruits, including those with the most allergy-sensitizing impact, such as peanuts, kiwis, avocados, bananas, or celery (Castelain 2011). But also various kinds of seafood, industrial food, spices, and herbs are nowadays widespread around the globe.

Globalization has led to a severe rise in allergies to cashews, Brazil nuts, sesame, and seafood. Labelling requirements that ensure that warnings against potential

allergens are declared on the products are often insufficient. Because the traceability of processed raw materials, especially from developing countries, is very difficult, cross-contamination is a likely consequence (Taylor and Baumert 2010).

A new emerging serious threat not to be underestimated is the spread of genetically modified (GM) foods, which often contain proteins that were previously not present in human food. Typical GM foods such as soybeans or crops spread from the USA act as potential sources of allergic reactions that impair human health (Bawa and Anilakumar 2013).

3 The Ethical Dimension of Allergic Diseases

3.1 Fundamental Ethical Implications of the Allergic Epidemic

As described above, allergies need to be ranked as severe chronic illnesses that cause various morbidities including irritable disorders such as dermatitis as well as disabling conditions associated with a high mortality risk, such as asthma and anaphylaxis. These medical conditions considerably reduce the patients' quality of life (Michaud et al. 2006). In combination with the epidemic-like prevalence, allergies constitute a major ethical issue on a global scale. This especially becomes obvious against the background of the human right to health which is defined in the constitution of the WHO as: "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being" (World Health Organization 1948). As can be seen impressively from the currently ongoing COVID-19-pandemic, maintaining and adhering to the human right to health is in no way an automatism, it rather requires insistent and globally concerted political action.

On the one hand, this right constitutes an urgent and immediate moral obligation of the international community to implement and intensify health strategies that pointedly address allergic diseases in terms of therapy. On the other hand, a major pillar of such strategies is prevention, i.e. the mitigation of the above-mentioned risk factors, especially climate change and globalization. In this respect, restoring and sustaining a health-promoting environment is of vital importance. For obvious reasons, an intact environment is an essential prerequisite for implementing human rights – be it in terms of health, food and water supply or even self-determination. This connection was recognized for the first time in the UN Convention on the Rights of the Child (UN General Assembly 1989). Specifically, this convention emphasizes the need to address environmental issues in child disease control. The scientific evidence for the adverse health effects of environmental pollution and climate change underpins the urgent call for ethically motivated action to fight the allergic epidemic.

3.2 Matters of Distributional Justice

Besides this basic moral obligation, allergic diseases involve crucial matters of distributional justice that need to be addressed by ethically motivated corrective action and related health programs. Clearly, the allergic epidemic is boosted by recently emerging and reinforcing risk factors rooted in the anthropogenic influence on the natural environment as well as in processes associated with globalization (Traidl-Hoffmann 2017). However, the question of vulnerability to allergic diseases crucially depends on social determinants.

Allergic sensitization indeed occurs in all social classes and ethnic groups, but the distribution of the pathology follows uneven patterns. Specifically, there is a strong negative correlation between the socioeconomic status and morbidity from allergic diseases (Almqvist et al. 2005). For instance, hospitalizations for asthma mainly occur in low and middle socioeconomic classes, and asthma morbidity primarily affects ethnic minorities (Foggs 2005). This socioeconomic gradient in terms of allergy suffering apparently does not depend on universally granted access to public health services, as has been shown in a respective study for Canada (Behrmann 2010). Raised morbidity rates among lower classes are tied to factors of social deprivation. For instance, poverty stricken children in urban livelihoods are frequently exposed to cockroaches, rodents, mold, and dust due to inadequate housing standards (Breysse et al. 2004). Additionally, ethnic minorities or financially weak parts of the population are forced into neighborhoods with low housing costs which typically feature increased levels of environmental pollution and thus involve a higher risk for developing allergies. These groups also have to frequently cope with cheap (and potentially bioengineered) groceries and limited diets which may trigger food (and other) allergies. To sum up, certain populations such as children, ethnic minorities, and members of lower socioeconomic classes are particularly vulnerable to allergy and asthma morbidity.

However, this socioeconomic gradient in terms of developing allergies does not only apply for different classes of population, but also for countries or world regions as a whole. In this sense, allergic diseases and asthma are increasing particularly in low and middle income countries, due to specific poverty-related risk factors (Pawankar 2014). People in these countries frequently use solid fuel such as wood, cow dung, or crop residues, which is burned in simple stoves or open fire in order to generate domestic energy (Pawankar et al. 2013). Moreover, in middle income countries people have reached a sufficient level of wealth to consume tobacco products. Taken together, estimates suggest that indoor pollution is five times higher in poor countries compared to industrialized ones (World Health Organization 2007) To aggravate the situation, developing countries typically set lower priorities on environmental protection compared to economic growth. Therefore, there are higher levels of outdoor pollution in developing countries, which enhances the prevalence of allergic diseases (Pawankar et al. 2013). Additionally, these countries are especially vulnerable to the impacts of climate change, inducing an additional boost to related allergy risk factors (Heuson and Traidl-Hoffmann 2018).

Obviously, this socioeconomic gradient in terms of allergy prevalence across population groups and countries constitutes a serious injustice, since factors beyond the control of an individual such as being a member of an ethnic minority, population class or country cause an increased risk of allergy and asthma morbidity. Consequently, distributional justice necessarily needs to serve as guiding principle for the setting of goals within global strategies and programs to mitigate the allergic epidemic.

4 Policy Implications and Conclusion

The ethical dimension of the allergic epidemic depicted above has two major policy implications. First, the severity and extent of this epidemic requires a comprehensive and globally concerted strategy and program in order to sustainably tackle allergies and thus adhere to the human right to health proclaimed by the WHO (EAACI 2016). Second, seeing that the prevalence of allergies follows a steep socioeconomic gradient both in terms of population groups and countries, the stated strategies and programs need to be conceptualized and prioritized according to the principle of distributional justice.

4.1 Globally Concerted Strategy and Program to Sustainably Tackle Allergies

A comprehensive answer to the allergic epidemic must include a broad range of policy measures (EAACI 2014). Since the severity of allergic diseases is frequently underrated, the initial task would be to raise the awareness of allergic diseases and their priority both in the general public and among policy makers. Subsequently, national policies and interventions in terms of treating and alleviating the burden of allergic diseases need to be developed and interlinked between countries and world regions. This includes the promotion of capacity building and the improvement of health care delivery with respect to accessibility and affordability to treatment. Naturally, an essential prerequisite is to support research on increasing the tolerance, on early intervention, prevention and control of allergic diseases. However, the most promising and efficient strategy to tackle the allergic epidemic requires prevention and with that addressing its roots and the abovementioned risk factors – most notably climate change and globalization.

In terms of climate change mitigation, a mix of environmental policy instruments is the most promising approach. The central pillar of this mix is provided by tradable emission licenses that guarantee both the ecologically effective and economically efficient reduction of GHGs (Heuson 2010). The GHG emissions trading market addresses the majority of climate-related air pollutants. However, it should be expanded to include previously not covered emission sources and sectors. Furthermore, the quota of licenses should be significantly reduced compared to the status quo. Currently, the legally permitted emissions are far too high – not only in terms of

climate change mitigation and allergy prevention, but also with respect to the license market's economic efficiency. In addition to this, other allergy-relevant air pollutants that are not directly related to GHG emissions can and should be regulated in an efficient manner through emission taxes. However, if the priority is to meet a certain emission threshold – for example due to serious health impairments of the respective pollutant – quantitative regulatory instruments, in particular emission quotas are preferable. Suasoric approaches merely play a complementary role due to their vague ecological effectiveness. Examples are promoting information campaigns on the acceptance of "harsher" environmental interventions or on environmentally friendly behavior at the individual level.

Despite its benefits on the economic and cultural level, globalization comes with severe risks and drawbacks in terms of allergies. As world trade gathers momentum the complexities also increase more and more. For this reason, allergens contained in food, animals, plants, commodities, and packaging are distributed all over the world, thus exposing people with new and more allergens. In principle, product standards, regulations on processing methods or imports should be sufficient to address these concerns. However, relevant legislation often falls short of the required standard unless it is unilaterally issued by states or confederations, as can be seen in case of the EU. This is due to the dramatic increase in the volume of imports, which is associated with many new allergen-sources and ways of circumventing EU law. Additionally, online trade and counterfeiting similarly undermine respective unilateral legislations (Castelain 2011). For this reason, a sustainable strategy to mitigate the increasing prevalence of allergies induced by globalization necessarily requires international efforts to conceptualize, issue, and finally enforce uniform trade- and product-related legislation. However, seeing that such legislation can never cope with the rapid development of globalization and associated trade flows completely, the strategy needs to involve continuously updated campaigns of information to consumers.

4.2 Conceptualizing and Prioritizing Allergy Programs According to the Principle of Distributional Justice

Theories of social justice serve as useful approach to tackle socially unequal and thus unjust distributions of diseases such as the allergic epidemic (Behrmann 2010). In particular, the most influential theory of justice – especially with respect to health policy –is given by John Rawls's "justice as fairness" (Daniels 2008). This theory places the focus on the premise of equality of opportunity, claiming that people should possess equal liberties and potentials to pursue their goals of life (Rawls 2003). This principle emphasizes the responsibility for social institutions to implement policies that guarantee equal opportunity to all members of society. In this sense, allergy-related policies ought to reduce allergy morbidity amongst the whole range of allergy sufferers in equal manner, independent of their social or ethnical background. Commercial interests or similar influences as for example asserted by

lobbying of particular interest groups must not distort this equal treatment of allergic patients.

The second major principle of the Rawlsian theory refers to the moral imperative for social institutions to take precautions against discrimination. Along these lines, health policies ought to fight against the stigmatization of parts of the population suffering from a specific disease. This includes framing health policy measures in a way that patients do not accidentally get discriminated. For instance, this applies to the support of socially weak individuals with respect to the prevention or treatment of allergies that emanate from poor housing conditions.

In conclusion, these principles justify the pooling of health benefit resources towards especially underprivileged allergy patients. Moreover, the Rawlsian theory can be used to develop schemes and algorithms to prioritize and choose among competing allergy policies in terms of prevention and treatment (Behrmann 2010).

References

Abel GJ, Brottrager M, Crespo Cuaresma J, Muttarak R (2019) Climate, conflict and forced migration. Glob Environ Chang 54:239–249

Adkinson NF Jr (2008) Middleton's allergy 2-volume set: principles and practice, 7th edn. Mosby

Almqvist C, Pershagen G, Wickman M (2005) Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clin Exp Allergy 35(5):612–618

Barbeau DN, Grimsley LF, White LE, El-Dahr JM, Lichtveld M (2010) Mold exposure and health effects following hurricanes Katrina and Rita. Annu Rev Public Health 31:165–178. 1 p following 178

Bawa AS, Anilakumar KR (2013) Genetically modified foods: safety, risks and public concerns-a review. J Food Sci Technol 50(6):1035–1046

Beck I, Jochner S, Gilles S, McIntyre M, Buters JTM, Schmidt-Weber C, Behrendt H, Ring J, Menzel A, Traidl-Hoffmann C (2013) High environmental ozone levels lead to enhanced allergenicity of birch pollen. PLoS One 8(11)

Beggs PJ (ed) (2016) Impacts of climate change on allergens and allergic diseases. Cambridge University Press, Cambridge

Behrmann J (2010) Allergies and asthma: employing principles of social justice as a guide in public health policy development. Les ateliers de l'éthique 5(1):119

BfN (2018) FloraWeb: Daten und Informationen zu Wildpflanzen und zur Vegetation Deutschlands. http://floraweb.de/pflanzenarten/neophyten.html. Accessed 7 Aug 2019

Breysse P, Farr N, Galke W, Lanphear B, Morley R, Bergofsky L (2004) The relationship between housing and health: children at risk. Environ Health Perspect 112(15):1583–1588

Burbach GJ, Heinzerling LM, Röhnelt C, Bergmann K-C, Behrendt H, Zuberbier T (2009) Ragweed sensitization in Europe – GA(2)LEN study suggests increasing prevalence. Allergy 64(4):664–665

Burks AW (2015) The changing field of food allergy. The journal of allergy and clinical immunology. In Pract 3(1):39–41

Burney PGJ, Potts J, Kummeling I, Mills ENC, Clausen M, Dubakiene R, Barreales L, Fernandez-Perez C, Fernandez-Rivas M, Le T-M, Knulst AC, Kowalski ML, Lidholm J, Ballmer-Weber BK, Braun-Fahlander C, Mustakov T, Kralimarkova T, Popov T, Sakellariou A, Papadopoulos NG, Versteeg SA, Zuidmeer L, Akkerdaas JH, Hoffmann-Sommergruber K, van Ree R (2014) The prevalence and distribution of food sensitization in European adults. Allergy 69(3):365–371

Castelain M (2011) Globalisation and allergy. Eur J Dermatol 21(4):472–478

Chew FT, Lim SH, Shang HS, Dahlia MD, Goh DY, Lee BW, Tan HT, Tan TK (2000) Evaluation of the allergenicity of tropical pollen and airborne spores in Singapore. Allergy 55(4):340–347

Church JA, Clark PU, Cazenave A, Gregory JM, Jevrejeva S, Levermann A, Merrifield MA, Milne RS (eds) (2013) Sea level change. Climate change 2013: the physical science basis. Contribution of working group I to the fifth assessment report of the Intergovernmental Panel on climate change

Connett GJ, Gerez I, Cabrera-Morales EA, Yuenyongviwat A, Ngamphaiboon J, Chatchatee P, Sangsupawanich P, Soh S-E, Yap G-C, Shek LP-C, Lee B-W (2012) A population-based study of fish allergy in the Philippines, Singapore and Thailand. Int Arch Allergy Immunol 159 (4):384–390

Costello A, Abbas M, Allen A, Ball S, Bell S, Bellamy R, Friel S, Groce N, Johnson A, Kett M, Lee M, Levy C, Maslin M, McCoy D, McGuire B, Montgomery H, Napier D, Pagel C, Patel J, de Oliveira JAP, Redclift N, Rees H, Rogger D, Scott J, Stephenson J, Twigg J, Wolff J, Patterson C (2009) Managing the health effects of climate change. Lancet 373 (9676):1693–1733

Curin M, Hilger C (2017) Allergy to pets and new allergies to uncommon pets. Allergol Select 1 (2):214–221

D'Amato G, Cecchi L, Annesi-Maesano I (2012) A trans-disciplinary overview of case reports of thunderstorm-related asthma outbreaks and relapse. Eur Respir Rev 21(124):82–87

D'Amato G, Pawankar R, Vitale C, Lanza M, Molino A, Stanziola A, Sanduzzi A, Vatrella A, D'Amato M (2016a) Climate change and air pollution: effects on respiratory allergy. Allergy Asthma Immunol Res 8(5):391–395

D'Amato G, Vitale C, D'Amato M, Cecchi L, Liccardi G, Molino A, Vatrella A, Sanduzzi A, Maesano C, Annesi-Maesano I (2016b) Thunderstorm-related asthma: what happens and why. Clin Exp Allergy 46(3):390–396

Daniels N (2008) Just health. Meeting health needs fairly. Cambridge University Press, Cambridge

Demain JG (2018) Climate change and the impact on respiratory and allergic disease: 2018. Curr Allergy Asthma Rep 18(4):22

EAACI (2014) Global atlas of allergy. Eur Acad Allergy Clin Immunol

EAACI (2016) Tackling the allergy crisis in Europe – concerted policy action needed. EAACI Advocacy Manifesto. https://www.eaaci.org/documents/EAACI_Advocacy_Manifesto.pdf. Accessed 23 Jul 2019

Fahey L, Robinson G, Weinberger K, Giambrone AE, Solomon AB (2017) Correlation between aeroallergen levels and new diagnosis of eosinophilic esophagitis in NYC. J Pediatr Gastroenterol Nutr 64(1):22–25

Fisk WJ, Lei-Gomez Q, Mendell MJ (2007) Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. Indoor Air 17(4):284–296

Foggs MB (2005) Need for better adherence to asthma guidelines in Chicago. Ann Allergy Asthma Immunol 95(1):1–3

GBD 2017 Risk Factor Collaborators (2017) Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet 390(10100):1345–1422

Gilles S, Fekete A, Zhang X, Beck I, Blume C, Ring J, Schmidt-Weber C, Behrendt H, Schmitt-Kopplin P, Traidl-Hoffmann C (2011) Pollen metabolome analysis reveals adenosine as a major regulator of dendritic cell-primed T(H) cell responses. J Allergy Clin Immunol 127(2):454–461. e1–9

Gilles-Stein S, Beck I, Chaker A, Bas M, McIntyre M, Cifuentes L, Petersen A, Gutermuth J, Schmidt-Weber C, Behrendt H, Traidl-Hoffmann C (2016) Pollen derived low molecular compounds enhance the human allergen specific immune response in vivo. Clin Exp Allergy 46(10):1355–1365

Guttal S (2007) Globalisation. Dev Pract 17(4–5):523–531

Haines A, Ebi K (2019) The imperative for climate action to protect health. N Engl J Med 380 (3):263–273
Han Y, Chung S-J, Kim J, Ahn K, Lee S-i (2009) High sensitization rate to food allergens in breastfed infants with atopic dermatitis. Ann Allergy Asthma Immunol 103(4):332–336
Heuson C (2010) Weitzman revisited: emission standards versus taxes with uncertain abatement costs and market power of polluting firms. Environ Resource Econ 47(3):349–369
Heuson C, Traidl-Hoffmann C (2018) Bedeutung von Klima- und Umweltschutz für die gesundheit mit besonderer Berücksichtigung von Schädigungen der Hautbarriere und allergischen Folgeerkrankungen (the significance of climate and environment protection for health under special consideration of skin barrier damages and allergic sequelae). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 61(6):684–696
Hidaka T, Ogawa E, Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Fujimura T, Aiba S, Nakayama K, Okuyama R, Yamamoto M (2017) The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. Nat Immunol 18(1):64–73
IPCC (2014) Climate change 2014 synthesis report. Contribution of working group I to the fifth assessment report of the Intergovernmental Panel on climate change. Summary for policymakers
Irvine AD, McLean WHI, Leung DYM (2011) Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 365(14):1315–1327
Katelaris CH, Beggs PJ (2018) Climate change: allergens and allergic diseases. Intern Med J 48 (2):129–134
Kinney PL (2008) Climate change, air quality, and human health. Am J Prev Med 35(5):459–467
Laaidi M, Laaidi K, Besancenot J-P, Thibaudon M (2003) Ragweed in France: an invasive plant and its allergenic pollen. Ann Allergy Asthma Immunol 91(2):195–201
Labonté R, Mohindra K, Schrecker T (2011) The growing impact of globalization for health and public health practice. Annu Rev Public Health 32:263–283
Lammintausta K, Zimerson E, Winhoven S, Susitaival P, Hasan T, Gruvberger B, Williams J, Beck M, Bruze M (2010) Sensitization to dimethyl fumarate with multiple concurrent patch test reactions. Contact Dermatitis 62(2):88–96
Lang-Yona N, Shuster-Meiseles T, Mazar Y, Yarden O, Rudich Y (2016) Impact of urban air pollution on the allergenicity of Aspergillus fumigatus conidia: outdoor exposure study supported by laboratory experiments. Sci Total Environ 541:365–371
Lin S, Luo M, Walker RJ, Liu X, Hwang S-A, Chinery R (2009) Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. Epidemiology 20(5):738–746
Livideanu C, Giordano-Labadie F, Paul C (2007) Cellular phone addiction and allergic contact dermatitis to nickel. Contact Dermatitis 57(2):130–131
Mahajan VK, Sharma NL, Sharma RC (2004) Parthenium dermatitis: is it a systemic contact dermatitis or an airborne contact dermatitis? Contact Dermatitis 51(5–6):231–234
Maio S, Cerrai S, Simoni M, Sarno G, Baldacci S, Viegi G (2013) Section 3.3 environmental risk factors: indoor and outdoor pollution. In: Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss M (eds) WAO white book on allergy update 2013. World Allergy Organization, Milwaukee, p 92. https://www.worldallergy.org
Marmot M, Friel S, Bell R, Houweling TAJ, Taylor S (2008) Closing the gap in a generation: health equity through action on the social determinants of health. Lancet 372(9650):1661–1669
McMichael AJ (2013) Globalization, climate change, and human health. N Engl J Med 368 (14):1335–1343
Michaud CM, McKenna MT, Begg S, Tomijima N, Majmudar M, Bulzacchelli MT, Ebrahim S, Ezzati M, Salomon JA, Gaber Kreiser J, Hogan M, Murray CJL (2006) The burden of disease and injury in the United States 1996. Popul Health Metr 4:11
Motta AC, Marliere M, Peltre G, Sterenberg PA, Lacroix G (2006) Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. Int Arch Allergy Immunol 139(4):294–298

Myers SS, Zanobetti A, Kloog I, Huybers P, Leakey ADB, Bloom AJ, Carlisle E, Dietterich LH, Fitzgerald G, Hasegawa T, Holbrook NM, Nelson RL, Ottman MJ, Raboy V, Sakai H, Sartor KA, Schwartz J, Seneweera S, Tausz M, Usui Y (2014) Increasing CO2 threatens human nutrition. Nature 510(7503):139–142

Pawankar R (2014) Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J 7(1):12

Pawankar R, Holgate ST, Canonica GW, Lockey RF, Blaiss MS (2013) WAO White book on allergy. Update 2013

Platts-Mills T, Vervloet D, Thomas W, Aalberse R, Chapman M (1997) Indoor allergens and asthma: report of the third international workshop. J Allergy Clin Immunol 100(6):S2–S24

Popescu F-D (2015) Cross-reactivity between aeroallergens and food allergens. World J Methodol 5(2):31–50

Rawls J (2003) A theory of justice, rev. edn. 5–6. Printing. Belknap Press of Harvard Univ. Press, Cambridge

Ring J, Akdis C, Behrendt H, Lauener RP, Schäppi G, Akdis M, Ammann W, de Beaumont O, Bieber T, Bienenstock J, Blaser K, Bochner B, Bousquet J, Crameri R, Custovic A, Czerkinsky C, Darsow U, Denburg J, Drazen J, de Villiers EM, Fire A, Galli S, Haahtela T, Zur Hausen H, Hildemann S, Holgate S, Holt P, Jakob T, Jung A, Kemeny M, Koren H, Leung D, Lockey R, Marone G, Mempel M, Menné B, Menz G, Mueller U, von Mutius E, Ollert M, O'Mahony L, Pawankar R, Renz H, Platts-Mills T, Roduit C, Schmidt-Weber C, Traidl-Hoffmann C, Wahn U, Rietschel E (2012) Davos declaration: allergy as a global problem. Allergy 67(2):141–143

Rogerieux F, Godfrin D, Sénéchal H, Motta AC, Marlière M, Peltre G, Lacroix G (2007) Modifications of *Phleum pratense* grass pollen allergens following artificial exposure to gaseous air pollutants (O(3), NO(2), SO(2)). Int Arch Allergy Immunol 143(2):127–134

Rogers CA, Wayne PM, Macklin EA, Muilenberg ML, Wagner CJ, Epstein PR, Bazzaz FA (2006) Interaction of the onset of spring and elevated atmospheric CO2 on ragweed (*Ambrosia artemisiifolia* L.) pollen production. Environ Health Perspect 114(6):865–869

Sasseville D (2009) Dermatitis from plants of the new world. Eur J Dermatol 19(5):423–430

Scheelbeek PFD, Bird FA, Tuomisto HL, Green R, Harris FB, Joy EJM, Chalabi Z, Allen E, Haines A, Dangour AD (2018) Effect of environmental changes on vegetable and legume yields and nutritional quality. Proc Natl Acad Sci U S A 115(26):6804–6809

Sikoparija B, Skjøth CA, Celenk S, Testoni C, Abramidze T, Alm Kübler K, Belmonte J, Berger U, Bonini M, Charalampopoulos A, Damialis A, Clot B, Dahl Å, de Weger LA, Gehrig R, Hendrickx M, Hoebeke L, Ianovici N, Kofol Seliger A, Magyar D, Mányoki G, Milkovska S, Myszkowska D, Páldy A, Pashley CH, Rasmussen K, Ritenberga O, Rodinkova V, Rybníček O, Shalaboda V, Šaulienė I, Ščevková J, Stjepanović B, Thibaudon M, Verstraeten C, Vokou D, Yankova R, Smith M (2017) Spatial and temporal variations in airborne Ambrosia pollen in Europe. Aerobiologia 33(2):181–189

Smith M, Jäger S, Berger U, Sikoparija B, Hallsdottir M, Sauliene I, Bergmann K-C, Pashley CH, de Weger L, Majkowska-Wojciechowska B, Rybníček O, Thibaudon M, Gehrig R, Bonini M, Yankova R, Damialis A, Vokou D, Gutiérrez Bustillo AM, Hoffmann-Sommergruber K, van Ree R (2014) Geographic and temporal variations in pollen exposure across Europe. Allergy 69 (7):913–923

Tanner T, Horn-Phathanothai L (2014) Climate change and development. Routledge perspectives on development. Routledge, London

Taylor SL, Baumert JL (2010) Cross-contamination of foods and implications for food allergic patients. Curr Allergy Asthma Rep 10(4):265–270

Tham R, Dharmage SC, Taylor PE, Katelaris CH, Vicendese D, Abramson MJ, Erbas B (2014) Outdoor fungi and child asthma health service attendances. Pediatr Allergy Immunol 25 (5):439–449

Thyssen JP, Menné T, Johansen JD (2009) Nickel release from inexpensive jewelry and hair clasps purchased in an EU country – are consumers sufficiently protected from nickel exposure? Sci Total Environ 407(20):5315–5318

Traidl-Hoffmann C (2017) Allergie – eine Umwelterkrankung! (Allergy – an environmental disease). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 60(6):584–591

UN General Assembly (1989) Convention on the rights of the child. https://www.ohchr.org/Documents/ProfessionalInterest/crc.pdf. Accessed 16 Apr 2019

United Nations (2019) World Population Prospects – Population Division – United Nations. https://population.un.org/wpp/. Accessed 13 Aug 2019

USGCRP (2016) The impacts of climate change on human health in the United States: a scientific assessment. https://www.globalchange.gov/browse/reports/impacts-climate-change-human-health-united-states-scientific-assessment. Accessed 9 Aug 2019

Weiss C, Muñoz-Furlong A, Furlong TJ, Arbit J (2004) Impact of food allergies on school nursing practice. J Sch Nurs 20(5):268–278

Weisse K, Lehmann I, Heroux D, Kohajda T, Herberth G, Röder S, von Bergen M, Borte M, Denburg J (2012) The LINA cohort: indoor chemical exposure, circulating eosinophil/basophil (Eo/B) progenitors and early life skin manifestations. Clin Exp Allergy 42(9):1337–1346

Werchan B, Werchan M, Mücke H-G, Gauger U, Simoleit A, Zuberbier T, Bergmann K-C (2017) Spatial distribution of allergenic pollen through a large metropolitan area. Environ Monit Assess 189(4):169

Witt C, Schubert AJ, Jehn M, Holzgreve A, Liebers U, Endlicher W, Scherer D (2015) The effects of climate change on patients with chronic lung disease. A systematic literature review. Deutsch Arztebl Int 112(51–52):878–883

World Allergy Organization WAO (2011) The economic burden of allergy. https://www.worldallergy.org/UserFiles/file/Economic-Burden-of-Allergy.pdf. Accessed 24 Jul 2019

World Health Organization (1948) Constitution of the World Health Organization. https://www.who.int/governance/eb/who_constitution_en.pdf. Accessed 16 Apr 2019

World Health Organization (2007) Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach

Zhao F, Elkelish A, Durner J, Lindermayr C, Winkler JB, Ruëff F, Behrendt H, Traidl-Hoffmann C, Holzinger A, Kofler W, Braun P, von Toerne C, Hauck SM, Ernst D, Frank U (2016) Common ragweed (*Ambrosia artemisiifolia* L.): allergenicity and molecular characterization of pollen after plant exposure to elevated NO2. Plant Cell Environ 39(1):147–164

Zhao F, Durner J, Winkler JB, Traidl-Hoffmann C, Strom T-M, Ernst D, Frank U (2017) Pollen of common ragweed (*Ambrosia artemisiifolia* L.): Illumina-based de novo sequencing and differential transcript expression upon elevated NO2/O3. Environ Pollut 224:503–514. Barking, Essex: 1987

Ziello C, Sparks TH, Estrella N, Belmonte J, Bergmann KC, Bucher E, Brighetti MA, Damialis A, Detandt M, Galán C, Gehrig R, Grewling L, Gutiérrez Bustillo AM, Hallsdóttir M, Kockhans-Bieda M-C, de Linares C, Myszkowska D, Pàldy A, Sánchez A, Smith M, Thibaudon M, Travaglini A, Uruska A, Valencia-Barrera RM, Vokou D, Wachter R, de Weger LA, Menzel A (2012) Changes to airborne pollen counts across Europe. PLoS One 7(4)

Ziska LH, Yang J, Tomecek MB, Beggs PJ (2016) Cultivar-specific changes in Peanut yield, biomass, and allergenicity in response to elevated atmospheric carbon dioxide concentration. Crop Sci 56(5):2766

Zuberbier T, Lötvall J, Simoens S, Subramanian SV, Church MK (2014) Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy 69(10):1275–1279

Part VII

Diagnostics

Update on Type-1 Allergy Diagnostics

Regina Treudler and Jan-Christoph Simon

Contents

Abstract

Diagnostics in type-1 allergy rely on medical history and clinical examination. Extent and severity of signs and symptoms can be documented by standardized scores and questionnaires. Both skin prick test and intradermal test are useful for search of immunoglobulin E-mediated sensitizations but the availability of commercially available diagnostic extracts has been markedly reduced during the last years. Investigation of total and of specific serum IgE is the most important in vitro diagnostic analyte in type-1 allergy. Identification of the individual molecules to which patients are sensitized, known as molecular or component-resolved diagnostics (CRD), has recently markedly improved management of type-1 allergy to pollen, food and hymenoptera venoms. Main features of CRD are increased analytic sensitivity, detection of cross-reactivity and determination of individual sensitization profiles which allow for risk assessment and facilitate decisions for or against allergen immunotherapy. Basophil activation test as well as determination of selected biomarkers (e.g. tryptase) may also be helpful in

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some cases. If any allergy test is positive, one will have to distinguish reactions, which are clinically relevant, from those, which are not. In vivo provocation tests (e.g. nasal provocation, oral drug or food challenge) may help to clarify the relevance of a sensitization.

Keywords

Component-resolved diagnostics · Diagnostics · Provocation test · Review · Skin prick test · Type-1 allergy

1 Introduction

Type-1 (immediate type) allergy involves immunoglobulin E (IgE) mediated mast cell degranulation and release of histamine and other inflammatory mediators (see Part II, Chap. 1). Typical type-1 allergens are pollen, mites, animal dander, moulds, foods, drugs, insect venoms, etc. As a result of allergen exposure, i.e. by ingestion, inhalation, injection or direct contact, the clinical reactions may become manifest as allergic rhinitis or hay fever, allergic conjunctivitis, hives, atopic eczema, or erythema, angioedema, allergic asthma or anaphylaxis (Abbas et al. 2020). Non-IgE-mediated mechanisms may also be responsible for mast cell degranulation, which clinically is not distinguishable from IgE-mediated allergy (Redegeld et al. 2018). Both in vivo and in vitro tests are used in the diagnosis of type-1 hypersensitivity.

2 Medical History and Examination

The diagnosis of type-1 hypersensitivity relies on a thorough clinical history and physical examination. Information about the patient's history should include: signs and symptoms as well as timing with onset, allergen exposure (e.g. indoor, outdoor, professional), prior history of allergic reactions, (family) history of atopy or food allergies (Abbas et al. 2020). Scoring of clinical signs and symptoms may help to categorize the activity/severity of the disease and for therapeutic decision making (Table 1). Spirometry and measurement of fractional exhaled nitric oxide (FeNO) may be helpful for investigation of lung function, eosinophil count in nasal smear may be seen in allergic rhinoconjunctivitis (Ansotegui et al. 2020). Health related quality of life can be measured by several standardized questionnaires (Alvarado et al. 2019; Apfelbacher et al. 2016; Beyer et al. 2016; Fischer et al. 2011; Lanario et al. 2020; Muraro et al. 2018; Pariser et al. 2020; Steinke et al. 2018; Stone et al. 2020; Weller et al. 2020; Wise et al. 2018; Zuberbier et al. 2018) (Table 1). History taking should also include evaluation of possible comorbidities, e.g. psychosocial or autoimmune comorbidities in atopic dermatitis or mastocytosis in anaphylaxis (Kage et al. 2020; Treudler et al. 2018; Treudler et al. 2020; Worm et al. 2018). Once the history has been collected, one of several primary confirmatory tests for sensitization can be performed to detect allergen-specific IgE in the skin or blood.

Table 1 Instruments for measurement of activity, severity and health related quality of life in selected manifestations of type-1 allergy

Disease	Activity/severity	Health related quality of life (QOL)
Allergic rhinoconjunctivitis	Allergic rhinitis and its impact on asthma (ARIA) classification	Rhinoconjunctivitis QOL questionnaire – RQLQ
Allergic asthma	Global initiative for *Asthma classification (GINA)*	Severe asthma questionnaire – SAQ
Anaphylaxis (insect, food, drug)	Ring & Messer Scale, Müller scale, et al.	Food allergy QOL questionnaire – FAQOLQ
Urticaria	Urticaria control score – UCS Urticaria activity score – UAS7	Urticaria QoL questionnaire – UQOL
Angioedema	Angioedema control test – AECT	Angioedema QOL questionnaire – AEQOL
Atopic dermatitis (AD)	Severity scoring of AD – SCORAD Eczema activity and severity index – EASI AD control test – ADCT	Dermatology life quality index – DLQI

3 Skin Tests

Skin tests must be performed under medical supervision, with emergency equipment available for the treatment of possible anaphylaxis, especially in drug allergy. (Ansotegui et al. 2020; Aurich et al. 2017) Usually, skin tests are performed on healthy volar skin of one or both forearms. Special recommendations on how to perform allergy skin tests in drug allergy or in occupational allergy exist (Brockow et al. 2013; Brockow et al. 2015; Raulf et al. 2014; Wurpts et al. 2020). Negative and positive controls (e.g. saline and histamine hydrochloride solution) are required. Importantly, drugs can suppress skin test results, e.g. antihistamines tricyclic antidepressants, oral glucocorticosteroids >10 mg prednisolone per day (Bousquet et al. 2012; Malling 1993). It is recommended to use standardized test extracts, which, however, may show large differences between extracts from different manufacturers (Heinzerling et al. 2009; Ruëff et al. 2011). Also, the availability of commercially available diagnostic extracts, used for skin and for provocation tests, has been markedly reduced in the European Union since they have been defined as medicinal products (EU-Directives 89/342/EEC, 2001/83 EC) (Klimek et al. 2020). Accordingly, to an increasing degree native allergens have to be used (e.g. in food and drug allergy).

In *skin prick test (SPT),* a specific allergen is introduced via a lancet into the skin and degranulation of dermal mast leads to wheal and flare reaction in sensitized people. After 15 min, the largest and perpendicular diameter of the each wheal's size is measured in millimetres (mm) with a ruler, then the largest plus perpendicular diameter/2 is calculated. The positive control should optimally show a wheal diameter ≥3 mm. SPT should be interpreted as being positive if the wheal diameter is 3 mm greater than the negative control and negative if the wheal diameter is less

than 3 mm with a positive simultaneous histamine control (Ansotegui et al. 2020). False-positive skin tests may result from dermographism or may be caused by 'irritant' reactions or a nonspecific enhancement from a nearby strong reaction (Bousquet et al. 2012). False-negative skin tests can be caused by extracts of poor potency, drugs modulating the allergic reaction, diseases attenuating the skin response, improper technique, limited local IgE production, for example, only in the nose or in the eye. (Bousquet et al. 2012).

Intradermal skin test (IDT) should be performed only if the patient's history indicates relevant sensitization and a negative SPT result was obtained (Malling 1993). IDT is more technically demanding than SPT and carries a higher risk of adverse reactions. Allergens (usually, 0.02 mL) are injected intradermally with small needles to produce a small bleb, and the outcome measure is an increase in the size of the wheal with flare reaction at 20 min. Allergenic extract must be diluted (10–1,000-fold or more) from the concentrations used for SPT (Ansotegui et al. 2020). IDT may be helpful in drug or in insect allergy but is said to be not useful for allergy diagnosis with inhalant allergens (Bousquet et al. 2012). Interpretation of IDT results is less standardized than in SPT and there is no true consensus (Malling 1993). According to German Guidelines, IDT is regarded positive if the mean wheal diameter is $\geq$5 mm(Ruëff et al. 2011). The International Consensus Statement on Allergy and Rhinology considers IDT positive if the diameter of the resulting wheal is at least 7 mm, and at least 2 mm wider than the control (saline, glycerin solution) (Wise et al. 2018).

4 In Vitro Tests

Total IgE may be elevated in atopic disorders; however, abnormal levels may also be seen in several entities, not only in allergy (Ansotegui et al. 2020). *Allergen-specific (s)IgE antibody* is the most important analyte in the diagnosis of type1 hypersensitivity reactions. The measurement of sIgE recognizing allergenic epitopes can be achieved both through the usage of single reagents (singleplex) or with a pre-defined panel more than hundred of molecules to be tested simultaneously (multiplex) (Treudler 2012; Treudler and Simon 2013). IgE is usually measured by using a fluorescence enzyme immunoassay in singleplex platforms. When comparing the singleplex and multiplex assays, concordance of results vary between allergens tested, and the sensitivity of multiplex platform is lower than that of singleplex, particularly when sIgE levels are low. Otherwise singleplex platforms are quantitative assays and multiplex are semiquantitative (Treudler 2012). Purified native or recombinant allergens, identifying the individual molecules to which patients are sensitized, can be determined by the so-called molecular or *component-resolved diagnostics (CRD)* with the following specialized features (Matricardi et al. 2016; Treudler 2012; Treudler and Simon 2013): standardization of allergen extracts by use of individual allergens, increase of analytic sensitivity by replacement/supplementation of relevant individual allergens in the test extract, detection of cross-reactions, determination of individual sensitization profiles, no cross-reacting

carbohydrate chains (CCD). An increasing number of allergens have found their way into routine diagnostics in recent years and individual IgE profiles and allergen patterns allow for closer examinations of cross-reactivity, molecules of risk and prognostically significant sensitizations. Overall, CRD has improved management of the allergic patient as it allows to some extent to discriminate between clinically significant and irrelevant sIgE results and to establish sensitization patterns with particular prognostic outcomes (Matricardi et al. 2016). Reliable detection of sIgE requires allergen reagents with a sufficient representation of all relevant allergen components. As this might not be the case in all reagents, some of them are meanwhile enriched with recombinant allergens (also known as spiking). Examples for reagents with enriched recombinant allergen components are hazel and nut mix (enriched with Cor a 1), latex (Hev b 5), or wasp (Ves v 5) (Treudler 2012; Treudler and Simon 2013). In *pollen allergies* with determination of the respective major allergens (i.e. Bet v 1: birch, Phl p 1/5: grass) clinically relevant sensitizations can be differentiated from those to cross-reacting, clinically less relevant panallergens such as profilins (i.e. Bet v 2/4, Phl p 7/12). These diagnostics allow for establishing a more precise indication for specific immunotherapy. In food allergies, sensitizations to storage (i.e. Ara h 2/ peanut) or lipid transfer proteins (i.e. Pru p 3/peach) signal a high risk of anaphylaxis, while sensitizations to Bet v 1 homologues (e.g. Ara h 8/peanut) are usually associated with milder symptoms (Table 2). By determination of the major allergens Api m 1 (bee) and Ves v 1 and Ves v 5 (wasp) double sensitizations can already today be better differentiated from cross-reactivities in

Table 2 Main sensitizing plant allergen families in type-1 allergy

Family	Characteristics	Examples
Bet v 1 homologue	Major allergen of birch *Betula verrucosa.* Similar proteins are termed Bet v 1 homologues or pathogenesis-related proteins (PR) 10	rAra h 8 – Peanut rCor a 1 – Hazel rGly m 4 – Soy
Lipid transfer Proteins	Sensitizations usually in southern Europe, severe reactions, gastrointestinal sensitization	rAra h 9 – Peanut rPru p 3 – Peach rCor a 8 – Hazel
Profilins	Little clinical relevance, often responsible for cross-reactions	rBet v 2 – Birch rPhl p 12 – Grass
Storage proteins	Stable proteins represent a large proportion of proteins in nuts, seeds, legumes and cereals	rAra h 2 and 3 – Peanut rGly m 5 and 6 – Soy rTri a 19 – Wheat

hymenoptera venom allergies than previously. Further promising improvements in diagnostics are expected from additional, not yet commercially available molecules of risk. Elevation of *serum tryptase* indicates degranulation of mast cells. An acute rise in tryptase levels starts to be detected in serum within minutes of anaphylaxis. In contrast to serum histamine, which has a very short half-life, the serum tryptase level gradually reverts to normal over 6–24 h. Persistently elevated serum tryptase levels are seen in mastocytosis but may also be present in other entities like chronic kidney disease (Lee 2020).

The *Basophil activation test (BAT)* uses flow cytometry to measure the expression of activation markers on the surface of basophils that are upregulated following the cross-linking of IgE antibodies bound to the high-affinity IgE receptor (FcεRI) that result from allergen or anti-IgE stimulation. BAT can be used to support the diagnosis of various allergic conditions, such as food, drug, respiratory and insect venom allergies, and the assessment of clinical response to allergen-specific immunotherapy and other immunomodulatory treatments (Hemmings et al. 2018). There are several other analytes that may be used outside the clinical routine and/or for research purposes, e.g. allergen-specific IgG (as parameter for course of allergen-specific immunotherapy), indoor aeroallergen quantitation in surface dust, IgE-specific autoantibodies (in chronic spontaneous urticaria), eosinophil cationic protein mediators, leukotriene C4, prostaglandin D2, proteoglycans, mast cell chymase/carboxypeptidase, cathepsin, different cytokines (e.g. Interferon-gamma, Interleukin (IL)-4, IL-5, IL-13).(Ansotegui et al. 2020)

5 In Vivo Provocation Tests

In -vivo provocation tests (Table 3) are considered confirmatory tests that are available when one needs to adjudicate the correctness of discordant clinical history and results from allergen-specific IgE antibody skin or serologic tests (Hamilton 2010). Provocation tests are more difficult to perform in a reproducible manner than skin or blood tests for IgE antibodies, and they place the patient at some risk for a

Table 3 In vivo provocation tests in type-1 allergy

In vivo tests	Disease
Conjunctival/nasal provocation test, rhinomanometry	Allergic rhinoconjunctivitis
Bronchial inhalation challenge (e.g. allergen, methacholine, histamine)	
Oral food challenge (open/single or double blind/placebo controlled)	Food allergy
Physical exercise test	Exercise induced anaphylaxis
Drug provocation test (oral, subcutaneous, intravenous, open/single or double blind/placebo controlled)	Drug allergy
Physical tests (e.g. temp test, Fric test, ultraviolet light)	Chronic inducible urticaria
Sting challenge (only recommended under venom immunotherapy)	Insect allergy

reaction because they involve a direct allergen challenge. Interpretation of their results can also be difficult because they often involve subjective endpoints that can be altered by observer and patient bias (Brockow et al. 2015; Muraro et al. 2014a, b; Sampson et al. 2012; Treudler et al. 2016; Wurpts et al. 2020).

6 Conclusion

Most important diagnostics in type-1 allergy are history taking, allergy skin tests (e.g. SPT) and in vitro tests (e.g. specific IgE, tryptase, BAT). If any test is positive, one will have to distinguish reactions, which are clinically relevant, from those, which are not. Provocation tests may help to clarify the relevance of a sensitization.

References

Abbas M, Moussa Mohamed, Akel Hassan (2020) Type 1 hypersensitivity reaction. https://www.ncbi.nlm.nih.gov/books/NBK560561/

Alvarado SA, Nassiri M, Bahna SL (2019) Scoring systems for allergies and asthma in clinical research and practice. Allergy Asthma Proc 40:93–102. https://doi.org/10.2500/aap.2019.40.4196

Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, Passalacqua G, Savi E, Ebo D, Gómez RM, Luengo Sánchez O, Oppenheimer JJ, Jensen-Jarolim E, Fischer DA, Haahtela T, Antila M, Bousquet JJ, Cardona V, Chiang WC, Demoly PM, DuBuske LM, Ferrer Puga M, van Gerth WR, González Díaz SN, Gonzalez-Estrada A, Jares E, Kalpaklioğlu AF, Kase Tanno L, Kowalski ML, Ledford DK, Monge Ortega OP, Morais Almeida M, Pfaar O, Poulsen LK, Pawankar R, Renz HE, Romano AG, Rosário Filho NA, Rosenwasser L, Sánchez Borges MA, Scala E, Senna G-E, Sisul JC, Tang MLK, Thong BY-H, Valenta R, Wood RA, Zuberbier T (2020) IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J 13:100080. https://doi.org/10.1016/j.waojou.2019.100080

Apfelbacher CJ, Jones CJ, Frew A, Smith H (2016) Validity of three asthma-specific quality of life questionnaires: the patients' perspective. BMJ Open 6. https://doi.org/10.1136/bmjopen-2016-011793

Aurich S, Schüürmann M, Simon J-C, Treudler R (2017) Anaphylactic shock caused by intradermal testing with cefuroxime. J Dtsch Dermatol Ges 15:668–670. https://doi.org/10.1111/ddg.13246

Beyer S, Franke A, Simon JC, Treudler R (2016) Measurement of health-related quality of life in adult patients with birch pollen-associated food allergy. J Dtsch Dermatol Ges 14:397–404. https://doi.org/10.1111/ddg.12731

Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, Canonica GW, Carlsen KH, Cox L, Haahtela T, Lodrup Carlsen KC, Price D, Samolinski B, Simons FER, Wickman M, Annesi-Maesano I, Baena-Cagnani CE, Bergmann KC, Bindslev-Jensen C, Casale TB, Chiriac A, Cruz AA, Dubakiene R, Durham SR, Fokkens WJ, Gerth-van-Wijk R, Kalayci O, Kowalski ML, Mari A, Mullol J, Nazamova-Baranova L, O'Hehir RE, Ohta K, Panzner P, Passalacqua G, Ring J, Rogala B, Romano A, Ryan D, Schmid-Grendelmeier P, Todo-Bom A, Valenta R, Woehrl S, Yusuf OM, Zuberbier T, Demoly P (2012) Practical guide to skin prick tests in allergy to aeroallergens. Allergy 67:18–24. https://doi.org/10.1111/j.1398-9995.2011.02728.x

Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, Bircher A, Blanca M, Bonadonna B, Campi P, Castro E, Cernadas JR, Chiriac AM, Demoly P, Grosber M,

Gooi J, Lombardo C, Mertes PM, Mosbech H, Nasser S, Pagani M, Ring J, Romano A, Scherer K, Schnyder B, Testi S, Torres M, Trautmann A, Terreehorst I (2013) Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 68:702–712. https://doi.org/10.1111/all.12142

Brockow K, Przybilla B, Aberer W, Bircher AJ, Brehler R, Dickel H, Fuchs T, Jakob T, Lange L, Pfützner W, Mockenhaupt M, Ott H, Pfaar O, Ring J, Sachs B, Sitter H, Trautmann A, Treudler R, Wedi B, Worm M, Wurpts G, Zuberbier T, Merk HF (2015) Guideline for the diagnosis of drug hypersensitivity reactions: S2K-guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergology and Immunology (ÖGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of severe skin reactions and the German Federal Institute for Drugs and Medical Products (BfArM). Allergo J Int 24:94–105. https://doi.org/10.1007/s40629-015-0052-6

Fischer J, Feidt A, Giel KE, Martens U, Zipfel S, Biedermann T, Teufel M (2011) Quality-of-life in wasp venom allergy – validation of the German version of the "Vespid Allergy Quality of Life Questionnaire" (VQLQ-d). J Dtsch Dermatol Ges 9:379–385. https://doi.org/10.1111/j.1610-0387.2011.07622.x

Hamilton RG (2010) Clinical laboratory assessment of immediate-type hypersensitivity. J Allergy Clin Immunol 125:S284–S296. https://doi.org/10.1016/j.jaci.2009.09.055

Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, Bousquet-Rouanet L, Bousquet PJ, Bresciani M, Bruno A, Burney P, Canonica GW, Darsow U, Demoly P, Durham S, Fokkens WJ, Giavi S, Gjomarkaj M, Gramiccioni C, Haahtela T, Kowalski ML, Magyar P, Muraközi G, Orosz M, Papadopoulos NG, Röhnelt C, Stingl G, Todo-Bom A, von Mutius E, Wiesner A, Wöhrl S, Zuberbier T (2009) GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 64:1498–1506. https://doi.org/10.1111/j.1398-9995.2009.02093.x

Hemmings O, Kwok M, McKendry R, Santos AF (2018) Basophil activation test: old and new applications in allergy. Curr Allergy Asthma Rep 18:77. https://doi.org/10.1007/s11882-018-0831-5

Kage P, Simon J-C, Treudler R (2020) Atopic dermatitis and psychosocial comorbidities. J Dtsch Dermatol Ges 18:93–102. https://doi.org/10.1111/ddg.14029

Klimek L, Hoffmann HJ, Kalpaklioglu AF, Demoly P, Agache I, Popov TA, Muraro A, Schmid-Grendelmeier P, Bonini S, Bonertz A, Mahler V, Vieths S, Pfaar O, Zuberbier T, Jutel M, Schmidt-Weber C, Hellings PW, Dreborg S, Bonini M, Brough HA, Bousquet J, Hoffmann-Sommergruber K, Palomares O, Ollert M, Shamji MH, Cardona V (2020) In-vivo diagnostic test allergens in Europe: a call to action and proposal for recovery plan – an EAACI position paper. Allergy 75:2161–2169. https://doi.org/10.1111/all.14329

Lanario JW, Hyland ME, Menzies-Gow A, Mansur AH, Dodd JW, Fowler SJ, Jones RC, Masoli M (2020) Validation of subscales of the severe asthma questionnaire (SAQ) using exploratory factor analysis (EFA). Health Qual Life Outcomes 18:336. https://doi.org/10.1186/s12955-020-01593-9

Lee AYS (2020) Elevated serum Tryptase in non-anaphylaxis cases: a concise review. Int Arch Allergy Immunol 181:357–364. https://doi.org/10.1159/000506199

Malling H-J (1993) Methods of skin testing: EAACI position paper. Allergy 48:55–56

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Aalberse RC, Agache I, Asero R, Ballmer-Weber B, Barber D, Beyer K, Biedermann T, Bilò MB, Blank S, Bohle B, Bosshard PP, Breiteneder H, Brough HA, Caraballo L, Caubet JC, Crameri R, Davies JM, Douladiris N, Ebisawa M, Eigenmann PA, Fernandez-Rivas M, Ferreira F, Gadermaier G, Glatz M, Hamilton RG, Hawranek T, Hellings P, Hoffmann-Sommergruber K, Jakob T, Jappe U, Jutel M, Kamath SD, Knol EF, Korosec P, Kuehn A, Lack G, Lopata AL,

Mäkelä M, Morisset M, Niederberger V, Nowak-Węgrzyn AH, Papadopoulos NG, Pastorello EA, Pauli G, Platts-Mills T, Posa D, Poulsen LK, Raulf M, Sastre J, Scala E, Schmid JM, Schmid-Grendelmeier P, van Hage M, van Ree R, Vieths S, Weber R, Wickman M, Muraro A, Ollert M (2016) EAACI molecular allergology user's guide. Pediatr Allergy Immunol 27(Suppl 23):1–250. https://doi.org/10.1111/pai.12563

Muraro A, Dubois AEJ, DunnGalvin A, JOB H, de Jong NW, Meyer R, Panesar SS, Roberts G, Salvilla S, Sheikh A, Worth A, Flokstra-de Blok BMJ (2014a) EAACI food allergy and anaphylaxis guidelines. Food allergy health-related quality of life measures. Allergy 69:845–853. https://doi.org/10.1111/all.12405

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, duToit G, Eigenmann P, Fernandez Rivas M, Halken S, Hickstein L, Høst A, Knol E, Lack G, Marchisotto MJ, Niggemann B, Nwaru BI, Papadopoulos NG, Poulsen LK, Santos AF, Skypala I, Schoepfer A, van Ree R, Venter C, Worm M, Vlieg-Boerstra B, Panesar S, de Silva D, Soares-Weiser K, Sheikh A, Ballmer-Weber BK, Nilsson C, de Jong NW, Akdis CA (2014b) EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 69:1008–1025. https://doi.org/10.1111/all.12429

Muraro A, Fernandez-Rivas M, Beyer K, Cardona V, Clark A, Eller E, Hourihane JOB, Jutel M, Sheikh A, Agache I, Allen KJ, Angier E, Ballmer-Weber B, Bilò MB, Bindslev-Jensen C, Camargo CA, Cianferoni A, DunnGalvin A, Eigenmann PA, Halken S, Hoffmann-Sommergruber K, Lau S, Nilsson C, Poulsen LK, Rueff F, Spergel J, Sturm G, Timmermans F, Torres MJ, Turner P, van Ree R, Wickman M, Worm M, Mills ENC, Roberts G (2018) The urgent need for a harmonized severity scoring system for acute allergic reactions. Allergy 73:1792–1800. https://doi.org/10.1111/all.13408

Pariser DM, Simpson EL, Gadkari A, Bieber T, Margolis DJ, Brown M, Nelson L, Mahajan P, Reaney M, Guillemin I, Mallya UG, Eckert L (2020) Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the atopic dermatitis control tool (ADCT). Curr Med Res Opin 36:367–376. https://doi.org/10.1080/03007995.2019.1699516

Raulf M, Buters J, Chapman M, Cecchi L, de Blay F, Doekes G, Eduard W, Heederik D, Jeebhay MF, Kespohl S, Krop E, Moscato G, Pala G, Quirce S, Sander I, Schlünssen V, Sigsgaard T, Walusiak-Skorupa J, Wiszniewska M, Wouters IM, Annesi-Maesano I (2014) Monitoring of occupational and environmental aeroallergens – EAACI position paper. Concerted action of the EAACI IG occupational allergy and aerobiology & air pollution. Allergy 69:1280–1299. https://doi.org/10.1111/all.12456

Redegeld FA, Yu Y, Kumari S, Charles N, Blank U (2018) Non-IgE mediated mast cell activation. Immunol Rev 282:87–113. https://doi.org/10.1111/imr.12629

Ruëff F, Bergmann K-C, Brockow K, Fuchs T, Grübl A, Jung K, Klimek L, Müsken H, Pfaar O, Przybilla B, Sitter H, Wehrmann W (2011) Hauttests zur Diagnostik von allergischen Soforttyp-Reaktionen. Leitlinie der Deutschen Gesellschaft für Allergologie und klinischen Immunologie (DGAKI) (skin tests for diagnostics of allergic immediate-type reactions. Guideline of the German Society for Allergology and Clinical Immunology). Pneumologie 65:484–495. https://doi.org/10.1055/s-0030-1256476

Sampson HA, van Gerth WR, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, Dubois AEJ, Beyer K, Eigenmann PA, Spergel JM, Werfel T, Chinchilli VM (2012) Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 130:1260–1274. https://doi.org/10.1016/j.jaci.2012.10.017

Steinke S, Beikert FC, Langenbruch A, Fölster-Holst R, Ring J, Schmitt J, Werfel T, Hintzen S, Franzke N, Augustin M (2018) Measurement of healthcare quality in atopic dermatitis – development and application of a set of quality indicators. J Eur Acad Dermatol Venereol 32:2237–2243. https://doi.org/10.1111/jdv.15074

Stone RG, McDonald M, Elnazir B (2020) Global initiative for asthma 2019 guidelines: new changes to the treatment of mild asthmatics 12 years and older. Ir Med J 113:69

Treudler R (2012) Update on in vitro allergy diagnostics. J Dtsch Dermatol Ges 10:89–97.; quiz 98-9. https://doi.org/10.1111/j.1610-0387.2011.07860.x

Treudler R, Simon JC (2013) Overview of component resolved diagnostics. Curr Allergy Asthma Rep 13:110–117. https://doi.org/10.1007/s11882-012-0318-8

Treudler R, Franke A, Schmiedeknecht A, Ballmer-Weber BK, Worm M, Werfel T, Jappe U, Biedermann T, Schmitt J, Brehler R, Kleinheinz A, Kleine-Tebbe J, Brüning H, Ruëff F, Ring J, Saloga J, Schäkel K, Holzhauser T, Vieths S, Simon JC (2016) Standardization of double blind placebo controlled food challenge with soy within a multicentre trial. Clin Transl Allergy 6:39. https://doi.org/10.1186/s13601-016-0129-4

Treudler R, Zeynalova S, Walther F, Engel C, Simon JC (2018) Atopic dermatitis is associated with autoimmune but not with cardiovascular comorbidities in a random sample of the general population in Leipzig, Germany. J Eur Acad Dermatol Venereol 32:e44–e46. https://doi.org/10.1111/jdv.14495

Treudler R, Zeynalova S, Riedel-Heller SG, Zuelke AE, Roehr S, Hinz A, Glaesmer H, Kage P, Loeffler M, Simon JC (2020) Depression, anxiety and quality of life in subjects with atopic eczema in a population-based cross-sectional study in Germany. J Eur Acad Dermatol Venereol 34:810–816. https://doi.org/10.1111/jdv.16148

Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, Hawro T, Altrichter S, Krause K, Siebenhaar F, Metz M, Zuberbier T, Freier D, Maurer M (2020) Validation of the angioedema control test (AECT) – a patient-reported outcome instrument for assessing angioedema control. J Allergy Clin Immunol Pract 8:2050–2057.e4. https://doi.org/10.1016/j.jaip.2020.02.038

Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, Azar A, Baroody FM, Bachert C, Canonica GW, Chacko T, Cingi C, Ciprandi G, Corey J, Cox LS, Creticos PS, Custovic A, Damask C, DeConde A, DelGaudio JM, Ebert CS, Eloy JA, Flanagan CE, Fokkens WJ, Franzese C, Gosepath J, Halderman A, Hamilton RG, Hoffman HJ, Hohlfeld JM, Houser SM, Hwang PH, Incorvaia C, Jarvis D, Khalid AN, Kilpeläinen M, Kingdom TT, Krouse H, Larenas-Linnemann D, Laury AM, Lee SE, Levy JM, Luong AU, Marple BF, McCoul ED, McMains KC, Melén E, Mims JW, Moscato G, Mullol J, Nelson HS, Patadia M, Pawankar R, Pfaar O, Platt MP, Reisacher W, Rondón C, Rudmik L, Ryan M, Sastre J, Schlosser RJ, Settipane RA, Sharma HP, Sheikh A, Smith TL, Tantilipikorn P, Tversky JR, Veling MC, Wang DY, Westman M, Wickman M, Zacharek M (2018) International consensus statement on allergy and rhinology: allergic rhinitis. Int Forum Allergy Rhinol 8:108–352. https://doi.org/10.1002/alr.22073

Worm M, Francuzik W, Renaudin J-M, Bilo MB, Cardona V, Scherer Hofmeier K, Köhli A, Bauer A, Christoff G, Cichocka-Jarosz E, Hawranek T, Hourihane JOB, Lange L, Mahler V, Muraro A, Papadopoulos NG, Pföhler C, Poziomkowska-Gęsicka I, Ruëff F, Spindler T, Treudler R, Fernandez-Rivas M, Dölle S (2018) Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European Anaphylaxis Registry. Allergy 73:1322–1330. https://doi.org/10.1111/all.13380

Wurpts G, Aberer W, Dickel H, Brehler R, Jakob T, Kreft B, Mahler V, Merk HF, Mülleneisen N, Ott H, Pfützner W, Röseler S, Ruëff F, Sitter H, Sunderkötter C, Trautmann A, Treudler R, Wedi B, Worm M, Brockow K (2020) Guideline on diagnostic procedures for suspected hypersensitivity to beta-lactam antibiotics: guideline of the German Society for Allergology and Clinical Immunology (DGAKI) in collaboration with the German Society of Allergology (AeDA), German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Austrian Society for Allergology and Immunology (ÖGAI), and the Paul-Ehrlich Society for Chemotherapy (PEG). Allergol Select 4:11–43. https://doi.org/10.5414/ALX02104E

Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-

Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M (2018) The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 73:1393–1414. https://doi.org/10.1111/all.13397

Epicutaneous Patch Testing in Type IV Allergy Diagnostics: State of the Art and Best Practice Recommendations

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Abstract

This chapter summarises all relevant aspects of patch testing, closely following recommendations outlined in a recent European, and a German S3 guideline on diagnostic patch testing with contact allergens and medicinal products (drugs). Patch testing is indicated in patients suspected of suffering, or having been suffering, from delayed-type hypersensitivity leading to allergic contact dermatitis or other skin and mucosal diseases. Sections of this chapter include detailed indications, reasons for possibly postponing the test, considerations on choosing haptens (contact allergens) to test, various aspects of the application of patch test allergen preparations (storage, dosing) and of testing with individual materials provided by the patients. Special aspects of patch testing in cutaneous adverse drug reactions, children, or occupational contact dermatitis are outlined. Supplemental test methods, notably the repeated open application test, are briefly described. Finally, the final evaluation in terms of assessment of clinical relevance of reactions and patient counselling are outlined.

Keywords

Contact allergen · Contact allergy · Contact dermatitis · Delayed-type hypersensitivity · Diagnostics · Diagnostic patch testing · Drug allergy · Guideline · Hapten · Medicinal product · Skin and mucosal disease · Test methods

1 Introduction

This chapter addresses dermatologists, physicians of other specialties and further healthcare professionals (Uter et al. 2017; Mahler et al. 2019a, b), involved in the work-up of (allergic) contact dermatitis, other delayed hypersensitivity reactions and their differential diagnoses. It is based on the best practice recommendations developed within the current guideline of the European Society of Contact Dermatitis (ESCD) (Johansen et al. 2015) and the recently published German S3-guideline on *Epicutaneous patch testing with contact allergens and drugs* (Mahler et al. 2019a, b).

Throughout the chapter, the following definitions are used (Johansen et al. 2015):

- *Contact dermatitis* is an inflammatory skin reaction due to direct contact with noxious agents in the environment. The pathomechanism may involve immunological hypersensitivity (allergy) or not (irritant contact dermatitis), or may be of mixed aetiology (Johansen et al. 2015).
- *Contact allergy* is an altered immune status of an individual induced by a particular sensitising substance, a contact allergen. This involves a clinically inapparent sensitisation phase, also called induction (Johansen et al. 2015).
- The *induction phase* results in the expansion of a clone of allergen-specific T cells. At this point an individual is immunologically sensitised. Upon re-exposure with the same, or a cross-reacting allergen/antigen, the elicitation phase is

triggered. In humans, the majority of T cells found in the epidermis are memory $CD8^+$ T cells (Martin and Bonefeld 2021).

- The *elicitation phase* leads to specific T-cell activation with clinically visible disease, that is, allergic contact dermatitis. In this chapter the term contact allergy is used synonymously with *contact sensitivity* (Johansen et al. 2015).
- *Haptens:* The substances inducing contact allergy are reactive chemicals, usually with a molecular weight of less than 500 Da. These substances (also referred to as *haptens)* are generally not antigenic by themselves, but only after protein binding (*haptenisation*). In this haptenisation process electrophilic organic chemicals covalently bind to sulfhydryl (SH) groups of the amino acids histidine or cysteine or to the ε-amino groups of lysine. Metal ions can form complexes with SH groups (Martin and Bonefeld 2021). In this chapter the term *allergen* will be used to include haptens (Johansen et al. 2015).
- *Allergic contact dermatitis* is also termed allergic contact eczema. The typical morphology includes erythema, (papular) infiltration, oedema and possibly vesicles. At a later stage, if exposure to the allergen continues, the dermatitis may become chronic and present with scaling, fissures and lichenification (Johansen et al. 2015).
- *Cross-sensitivity* occurs when a person initially sensitised to an allergen reacts to another allergen he or she has never been exposed to before (Benezra and Maibach 1984). The allergens involved are usually chemically similar, sometimes after oxidation or metabolic transformation in the skin (Johansen et al. 2015).

A special case is allergic ("immunologic") contact urticaria/protein contact dermatitis, where high molecular allergens such as peptides induce a specific IgE response (type I hypersensitivity), which may result in urticarial as well as eczematous lesions. Diagnostic work-up is different and will thus not be dealt with in this chapter (Mahler et al. 2019a).

2 Indications for Patch Testing

The standard procedure to diagnose contact allergy due to type IV hypersensitivity is patch testing. This in vivo test aims to reproduce the elicitation phase of the reaction to a contact allergen, i.e. allergic contact dermatitis. The patch test is performed by applying allergens under occlusion on the skin under standardised conditions. It is undertaken on patients with a history of dermatitis (eczema) in order to determine whether they have a contact allergy and then evaluate the relation (if any) of the contact allergy to their dermatitis (Mahler et al. 2019a). Patch testing should be done in all patients in whom contact allergy is suspected or needs to be excluded, regardless of, e.g. age or anatomical site of dermatitis (Mahler et al. 2019a). This also includes (1) other conditions that may represent a contact allergic reaction such as erythema multiforme-like, lichen planus-like, psoriasis (of the hands), or granulomatous or lymphomatoid reactions (Johansen et al. 2021), (2) worsening of pre-existing dermatitis such as stasis, atopic, or seborrheic dermatitis, nummular

eczema, (3) certain drug eruptions (Johansen et al. 2021), (4) mucous membrane reactions (conjunctivitis, stomatitis (Johansen et al. 2021), vulvitis) or (5) implants (Schalock et al. 2012; Mahler et al. 2019a).

There are very rare reports that some biological materials, haptens such as ammonium persulfate (Perfetti et al. 2000) or chlorocresol, chloroxylenol and thiourea (Mehrtens and Reckling 2019), or drugs have been associated with anaphylactic reactions when patch tested in patients with strong immediate type hypersensitivity (Johansen et al. 2015). These patients should undergo investigations for type I hypersensitivity (Johansen et al. 2015) if the medical history leading to the patch test is indicative for immediate type hypersensitivity these tests should performed prior to patch testing (Mahler et al. 2019a). It is at the discretion of the physician to include these substances in the patch test programme of these individuals after considering risk-benefit for the patient (Johansen et al. 2015).

Postponing of patch test investigations should be considered in patients with the following conditions (Johansen et al. 2015):

- Severe or generalised active dermatitis
- Systemic immunosuppressive treatment in relevant doses where a pause is foreseen or possible
- Dermatitis on the upper back or other body areas chosen to apply patch tests
- Test sites recently treated with topical corticosteroids because these suppress, at least to some extent, the elicitation reaction (Green 1996); according to current practice 7 days are considered adequate (Ring 1991) although there are no investigations concerning this
- Recent UV exposure of the test area
- Patch testing during pregnancy or lactation is not known to be harmful, but most dermatologists postpone testing during pregnancy and lactation as general precaution.

These and several other factors, which may affect the outcome of patch testing, are reviewed in (Johansen et al. 2021, 2015; Mahler et al. 2019a).

Patients should be informed about the purpose, benefits and potential adverse reactions of patch testing, how patch testing is done and symptoms that may occur (Johansen et al. 2015). It is necessary to inform about avoidance of showers, wetting the test sites, UV irradiation and excessive exercise, loosening of patches and about symptoms such as itch and severe or late reactions (Johansen et al. 2015). Patients should receive written information about the patch test procedure. There are various national regulations concerning patch testing. The dermatologist should be aware of the national legal framework within their respective countries (Johansen et al. 2015).

3 Patch Test Materials

Patch test allergens are medicinal products (drugs) according to European Directive 2001/83/EC. According to Article 6 of this Directive, a medicinal product may only be placed on the market in an EU Member State once the marketing authorisation has been granted by the competent authority in charge. However, in accordance with legislation in force and to fulfil special needs, a Member State may (according to Article 5) exclude from the provisions of this Directive medicinal products [...] formulated in accordance with the specifications of an authorised health-care professional and for use in an individual patient under his direct personal responsibility (Named patient products). This gives room to different interpretation and approaches leading up to date to an inhomogeneous regulatory landscape regarding in vivo test allergens (Mahler 2018). Information on patch test material producers can be found on the ESCD website (www.escd.org). To date, some patch test allergens and systems, respectively, are of pharmaceutical quality and are licensed as drugs, others are not.

3.1 Active Ingredients and Vehicles

For the most part, allergens are dispersed in white soft paraffin (petrolatum) and are supplied in labelled syringes with the name and concentration of the substance on the label, together with an expiry date (Johansen et al. 2015). Petrolatum is inexpensive, practical, gives good occlusion and can be mixed thoroughly with most substances (Johansen et al. 2015). However, some substances are better tested in solution in, e.g. water or ethanol (Johansen et al. 2015). For dosing the allergen and loading test chambers: see below (patch testing technique) (Johansen et al. 2015). Test concentrations have been selected based on best practice experience to elicit an allergic response in previously sensitised and no reaction in non-sensitised individuals (Johansen et al. 2015). For these allergens patch test sensitisation ("active sensitisation") is considered to be extremely rare (Jensen et al. 2006). For practical reasons and standardisation, test allergens are grouped into test series – most often according to their concomitant fields of exposure (special series) or prevalence (baseline series) (Mahler et al. 2019a; Johansen et al. 2015).

Pre-packaged tests are also available as licensed medicinal products – but only for a limited number of allergens, not fully covering, e.g. the European baseline series (Mahler et al. 2019a). They contain homogeneously dispersed allergens in standardised concentrations in a hydrophilic gel base (hydroxypropyl cellulose or povidone) mounted on an acrylic-based adhesive tape (Mahler et al. 2019a).

Several hundred test allergens are commercially available from suppliers, and others can be prepared from the patient's own materials based on exposure evaluation (Johansen et al. 2021; Mahler et al. 2017). If not covered by commercial allergens, it is sometimes necessary to obtain constituent ingredients directly from the manufacturer of the suspected culprit product in order to identify the causative allergen. Thereby, new allergens may be identified for further evaluation (Johansen

et al. 2015). Product constituents can be made up for patch testing, but the appropriate test concentration and vehicle need to be determined with care (de Groot 2018). Moreover, issues concerning purity, original concentration and reliability of materials and information obtained from the manufacturer should prompt extra caution (Mahler et al. 2019a; Johansen et al. 2015).

3.2 Test Exposure Systems

Test exposure systems are medical devices. Different systems are used to occlude and apply the allergens (Johansen et al. 2015): In one commonly used system, the chambers are supplied in strips of five or ten and consist of small aluminium disks mounted on non-occlusive tape that has been chosen for its adhesive properties and hypoallergenic acrylic-based adhesive (Fischer and Maibach 1984). Other systems consist of square plastic chambers on hypoallergenic tape (Mahler et al. 2019a; Johansen et al. 2015). The little impressions that the chambers leave on the skin when removing the test allow for assessing correct application and tight fit of patches. There is no documentation that proves one test system superior to the others; however, concerning some allergens, notably fragrance mix I, it is well documented that the sensitivity of the TRUE Test is considerably less (Uter 2015). The choice of patch test system in a clinic is mostly based on tradition and experience (Mahler et al. 2019a; Johansen et al. 2015).

3.3 Storage and Stability

Patch test materials should be stored at 4°C and protected from light (Mahler et al. 2019a; Johansen et al. 2015). Contact allergens with high vapour pressure such as some fragrance chemicals, acrylates and isocyanates are instable and require more frequent renewal and strict storage conditions (Mose et al. 2012; Mowitz et al. 2014). For some of the products (or patch test substances) storage at −18°C is recommended, e.g. some diisothiocyanates (Johansen et al. 2015). Glutaraldehyde in petrolatum and formaldehyde in aqueous solution are also subject to instability and deterioration (Johansen et al. 2015). It is necessary to respect expiration dates (Siegel et al. 2014).

3.4 Selection of Patch Test Materials

The history and examination of a patient offer clues to the possible sensitiser and should guide the choice of patch test materials. Unfortunately, it is not sufficient to patch test only with one or a few suspected sensitisers, as unsuspected ones frequently turn out to be relevant (Cronin 1972; Podmore et al. 1984). This failure to predict sensitisation correctly is the reason why a “baseline series” of test allergens should be applied in the evaluation of all patients suspected of having a contact dermatitis (Mahler et al. 2019a). An allergen is suggested for inclusion in the

baseline series when routine ("consecutive") patch testing of patients with suspected contact dermatitis results in a proportion of contact allergy to the substance exceeds 0.5–1.0% and at the same time this particular allergen is ubiquitous and/or clinically highly relevant (Bruze et al. 1999). The composition of the European baseline series valid at the time of writing is shown in Table 1, taken from (Wilkinson et al. 2019). New allergens emerge and some are phased out. The European baseline series is dynamic and subject to continuous evaluation and occasional modification depending on population exposures and prevalence of contact allergy. It can be complemented to include allergens of regional importance to specific dermatology departments.

A number of allergens, mainly fragrances and rubber compounds, are compiled into mixes (Johansen et al. 2015). The basic concept of using mixes of allergens instead of single allergens is to save space (Mahler et al. 2019a). However, a positive reaction to some of the mixes, such as the fragrance mixes, should prompt a subsequent break-down test of its single ingredients to provide specific information to the patient (Johansen et al. 2015). In addition, where allergy is suspected, a mix should not be relied on to detect the allergy, and the individual components and additional allergens should be tested in addition (Johansen et al. 2015). The mixes are frequently a compromise trying to balance sensitivity to detect contact allergy to every single ingredient of the mix by including them in sufficient concentrations against the risk of irritation from the combination of several constituents in one test preparation (Johansen et al. 2015). Consequently false-negative reactions occur (Johansen et al. 2015). Of note, in most cases application of just the baseline series is insufficient to diagnose all relevant contact allergies and additional patch test substances or series, tailored to the history and exposures of the patient, are necessary and recommended.

4 Patch Testing Technique

4.1 Dosing of Chambers

The critical factor for sensitisation and elicitation of contact allergy is the "dose per unit area" (Friedmann 2006). Therefore, it is important that the dose of allergen is standardised for each type of test chamber (Johansen et al. 2015; Mahler et al. 2019a). For example, for 8 mm Finn Chambers® 20 mg of each allergen in petrolatum (approximately 40 mg/cm^2) is deposited from the syringe into the chamber such that it fills the well of the disk but does not extrude when the patch is applied to the back (Bruze et al. 2007b). For aqueous-based allergens, small filter-papers are placed in the well and these will hold around 15 μL of liquid. The dosing of liquids is strongly recommended by means of a micropipette (Frick-Engfeldt et al. 2010). If the same amount/volume of a test preparation is applied all the time with the same test technique (same area of skin) and occlusion time, it is appropriate to use concentration as a dose parameter (Johansen et al. 2015). For most allergens, petrolatum (pet.) is an appropriate vehicle as it is stable and seems to prevent/

Table 1 The current European baseline patch test series. The patch test concentrations are shown (aq., water; pet., petrolatum) for a manually loaded chamber system. Note that the compositions are periodically adapted; the present list is taken from (Wilkinson et al. 2019). Single components of the mixes are additionally given

Allergen	Conc. (%)	mg/cm^2	Vehicle
Potassium dichromate	0.5	0.2	pet.
p-Phenylenediamine (free base)	1.0	0.4	pet.
Thiuram mix	1.0	0.4	pet.
Tetramethylthiuram monosulfide (TMTM)	0.25	0.1	
Tetramethylthiuram disulfide (TMTD)	0.25	0.1	
Tetraethylthiuram disulfide (TETD)	0.25	0.1	
Dipentamethylenethiuram disulfide (PTD)	0.25	0.1	
Neomycin sulfate	20	8.0	pet.
Cobalt chloride	1.0	0.4	pet.
Caine mix III	10.0	4.0	pet.
Benzocaine	5.0	2.0	
Cinchocaine	2.5	1.0	
Tetracaine	2.5	1.0	
Nickel sulfate	5.0	2.0	pet.
2-Hydroxyethyl methacrylate	2.0	0.8	pet.
Colophonium	20	8.0	pet.
Paraben mix	16	6.4	pet.
Methylparaben	4	1.6	
Ethylparaben	4	1.6	
Propylparaben	4	1.6	
Butylparaben	4	1.6	
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD)	0.1	0.04	pet.
Lanolin alcohols (wool alcohols)	30	12.0	pet.
Mercapto mix	2.0	0.8	pet.
N-Cyclohexylbenzothiazyl sulphenamide	0.5	0.2	
Mercaptobenzothiazole	0.5	0.2	
Dibenzothiazyl disulphide	0.5	0.2	
Morpholinylmercaptobenzothiazole	0.5	0.2	
Epoxy resin	1.0	0.4	pet.
Myroxylon pereirae (Balsam of Peru)	25	10	pet.
p-tert-Butylphenol-formaldehyde resin (PTBP resin)	1.0	0.4	pet.
Mercaptobenzothiazole	2.0	0.8	pet.
Formaldehyde	2.0	0.6	aq.
Fragrance mix I	8.0	3.2	pet.
Cinnamyl alcohol	1.0	0.4	
Cinnamal	1.0	0.4	
Hydroxycitronellal	1.0	0.4	
Amyl cinnamal	1.0	0.4	
Geraniol	1.0	0.4	

(continued)

Table 1 (continued)

Allergen	Conc. (%)	mg/cm^2	Vehicle
Eugenol	1.0	0.4	
Isoeugenol	1.0	0.4	
Evernia prunastri extract (Oak moss abs.)	1.0	0.4	
Sesquiterpene lactone mix	0.1	0.04	pet.
Alantolactone	0.033	0.013	
Dehydrocostus lactone and costunolide	0.067	0.027	
Quaternium-15	1.0	0.4	pet.
Propolis	10.0	4.0	pet.
Methylchloroisothiazolinone and methylisothiazolinone, 3:1	0.02	0.006	aq.
Budesonide	0.01	0.004	pet.
Tixocortol pivalate	0.1	0.04	pet.
Methyldibromo glutaronitrile	0.5	0.2	pet.
Fragrance mix II	14	5.6	pet.
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	2.5	1.0	
Citral	1.0	0.4	
Farnesol	2.5	1.0	
Coumarin	2.5	1.0	
Citronellol	0.5	0.2	
Hexyl cinnamal	5.0	2.0	
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	2.0	pet.
Methylisothiazolinone	0.2	0.06	aq.
Textile dye mix	6.6	2.64	pet.
Disperse blue 35	1.0	0.4	
Disperse yellow 3	1.0	0.4	
Disperse orange 1	1.0	0.4	
Disperse orange 3	1.0	0.4	
Disperse red 1	1.0	0.4	
Disperse red 17	1.0	0.4	
Disperse blue 106	0.3	0.12	
Disperse blue 124	0.3	0.12	

diminish degradation as well as oxidation and polymerisation but not evaporation, of the incorporated allergen (Isaksson et al. 2000b; Mowitz et al. 2012). Dosing of petrolatum-based allergens needs training and experience to keep the variation within a limited range (Bruze et al. 2007a). The use of dispenser devices may help in standardisation (Tournoux et al. 2016). When other test chambers are used the same dose/unit area skin can be used (Johansen et al. 2015). Concerning the optimal dose of petrolatum and liquid preparations, respectively, in different, commonly used chambers, see (Johansen et al. 2015). Generally, petrolatum-based patch test substances should be loaded into the chambers shortly before application of the patches (no longer than a few hours), liquids and some volatile petrolatum-based substances (e.g. acrylates) at the time of application (Johansen et al. 2015).

4.2 Anatomical Site of Patch Test Application

For practical reasons, the upper back is chosen (Johansen et al. 2015). The back offers a flat surface for good occlusion and usually a large enough surface for application of the necessary number of patch test substances. It is not regularly exposed to sun and is not in reach for scratching (Johansen et al. 2015). Sometimes the outer surface of the upper arms or thighs can also be used if the surface on the back of the patients is insufficient or cannot be used for other reasons, e.g. scars, acne, giant tattoos (Johansen et al. 2015).

There are known variations in reactivity of the skin between different anatomical regions (Johansen et al. 2015). For example, the forearm is less sensitive than the back to elicitation of contact allergy to nickel (Memon and Friedmann 1996). Some studies showed a higher reactivity of the upper back especially when using laser Doppler flowmetry for evaluation (van Strien and Korstanje 1994) compared to the lower back but other studies (Memon and Friedmann 1996; Simonetti et al. 1998) have not confirmed such a difference. For comparability and standardisation it is important to always use (if possible) the same anatomical site (Johansen et al. 2015).

4.3 Occlusion Time

Occlusion time is the duration of application of the patch test allergen to the skin (Johansen et al. 2015). Exposure of the outer surface of the horny layer to the haptens is obtained by an occlusive patch test chamber system (Johansen et al. 2015). Penetration of substances and the process of enhanced penetration with the help of occlusion (which facilitates the penetration of less lipophilic or mainly hydrophilic substances) vary considerably between different chemical substances (Johansen et al. 2015). The currently used occlusion time established for patch testing is a practical compromise, which makes it possible to patch test with many different substances at the same time (Johansen et al. 2015). Most handbooks and experts recommend an occlusion time of 2 days (Johansen et al. 2015).

It has been shown for nickel that 2 days occlusion time reveals a higher frequency of positive reactions compared to 1 day occlusion (Kalimo and Lammintausta 1984). Isaksson et al. (1999) compared 5, 24 and 48 h occlusion for several dilutions of budesonide in allergic subjects and found that 48 h occlusion method revealed most positive responses. In contact allergy studies on DNCB (Friedmann et al. 1983) longer duration of application at challenge evoked stronger responses because larger effective dose has been reached the skin immune system. Neither the literature study of Manuskiatti and Maibach (1996), nor the data of Brasch et al. (1995) revealed evidence for a general superiority of 1 versus 2 days occlusion. Hence, as no definite conclusion can be drawn from studies of different methodology, most handbooks and authors recommend an occlusion time of 2 days (Mahler et al. 2019a; Johansen et al. 2015). Longer application periods are not recommended.

In one study, just one case of putative, and no case of confirmed, active sensitisation to *p*-phenylenediamine (PPD) was observed after 1 day application, in contrast to 2 days (Hillen et al. 2006). In studies on PPD-allergic subjects it was shown that with longer occlusion time lower concentrations of PPD were necessary to elicit a positive response (Hextall et al. 2002). In case of strong contact allergy to PPD 30 min application of PPD 1% in pet. was sufficient to elicit positive responses, while this was not the case in patients with lower reactivity. For some contact allergens (in the particular case; photocontact allergen), e.g. ketoprofen (Manuskiatti and Maibach 1996) a much shorter occlusion (1 h instead of 48 h) seems to be as effective as the traditional occlusion period.

4.4 Reading Times

After test application (day 0) and allergen exposure for 2 days the patch test chambers are removed. The following reading times are often used in practice (Johansen et al. 2015):

- D2 and D3 or D4 and around D7 (optimum)
  Usually, 15–60 min after patch removal, allowing for the resolution of pressure effects, the test reaction is read for the first time (Magnusson et al. 1966; Bourke et al. 2009; Johansen et al. 2021). A second reading at day 3 or day 4 is obligatory (Magnusson et al. 1966; Bourke et al. 2009). A reading between D 5 and D10 is necessary concerning at least some allergens, e.g. corticosteroids and aminoglycoside antibiotics, where 7 to 30% of contact sensitisations will be missed if a reading around day 7 is not performed in addition to the reading on day 3 or 4 (Macfarlane et al. 1989; Isaksson et al. 2000a; Jonker and Bruynzeel 2000).
- D3 or D4 and around D7 (fair alternative)
  In some countries the first reading is on day 3 or day 4.
- D2 and D3 or (preferably) D4 (acceptable)
  If organisational circumstances dictate, two readings as above will allow for the diagnosis of the vast majority of contact allergies to most allergens with, however, a risk of false-negative results in particular for some allergens (see above).
- D4 only (not recommended as routine)
  In a study where patch-tested individuals were read several times in the range day 2 – day 9, the single day which traced most contact allergy was day 4 but to trace all contact allergy 2 readings on day 4 and day 7 were required (Macfarlane et al. 1989). A D2 reading as only reading is not appropriate (Uter et al. 1996).

  Due to geographic or organisational circumstances the reading times may vary.

4.5 Morphology

The reading of patch test reactions is based on inspection and palpation of the morphology (erythema, infiltrate, papules, vesicles) (Mahler et al. 2019a; Johansen et al. 2015). The globally acknowledged reading criteria of the ICDRG (Magnusson et al. 1966) are shown in Table 2.

Morphologically positive patch test reactions ("+", "++" or "+++") at day 3 or later are usually assessed as allergic (Mahler et al. 2019a; Johansen et al. 2015). Doubtful reactions (?+) can sometimes be clinically relevant and important for the individual patient (Bruze et al. 1999; Andersen and Andersen 2008) and may need further work-up (e.g. repetition of the patch test with several concentrations/serial dilutions, use test). Substances in a liquid vehicle may lead to a ring-shaped test reaction, e.g. observed in serial dilution tests with corticosteroids where clear allergic reactions were observed to other concentrations of the same allergen (Isaksson et al. 1999). Sharp-edged margins and fine wrinkling of the surface of the test area point towards irritant reactions (Johansen et al. 2015). Recently, inter-observer variability has been identified in the discrimination between doubtful and irritant reactions and in the distinction between doubtful and weak positive reactions (Andersen and Andersen 2008; Svedman et al. 2012). Continuous standardisation and reading training is advisable (Svedman et al. 2012).

Different types of irritant reactions have been described (Johansen et al. 2015). Well demarcated erythematous reactions are often seen with fragrance mix and thiuram mix. Reactions appearing purpuric are commonly caused by metal salts, e.g. cobalt chloride (Johansen et al. 2015). Pustular reactions are seen mainly with non-noble metals like chromium, cobalt and nickel (Johansen et al. 2015). In special cases, pustular reactions may reflect contact sensitisation (Bernedo et al. 2001). For the interpretation it is necessary to keep in mind, that besides their properties as a patch test allergen, many patch test chemicals also have some irritant potential (Nosbaum et al. 2009), which is more predominant for some allergens (e.g. benzoyl peroxide, phenyl mercuric acetate, propylene glycol, benzalkonium chloride, octyl gallate, cocamidopropyl betaine, 1,3-diphenyl guanidine) frequently resulting in weak erythematous (doubtful) test reactions (Brasch and Henseler 1992; Geier et al. 2003; Brasch and Geier 2008). A relevant factor for the assessment of patch test results is the individual skin sensitivity and irritability of the individual tested at the time of patch testing (Mahler et al. 2019a). At times of individually

Table 2 reading criteria of the ICDRG (Magnusson et al. 1966) and ESCD (Johansen et al. 2015)

Symbol	Morphology	Assessment
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

increased skin irritability more nonspecific doubtful test reactions may occur (Mahler et al. 2019a). An irritant control patch test is done in some centres (e.g. SLS 0.25% aq., e.g. (Löffler et al. 2005)) where it is considered to provide help in the interpretation of weak reactions to allergens (Mahler et al. 2019a). The value of such "control" has not been unequivocally proven. After the reading of patch test reactions a conclusive interpretation is mandatory concerning the relevance of the test reactions in the respective case with regard to the patient's history, exposure and clinical course (Johansen et al. 2015).

5 Other Techniques

5.1 Repeated Open Application Test (ROAT)

The repeated open application test (ROAT) was developed by Hannuksela and Salo (1986). It is a standardised exposure test mimicking a use situation. It aims at eliciting allergic contact dermatitis in the test area (Johansen et al. 2015). By using this method it is possible to clarify the clinical importance (relevance) of selected patch test reactions (Johansen et al. 2015). In some cases contact allergy to a product can only be proven by this technique. The ROAT may be useful both in experimental studies and in the daily clinic (Johansen et al. 2015).

Test substances, either commercial products or test substances (note: off-label use) are applied twice daily, usually for 2 weeks and up to 4 weeks on the flexural (volar) aspect of the forearm near the ante-cubital fossa in a marked area of 3 × 3 cm to 5 × 5 cm (Johansen et al. 2015). The amount of test substance should cover the test area (Johansen et al. 2015). The applications continue until a reaction develops or until the end of the selected exposure period (Johansen et al. 2015). It may be advisable in selected cases to include a control substance on the contralateral arm, and the ROAT may also be performed in a blinded fashion (Johansen et al. 2015).

A positive response in the form of "eczematous" dermatitis may appear after a few days or later depending on dose/area, matrix effects and individual elicitation thresholds (Johansen et al. 2015). However, a negative ROAT after 1–2 weeks does not exclude a relevant contact allergy (Johansen et al. 2015). Therefore, in highly suspected cases extended application periods of 3–4 weeks may be important in order not to miss late appearing reactions (Johansen et al. 2015). Johansen and co-workers (1998, 2003) developed a scale for evaluation of ROAT responses. It is noteworthy that positive reactions often start with follicular papules in the application area (Johansen et al. 2015) (Table 3).

5.2 Other Test Methods

Further test modalities (semi-open test (Goossens 2009), open test (Johansen et al. 2015), photopatch test (Bruynzeel et al. 2004; Batchelor and Wilkinson 2006;

Table 3 Modified scale for reading use test results. The minimum requirement for a positive test is marked in bold, equivalent to that of 5 points (Johansen et al. 1998, 2003)

1. Involved area of application						
	0	1–24%	25–49%	50–89%	90–100%	
	0	1	**2**	3	4	
2. Erythema Involvement						
				. . . Strength		
None	Spotty	Homogeneous		Weak	Medium	Strong
0	**1**	2		**1**	2	3
3. Papules						
					Homogeneous infiltration	
None	<5	5–10	>10			
0	**1**	2	3			4
4. Vesicles						
None	<5	5–10	>10			Confluent
0	1	2	3			4

Each variable (1–4) must be scored. A positive reaction is characterised by erythema and infiltration as represented by papules, as a minimum, and the reaction should cover altogether at least 25% of the test area. The single scores are added and a positive reaction will range from 5 points to a maximum of 17 points

Gonçalo et al. 2013), lymphocyte proliferation test (LTT)) (Ständer et al. 2017; Spoerri et al. 2018) are summarised in Table 4.

6 Patch Testing of Patients' Own Materials

The textbook chapters in the references provide more detailed information on this subject (mainly in (Johansen et al. 2021)). Information in this section is based on practical observations and empirical evidence as no experimental data exists in this area (Johansen et al. 2015).

Patch testing patients' own products is especially important in occupational dermatology, because standardised commercial patch test substances of many occupationally used chemical compounds are lacking (Johansen et al. 2015): About 4000 contact allergens are known, but only several hundred commercially available allergen preparations exist (Johansen et al. 2015). Moreover, our environment is constantly changing, and workers and consumers are exposed to new chemicals, some of which are allergens (Johansen et al. 2015). Routine test substances will not identify new allergens (Johansen et al. 2015). Testing patients' own products is the only way of finding new allergens in the clinic (Johansen et al. 2015). In addition, patch testing patients' own materials often help assess the clinical relevance of an allergic reaction to standard allergens: for example, when a cosmetic product induces an allergic reaction and the patient also reacts to some of the ingredients labelled on

Table 4 Other test methods: brief summary of indication and technique

Test	Indication	Technique	References
Semi-open test	Products with suspected irritant properties, e.g., shampoos, detergents, paints, varnishes, cooling fluids, pharmaceuticals and cosmetics	Application (with a cotton swab) of approximately 15 μL product on 1 cm^2 skin, allow to dry completely, check for signs of contact urticaria (reading after 20-30 min), then cover with semipermeable acrylic tape. Dermatitis reactions may develop at days 2–4. Readings are performed as for patch testing	Goossens (2009)
Open test	First step, when testing poorly defined substances or products such as those brought by the patient (still same general information is necessary about the product composition!)	Product "as is" or dissolved in water or organic solvent (e.g. ethanol, acetone) is dripped onto the skin and allowed to dry. No occlusion is used. Usual test site is the volar forearm (note: less reactive than the upper back or the upper arm!) Readings at regular intervals during the first 30–60 min after application in order to detect immediate reactions. A second reading at 3–4 days. A negative open test can be explained by insufficient penetration, but indicates that one may proceed with an occlusive patch test	Johansen et al. (2015)
Photopatch test	Photoallergic contact dermatitis (where ultraviolet exposure is necessary to form the hapten), any dermatitis in photo-exposed areas or in photosensitivity from systemic drugs	In the photosensitive patient, it is recommended to first determine their reactivity to UV light (phototests performed on the day of application of the patches). The UV dose for irradiation of the test site should be only $\leq$75% of their Minimal Erythema Dose (Johansen et al. 2021). Test duplicate set of allergens applied on two corresponding areas of the back. After 1 or 2 days of occlusion one set of tests is irradiated with 5 J/cm^2 of UVA while the other is completely shielded from light until further reading. 2 day occlusion before irradiation showed to be more sensitive, however it was concluded that systematic studies were needed	Bruynzeel et al. (2004), Batchelor and Wilkinson (2006), Gonçalo et al. (2013)

(continued)

Table 4 (continued)

Test	Indication	Technique	References
		for definite conclusions. Readings should be performed before and immediately after irradiation and at least 2 days thereafter, if possible also later. Grading of the reactions follows the rules of patch test readings but for result interpretation comparison of reactions in the irradiated and non-irradiated sites is necessary: A positive photopatch tests occurs when there is no reaction at the non-irradiated site and a positive (+ to +++) on the irradiated one. Positive reactions on both sets of tests represent contact allergy. European baseline series for photopatch testing includes mostly UV filters of the different chemical families, non-steroidal anti-inflammatory drugs and a few older photosensitisers	
Lymphocyte transformation test (LTT, syn. Lymphocyte proliferation test) and related ex vivo tests	LTT bears considerable variability due to methodological factors (preanalytical, analytical and postanalytical confounders need to be addressed). Only in the hands of an experienced laboratory, the LTT may be a suitable and valid approach where a patch test cannot be performed (e.g. in patients with non-remitting generalised dermatitis). The MELISA test has been not yet been found to be sufficiently valid	In brief, peripheral blood mononuclear cells from heparinised full blood of patients and non-sensitised control individuals are separated via Ficoll density gradient centrifugation, then cultured with different (non-toxic) concentrations of the incriminated allergen for 5–6 days. The proliferation of the cells is most frequently measured by the 3H-thymidine incorporation	Ständer et al. (2017), Spoerri et al. (2018) MELISA: RKI committee (2008) and http://dkg.ivdk.org/melisa.html

the product, the allergen is probably the cause of the patient's problems (Johansen et al. 2015). However, a negative result to a patient's own product does not exclude contact allergy to some of its components (Johansen et al. 2015).

Efficient testing of patients' own substances requires experience and well-trained staff (Johansen et al. 2015). The concentration of an allergen in the product may be

too low to provoke an allergic reaction, i.e. a false-negative reaction (Johansen et al. 2015). Many products need to be diluted due to their irritant components (e.g. shampoos, toothpaste, etc.), which may lead to a false-negative test result (Johansen et al. 2015). Conversely, if the product is not sufficiently diluted, the irritant components can induce false-positive reactions (Johansen et al. 2015). Concentrations that are too high may lead to patch test sensitisation. The choice of test concentration is based on the characteristics of the product (skin irritant components, sensitising components, pH, etc.) (Johansen et al. 2015). Those ingredients of the product available as commercial test substances should also be tested at the initial patch test session (Johansen et al. 2015). As far as the concentration of ingredients in the product is known, the dilution of the product should achieve that none of the ingredients is above the recommended test concentration for this allergen (de Groot 2018). Contact dermatitis/occupational dermatology textbooks contain recommendations on test concentrations (Johansen et al. 2021; John et al. 2019).

Identification of a new allergen often requires serial testing because products are usually composed of many different chemical substances (Johansen et al. 2015). The components of the product are tested in the second phase, preferably with a dilution series down to negative concentrations (often ppm level) (Johansen et al. 2015). Very low concentrations can usually be increased, and the concentration should not exceed the recommended test concentrations for the type of product or chemical group (e.g. acrylates 0.1%, methacrylates 1 to 2%) (Johansen et al. 2015). A low threshold concentration itself strongly supports the allergic nature of the reactions, as irritant reactions to such low concentrations are rare (Johansen et al. 2015). Aspects of testing with specific product categories are outlined in detail (Johansen et al. 2015) which is recommended for further reading prior to testing patients´ own materials (Johansen et al. 2015). Table 5 outlines some basic rules.

The choice of vehicle depends on the characteristics of the product, solubility and pH (Johansen et al. 2015). When water-soluble chemicals are tested, it is important to check the pH before testing. Neutral products (pH 4–9) can be diluted with distilled water (Johansen et al. 2015). For testing more alkaline or acidic substances, the use of buffer solutions is recommended to reduce irritability and to allow higher concentrations (Johansen et al. 2015). Acid buffer is used for alkaline products ($pH > 9$) and alkaline buffer for acid products ($pH < 4$) while monitoring pH (Bruze 1984a). Water-insoluble chemicals are usually diluted or dispersed in petrolatum, but acetone, ethanol, olive oil and methyl ethyl ketone (MEK) are other alternatives (de Groot 2018).

It is advisable to use disposable containers, syringes, stirrers and spatulas for preparing the test substances (Johansen et al. 2015). Solid materials in crystal or powder form can be ground with a pestle and mortar (Johansen et al. 2015). Liquids are diluted by using pipettes and syringes, and the percentage is given by volume (volume/volume) (Johansen et al. 2015). When electronic scales are used, the percentage is given by weight (weight/weight) (Johansen et al. 2015). Thorough mixing is important for a homogeneous distribution of the allergen in the vehicle (Johansen et al. 2015). Serial dilutions can be prepared from these preparations

Table 5 Basic recommendations for patch testing of patients' own materials [modified from (Johansen et al. 2015)]

Test material	Recommended test preparation
Leave-on cosmetic preparations, protective creams, topical medicaments	"as is"
Rinse-off skin care products such as liquid soap, shampoos, shower gels	1% and 10% in aqua
Oil-based fresh and used metal-working fluids	50% in olive oil
Water-based fresh metal-working fluid Workplace concentration of water-based metal-working fluids *at 4% to 8%* Workplace concentration of water-based metal-working fluids *≥8%*	5% in aqua "as is" Dilute to 5% in aqua.
Acrylic compounds, epoxy diacrylates	0.5% in pet.
Dimethacrylates, such as dental composite resins	1–2% in pet.
Cyanoacrylate-based instant glues	1–10% in pet.
Methacrylates	2% in pet.
UV-curable inks and lacquers, other acrylate-containing products	0.01–0.1% in pet.
Paper, textile, plastic, rubber	"as is"
Ground dust, scrapings, glove pieces, textiles (moist with aqua or organic solvent)	"as is"
Plant material, tropical woods (irritant and sensitising; allergen content may vary)	No general recommendation (test concentration/vehicle depending on individual plant/wood)

(Johansen et al. 2015). The test substances should be stored in a fridge in tightly closed containers or syringes (Johansen et al. 2015). Of note, a negative result to the product does not exclude contact allergy to some of the product's components (Johansen et al. 2015).

7 Final Evaluation: Clinical Relevance and Diagnosis

7.1 Interpretation of Positive Patch Test Reactions and Clinical Relevance

A morphologically positive patch test reaction to a substance at a non-irritant patch test concentration is a sign that sensitisation to the substance in question has occurred (Johansen et al. 2015). However, diagnosing allergic contact dermatitis involves a process with two major steps: Demonstration of contact sensitisation and assessment of clinical relevance (Johansen et al. 2015). Clinical relevance is defined as (Bruze 1990):

1. Existing exposure to the sensitiser and
2. Presence of dermatitis, which is understandable and explainable with regard to the exposure on the one hand and type, anatomical site, and course of the dermatitis on the other.

A positive patch test reaction can be of current and/or past relevance or unknown relevance (Johansen et al. 2015). In case a substance "cross-reacts" with a diagnosed allergen, previous exposure and sensitisation to this cross-reacting substance are not necessary (Benezra and Maibach 1984). No commonly accepted relevance scoring system exists, but different systems have been suggested (Lachapelle 1997; Heisterberg et al. 2011; Fransway et al. 2013; Uter et al. 2018). The latest concept has added the element of the type of information, the evaluation of relevance is based upon – ranging from patient's report to labelling or material data sheet information, to spot testing and chemical analysis – thereby replacing concepts of "certain" vs. "probable" vs. "possible" relevance attribution, which have proven difficult to handle consistently (Uter et al. 2018).

7.2 Interpretation of Doubtful and Negative Reactions

A patch test reaction scored as doubtful means that the morphology is not clear-cut "irritant" or "allergic" (Johansen et al. 2015). This implies that further investigations may have to be done (Johansen et al. 2015): The patch test concentration used may be too low and if increased, a positive patch test reaction may develop, which may even be clinically relevant (Johansen et al. 2015). If, for instance, formaldehyde is tested only at 1% instead of 2% aq. positive reactions are missed, which were shown to be clinically relevant by use tests with formaldehyde containing creams (Hauksson et al. 2011). The weak patch test reaction may also be due to cross-reactivity to another substance which is the primary sensitiser (Johansen et al. 2015). Considerations should be given to the pattern of reactions (Johansen et al. 2015). If reactions to some chemicals from the same "family" are doubtful and others (strong) positive, such as reactions to formaldehyde releaser, rubber chemicals or fragrance substances, this may be a sign of the same contact allergy (Johansen et al. 2015). Evidently, "doubtful" allergic reactions regularly occur to low concentrations of an allergen clearly positive at higher concentrations in serial dilution testing (Johansen et al. 2015). The patch test concentration may also be marginally irritant and the doubtful reaction may then be a sign of skin irritation (Johansen et al. 2015). Repeated patch testing or serial dilution patch testing may be helpful in clarifying the nature of the reaction (Johansen et al. 2015).

As for doubtful patch test reactions, it should always be considered, particularly for non-standardised substances, that false-negative reactions are possible, e.g. due to inadequate patch test concentration and/or vehicle (Johansen et al. 2015). If strongly suspected, testing should be repeated (Johansen et al. 2015). Standardised tape-stripping of the patch test area prior to allergen application has been suggested, and proven, to increase sensitivity, albeit at the expense of specificity, i.e. with an

increase in false-positive reactions (Dickel et al. 2010). Moreover, the culprit substance may not have been included in the patch test programme at all (Johansen et al. 2015). It is also advisable to check for some of the individual factors which may influence a patch test response, especially if the test is unexpectedly negative (Johansen et al. 2015).

7.3 Final Diagnosis

In case *current clinical relevance* is found in a person with established contact allergy, the diagnosis *allergic contact dermatitis* can be made (Johansen et al. 2015). In case of unknown relevance, the person is sensitised, i.e. has a contact allergy, but the criteria for diagnosing allergic contact dermatitis have not been met currently (Johansen et al. 2015). However, the person is at risk of developing allergic contact dermatitis in the future if sufficiently exposed to the allergen (Johansen et al. 2015). Hence, also the contact allergy with unknown relevance must be mentioned in the list of diagnoses, and counselling of the patient should include the respective substance(s) (Johansen et al. 2015). Moreover, contact allergy to one hapten (or sometimes natural mixture) may explain different types of dermatitis, such as chromium allergy being of past occupational relevance for hand eczema in a previous construction worker and of current clinical relevance for foot dermatitis due to chromium tanned leather (Johansen et al. 2015). Documentation of cases should ideally be able to represent such complex diagnostic outcomes (Uter et al. 2018).

In some cases, exposure to a contact allergen may explain the dermatitis entirely, but dermatitis with multi-factorial background frequently occurs (Johansen et al. 2015). Besides the exposure to the contact allergen, constitutional factors may be of importance for the dermatitis and there may be exposure to irritants and other allergens (Johansen et al. 2015). It may be difficult to assess the relative significance of the various factors at a given time (Bruze 1990).

8 Influence of Individual Factors and Special Populations

When patch testing, it is important, among other factors, to consider the responsiveness of the patient (Johansen et al. 2015). Many factors may theoretically weaken the patch test response, including *medication, immunosuppression, UV light* and tanning resulting in false-negative reactions, whilst other factors may increase the response, such as *active dermatitis* (Mahler et al. 2019b; Johansen et al. 2015). Much evidence within this area is based on clinical experience, and limited controlled data are available (Johansen et al. 2015).

Little evidence is available about of the effect of *immunosuppressive agents* on allergic patch test reactions (Mahler et al. 2019b). In practice it may be difficult or impossible for patients to be removed from their immunosuppressive drugs, e.g. corticosteroids, azathioprine and ciclosporin A (Mahler et al. 2019b). In such

circumstances patch testing may be undertaken, but the clinician must be aware that false-negative reactions may occur (Mahler et al. 2019b). However, positive reactions may still occur despite immunosuppressive therapy (Wee et al. 2010), although their number and intensity decrease, e.g., after 20 mg/day prednisolone administration (Anveden et al. 2004). With respect to how many days in advance an oral treatment should be stopped to avoid a theoretical influence on patch testing, a period of 5 half-lives of the particular drug seems reasonable from a clinical point of view; however this is but a rule of thumb and pharmacodynamics need to be considered (e.g. receptor binding) (Mahler et al. 2019b).

Exposure to UVB may reduce risk of sensitization and temporarily diminish the ability to elicit allergic reactions in sensitised individuals (Mahler et al. 2019b). Whilst this seems not to be the case for UVA (Cooper et al. 1992; Skov et al. 1997), PUVA is reported to cause a reduction in patch test reactions (Thorvaldsen and Volden 1980). *UV irradiation* results in a reduction in epidermal Langerhans cell numbers (Seité et al. 2003).

Some patients with severe *generalised inflammatory, infectious or neoplastic disease* or certain cancer diseases may have an impaired capacity for contact sensitisation (Johnson et al. 1973; Grossman et al. 1975; van der Harst-Oostveen and van Vloten 1978). Nevertheless some still develop allergic contact dermatitis and, therefore, positive reactivity to a relevant allergen may occur (Mahler et al. 2019b). In most studies the frequency of positive patch tests in *atopic subjects* is similar to other dermatitis patients. Therefore, patch testing is encouraged for the same reasons as in other patients (Cronin 1972), albeit that the interpretation may be difficult due to their generally hyper-reactive skin with risk of false-positive reactions. Filaggrin mutations, leading to an impaired epidermal barrier function, seem to increase the risk of contact allergy slightly (Thyssen et al. 2013), particularly, the risk of "polysensitisation" (Elhaji et al. 2019).

Children, whether atopic or not, may become sensitised to environmental chemicals such as topical pharmaceuticals and cosmetic products, to topical products used by their caregivers (dermatitis by proxy), or to any other material in prolonged contact with the skin (Schena et al. 2012; Simonsen et al. 2014; Netterlid et al. 2014). Adolescents are more likely to become sensitised to similar allergens as adults, including initial contacts with occupational sensitiser. Patch testing in children is considered safe and recommended when allergic contact dermatitis is suspected or needs to be excluded, as in adults (Moustafa et al. 2011). Contact allergens found mainly in occupational settings, e.g. epoxy resin, can be omitted, whereas patch testing with the products children actually are exposed to, such as topical products, antiseptics, toys, etc., along with their potential ingredients, is crucial (Mahler et al. 2019b). In young children, in particular, these may sometimes be the only allergens to be tested. In case of contact dermatitis after a "henna tattoo", concentrations of PPD much lower than 1% pet. or shorter exposure times (Hextall et al. 2002) or open testing may be advisable to avoid unnecessarily strong patch test reactions (Spornraft-Ragaller et al. 2011).

Patients presenting with possibly *work-related contact dermatitis* require a number of special considerations (Johansen et al. 2015). A consensus-based

recommendation on the general management of patients with occupational dermatitis, including an approach to diagnostics, is found in (Alfonso et al. 2017). In brief, in addition to a standard history, the present and previous employment(s), occupational exposures, work tasks and other relevant aspects need to be documented in detail (and may be required later for medico-legal purposes) (Johansen et al. 2021; John et al. 2019). Photographs (enabled by mobile phones) provided by the patient can be very helpful in identifying an exposure-related problem (Johansen et al. 2015). In particular cases, a visit to the patient's workplace may reveal crucial information concerning the exposure (Johansen et al. 2015). The application of special patch test series, such as hairdresser series, cutting fluid series, etc., and a case-by-case extension of these requires sufficient knowledge of the patient's exposure (Johansen et al. 2015). Concerning patch testing of workplace materials, recommendations found above in this chapter should be followed (Johansen et al. 2015). In practice, it may be difficult to obtain (1) a list of ingredients and (2) the set of actual chemicals, to prepare allergens from these for patch testing (Johansen et al. 2015). Difficulties may be due to company secrets, unwillingness of employers, retailers or manufacturers to respond, lack of information of downstream manufacturers or importers, lack of time, dedication or knowledge by the physician, and the patient's unwillingness to undergo further testing (Johansen et al. 2015). If successful, however, such detailed work-up can profoundly assist patient management and may prompt preventive measures in the work place (Johansen et al. 2015). A missed allergen or allergens, besides other problems, must be suspected in case of persisting skin problems (Johansen et al. 2015). Referral to specialised institutions is advised (Johansen et al. 2015).

For patch testing in *drug eruptions* see (Mahler et al. 2019a) and (Brockow et al. 2013).

9 Potential Adverse Effects of Patch Testing

The following section on adverse reactions to the patch test refers to patch tests performed appropriately, following the published guidelines (Johansen et al. 2015; Mahler et al 2019b):

- *Unexpected irritant reaction.* These may be seen when non-standard allergens or products are tested, despite appropriate dilution based on the available product information.
- *Patch test sensitization.* Although sensitisation by patch testing is uncommon, it is an important potential complication of patch testing. It is defined as a positive patch test reaction generally beyond 2 weeks after an initially negative response at the same site. In practice, it may be difficult to differentiate between induction of sensitisation due to allergen exposure from the patch test and a delayed patch test elicitation reaction (Hillen et al. 2001). To confirm the diagnosis of active sensitisation, repeat patch testing can be performed. A positive reaction, with "normal" latency of elicitation (one to a few days) supports patch test

sensitisation, particularly if there is a positive reaction to the test preparation diluted 10–100 times (Bruze 1984b) although a boosting of a pre-existing, but weak sensitisation cannot be ruled out. Several allergens are known to carry some risk of patch test sensitisation, examples include: *p*-phenylenediamine (Hillen et al. 2006), *p-tert*-butylcatechol (Estlander et al. 1998; Hillen et al. 2001), acrylates tested in historically higher than the present concentrations (Kanerva et al. 1988), chloroacetamide (Fonia et al. 2009), Compositae mix (Wilkinson and Pollock 1999), methyl octynoate (Heisterberg et al. 2010), primula extracts and isothiazolinones (Johansen et al. 2021). The risk of sensitisation by patch testing is very low and the benefit far outweighs any risk (Mahler et al. 2019b; Johansen et al. 2015).

- *Pigmentation changes.* A patch test reaction may rarely result in localised transient hyper- or hypopigmentation.
- *Flare up of clinical dermatitis.* Flare of an existing, or sometimes a previous dermatitis, may occur in the course of a (usually) strong positive reaction. Such flare-up reactions usually indicate that the responsible allergen is the culprit for the current dermatitis (Mose et al. 2010).
- *Persisting reaction.* A positive patch test reaction can sometimes persist up to several weeks. Uchida et al. reported a case with positive patch test reaction to *p*-phenylenediamine that persisted for more than 1 month (Uchida et al. 2013). Gold chloride 0.5% aq. is notorious for causing persisting reactions (Sperber et al. 2003). Palladium salts have been described to cause persisting granulomatous patch test reactions (Goossens et al. 2006; Thyssen et al. 2011).
- *Scarring and necrosis.* While most experts consider this entirely unlikely if the present guidelines are adhered to, some consider the exceptional possibility that secondary scarring may occur after strong (allergic and especially irritant) patch test reactions, in particular, if scratching or superinfection occurs.
- *Subjective complaints.* Itching at the site of applying the patches is commonly observed, it can either be due to a positive patch test reaction or as a result of tape irritation. However, some patients experience more itch immediately after removal of the tape (Mose et al. 2010; Curto et al. 2014). Various subjective complaints of patch-tested patients have occasionally been reported in the literature (Fowler and Zirwas 2018). There is no evidence of a cause-effect relationship.

10 Patient Education on Allergen Avoidance

Allergic contact dermatitis may completely resolve following successful education of the patient on allergen avoidance, addressing workplace conditions (employer, accident insurance) as required, provided that exposure can be sufficiently reduced (Johansen et al. 2015). Sufficient time should be allowed to go over the allergies in detail with the patient, explaining potential sources of exposure (Katta 2008) and to advise on how to avoid future skin contact with the allergen (Johansen et al. 2015).

The use of written, regularly updated information containing the INCI (International nomenclature of cosmetic ingredients) names (in the realm of cosmetics), as well as the different chemical names of the compound, together with the sources of exposure, is necessary (Johansen et al. 2015). This is particularly import for patients with positive patch test reactions to fragrance substances and preservatives (Noiesen et al. 2007). There is some evidence that written information can be superior to oral information regarding a patient's perception (Woo et al. 2003; Noiesen et al. 2004). Marketing terms such as "fragrance-free", "dermatology recommended", "organic" or "does not contain synthetic fragrances" are often misleading and cannot be used for guidance (Johansen et al. 2015). Many clinics provide a card with the allergen names printed, which the patient can have in their wallet and easily access when shopping (Johansen et al. 2015).

Conflict of Interests VM: Has received speaker's fees from SmartPractice Germany, Almirall Hermal, GlaxoSmithKline (prior to current position at PEI); The views expressed in this chapter are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authority, the European Medicines Agency, or one of its committees or working parties. **WU**: Accepted travel reimbursement for presentations given to cosmetic industry (associations) by them. Lecture fee from mixed dermatopharmaceutical sponsors and from PEI, respectively, for educative lectures on contact allergy.

References

Alfonso JH, Bauer A, Bensefa-Colas L et al (2017) Minimum standards on prevention, diagnosis and treatment of occupational and work-related skin diseases in Europe – position paper of the COST action StanDerm (TD 1206). J Eur Acad Dermatol Venereol 31(Suppl 4):31–43. https://doi.org/10.1111/jdv.14319

Andersen KE, Andersen F (2008) The reaction index and positivity ratio revisited. Contact Dermatitis 58:28–31. https://doi.org/10.1111/j.1600-0536.2007.01252.x

Anveden I, Lindberg M, Andersen KE et al (2004) Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel. Contact Dermatitis 50:298–303. https://doi.org/10.1111/j.0105-1873.2004.00340.x

Batchelor RJ, Wilkinson SM (2006) Photopatch testing – a retrospective review using the 1 day and 2 day irradiation protocols. Contact Dermatitis 54:75–78. https://doi.org/10.1111/j.0105-1873.2006.00760.x

Benezra C, Maibach H (1984) True cross-sensitization, false cross-sensitization and otherwise. Contact Dermatitis 11:65–69

Bernedo N, González I, Gastaminza G et al (2001) Positive patch test in vancomycin allergy. Contact Dermatitis 45:43

Bourke J, Coulson I, English J, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee (2009) Guidelines for the management of contact dermatitis: an update. Br J Dermatol 160:946–954. https://doi.org/10.1111/j.1365-2133.2009.09106.x

Brasch J, Geier J (2008) How to use the reaction index and positivity ratio. Contact Dermatitis 59:63–65. https://doi.org/10.1111/j.1600-0536.2008.01360.x

Brasch J, Geier J, Henseler T (1995) Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the information network of departments of dermatology (IVDK). Contact Dermatitis 33:375–380

Brasch J, Henseler T (1992) The reaction index: a parameter to assess the quality of patch test preparations. Contact Dermatitis 27:203–204

Brockow K, Garvey LH, Aberer W et al (2013) Skin test concentrations for systemically administered drugs – an ENDA/EAACI drug allergy interest group position paper. Allergy 68:702–712. https://doi.org/10.1111/all.12142

Bruynzeel DP, Ferguson J, Andersen K et al (2004) Photopatch testing: a consensus methodology for Europe. J Eur Acad Dermatol Venereol 18:679–682. https://doi.org/10.1111/j.1468-3083.2004.01053.x

Bruze M (1984a) Use of buffer solutions for patch testing. Contact Dermatitis 10:267–269

Bruze M (1990) What is a relevant contact allergy? Contact Dermatitis 23:224–225

Bruze M (1984b) Simultaneous patch test sensitization to 4 chemically unrelated compounds in a standard test series. Contact Dermatitis 11:48–49

Bruze M, Condé-Salazar L, Goossens A et al (1999) Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. Contact Dermatitis 41:241–250

Bruze M, Frick-Engfeldt M, Gruvberger B, Isaksson M (2007a) Variation in the amount of petrolatum preparation applied at patch testing. Contact Dermatitis 56:38–42. https://doi.org/10.1111/j.1600-0536.2007.00985.x

Bruze M, Isaksson M, Gruvberger B, Frick-Engfeldt M (2007b) Recommendation of appropriate amounts of petrolatum preparation to be applied at patch testing. Contact Dermatitis 56:281–285. https://doi.org/10.1111/j.1600-0536.2007.01098.x

Cooper KD, Oberhelman L, Hamilton TA et al (1992) UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, CD1a-DR+ epidermal macrophage induction, and Langerhans cell depletion. Proc Natl Acad Sci U S A 89:8497–8501

Cronin E (1972) Clinical prediction of patch test results. Trans St Johns Hosp Dermatol Soc 58:153–162

Curto L, Carnero L, López-Aventin D et al (2014) Fast itch relief in an experimental model for methylprednisolone aceponate topical corticosteroid activity, based on allergic contact eczema to nickel sulphate. J Eur Acad Dermatol Venereol 28:1356–1362. https://doi.org/10.1111/jdv.12292

de Groot AC (2018) Patch testing, vol 4. Acdegroot Publishing, Wapserveen

Dickel H, Kreft B, Kuss O et al (2010) Increased sensitivity of patch testing by standardized tape stripping beforehand: a multicentre diagnostic accuracy study. Contact Dermatitis 62:294–302. https://doi.org/10.1111/j.1600-0536.2010.01710.x

Elhaji Y, Sasseville D, Pratt M et al (2019) Filaggrin gene loss-of-function mutations constitute a factor in patients with multiple contact allergies. Contact Dermatitis. https://doi.org/10.1111/cod.13268

Estlander T, Kostiainen M, Jolanki R, Kanerva L (1998) Active sensitization and occupational allergic contact dermatitis caused by para-tertiary-butylcatechol. Contact Dermatitis 38:96–100

Fischer T, Maibach H (1984) Finn chamber patch test technique. Contact Dermatitis 11:137–140

Fonia A, White JML, McFadden JP, White IR (2009) Active sensitization to chloracetamide. Contact Dermatitis 60:58–59. https://doi.org/10.1111/j.1600-0536.2008.01457.x

Fowler JF, Zirwas M (2018) Fisher's contact dermatitis, 7th edn. Contact Dermatitis Institute, Phoenix

Fransway AF, Zug KA, Belsito DV et al (2013) North American contact dermatitis group patch test results for 2007-2008. Dermat Contact Atopic Occup Drug 24:10–21. https://doi.org/10.1097/DER.0b013e318277ca50

Frick-Engfeldt M, Gruvberger B, Isaksson M et al (2010) Comparison of three different techniques for application of water solutions to Finn Chambers®. Contact Dermatitis 63:284–288. https://doi.org/10.1111/j.1600-0536.2010.01797.x

Friedmann PS (2006) Contact sensitisation and allergic contact dermatitis: immunobiological mechanisms. Toxicol Lett 162:49–54. https://doi.org/10.1016/j.toxlet.2005.10.008

Friedmann PS, Moss C, Shuster S, Simpson JM (1983) Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects. Clin Exp Immunol 53:709–715

Geier J, Uter W, Lessmann H, Schnuch A (2003) The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. Contact Dermatitis 48:280–282

Gonçalo M, Ferguson J, Bonevalle A et al (2013) Photopatch testing: recommendations for a European photopatch test baseline series. Contact Dermatitis 68:239–243. https://doi.org/10.1111/cod.12037

Goossens A (2009) Alternatives to patch tests. Ann Dermatol Venereol 136:623–625. https://doi.org/10.1016/j.annder.2009.06.007

Goossens A, De Swerdt A, De Coninck K et al (2006) Allergic contact granuloma due to palladium following ear piercing. Contact Dermatitis 55:338–341. https://doi.org/10.1111/j.1600-0536.2006.00952.x

Green C (1996) The effect of topically applied corticosteroid on irritant and allergic patch test reactions. Contact Dermatitis 35:331–333

Grossman J, Baum J, Gluckman J et al (1975) The effect of aging and acute illness on delayed hypersensitivity. J Allergy Clin Immunol 55:268–275

Hannuksela M, Salo H (1986) The repeated open application test (ROAT). Contact Dermatitis 14:221–227

Hauksson I, Pontén A, Gruvberger B et al (2011) Clinically relevant contact allergy to formaldehyde may be missed by testing with formaldehyde 1·0%. Br J Dermatol 164:568–572. https://doi.org/10.1111/j.1365-2133.2010.10151.x

Heisterberg MV, Menné T, Johansen JD (2011) Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. Contact Dermatitis 65:266–275. https://doi.org/10.1111/j.1600-0536.2011.01962.x

Heisterberg MV, Vigan M, Johansen JD (2010) Active sensitization and contact allergy to methyl 2-octynoate. Contact Dermatitis 62:97–101. https://doi.org/10.1111/j.1600-0536.2009.01664.x

Hextall JM, Alagaratnam NJ, Glendinning AK et al (2002) Dose-time relationships for elicitation of contact allergy to para-phenylenediamine. Contact Dermatitis 47:96–99

Hillen U, Frosch PJ, John SM et al (2001) Patch test sensitization caused by para-tertiary-butylcatechol. Results of a prospective study with a dilution series. Contact Dermatitis 45:193–196

Hillen U, Jappe U, Frosch PJ et al (2006) Late reactions to the patch-test preparations para-phenylenediamine and epoxy resin: a prospective multicentre investigation of the German Contact Dermatitis Research Group. Br J Dermatol 154:665–670. https://doi.org/10.1111/j.1365-2133.2006.07159.x

Isaksson M, Andersen KE, Brandão FM et al (2000a) Patch testing with corticosteroid mixes in Europe. A multicentre study of the EECDRG. Contact Dermatitis 42:27–35

Isaksson M, Bruze M, Goossens A, Lepoittevin JP (1999) Patch testing with budesonide in serial dilutions: the significance of dose, occlusion time and reading time. Contact Dermatitis 40:24–31

Isaksson M, Gruvberger B, Persson L, Bruze M (2000b) Stability of corticosteroid patch test preparations. Contact Dermatitis 42:144–148

Jensen CD, Paulsen E, Andersen KE (2006) Retrospective evaluation of the consequence of alleged patch test sensitization. Contact Dermatitis 55:30–35. https://doi.org/10.1111/j.0105-1873.2006.00863.x

Johansen JD, Aalto-Korte K, Agner T et al (2015) European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. Contact Dermatitis 73:195–221. https://doi.org/10.1111/cod.12432

Johansen JD, Bruze M, Andersen KE et al (1998) The repeated open application test: suggestions for a scale of evaluation. Contact Dermatitis 39:95–96

Johansen JD, Mahler V, Lepoittevin JP, Frosch PJ (eds) (2021) Contact dermatitis, 6th edn. Springer, Cham

Johansen JD, Frosch PJ, Svedman C et al (2003) Hydroxyisohexyl 3-cyclohexene carboxaldehyde-known as Lyral: quantitative aspects and risk assessment of an important fragrance allergen. Contact Dermatitis 48:310–316

John SM, Johansen JD, Rustemeyer T et al (eds) (2019) Kanerva's occupational dermatology, 3rd edn. Springer, Berlin

Johnson MW, Maibach HI, Salmon SE (1973) Brief communication: quantitative impairment of primary inflammatory response in patients with cancer. J Natl Cancer Inst 51:1075–1076

Jonker MJ, Bruynzeel DP (2000) The outcome of an additional patch-test reading on days 6 or 7. Contact Dermatitis 42:330–335

Kalimo K, Lammintausta K (1984) 24 and 48 h allergen exposure in patch testing. Comparative study with 11 common contact allergens and NiCl2. Contact Dermatitis 10:25–29

Kanerva L, Estlander T, Jolanki R (1988) Sensitization to patch test acrylates. Contact Dermatitis 18:10–15

Katta R (2008) Common misconceptions in contact dermatitis counseling. Dermatol Online J 14:2

Lachapelle JM (1997) A proposed relevance scoring system for positive allergic patch test reactions: practical implications and limitations. Contact Dermatitis 36:39–43

Löffler H, Becker D, Brasch J et al (2005) Simultaneous sodium lauryl sulphate testing improves the diagnostic validity of allergic patch tests. Results from a prospective multicentre study of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). Br J Dermatol 152:709–719. https://doi.org/10.1111/j.1365-2133.2004.06465.x

Macfarlane AW, Curley RK, Graham RM et al (1989) Delayed patch test reactions at days 7 and 9. Contact Dermatitis 20:127–132

Magnusson B, Blohm SG, Fregert S et al (1966) Routine patch testing. II. Proposed basic series of test substances for Scandinavian countries and general remarks on testing technique. Acta Derm Venereol 46:153–158. 102340/0001555546153158

Mahler V (2018) Test allergens: current state of availability from a regulatory point of view. Dermatol Beruf Umw 66:140–144

Mahler V, Dickel H, Diepgen TL et al (2017) Statement of the German Contact Dermatitis Research Group (DKG) and the German Dermatological Society (DDG) on liability issues associated with patch testing using a patient's own materials. J Dtsch Dermatol Ges 15:202–204. https://doi.org/10.1111/ddg.12898

Mahler V, Nast A, Bauer A et al (2019a) S3 guidelines: Epicutaneous patch testing with contact allergens and drugs – short version, part 1. J Dtsch Dermatol Ges 17:1076–1093. https://doi.org/10.1111/ddg.13956

Mahler V, Nast A, Bauer A et al (2019b) S3 guidelines: Epicutaneous patch testing with contact 881 allergens and drugs – short version, part 2. J Dtsch Dermatol Ges 17:1187–1207. https://doi.org/10.1111/ddg.13971

Manuskiatti W, Maibach HI (1996) 1- versus 2- and 3-day diagnostic patch testing. Contact Dermatitis 35:197–200

Martin SF, Bonefeld CM (2021) Mechanisms of irritant and allergic contact dermatitis. In: Johansen JD, Mahler V, Lepoittevin JP, Frosch PJ (eds) Contact dermatitis, 6th edn. Springer, Cham. https://doi.org/10.1007/978-3-030-36335-2_59

Mehrtens SH, Reckling C (2019) Contact urticaria with anaphylaxis caused by chlorocresol, chloroxylenol, and thiourea. Contact Dermatitis 80:311–313. https://doi.org/10.1111/cod.13194

Memon AA, Friedmann PS (1996) Studies on the reproducibility of allergic contact dermatitis. Br J Dermatol 134:208–214

Mose AP, Steenfeldt N, Andersen KE (2010) Flare-up of dermatitis following patch testing is more common in polysensitized patients. Contact Dermatitis 63:289–290. https://doi.org/10.1111/j.1600-0536.2010.01761.x

Mose KF, Andersen KE, Christensen LP (2012) Stability of selected volatile contact allergens in different patch test chambers under different storage conditions. Contact Dermatitis 66:172–179. https://doi.org/10.1111/j.1600-0536.2011.02035.x

Moustafa M, Holden CR, Athavale P et al (2011) Patch testing is a useful investigation in children with eczema. Contact Dermatitis 65:208–212. https://doi.org/10.1111/j.1600-0536.2011.01900.x

Mowitz M, Svedman C, Zimerson E, Bruze M (2014) Fragrance patch tests prepared in advance may give false-negative reactions. Contact Dermatitis 71:289–294. https://doi.org/10.1111/cod.12300

Mowitz M, Zimerson E, Svedman C, Bruze M (2012) Stability of fragrance patch test preparations applied in test chambers. Br J Dermatol 167:822–827. https://doi.org/10.1111/j.1365-2133.2012.11143.x

Netterlid E, Hindsén M, Ekqvist S et al (2014) Young individuals with atopic disease and asthma or rhinoconjunctivitis may have clinically relevant contact allergies. Dermat Contact Atopic Occup Drug 25:115–119. https://doi.org/10.1097/DER.0000000000000037

Noiesen E, Larsen K, Agner T (2004) Compliance in contact allergy with focus on cosmetic labelling: a qualitative research project. Contact Dermatitis 51:189–195. https://doi.org/10.1111/j.0105-1873.2004.00442.x

Noiesen E, Munk MD, Larsen K et al (2007) Difficulties in avoiding exposure to allergens in cosmetics. Contact Dermatitis 57:105–109. https://doi.org/10.1111/j.1600-0536.2007.01170.x

Nosbaum A, Vocanson M, Rozieres A et al (2009) Allergic and irritant contact dermatitis. Eur J Dermatol 19:325–332. https://doi.org/10.1684/ejd.2009.0686

Perfetti L, Galdi E, Biale C et al (2000) Anaphylactoid reaction to patch testing with ammonium persulfate. Allergy 55:94–95

Podmore P, Burrows D, Bingham EA (1984) Prediction of patch test results. Contact Dermatitis 11:283–284

Ring J (1991) Angewandte allergologie. MMW Medizinverlag, München

Schalock PC, Menné T, Johansen JD et al (2012) Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. Contact Dermatitis 66:4–19. https://doi.org/10.1111/j.1600-0536.2011.01971.x

Schena D, Papagrigoraki A, Tessari G et al (2012) Allergic contact dermatitis in children with and without atopic dermatitis. Dermat Contact Atopic Occup Drug 23:275–280. https://doi.org/10.1097/DER.0b013e318273a3e0

Seité S, Zucchi H, Moyal D et al (2003) Alterations in human epidermal Langerhans cells by ultraviolet radiation: quantitative and morphological study. Br J Dermatol 148:291–299

Siegel PD, Fowler JF, Law BF et al (2014) Concentrations and stability of methyl methacrylate, glutaraldehyde, formaldehyde and nickel sulfate in commercial patch test allergen preparations. Contact Dermatitis 70:309–315. https://doi.org/10.1111/cod.12169

Simonetti V, Manzini BM, Seidenari S (1998) Patch testing with nickel sulfate: comparison between 2 nickel sulfate preparations and 2 different test sites on the back. Contact Dermatitis 39:187–191

Simonsen AB, Deleuran M, Mortz CG et al (2014) Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multicentre study. Contact Dermatitis 70:104–111. https://doi.org/10.1111/cod.12129

Skov L, Hansen H, Barker JN et al (1997) Contrasting effects of ultraviolet-A and ultraviolet-B exposure on induction of contact sensitivity in human skin. Clin Exp Immunol 107:585–588

Sperber BR, Allee J, Elenitsas R, James WD (2003) Papular dermatitis and a persistent patch test reaction to gold sodium thiosulfate. Contact Dermatitis 48:204–208

Spoerri I, Bircher AJ, Link S et al (2018) Delayed-type allergy to cobalt-comparison of a flow cytometric lymphocyte proliferation test with patch testing. Contact Dermatitis 79:31–33. https://doi.org/10.1111/cod.12990

Spornraft-Ragaller P, Schnuch A, Uter W (2011) Extreme patch test reactivity to p-phenylenediamine but not to other allergens in children. Contact Dermatitis 65:220–226. https://doi.org/10.1111/j.1600-0536.2011.01930.x

Ständer S, Oppel E, Thomas P, Summer B (2017) Evaluation of lymphocyte transformation tests as compared with patch tests in nickel allergy diagnosis. Contact Dermatitis 76:228–234. https://doi.org/10.1111/cod.12751

Svedman C, Isaksson M, Björk J et al (2012) "Calibration" of our patch test reading technique is necessary. Contact Dermatitis 66:180–187. https://doi.org/10.1111/j.1600-0536.2011.02044.x

Thorvaldsen J, Volden G (1980) PUVA-induced diminution of contact allergic and irritant skin reactions. Clin Exp Dermatol 5:43–46

Thyssen JP, Johansen JD, Jellesen MS, Menné T (2011) Provocation test with metallic palladium in a palladium-allergic patient. Contact Dermatitis 65:304–306. https://doi.org/10.1111/j.1600-0536.2011.01959.x

Thyssen JP, Linneberg A, Ross-Hansen K et al (2013) Filaggrin mutations are strongly associated with contact sensitization in individuals with dermatitis. Contact Dermatitis 68:273–276. https://doi.org/10.1111/cod.12021

Tournoux M, Zhu H, Maibach HI (2016) Reliability of dispensers for patch testing. Contact Dermatitis 74:382–383. https://doi.org/10.1111/cod.12574

Uchida S, Oiso N, Matsunaga K, Kawada A (2013) Patch test reaction to p-phenylenediamine can persist for more than 1 month. Contact Dermatitis 69:382–383. https://doi.org/10.1111/cod.12119

Uter W (2015) Fragrance mix I: TRUE Test(®) versus pet.-based patch test. Contact Dermatitis 72:256–258. https://doi.org/10.1111/cod.12352

Uter W, Bauer A, Bensefa-Colas L et al (2018) Pilot study on a new concept of documenting the clinical relevance of patch test results in contact dermatitis patients. Contact Dermatitis 79:370–377. https://doi.org/10.1111/cod.13097

Uter W, Bruze M, Rustemeyer T et al (2017) Re "International survey on skin patch test procedures, attitudes and interpretation" L.K. Tanno et al. WAOJ (2016) 9:8. World Allergy Organ J 10:18. https://doi.org/10.1186/s40413-017-0149-0

Uter WJ, Geier J, Schnuch A (1996) Good clinical practice in patch testing: readings beyond day 2 are necessary: a confirmatory analysis. Members of the Information Network of Departments of Dermatology. Am J Contact Dermat Off J Am Contact Dermat Soc 7:231–237

van der Harst-Oostveen CJ, van Vloten WA (1978) Delayed-type hypersensitivity in patients with mycosis fungoides. Dermatologica 157:129–135

van Strien GA, Korstanje MJ (1994) Site variations in patch test responses on the back. Contact Dermatitis 31:95–96

Wee JS, White JML, McFadden JP, White IR (2010) Patch testing in patients treated with systemic immunosuppression and cytokine inhibitors. Contact Dermatitis 62:165–169. https://doi.org/10.1111/j.1600-0536.2009.01695.x

Wilkinson M, Gonçalo M, Aerts O et al (2019) The European baseline series and recommended additions: 2019. Contact Dermatitis 80:1–4. https://doi.org/10.1111/cod.13155

Wilkinson SM, Pollock B (1999) Patch test sensitization after use of the Compositae mix. Contact Dermatitis 40:277–278

Woo PN, Hay IC, Ormerod AD (2003) An audit of the value of patch testing and its effect on quality of life. Contact Dermatitis 48:244–247

Robert Koch Institut (RKI) Committee (2008) Methods and quality assurance in environmental medici report by the committee. Quality assurance in the lymphocyte transformation test–addendum to the LTT publication. Methods and quality assurance in environmental medicine. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. September 51:1070–1076

Part VIII

Allergy Prevention

Effective Ways to Prevent Allergic Diseases: Where Do We Stand?

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Abstract

Since allergic diseases are of great public health relevance, effective primary prevention strategies are urgently needed. This chapter gives an overview of existing primary prevention programs on environmental exposures and dietary strategies based on epidemiological studies which have defined risk- and protective factors for the development of allergic diseases.

The allergy protective effect mediated by growing up on a traditional farm environment is well studied. But the exact underlying mechanisms have still not been fully clarified and have not yet led to concrete prevention strategies. The beneficial effect of avoiding cigarette smoke exposure, indoor moisture and molds in pregnancy and childhood on the development of asthma is well documented. Whereas the avoidance of house dust mite exposure is not recommended to prevent eczema or allergy. Dietary supplementation with vitamins, pre- and probiotics in pregnant woman and their offspring is not harmful but evidence for the prevention of allergic diseases is still lacking. Fish oil consumption was shown to be asthma protective. The early introduction of peanuts and egg protein to prevent peanut and egg allergy in children with atopic dermatitis is promising. Further studies are needed to increase the overall evidence in allergy prevention. Most studies lack methodological standards such as randomization and blinding. More evidence is in demand on the potential beneficial impact of multifaceted interventional studies. The future of allergy prevention strategies might be based on individual risk assessment. Therefore, research in the immunological and molecular basis of allergic diseases needs to be promoted.

Keywords

Allergy · Eczema · Primary prevention

1 Introduction

With a high prevalence in developed countries allergic diseases are a major burden of public health relevance in all age groups. Allergic diseases include allergic asthma; allergic rhinitis; anaphylaxis; drug-, food-, and insect- allergy and eczema with highest level of suffering in children (Pawankar et al. 2013). The different forms of allergy are caused by complex and multiple pathophysiological changes in different organs, which cause manifold symptoms. Therefore, a "one size fits all" approach to prevent the different forms of allergic diseases is likely unrealistic. Nevertheless, there are promising findings from epidemiologic studies which detected distinct risk factors and also environmental and nutritional components decreasing the risk to develop allergic diseases. This chapter gives a brief overview of existing insights into promising intervention strategies and reveals gaps in evidence. Most atopic diseases are known to have its origin in the childhood. For this reason, we focus on interventional strategies in pregnancy and childhood.

2 Environmental Exposure in Interventions

Environmental exposure describes all particles and substances of different size which are in contact with the human body and might enter it through different barriers like the skin, the lung, the nose, and the digestive system. Environmental components have been associated with not only protective but also harmful effects on allergy development.

2.1 The More Microbes, the Better?!

2.1.1 Hygiene Hypothesis and Farm Environment

After David Strachan associated increased microbial exposure with decreased prevalence of hay fever in developed countries in 1989 (Strachan 1989), the "hygiene hypothesis" was born. Several following studies showed that microbes play an important role in tolerance induction by activating regulatory immune cells like regulatory T and B cells (Smits et al. 2016). In addition to the observation of Strachan, rural living such as "traditional" farming was shown to be associated with a decreased risk of allergy development. Numerous "farm studies" confirmed the protective effect and associated it with being exposed to cattle, their sheds and by the consumption of unprocessed cow's milk since early childhood. These effects were traced back to an increased diversity and richness of bacteria and fungi in the farm environment (Ober et al. 2017; von Mutius and Vercelli 2010; von Mutius and Smits 2020). Latest results of the Finnish birth cohort study LUKAS showed that microbiota composition in non-farm houses which are comparable to those of traditional farms also have allergy protective effects (Kirjavainen et al. 2019). These studies showed the influence of environmental microbes on the development of allergic diseases, but have not yet led to concrete guidelines or intervention studies.

2.1.2 Dogs and Cats

The influence of intense contact to dogs and cats in the development of allergies is still under debate. Observational studies on pet ownership and its association with allergy protection may be biased as dog/cat owners are unlikely to be allergic to their animals and keep them whereas allergic persons do not have cats or dogs in their home (Konradsen et al. 2015). Nevertheless dog ownership was associated with allergy protection. Marrs et al. showed that children growing up with more than one dog are likely to be protected from food allergy and house dust mite (HDM) sensitization until their 3rd year of life (Marrs et al. 2019). This effect was traced back to increased microbial diversity. Kettleson et al. revealed that homes with dogs contained four times more putative bacterial species compared to homes without a dog (Kettleson et al. 2015). In different studies, cat ownership was associated not only with protective but also with harmful effects on allergy development in the past. Discussion on the influence of cats in allergy development is still ongoing (Konradsen et al. 2015; Pawankar et al. 2013).

2.1.3 C-Section

The contact to maternal bacteria through natural birth seems to be important in the development of child's own gut microbiome. It has been shown that delivery by cesarean section (CS) is predisposed to the development of food allergy but not to atopic dermatitis in early childhood (Papathoma et al. 2016; Chernikova et al. 2019). CS without medical indication was also associated with an increased risk of childhood asthma (Chu et al. 2017). Highly standardized interventional studies with randomization are unfeasible but pregnant women should be encouraged to give birth naturally.

2.1.4 Day Care

Attending day care in early life was associated with a reduced risk to develop atopic dermatitis (Kantor and Silverberg 2017) to be sensitized against food- and aero-allergen (Gabet et al. 2016) and asthma development in high-risk children (Grabenhenrich et al. 2014). These results are consistent with Strachan's original hygiene theory. But these observational studies do not lead to evidence in allergy prevention.

3 Potentially Harmful Environmental Factors

3.1 Exposure to Molds

As children more and more spend time indoors than outdoors, indoor exposure plays an increasingly important role in allergy prevention. Indoor mold exposure is known to be a risk factor for respiratory diseases like asthma especially in moist homes (Casas et al. 2016). An intervention study in European schools reducing indoor mold exposition showed beneficial effects in asthma symptoms (Hauptman and Phipatanakul 2016). The mold free environment in schools and households might also be important for primary prevention of allergic and also other respiratory diseases. Of note a recently published review pointed out that indoor fungal diversity is associated with atopy protection. The harmful effect has been attributed to indoor moisture rather than molds by the author (Barnes 2019).

3.2 Exposure to Cigarette Smoke

The negative health effect of active and passive smoking is well studied. The risk of wheezing and asthma is increased by at least 20% in the offspring of active and passive smoking parents (Burke et al. 2012; Neuman et al. 2012; Hollams et al. 2014). The benefits of avoiding tobacco smoke during pregnancy, childhood, and ideally during the whole life is one of the best studied health promotion strategies, not exclusively for atopic diseases. Reduced asthma-associated hospital stays have already been reported after the smoke free legislation in the USA (Been et al. 2014). National anti-smoking campaigns, e.g. in Germany, are already showing signs of success. The frequency of smoking, especially among adolescents, is decreasing

(Zeiher et al. 2018). Encouraging pregnant women to raise their children in a smoke free environment needs to be the task for gynecologists and pediatricians.

The effects of the more and more upcoming "e-cigarettes" on allergy development are poorly studied and prevention strategies are not published yet.

3.3 House Dust Mite Exposure

One of the best studied environmental indoor allergens is the house dust mite (HDM). Numerous studies investigated the effects of reducing HDM at home, e.g. with special bed covers or chemical removal strategies. HDM avoidance strategies alone or in combination with additional allergen avoidance did not decrease the risk of atopic dermatitis (Bremmer and Simpson 2015) or allergy development (Arroyave et al. 2014) and should therefore not be recommended as it was in former years.

4 Climate Change and Air Pollution

The world allergy organization (WOA) summarized the influences of climate changes on allergy and asthma risk and development in one publication (D'amato et al. 2015). The most important changes which are relevant in allergic diseases are the extension of the pollen season as the global temperature increases and the spread of non-indigenous plants and their pollen like *Ambrosia* in middle Europe. Climate change will also lead to global wind changes affecting the distribution of pollen.

Air pollution is mostly referred to traffic-related air pollutants (TRAP), including elemental carbon, black soot, nitrogen dioxide (NO2), nitric oxide (NO), sulfur dioxide (SO2), carbon monoxide (CO), and carbon dioxide (CO2). It is uncontroversial that the concentration of these pollutants increased during the last century. A recently published review of air pollution effects on asthma, rhinitis, and atopic dermatitis concluded growing evidence for a significant association. But the authors pointed out that observational studies often lack standardized methodology (Hassoun et al. 2019). Climate changes and increase in TRAP have influences on the global burden of allergic diseases. For this reason, global programs against climate change might also have a positive impact on allergy prevalence.

5 Dietary Intervention Strategies

5.1 Supplements

Dietary supplements to prevent allergic diseases have been studied for years. This chapter will summarize the evidence of the supplementation with pro- and prebiotics, long chain polyunsaturated fatty acids (LC-PFUAs), and vitamins.

A systematic review summarized the effect of probiotics on the prevention of allergies and showed positive effects in the prevention of eczema in childhood when probiotics are taken in pregnancy and/or given to infants. But the authors found no

beneficial effects in the prevention of any allergy. They emphasize the lack of highly standardized RCTs and objective outcomes in the studies (Cuello-Garcia et al. 2015). Also other studies found some evidence for the eczema preventive effect of supplementation with *Bifidobacterium lactis* and *Lactobacillus rhamnosus* in pregnant women and their children. The evidence for allergy and asthma prophylaxis with pro- and prebiotics is still unclear, but could be advantageous in high-risk children (Mennini et al. 2017; Krzych-Falta et al. 2018). Research is needed to define the period, dose and composition of pre- and probiotic supplementation to prevent allergic diseases. Although the beneficial effect of prebiotics is still under debate, the WAO recommends prebiotic supplementation for all infants who are not breastfeed (Cuello-Garcia et al. 2016) and probiotics in pregnancy and early childhood for children at high risk to develop allergy. But the WAO has also highlighted the poor quality of the evidence (Fiocchi et al. 2015).

A systematic review on the effect of vitamin D supplementation did not conclude evidence for the prevention of allergy. The authors criticize the poor study quality of their included studies (Yepes-Nunez et al. 2018). Studies which investigated the effect of vitamin D supplementation in the development of asthma did also find no clear beneficial effect (Brustad et al. 2019; Shen et al. 2018). Therefore, supplementation with vitamin D is not recommended for the prevention of allergic diseases.

N-3 long chain polyunsaturated fatty acids (LCPFUAs), most importantly omega-3 and omega-6 fatty acids were shown to influence immunological cells and act immunosuppressive in different cell culture and animal models. They modulate T-cell proliferation, decrease pro-inflammatory cytokine production, and can increase IL-10 secretion in vitro (Hoppenbrouwers et al. 2019). Although these effects were striking, consumption of LCPFUAs in pregnancy during breastfeeding periods and in early childhood did not show evidence in the prevention of allergy or dermatitis/eczema and insufficient evidence for the prevention of allergic rhinitis (Schindler et al. 2016; Gunaratne et al. 2015). The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) showed promising results in the prevention of wheezing and asthma development in the offspring with fish oil supplementation in pregnancy. The study consortium detected reduced wheezing and asthma prevalence in 5-year-old children whose mothers took 2.4 g of fish oil capsules daily from the 24th pregnancy week until 1 week after birth, compared to the control group supplemented with olive oil. They did not observe a reduced risk for allergic sensitization, rhinoconjunctivitis, or eczema (Bisgaard et al. 2016). A recently published study associated the consumption of fish or cod liver oil in the first year of life with a reduced risk for eczema, asthma, and wheeze at 6 years of age using data from the PACT study in Norway (Oien et al. 2019). Whereas evidence for asthma prevention with fish oil consumption is increasing, it is still lacking for other allergic diseases.

5.2 Solid Food Introduction

Recommendations on solid food introduction in young children are manifold and emotionally discussed. The current practice of gradually introducing solid foods in children and avoiding potentially allergenic foods is likely to be outdated.

Different studies showed an association between the avoidance of egg, fish, milk, and tree nuts in pregnancy and early life on decreased rates of asthma, rhinitis, and atopy but not for food allergy (Zeiger and Heller 1995; Arshad et al. 2007). Whereas the Cochrane review of Kramer and Kakuma did not find evidence for positive effects of antigen avoidance in pregnancy for the offspring's eczema or food allergy risk. They concluded that avoiding potentially antigenic foods during pregnancy is not recommended to prevent eczema or food allergies in the offspring (Kramer and Kakuma 2012). In more recent studies the early introduction of potentially allergenic food was studied. The early introduction of peanut- and egg-protein to avoid peanut and egg allergy was shown to be successful in children being at risk to develop food allergy in the Learning Early About Peanut (LEAP) and Enquiring About Tolerance (EAT) studies. The authors did not show reduction or increase of other food allergies or eczema (Fisher et al. 2018). These results go along with a recently published multicenter cluster randomized prevention study which concluded not only no beneficial but also no harmful effect of early introduction (starting 3 month after birth) of peanut, cow's milk, wheat, and egg on the prevention of eczema at 12 months of age. The assessment of food allergy will be a primary outcome of the follow-up protocol after 36 months (Skjerven et al. 2020). These results were striking because they brought about a paradigm shift, which is also supported by the biodiversity hypothesis which recommends as much diverse contact to natural environment early in life as possible which includes exposure to various food products (Haahtela 2019). "The Guidelines for the Diagnosis and Management of Peanut and Tree Nut Allergy in the United Kingdom" thereupon recommends the early introduction of peanuts (at least 2 g of peanut protein three times a week) for children at risk to develop peanut allergy. High risk is defined by severe eczema or egg allergy. Non-risk children consuming peanuts do not have any increased risk to develop peanut allergy (Stiefel et al. 2017). The American Academy of Allergy guidelines also recommends the consumption of potentially allergenic food in young age and highlights that avoidance of egg, dairy, peanut, tree nuts, fish, and shellfish might even increase the child's risk to become food allergic (American Academy of Allergy, Asthma, and Immunology 2019).

5.3 Breastfeeding

The positive effects of breastfeeding for mother and child are well studied. But the protective effects on allergy and asthma development are still under debate. RTC studies are not feasible as well as blinding. Although no evidence for allergy and asthma prevention exists, breast feeding is highly recommended for the first 4 months of life (Heinrich 2017; Victora et al. 2016).

6 Conclusion

Many attempts to prevent allergic diseases have been taken, but so far no conclusive evidence for general allergy prevention recommendations exists. Avoidance of passive and active cigarette smoke exposure for pregnant women and children and avoidance of indoor moisture and mold is beneficial for the prevention of wheezing and asthma. Whereas the avoidance of HDM allergens to prevent HDM allergy is not recommended anymore. There are epidemiological studies which associated the traditional farm environment with allergy reduction but primary prevention studies are not published yet. Supplementation with vitamins, pre- and probiotics is not harmful but evidence for the prevention of allergic diseases is still lacking. Supplementation with LCPFUAs was shown to be asthma but not allergy protective. Best evidence was shown in the early introduction of peanuts in children with egg sensitization or eczema to prevent peanut allergy.

The evidence for allergy prevention in total can be classified as low. The lack of RCTs has a major impact on evidence generation. With regard to behavioral studies, blinding or randomization is hardly feasible, which makes the evaluation of evidence more difficult. Most of the prevention strategies are based on observational studies which are less meaningful than RCTs and very hard to compare. Another factor associated with observational and intervention studies is a large influence of bias, especially when it comes to parents filling out questionnaires and describing their children's symptoms. Outcome assessment was mostly based on observation instead of evaluated objective measures like the skin prick tests, blood IgE levels, and/or lung function tests, just to mention a few. Research on reliable, easy-to-use and inexpensive biomarkers that can be used in various body fluids, ideally non-invasive, is ongoing and will increase the quality and comparability of study results in future studies. Figure 1 summarizes beneficial strategies and research needs in allergy prevention.

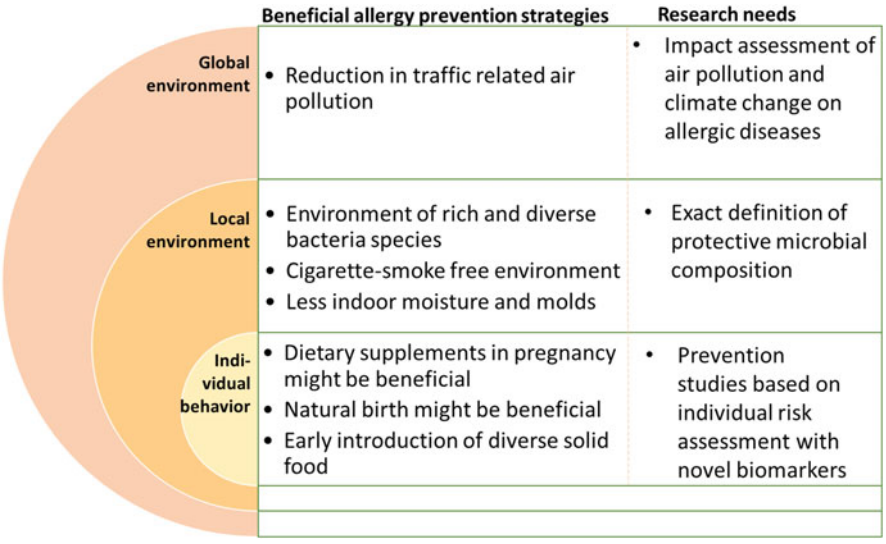

Fig. 1 An overview of prevention strategies and research needs to reduce allergic diseases in three dimensions, including individual behavior, local and global environment

Targeted prevention based on individual risk assessment with the help of evaluated biomarkers could be one future strategy to overcome the burden of allergic diseases. With profound knowledge in cellular and molecular signal processing in allergy sufferers, these strategies will be improved. Although all quoted studies in this chapter focusing on one intervention strategy or one outcome, the future in prevention of allergy and atopic diseases may also lie in multifaceted allergy prevention programs. They can combine best evidence studies in a national program where forces are bundled and which includes stakeholders, communities, patients, and their parents already in the conceptual stage to develop prevention strategies on a population level like the Finnish allergy program (Pelkonen et al. 2012).

References

American Academy of Allergy, Asthma, and Immunology (2019) Prevention of allergies and asthma in children. [Online]. https://www.aaaai.org/conditions-and-treatments/library/allergy-library/prevention-of-allergies-and-asthma-in-children. Accessed 24 Oct 2019

Arroyave WD, Rabito FA, Carlson JC, Friedman EE, Stinebaugh SJ (2014) Impermeable dust mite covers in the primary and tertiary prevention of allergic disease: a meta-analysis. Ann Allergy Asthma Immunol 112:237–248

Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM (2007) Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. J Allergy Clin Immunol 119:307–313

Barnes C (2019) Fungi and atopy. Clin Rev Allergy Immunol 57:439–448

Been JV, Nurmatov UB, Cox B, Nawrot TS, Van Schayck CP, Sheikh A (2014) Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. Lancet 383:1549–1560

Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadottir E, Schoos AM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdottir S, Folsgaard NV, Fink NR, Thorsen J, Pedersen AG, Waage J, Rasmussen MA, Stark KD, Olsen SF, Bonnelykke K (2016) Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med 375:2530–2539

Bremmer SF, Simpson EL (2015) Dust mite avoidance for the primary prevention of atopic dermatitis: a systematic review and meta-analysis. Pediatr Allergy Immunol 26:646–654

Brustad N, Eliasen AU, Stokholm J, Bonnelykke K, Bisgaard H, Chawes BL (2019) High-dose vitamin D supplementation during pregnancy and asthma in offspring at the age of 6 years. JAMA 321:1003–1005

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, Mckeever TM (2012) Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 129:735–744

Casas L, Tischer C, Taubel M (2016) Pediatric asthma and the indoor microbial environment. Curr Environ Health Rep 3:238–249

Chernikova D, Yuan I, Shaker M (2019) Prevention of allergy with diverse and healthy microbiota: an update. Curr Opin Pediatr 31:418–425

Chu S, Chen Q, Chen Y, Bao Y, Wu M, Zhang J (2017) Cesarean section without medical indication and risk of childhood asthma, and attenuation by breastfeeding. PLoS One 12: E0184920

Cuello-Garcia CA, Brozek JL, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Terracciano L, Gandhi S, Agarwal A, Zhang Y, Schunemann HJ (2015) Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 136:952–961

Cuello-Garcia CA, Fiocchi A, Pawankar R, Yepes-Nunez JJ, Morgano GP, Zhang Y, Ahn K, Al-Hammadi S, Agarwal A, Gandhi S, Beyer K, Burks W, Canonica GW, Ebisawa M, Kamenwa R, Lee BW, Li H, Prescott S, Riva JJ, Rosenwasser L, Sampson H, Spigler M, Terracciano L, Vereda A, Waserman S, Schunemann HJ, Brozek JL (2016) World Allergy Organization-Mcmaster University guidelines for allergic disease prevention (Glad-P): prebiotics. World Allergy Organ J 9:10

D'amato G, Holgate ST, Pawankar R, Ledford DK, Cecchi L, Al-Ahmad M, Al-Enezi F, Al-Muhsen S, Ansotegui I, Baena-Cagnani CE, Baker DJ, Bayram H, Bergmann KC, Boulet LP, Buters JT, D'amato M, Dorsano S, Douwes J, Finlay SE, Garrasi D, Gomez M, Haahtela T, Halwani R, Hassani Y, Mahboub B, Marks G, Michelozzi P, Montagni M, Nunes C, Oh JJ, Popov TA, Portnoy J, Ridolo E, Rosario N, Rottem M, Sanchez-Borges M, Sibanda E, Sienra-Monge JJ, Vitale C, Annesi-Maesano I (2015) Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. World Allergy Organ J 8:25

Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, Beyer K, Burks W, Canonica GW, Ebisawa M, Gandhi S, Kamenwa R, Lee BW, Li H, Prescott S, Riva JJ, Rosenwasser L, Sampson H, Spigler M, Terracciano L, Vereda-Ortiz A, Waserman S, Yepes-Nunez JJ, Brozek JL, Schunemann HJ (2015) World Allergy Organization-Mcmaster University guidelines for allergic disease prevention (Glad-P): probiotics. World Allergy Organ J 8:4

Fisher HR, Du Toit G, Bahnson HT, Lack G (2018) The challenges of preventing food allergy: lessons learned from Leap and eat. Ann Allergy Asthma Immunol 121:313–319

Gabet S, Just J, Couderc R, Seta N, Momas I (2016) Allergic sensitisation in early childhood: patterns and related factors in Paris birth cohort. Int J Hyg Environ Health 219:792–800

Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, Forster J, Schuster A, Schramm D, Bauer CP, Hoffmann U, Beschorner J, Wagner P, Bergmann R, Bergmann K, Matricardi PM, Wahn U, Lau S, Keil T (2014) Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. J Allergy Clin Immunol 133:979–988

Gunaratne AW, Makrides M, Collins CT (2015) Maternal prenatal and/or postnatal N-3 long chain polyunsaturated fatty acids (Lcpufa) supplementation for preventing allergies in early childhood. Cochrane Database Syst Rev:Cd010085

Haahtela T (2019) A biodiversity hypothesis. Allergy 74:1445–1456

Hassoun Y, James C, Bernstein DI (2019) The effects of air pollution on the development of atopic disease. Clin Rev Allergy Immunol 57(3):403–414

Hauptman M, Phipatanakul W (2016) Recent advances in environmental controls outside the home setting. Curr Opin Allergy Clin Immunol 16:135–141

Heinrich J (2017) Modulation of allergy risk by breast feeding. Curr Opin Clin Nutr Metab Care 20:217–221

Hollams EM, De Klerk NH, Holt PG, Sly PD (2014) Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. Am J Respir Crit Care Med 189:401–407

Hoppenbrouwers T, Cvejic Hogervorst JH, Garssen J, Wichers HJ, Willemsen LEM (2019) Long chain polyunsaturated fatty acids (Lcpufas) in the prevention of food allergy. Front Immunol 10:1118

Kantor R, Silverberg JI (2017) Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol 13:15–26

Kettleson EM, Adhikari A, Vesper S, Coombs K, Indugula R, Reponen T (2015) Key determinants of the fungal and bacterial microbiomes in homes. Environ Res 138:130–135

Kirjavainen PV, Karvonen AM, Adams RI, Täubel M, Roponen M, Tuoresmäki P, Loss G, Jayaprakash B, Depner M, Ege MJ, Renz H, Pfefferle PI, Schaub B, Lauener R, Hyvärinen A, Knight R, Heederik DJJ, Von Mutius E, Pekkanen J (2019) Farm-like indoor microbiota in non-farm homes protects children from asthma development. Nat Med 25:1089–1095

Konradsen JR, Fujisawa T, Van Hage M, Hedlin G, Hilger C, Kleine-Tebbe J, Matsui EC, Roberts G, Ronmark E, Platts-Mills TA (2015) Allergy to furry animals: new insights, diagnostic approaches, and challenges. J Allergy Clin Immunol 135:616–625

Kramer MS, Kakuma R (2012) Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev: Cd000133

Krzych-Falta E, Furmanczyk K, Tomaszewska A, Olejniczak D, Samolinski B, Samolinska-Zawisza U (2018) Probiotics: myths or facts about their role in allergy prevention. Adv Clin Exp Med 27:119–124

Marrs T, Logan K, Craven J, Radulovic S, Irwin McLean WHA, Lack G, Flohr C, Perkin MR (2019) Dog ownership at three months of age is associated with protection against food allergy. EAT Study Team Allergy 74(11):2212–2219. https://doi.org/10.1111/all.13868

Mennini M, Dahdah L, Artesani MC, Fiocchi A, Martelli A (2017) Probiotics in asthma and allergy prevention. Front Pediatr 5:165

Neuman A, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, Gehring U, Granell R, Henderson J, Heinrich J, Lau S, Nieuwenhuijsen M, Sunyer J, Tischer C, Torrent M, Wahn U, Wijga AH, Wickman M, Keil T, Bergstrom A (2012) Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. Am J Respir Crit Care Med 186:1037–1043

Ober C, Sperling AI, Von Mutius E, Vercelli D (2017) Immune development and environment: lessons from Amish and Hutterite children. Curr Opin Immunol 48:51–60

Oien T, Schjelvaag A, Storro O, Johnsen R, Simpson MR (2019) Fish consumption at one year of age reduces the risk of eczema, asthma and wheeze at six years of age. Nutrients 11

Papathoma E, Triga M, Fouzas S, Dimitriou G (2016) Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. Pediatr Allergy Immunol 27:419–424

Pawankar R, Holgate ST, Canonica GW, Lockey RF, Blaiss MS (2013) Wao White book on allergy 2013 update. https://www.worldallergy.org/wao-white-book-on-allergy

Pelkonen AS, Kuitunen M, Dunder T, Reijonen T, Valovirta E, Makela MJ (2012) Allergy in children: practical recommendations of the Finnish Allergy Programme 2008-2018 for prevention, diagnosis, and treatment. Pediatr Allergy Immunol 23:103–116

Schindler T, Sinn JK, Osborn DA (2016) Polyunsaturated fatty acid supplementation in infancy for the prevention of allergy. Cochrane Database Syst Rev 10:Cd010112

Shen SY, Xiao WQ, Lu JH, Yuan MY, He JR, Xia HM, Qiu X, Cheng KK, Lam KBH (2018) Early life vitamin D status and asthma and wheeze: a systematic review and meta-analysis. BMC Pulm Med 18:120

Skjerven HO, Rehbinder EM, Vettukattil R, Leblanc M, Granum B, Haugen G, Hedlin G, Landrø L, Marsland BJ, Rudi K, Sjøborg KD, Söderhäll C, Staff AC, Carlsen KH, Asarnoj A, Bains KES, Carlsen OCL, Endre KMA, Granlund PA, Hermansen JU, Gudmundsdóttir HK, Hilde K, Håland G, Kreyberg I, Olsen IC, Mägi CO, Nordhagen LS, Saunders CM, Skrindo I, Tedner SG, Værnesbranden MR, Wiik J, Jonassen CM, Nordlund B, Carlsen KCL (2020) Skin emollient and early complementary feeding to prevent infant atopic dermatitis (Preventadall): a factorial, multicentre, cluster-randomised trial. Lancet 395:951–961

Smits HH, Hiemstra PS, Prazeres Da Costa C, Ege M, Edwards M, Garn H, Howarth PH, Jartti T, De Jong EC, Maizels RM, Marsland BJ, Mcsorley HJ, Muller A, Pfefferle PI, Savelkoul H, Schwarze J, Unger WW, Von Mutius E, Yazdanbakhsh M, Taube C (2016) Microbes and asthma: opportunities for intervention. J Allergy Clin Immunol 137:690–697

Stiefel G, Anagnostou K, Boyle RJ, Brathwaite N, Ewan P, Fox AT, Huber P, Luyt D, Till SJ, Venter C, Clark AT (2017) Bsaci guideline for the diagnosis and management of Peanut and tree nut allergy. Clin Exp Allergy 47:719–739

Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299:1259–1260

Victora CG, Bahl R, Barros AJ, Franca GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC (2016) Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 387:475–490

Von Mutius E, Smits HH (2020) Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. Lancet 396:854–866

Von Mutius E, Vercelli D (2010) Farm living: effects on childhood asthma and allergy. Nat Rev Immunol 10:861–868

Yepes-Nunez JJ, Brozek JL, Fiocchi A, Pawankar R, Cuello-Garcia C, Zhang Y, Morgano GP, Agarwal A, Gandhi S, Terracciano L, Schunemann HJ (2018) Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies. Allergy 73:37–49

Zeiger RS, Heller S (1995) The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol 95:1179–1190

Zeiher J, Finger JD, Kuntz B, Hoebel J, Lampert T, Starker A (2018) Trends in smoking among adults in Germany : evidence from seven population-based health surveys from 1991-2015. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 61:1365–1376

Secondary and Tertiary Prevention: Medical Rehabilitation

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Abstract

Allergies are a major public health burden, and targeted measures are required in terms of prevention and treatment. The most common allergic conditions encompass atopic dermatitis (AD), food allergy (FA), allergic asthma (AA), and allergic rhino-conjunctivitis (AR). Primary prevention aims at preventing the onset of allergic disease, before the disease process begins. Secondary prevention aims at preventing progression and exacerbation of allergic disease whereas tertiary prevention aims at reducing disease burden in patients with established disease, by allergen immunotherapy (AIT) or medical rehabilitation. Rehabilitation programs are used for treatment of AA and AD and usually consist of extensive patient assessment, optimization of treatment management, patient education, and behavioral interventions, ideally involving a multidisciplinary treatment team and sometimes provided in a specific climate, usually alpine or maritime. Similarly, prevention of occupational skin diseases requires interdisciplinary approaches on the level of secondary and tertiary preventive intervention; if this is provided, then prevention programs have proven highly (cost-) effective. Unfortunately, the recently published *Minimal Standards of Prevention* of these dermatoses, underlining especially the importance of meticulous allergological diagnosis and subsequent multidisciplinary patient education, are so far being adhered to only in very few European countries.

Keywords

Allergic disease · Climate · Multidisciplinary · Occupational skin disease · Prevention · Rehabilitation

1 The Cascade of Primary, Secondary, Tertiary Prevention

As allergies frequently have their onset early in life and children already start to get first symptoms before the age of 1, research focus should be placed on the prevention of allergies – ideally on primary prevention (Nowak und Schaub 2018). The key challenge in primary allergy prevention remains the identification of patients at risk. Family history should always be considered and children of atopic parents should be closely monitored. Clinical surveillance, straight-forward prevention practices, and regular follow-up care are needed. Furthermore, parents of allergic children need to be trained on how to carry out the required prevention or treatment measures. Since primary prevention is far from being widely implemented, issues of secondary and tertiary prevention become important.

Secondary prevention aims at preventing progression and exacerbation of allergic disease. Early intervention with adequate anti-inflammatory and anti-allergic medication is the key to increase quality of life of allergic patients. In sensitized subjects, secondary prevention includes strict allergen avoidance and possibly allergen immunotherapy (AIT). Tertiary allergy prevention seeks to reduce end-organ allergic disease in patients with established allergy. The most common currently applied example is medical rehabilitation or AIT.

Medical rehabilitation is used in the treatment of several chronic diseases. It consists of multidisciplinary treatment usually involving several health professionals and usually involves multiple elements depending on the disease. For the rehabilitation of allergic disease, there are several rehabilitation programs available, which are used in the treatment of asthma and atopic dermatitis.

Pulmonary rehabilitation, for example, is defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and emotional condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors by the 2013 American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation (Spruit et al. 2013). Pulmonary rehabilitation is increasingly used in the management of asthma.

Dermatologic rehabilitation for atopic dermatitis consists mainly of multidisciplinary treatment programs provided in clinical or outpatient settings. No formal definition has been established. Most existing rehabilitation programs address young children and there are fewer options for adolescents or adults. While the importance of education and the psychosocial consequences of AD are recognized in almost every international treatment guideline, psychosomatic counseling or dermatologic rehabilitation in the alpine climate are indicated in the 2015 and 2020 European position papers.

2 Tertiary Prevention: Medical Rehabilitation

Rehabilitation programs vary between clinics and countries. However most clinics provide multidisciplinary interventions which can be individualized to a certain extent and address multiple outcome areas of importance for patients. Existing rehabilitation programs vary across countries in duration, setting, and content (Spruit et al. 2014). There is no consensus on the optimal duration of a rehabilitation program. Programs range from 2–4 weeks to 6–8 weeks to 12–24 weeks, depending on the content (Ries et al. 2007). While most programs are institutional and provided in an inpatient setting, there are also outpatient programs or community-based or home-based programs. While rehabilitation programs are designed to provide the right treatment to the individual patient, depending on personal needs and goals, there are certain components that may be present in most rehabilitation programs.

2.1 Patient Assessment

An extensive assessment including impairments in different areas of life is done either before the start of the rehabilitation or as part of the rehabilitation. The International Classification of Functioning, Disability and Health (ICF) is a classification of the health components of functioning and disability and contains activities, participation, body structures and functions, personal factors, activity limitations, functional limitations, environmental factors, and participation restrictions. Several validated questionnaires assessing disease-specific quality of life, such as the Dermatology Life Quality Index (DLQI) and Asthma Quality of Life Questionnaire (AQLQ), contain these health components and are therefore valuable tools that can be used during the assessment.

The goal of the extensive assessment is to identify the problems in the different areas which are most troubling for the patient and provide guidance for treatment, thereby constructing the rehabilitation as effective as possible. In some clinics the assessment is part of the rehabilitation program and because the patient can be observed for a longer period of time, previously unknown factors that may compromise treatment outcomes could be identified early. In some countries an extensive assessment including a prognosis for the expected success of rehabilitation is required before the start of the rehabilitation program, for example in Germany (Buhles et al. 2011). Differential diagnosis, physical examination, and detailed clinical history are essential in the assessment process. In the case of difficult to treat disease, this sometimes leads to a different diagnosis than previously given. Therefore, it is very important to systematically assess any obstacles or problems a patient experiences.

2.2 Optimization of Treatment and Treatment Management

An important component of any rehabilitation program is the optimization of medical treatment and checking the prerequisites for effective treatment. This is done by assessing the current pharmacological options for effective treatment and choosing the most appropriate treatment for the patient, preferably also taking possible obstacles to optimal adherence into account.

Furthermore, the presence of a written action plan for asthma or AD has been shown to be very effective in treatment (Gibson and Powell 2004; Sauder et al. 2016). In asthma as well as AD, a written action plan for the early recognition and adequate treatment of exacerbations is developed and trained with the patient. Self-management education centered around an action plan for exacerbations led to a substantial reduction in health care utilization (Gibson et al. 2003). However, a more recent Cochrane review on the use of personalized action plans in adults with asthma identified studies providing low or very low quality of evidence (Gatheral et al. 2017).

Observing how a patient uses his medication usually identifies several areas of improvement. For asthma, this means assessment of inhalation technique. Poor inhaler technique has been linked to poor asthma outcomes and specific critical

errors have been identified in a large cohort of adult asthma patients (Price et al. 2017). For AD, this means observation of application of topical treatments. In AD, adherence to treatment is a problem and several factors leading to poor adherence and poor patient outcomes have been identified (Sokolova and Smith 2015). Especially in a chronic disease, continuous reinforcement is important to make sure treatment management stays according to expected standards.

2.3 Patient Education

The objective of patient education is to improve health literacy, which will lead to improved self-management and positively affect health-related quality of life and other relevant patient outcomes. Health literacy is defined as the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information to make appropriate health decisions. (Myers and Murray 2019) Adequate health literacy is especially important in the management of a chronic disease like asthma or atopic dermatitis. Both diseases are characterized by exacerbations and remissions and self-management is required over a long period of time. Low or inadequate health literacy is associated with poor longitudinal asthma outcomes, increased emergency department utilization, increased symptoms, and significant adverse outcomes in adults with asthma (Mancuso and Rincon 2006).

Several educational programs have been developed for children, adolescents or parents and adults to be used in adjunct to standard medical care (Ersser et al. 2014; Heratizadeh et al. 2017; Staab et al. 2006). Education may be lecture-based focusing on the transfer of knowledge, or more interactive based on the theory that learning is an active and social process and cognitive activation and adaptation to the patient group considering the needs and views of the target group is required (Bauerle et al. 2017). Several educational group trainings have also been developed for parents of children with AD (Ricci et al. 2009; Staab et al. 2002).

Therapeutic patient education (TPE) programs are distinguished from conventional educational programs by explicitly focusing on the transfer of skills instead of providing information and by offering tailored education (Stalder et al. 2013).

2.4 Psychological and Behavioral Interventions

Psychological and behavioral interventions are major components of most pulmonary and dermatological rehabilitation programs. Recent studies have supported the link between asthma (severity and control), psychological aspects (subjective perception, coping style), and mental health (anxiety, depression) (Baiardini et al. 2015). Living with asthma has been linked with psychological comorbidities including anxiety, depression, and panic attacks and psychological comorbidities are more present in patients with difficult to control disease (Smith and Jones 2015). For asthma, psychological interventions included in the rehabilitation program are aimed at adherence to treatment, coping with a chronic disease and dealing with functional

limitations in daily life. Furthermore exercise training, self-management, and therapy of dysfunctional breathing are of special importance in asthma. For AD, psychological interventions are usually aimed at coping with itch, relaxation techniques and other techniques to minimize scratching, and sleeping problems. Other interventions may focus on improvement of emotional and practical challenges in disease management, self-confidence, or sleep problems. Special counseling on social and job-related problems may be provided. Psycho-educational interventions involve education, self-management training, and psychosocial issues (Smith et al. 2007).

2.5 Inpatient Setting

Medical rehabilitation programs are usually provided in an inpatient setting. Patients with asthma or AD are usually treated in an outpatient setting and hospital admission is rarely needed. However in case of severe exacerbations, with insufficient response to standard outpatient treatment, hospital admission provides an excellent opportunity to assess self-management and to improve disease control (Cathcart and Theos 2011). The inpatient setting offers several advantages over an outpatient setting. Maximal compliance with pharmacological treatment is guaranteed through nurse supervision and assistance with treatment. There is more time for the treatment team to observe the behavior of the patient and to identify possible pitfalls over a longer period of time. Additional problems may become apparent during the rehabilitation program. Furthermore, the clinical stay can easily be combined with a structured treatment and education program, offering a large variety of psychological treatment possibilities, individual or in groups and physiotherapy or sports therapy.

3 The Multidisciplinary Treatment Team

The multidisciplinary team providing pulmonary or dermatologic rehabilitation includes medical specialists (pulmonologists, dermatologists, allergists), specialized nurses or nurse practitioners, psychologists, physiotherapists, respiratory therapists, exercise physiologists, occupational therapists, dieticians, and social workers. The composition of the team may change according to the needs of the patient or the possibilities of the clinic. Because patients who are in need of rehabilitation programs are often complex, programs usually provide integrative care, whilst also addressing other comorbidities and behavior change.

4 Results of Pulmonary and Dermatological Rehabilitation: Examples of Successful Programs

Several pulmonary and dermatologic rehabilitation programs have been developed for children and adults with asthma or atopic dermatitis (LeBovidge et al. 2016; Spruit et al. 2014). Randomized trials and observational studies have shown positive effects regarding clinical symptoms, exacerbations, quality of life, physical function, and use of health care resources. (Emtner et al. 1996; Cambach et al. 1997; Nathell 2005; Trevor et al. 2015; Spielman et al. 2015) However, there are few randomized controlled trials providing evidence for the benefits of pulmonary or dermatologic rehabilitation leading to limited available data regarding the effectiveness of rehabilitation programs for patients with asthma or atopic dermatitis (Schultz et al. 2017). Also, there are few studies exploring the mechanisms underlying its effectiveness. Most available studies concern the effectiveness of the provided rehabilitation program in a specific clinic or specific climate, but usually there is no dismantling of the intervention to find out which aspects might be the most useful. It is also quite difficult to distinguish the efficacy of a rehabilitation program, because management of allergic disease involves a multicomponent strategy, including pharmacological treatment, patient education, allergen avoidance, or immunological interventions.

4.1 Example Program for Asthma

The National Jewish Pediatric Day Program is a program in the USA for pediatric patients with severe asthma employing a day treatment model: children and their families participate from morning until evening and leave nights and weekends. (Bratton et al. 2001) The program provides an opportunity for extended multidisciplinary observation, teaching, and intervention, including behavior management for both the patient and the family (Bratton et al. 2001). The medical goals of this program are to establish diagnosis, identify exacerbating factors, determine the maximal function and the appropriate medical approach to maintain function, to minimize and treat side effects of pharmacological management. (Bratton et al. 2001) Rehabilitation needs are addressed with an assessment of functional endurance, overall physical fitness, and the ability to keep up with peers in activities of daily living (Bratton et al. 2001). Psychosocial evaluation includes assessment of family coping skills, observation of the family asthma management system, individual assessment of emotional functioning and identification of factors associated with chronic illness considered to compromise treatment or adherence with therapy (Bratton et al. 2001). Three asthma education classes are provided in addition to personalized feedback with nursing staff to improve information base, medication administration techniques, adherence, and self-assessment. (Bratton et al. 2001) An individualized, multidisciplinary therapeutic program was developed with written recommendations for home implementation (Bratton et al. 2001). The program significantly contributed to improvement in asthma severity, quality of life, and reduction in healthcare costs.

4.2 Example Program for Eczema

Several multidisciplinary programs are designed for the multidisciplinary treatment of AD (Spielman et al. 2015). Besides improving disease activity, these programs also address itching and scratching, sleep disruption, parental challenges in disease management, education of children and their families, psychosocial problems and adherence to treatment to improve disease activity.

PIM is an example of a program that has been successfully used for children with difficult to treat atopic dermatitis in Europe (Fieten et al. 2019b). It starts with a systematic assessment of AD, other atopic, pediatric, and mental health comorbidities and general well-being which is combined with patient designed treatment goals based on the problems experienced by the child/parents. The identified problems are prioritized regardless of the nature of the problems and a structured treatment plan using a goal-oriented approach is created and discussed among the multidisciplinary treatment team. Several health professionals work simultaneously on the treatment goals, using treatment strategies from their own field of expertise that best fit the individual child or family situation.

The dermatologist evaluates medical history and explains the course of AD with exacerbations and remissions, provides an overview of currently available AD treatment, and optimizes treatment and specific instructions for use. A personal written action plan is provided indicating how to phase out or step up treatment. Symptoms of allergic asthma, rhinitis, and food allergy are assessed and amount and side effects of total used medication and general health status, including physical activity and obesity are assessed. The psychologist assesses disease management abilities, cognitive abilities, and mental health issues, provides advice on sleep hygiene, and uses habit reversal or cognitive behavioral therapy to control scratching behavior. Adherence to treatment is optimized by providing a treatment regimen including all prescribed medications and taking school and family life into account. Guiding autonomy development leads to independence, where the child is responsible for his own treatment. Throughout the program, attention is paid on how to sustain the treatment goals after the end of the program.

5 Medical Rehabilitation in Specific Environments: Alpine Climate and Maritime Climate

Some of the rehabilitation clinics specialized in pulmonary or dermatological rehabilitation are situated in specific climates, mostly alpine climate or maritime climate.

The characteristics of the alpine climate (low allergen exposure, especially to house dust mite (HDM), low pollution rates, and high UV exposure) are thought to be beneficial for atopic patients. Allergen avoidance has been proposed as an important factor for the observed clinical improvement after rehabilitation in the alpine climate. Exposure to HDM has been identified as an important trigger for sensitized patients because it contributes to disease severity in patients who are exposed to HDM allergens (Custovic et al. 1996). However, reducing exposure to

HDM with physical (mainly mattress covers) and chemical methods appears to have limited effects on reducing asthma symptoms (Gotzsche and Johansen 2008). Indoor avoidance of HDM and molds has also been proposed in the disease management of refractory atopic dermatitis (Salt et al. 2007). However, several placebo-controlled studies with HDM reducing measures found significant reduction in exposure to HDM, especially the main allergen Der p 1, but no obvious improvement in AD severity (Holm et al. 2001; Oosting et al. 2002; Ricci et al. 2000). The alpine climate is a natural environment with low allergen exposure and could therefore be beneficial to sensitized patients with severe allergic asthma. However, studies indicating low HDM allergen exposure in the alpine climate are relatively old (Spieksma et al. 1971; Vervloet et al. 1982). A recent study carried out in alpine regions in Germany and Austria has demonstrated that there is no significant change in HDM concentration with increasing altitude and clinically relevant concentrations of HDM allergens were also detected in regions located above 1,500 m altitude (Grafetstatter et al. 2016). However, other aeroallergens such as birch or grass pollen are less prevalent in the alpine climate and clinically relevant concentrations are only found a few days per year (MeteoSchweiz 2019). Decreasing exposure to indoor allergens is a well-accepted part of treatment for allergic disease, but allergen avoidance measures need to be multifaceted (Platts-Mills 2008). It could be that allergen avoidance would be most beneficial for sensitized patients, but for asthma, several studies have shown that there is similar improvement in sensitized and non-sensitized patients after alpine climate treatment (Bersuch et al. 2017; Karagiannidis et al. 2006; Rijssenbeek-Nouwens et al. 2012). This suggests that factors other than allergen avoidance contribute to the results of rehabilitation in the alpine climate.

5.1 Air Pollution

Air pollution is considered a major environmental health issue (Brunekreef and Holgate 2002). Long-term exposure to relatively low levels of air pollution is associated with a higher prevalence of respiratory symptoms and a decline in lung function in adults (Zemp et al. 1999). Exposure to particulate matter and volatile organic compounds is associated with worse respiratory health, and an increased risk of hospitalizations and ICU admissions for asthma, especially in children (O'Connor et al. 2008; Silverman and Ito 2010). Furthermore, nitrogen dioxide and ozone may exacerbate severe asthma and increase the risk of death among patients with asthma (Sunyer et al. 2002). Long- and short-term exposure to air pollution has adverse effects on lung function, respiratory symptoms, and airway inflammation in children and adults, whereas reduction of exposure to air pollution improves lung function and respiratory health (Avol et al. 2001; Renzetti et al. 2009).

Recently, the adverse effects of air pollution on atopic dermatitis have gained more interest (Ahn 2014). Some studies suggest that outdoor air pollutants may act as risk factors for the development or exacerbations of AD (Kim et al. 2013; Lee et al. 2008). The alpine climate is characterized by lower levels of PM10 and other traffic-related air pollution (European Environment Agency 2017). However, there

are likely multiple mechanisms for the harmful effects of different air pollutants and these have not been elucidated yet. Furthermore, the duration of the rehabilitation programs in the alpine climate usually vary from 3- to 6 weeks and it is not clear if this period is long enough to contribute to a reduction in disease severity because of reduced exposure to air pollutants.

5.2 UV Radiation

Another environmental characteristic of the alpine climate is its increased UV exposure. In AD treatment, phototherapy with narrowband UVB and UVA1 are used (Garritsen et al. 2014). Therefore, it is possible that increased exposure to UV radiation during alpine climate treatment could contribute to the observed improved disease severity. However, studies assessing the relation between AD prevalence and UV exposure show conflicting results (Sargen et al. 2014; Silverberg et al. 2013). Furthermore, the actual individual UV exposure also depends on the hours spent outside, clothing, season, and on the use, quality, and potency of the used sunscreen products. For asthma, the beneficial influence of more exposure to UV would most likely lie in its role in vitamin D synthesis.

A maritime climate also provides a lack of allergens and pollutants and increased UV radiation (Vocks et al. 1994). In addition, the salty air and a higher humidity are deemed important characteristics for treatment of allergic diseases (Schuh 2009). Furthermore, antibacterial effects of sea water have been thought to be beneficial (Purschel 1973). Several rehabilitation programs in the maritime climate exist, for example on the German North Sea Islands, the French Atlantic and Mediterranean coast, the Baltic sea coast, the Caspian sea, or the Turkish coast. However, there are few validated scientific findings of its effectiveness (Schuh 1995; Vocks 2006). Some observational studies report a reduction of AD symptoms, a reduction in required corticosteroid treatment, and a reduction of eosinophils in the peripheral blood and decreased total and specific IgE levels after treatment on the German North Sea Islands (Fischer et al. 1990; Pürschel 1987; Purschel and Pahl 1985). A lasting effect up to 12 months was also reported for asthmatic patients after treatment during summer on the German North Sea Islands (Menger 1989).

Climatotherapy in the subtropical humid climate of the Canary Islands has mainly been used by Nordic countries for the treatment of AD in children as well as adults. Adults with moderate to severe AD stayed for 2- or 3-weeks in the Canary Islands and reported improved disease severity, quality of life and less use of topical corticosteroids up to 3 months (Autio et al. 2002). The treatment program has been adjusted with more focus on meeting peers, sharing experiences, adopting a healthy life style, improving physical, psychological, and social well-being and coping with the disease guided by health care experts. This also resulted in improved disease activity and improved quality of life up to 3 months (Karppinen et al. 2017; Karppinen et al. 2015). A study with pediatric patients with atopic dermatitis going for 4 weeks to the Canary Islands also reported improvements in disease severity,

health-related quality of life, reduced bacterial skin colonization with S aureus and less use of topical corticosteroids up to 3 months (Byremo et al. 2006).

Dead Sea climatotherapy, composed of increasing sun exposure after regular sea baths, has also been used in the treatment of children or adults with AD (Harari et al. 2000). Treatment during 28 consecutive days, with gradually increasing sun exposure, resulted in improved AD severity and a significantly reduced need for corticosteroids up to 3 months, with an increasing need for topical corticosteroids during the remainder of the 18-month follow-up (Adler-Cohen et al. 2012; Marsakova et al. 2019).

However, no randomized controlled trials or formal cost-effectiveness analyses of these treatments have been carried out.

6 Long-Term Results

Several studies have looked into the long-term effects of pulmonary or dermatologic rehabilitation programs. Long-term effects are important for the patients who are treated, but in terms of cost-effectiveness also for society and public health services.

Several observational studies have assessed long-term outcomes of pulmonary rehabilitation programs. One study assessed asthma control up to 1 year after completing a 3-week pulmonary rehabilitation program. About half of the patients indicated well-controlled asthma after 1 year and a significantly improved health-related quality of life (Lingner et al. 2015). Another study also showed improved asthma control, knowledge of asthma and improved health-related quality of life 12 months after completing a 3-week pulmonary rehabilitation program (Bauerle et al. 2017). A recent randomized trial (EPRA trial) comparing a 3-week pulmonary rehabilitation program with usual care demonstrated significant differences in asthma control and asthma related quality of life in favor of the rehabilitation program up to 3 months follow-up (Schultz et al. 2019). More than 50% of the study sample demonstrated sufficient asthma control after 12 months follow-up (Schultz et al. 2019). An outpatient pulmonary rehabilitation program for patients with asthma resulted in improved health-related quality of life, despite a loss of improvement in exercise tolerance, after 12 months (Foglio et al. 1999). Less exacerbations and hospital admissions in the year after pulmonary rehabilitation have also been observed in several studies (Foglio et al. 1999; Ochmann et al. 2012). A decrease in emergency room visits up to 3 years after a 10-week rehabilitation program has also been reported (Emtner et al. 1998). A significant decrease in asthma symptoms up to 3 years was only observed in a subgroup of patients who exercised one to two times a week (Emtner et al. 1998).

The long-term outcomes of pulmonary rehabilitation programs in the alpine or maritime climate has never been directly compared with the long-term outcomes of a rehabilitation program in another climate. One observational study reports sustained asthma control, health-related quality of life and less exacerbations and hospitalizations 12 months after rehabilitation in the alpine climate for patients with severe asthma. (Fieten et al. 2019a) Other observational studies report on the

long-term outcomes of climate therapy on atopic dermatitis. A three-week rehabilitation program in the alpine climate leads to a self-reported sustained improvement up to 1 year in 19% of 97 adult patients (A Porta et al. 2000). However, most patients (60%) noticed the first deterioration within 2 months. The only randomized trial with children with moderate to severe AD reported no significant differences 6 months after treatment compared to a similar outpatient rehabilitation program in the Netherlands (Fieten et al. 2018).

In the absence of any maintenance strategy benefits of pulmonary rehabilitation, irrespective of the climate, appear to diminish over 6–12 months (Spruit et al. 2013). There are several suggested reasons for this decline, including decrease in adherence to therapy, progression of comorbidities, or exacerbations. Several maintenance strategies, such as exercise training programs, ongoing communication to improve adherence with regular telephone follow-up, or peer support have been examined (Spruit et al. 2013). Developing ways to retain the effects of pulmonary rehabilitation is important. However, in order to maintain substantial long-term impact on a chronic disease, it has been pointed out that permanent health behavioral changes are needed (Nici and ZuWallack 2014). Furthermore, sustained disease control could be related to other factors, such as psychosocial characteristics related with disease acceptance or adherence to treatment, or families with multiple problems. When family factors are important in the ability to sustain a treatment effect, it is essential that these are explicitly addressed during the treatment program and support is also provided during follow-up. It is also possible that distinct disease phenotypes with more refractory disease prevent sustained benefits of rehabilitation programs.

7 Cost-Effectiveness of Programs

Several studies have looked at cost-effectiveness of rehabilitation programs and specific factors associated with increased medical charges (Bratton et al. 2001; Goldstein et al. 1997; Griffiths et al. 2001). Medical charges are composed of hospital inpatient care, visits to the emergency department, physician charges (visits to the doctor's office), and costs of medication. Several studies concerning children or adolescents with asthma demonstrated significant and continued reduction in health care charges during multiple years of follow-up, for hospital days, emergency department visits, physician fees and overall utilization of medical care encounters, relative to the year before pulmonary rehabilitation (Bratton et al. 2001; Weinstein et al. 1996). Treatment duration for these programs was around 15 days. In 2010 the Centers for Medicare and Medicaid Services began funding pulmonary rehabilitation in the USA. Although the funding was considered insufficient to cover total costs, it does reflect acceptance of pulmonary rehabilitation (Nici and ZuWallack 2014). A Canadian cost-effectiveness study on a pulmonary rehabilitation program involving 2 months of inpatient rehabilitation followed by 4 months outpatient supervision estimated total costs of Canadian $11,597, to which hospitalization costs contributed the most, or recalculated to 190 Euro per patient per day (Goldstein et al. 1997). Treatment costs per day for the rehabilitation program in the Canary

Islands have been estimated at 205 Euros per day per patient including travel and accommodation, half-board and medical staff (Autio et al. 2002). On the other hand, costs of a purely outpatient pulmonary rehabilitation program were estimated at £725 by a British in-depth cost-effectiveness analysis (Griffiths et al. 2001). This would make outpatient pulmonary rehabilitation very cost-effective in comparison with a program using inpatient care. Further cost reduction might be possible without compromising therapeutic results when the most effective elements of the rehabilitation program are provided. Estimated cost for a home-based rehabilitation program during 8 weeks was 1983 Euro per patient, i.e. 35 Euro per day (Renolleau-Courtois et al. 2014). However, the effect on subsequent health service costs should also be incorporated in the cost-effectiveness analysis. The ongoing EPRA trial for patients with asthma will also assess cost-effectiveness up to 1 year follow-up (Schultz et al. 2017). Comparisons of cost-effectiveness between studies are difficult because of differences in content and intensity of the rehabilitation program, the case mix, used outcome measures and time points at which outcomes are measured. Furthermore, some cost-effectiveness analyses focus primarily on costs of health professionals and equipment, while other analyses also incorporate institutional overhead, transport costs, furniture, furnishings, stationery and incidental costs incurred in setting up a new rehabilitation center (Griffiths et al. 2001). There is less information available about the cost-effectiveness of rehabilitation programs for atopic dermatitis (LeBovidge et al. 2016).

8 Outlook on Medical Rehabilitation for Allergic Disease

Though medical rehabilitation programs traditionally are provided in an inpatient setting, several programs are provided in outpatient, home or community settings or use other modalities such as e-health. Use of these settings may be more convenient for patients, could decrease health care costs, and may improve accessibility for patients with severe disease or patients from rural areas. Pulmonary rehabilitation in any setting should contain key components of traditional pulmonary rehabilitation, such as individualized exercise prescription, self-management education, outcome measurement, and patient support (Garvey et al. 2018). A French study investigated the feasibility of a home-based respiratory rehabilitation program for asthma and designed a two-month protocol with education sessions, respiratory physiotherapy and an exercise training program at home and in groups supervised by an adapted physical activity instructor (Renolleau-Courtois et al. 2014). They reported a decrease in exacerbations during the year following the rehabilitation program and an increase in physical capacity. However, no disease specific quality of life or asthma control outcome measures were reported. Another study designed a 12-week rehabilitation program in a community setting, involving local physiotherapists who provide exercise training, patient education, relaxation techniques and recreational activities (Cambach et al. 1997). They reported increased exercise tolerance and quality of life up to 6 months after the end of the program.

Recently, telehealth pulmonary rehabilitation programs have been suggested to be as effective as institution-based rehabilitation at improving functional exercise capacity and health-related quality of life. (Selzler et al. 2018) However, broad implementation of home-base or e-health rehabilitation is lacking. Several barriers exist, such as concerns about safety, liability, supervision responsibilities, and outcome measurement (Garvey et al. 2018).

In the future, several steps are needed to improve the availability of rehabilitation programs for allergic disease. Well-designed studies with large sample sizes and a long-term follow-up are needed to determine effectiveness of other rehabilitation forms on health outcomes of allergic disease. Effectiveness and cost-effectiveness should be demonstrated in different settings and for different disease phenotypes, to further expand its impact and applicability. The accessibility to rehabilitation programs could be improved by developing alternative means of delivery, including the use of new technologies, and identifying and overcoming barriers to participation. The content of the existing programs could be harmonized and further improved, with a focus on long-term treatment success, including meaningful and sustainable behavioral change by developing collaborative self-management strategies and optimizing the impact of rehabilitation.

9 Secondary and Tertiary Prevention: Immunotherapy

Recently, the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Allergen Immunotherapy for Allergy Prevention has developed a guideline on secondary and tertiary allergy prevention (Halken et al. 2017). The mentioned guideline has been developed using the Appraisal of Guidelines for Research and Evaluation (AGREE II) framework, which involved a multidisciplinary expert working group, a systematic review of the underpinning evidence, and external peer-review of draft recommendations.

There is moderate-to-high-quality evidence indicating that allergen immunotherapy (applied subcutaneously or sublingually) can be recommended for short-term prevention up to 2 years post-AIT of asthma in children/adolescents with moderate/severe allergic rhinitis and pollen allergy who are suboptimally controlled despite appropriate pharmacotherapy, and there are data suggesting that this benefit persists after 2 years post-AIT as regards asthma symptoms and medication use. Allergen immunotherapy may even be considered in patients with milder allergic rhinitis, as it might modify the natural disease history (Halken et al. 2017). No recommendations have been made in favor or against AIT for the prevention of the development of new allergic sensitizations.

10 Occupational Allergic Skin Disease

10.1 Epidemiology of Occupational Allergic Skin Disease

Since occupational diseases are by definition preventable, appropriate preventive strategies are required to reduce their public health burden. To date, occupational dermatitis (2019: $n = 20{,}229$) comprises each year ca. 30% of all occupational disease notifications in Germany, and is thus the most frequent work-related disease. This will likely hold true in most industrialized countries, even though this frequently is not reflected in the official statistics due to gross underreporting (Moldovan et al. 2017).

The vast majority of cases of occupational dermatitis (90%) presents with hand dermatitis, which may be of irritant or allergic or atopic origin or a combination of these three main etiologic factors. A recent study has analyzed in depth the etiology of occupational hand dermatitis in a group with 1,670 severely affected workers from various professions hazardous to the skin. Solely *allergic* hand dermatitis occurred in only 3.6% of cases, whereas in combination with *irritant* dermatitis it comprised 15.3% of cases; solely *atopic* hand dermatitis was in 9.7% of cases. An *atopic* etiology in combination with other causes (irritant, allergic) was observed in 41.7%, the total frequency of atopy – alone or in combination – in this biggest thoroughly physician investigated and closely followed up occupational cohort of hand dermatitis patients was 51.3% (Skudlik et al. 2012).

10.2 Secondary Prevention

Recently, within the framework of the European research network *Horizon 2020 StanDerm* (www.standerm.eu) minimal standards of prevention, diagnosis and treatment of workers with work-related dermatitis (WRD) were defined in a Delphi procedure by 85 experts from 28 countries, who had been delegated by their national ministries of science (Alfonso et al. 2017). These minimal standards postulate the urgent need of an interlocking system of primary, secondary and tertiary prevention, with specifically tailored offers of patient education that are considered compulsory at all levels. Furthermore, they emphasize the necessity for extensive and meticulous patch testing for identifying allergic contact dermatitis in all cases suspicious of WRD. Patch testing is considered pivotal for qualified patient consultation and management. All preventive efforts will fail, if the culprit allergen of WRD is not identified. However, in many European countries, to date, patch tests for contact allergy are not conducted routinely in such patients, often not even in cases with chronic longstanding hand dermatitis and a history suggestive of allergic causation (Mahler et al. 2017). Even if the health systems would provide such services, in some countries the allergological expertise is simply not or not anymore available.

The minimal standards postulate extensive patient education, not only in secondary and tertiary prevention, with the aim to increase health literacy, provide a

positive attitude to using skin protection and rearranging work organization in a way to minimize hazardous skin contacts, e.g. towards potential allergens. As pointed out above, if primary prevention has failed, and a contact allergy to an occupational allergen is acquired, then continuation of work will only be possible by unfailingly avoiding contact, e.g. by substitution, unswerving use of adequate gloves, etc. This is what patients have to be specifically educated and motivated for, even in jobs where one would expect, that there is a relatively high degree of health literacy, e.g. in healthcare workers. Secondary prevention programs in affected healthcare workers relying mainly on skin health education have thus proven to be highly successful (Ibler et al. 2012).

10.3 Tertiary Prevention

For advanced cases of WRD– which all too frequently may have started with irritant contact dermatitis and in consequence of the resulting impaired barrier function and pro-inflammatory milieu consecutive allergic contact dermatitis has occurred – the minimum standards recommend maximum efforts in terms of tertiary prevention (rehabilitation) with an interdisciplinary *return-to-work* approach, including meticulous allergological diagnosis, health education and psychology, occupational therapy in a workplace simulator with optimal skin protection, smoking cessation consultations, etc. In Germany, and recently in Austria, there is specific experience with such a tertiary prevention program, where workers with severe hand eczema are hospitalized as inpatients for 3 weeks, then stay out of work under surveillance of their local dermatologists for another 3 weeks to allow a total of 6 weeks for complete recovery of epidermal barrier function before returning to work (Brans et al. 2014, 2016; Wilfinger and Aberer 2017). Even after 3 and 5 years this measure has proven to be sustainable in its effects; it could be shown that about 70% of patients could stay in their jobs; most of which would have lost their jobs before this measure was established (Skudlik and John 2020). Many of these patients have acquired occupational allergies. It is one of the major tasks of the tertiary prevention inpatient phase to most fastidiously identify occupational and private life allergens; an individual may easily be exposed to more than 300 potential sensitizers at the workplace (de Groot 2012). However, only if allergens are completely identified by extensive work-up, tailored preventive measures at the workplace can be implemented, e.g. replacement of an anticorrosive in a cutting fluid by changing the product, different workplace organization (no-touch techniques, encapsulation), provision of specific gloves, etc. Wherever possible, this will be conducted in close cooperation with the occupational physician.

10.4 Outlook on Tertiary Prevention of Occupational Dermatitis

The minimal standards are not yet implemented in most European countries; for that reason, patient management is very heterogeneous, and particularly detection of

occupational causes for dermatitis is as yet rudimentary in many countries or not even attempted at all (Mahler et al. 2017). Here common preventive efforts are needed to improve the situation for workers in skin hazardous professions in Europe, as every worker is entitled to a healthy workplace. In order to achieve that, the main task will be to overcome the current problem of gross underreporting of cases (Moldovan et al. 2017). If only a few cases are reported, there is no political impact to create change. WHO has identified this problem. For that reason, with the WHO ICD 11 (International Classification of Diseases, 11th Revision), which was finally endorsed by the World Health Assembly (WHA) and its 194 member states on 25 May 2019, coding for allergic (and irritant) contact dermatitis will automatically generate the question, whether the disease is of occupational origin as a *primary factor*, *cofactor*, *not occupational*, or *not known*. Also, common contact allergens are now available within the WHO ICD 11 database and, furthermore, the localization of the dermatitis can precisely be documented. If physicians make use of these entirely new options by ICD 11, the true magnitude of WRD, including the overwhelmingly frequent cases of allergic, atopic, or mixed origin, will be revealed on a global scale (implementation scheduled for 1 January 2022). That would then become a game changer for all efforts to prevent occupational allergic skin disease.

References

A Porta B, Barandun J, Wuthrich B (2000) Therapy of atopic dermatitis in high mountain climate. Schweizerische Rundschau fur Medizin/Praxis 89:1147–1153

Adler-Cohen C, Czarnowicki T, Dreiher J, Ruzicka T, Ingber A, Harari M (2012) Climatotherapy at the Dead Sea: an effective treatment modality for atopic dermatitis with significant positive impact on quality of life. Dermatitis 23:75–80. https://doi.org/10.1097/DER.0b013e31824a6141

European Environment Agency (2017) Air quality maps of Europe. www.eea.europa.eu/themes/air/airbase/air-quality-mapsof-europe. Accessed 2 May 2017

Ahn K (2014) The role of air pollutants in atopic dermatitis. J Allergy Clin Immunol 134:993–999. https://doi.org/10.1016/j.jaci.2014.09.023. discussion 1000, Epub 2014 Nov 5

Alfonso JH et al (2017) Minimum standards on prevention, diagnosis and treatment of occupational and work-related skin diseases in Europe – position paper of the COST Action StanDerm (TD 1206). J Eur Acad Dermatol Venereol 31(Suppl 4):31–43. https://doi.org/10.1111/jdv.14319

Autio P, Komulainen P, Larni HM (2002) Heliotherapy in atopic dermatitis: a prospective study on climatotherapy using the SCORAD index. Acta Derm Venereol 82:436–440. https://doi.org/10.1080/000155502762064575

Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM (2001) Respiratory effects of relocating to areas of differing air pollution levels. Am J Respir Crit Care Med 164:2067–2072. https://doi.org/10.1164/ajrccm.164.11.2102005

Baiardini I, Sicuro F, Balbi F, Canonica GW, Braido F (2015) Psychological aspects in asthma: do psychological factors affect asthma management? Asthma Res Pract 1:7. https://doi.org/10.1186/s40733-015-0007-1. eCollection 2015

Bauerle K, Feicke J, Scherer W, Sporhase U, Bitzer EM (2017) Evaluation of a standardized patient education program for inpatient asthma rehabilitation: impact on patient-reported health outcomes up to one year. Patient Educ Couns 100:957–965. https://doi.org/10.1016/j.pec.2016.11.023. Epub 2016 Nov 28

Bersuch E, Graf F, Renner ED, Jung A, Traidl-Hoffmann C, Lauener R, Roduit C (2017) Lung function improvement and airways inflammation reduction in asthmatic children after a rehabilitation program at moderate altitude Pediatr Allergy Immunol 28:768–775 doi:https://doi.org/10.1111/pai.12808. Epub 2017 Nov 2

Brans R et al (2014) Association between tobacco smoking and prognosis of occupational hand eczema: a prospective cohort study. Br J Dermatol 171:1108–1115. https://doi.org/10.1111/bjd.13169

Brans R et al (2016) Multicentre cohort study 'Rehabilitation of Occupational Skin Diseases – Optimization and Quality Assurance of Inpatient Management (ROQ)': results from a 3-year follow-up. Contact Dermatitis 75:205–212. https://doi.org/10.1111/cod.12614

Bratton DL, Price M, Gavin L, Glenn K, Brenner M, Gelfand EW, Klinnert MD (2001) Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. Pediatr Pulmonol 31:177–189

Brunekreef B, Holgate ST (2002) Air pollution and health. Lancet 360:1233–1242. https://doi.org/10.1016/S0140-6736(02)11274-8

Buhles N, Wehrmann J, Hinsch KD, Nurnberg W, German Society of Dermatology (DDG) and the German Dermatologists' Association (BVDD) (2011) S1 guideline: dermatological inpatient rehabilitation in adult atopic dermatitis. J Dtsch Dermatol Ges 9:558–561. https://doi.org/10.1111/j.1610-0387.2011.07686.x. Epub 2011 Apr 15

Byremo G, Rod G, Carlsen KH (2006) Effect of climatic change in children with atopic eczema Allergy 61:1403-1410. ALL1209 [pii]; https://doi.org/10.1111/j.1398-9995.2006.01209.x

Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC (1997) The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. Eur Respir J 10:104–113

Cathcart SD, Theos A (2011) Inpatient management of atopic dermatitis. Dermatol Ther 24:249–255. https://doi.org/10.1111/j.1529-8019.2011.01400.x

Custovic A, Taggart SC, Francis HC, Chapman MD, Woodcock A (1996) Exposure to house dust mite allergens and the clinical activity of asthma. J Allergy Clin Immunol 98:64–72

de Groot AC (2012) Patch test concentrations and vehicles for testing contact allergens. In: Rustemeyer T, Elsner P, John S-M, Maibach HI (eds) Kanerva's occupational dermatology. Springer, Berlin, pp 1849–1893. https://doi.org/10.1007/978-3-642-02035-3_200

Emtner M, Herala M, Stalenheim G (1996) High-intensity physical training in adults with asthma. A 10-week rehabilitation program. Chest 109:323–330

Emtner M, Finne M, Stalenheim G (1998) A 3-year follow-up of asthmatic patients participating in a 10-week rehabilitation program with emphasis on physical training. Arch Phys Med Rehabil 79:539–544

Ersser SJ et al (2014) Psychological and educational interventions for atopic eczema in children. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD004054.pub3

Fieten KB et al (2018) Effectiveness of alpine climate treatment for children with difficult to treat atopic dermatitis: results of a pragmatic randomized controlled trial (DAVOS trial). Clin Exp Allergy 48:186–195. https://doi.org/10.1111/cea.13058. Epub 2017 Dec 15

Fieten KB, Rijssenbeek-Nouwens LH, Hashimoto S, Bel EH, Weersink EJ (2019a) Less exacerbations and sustained asthma control 12 months after high altitude climate treatment for severe asthma. Allergy 74:628–630. https://doi.org/10.1111/all.13664. Epub 2018 Dec 9

Fieten KB, Schappin R, Zijlstra WT, Rijssenbeek-Nouwens L, Meijer Y, Pasmans S (2019b) Predictors of treatment success in children with difficult to treat atopic dermatitis using a personalized integrative multidisciplinary (PIM) treatment programme. J Eur Acad Dermatol Venereol 33:376–383. https://doi.org/10.1111/jdv.15244. Epub 2018 Oct 8

Fischer J, Schmidt-Wolf I, Raschke F (1990) Einfluss eines mehrwöchigen Aufenthaltes im Nordseeklima auf die Lymphozytensubpopulationen bei Patienten mit Neurodermitis und Atemwegserkrankungen. Z Phys Med Baln Med Klim 19:320–324

Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N (1999) Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. Eur Respir J 13:125–132

Garritsen FM, Brouwer MW, Limpens J, Spuls PI (2014) Photo(chemo)therapy in the management of atopic dermatitis: an updated systematic review with implications for practice and research. Br J Dermatol 170:501–513. https://doi.org/10.1111/bjd.12645

Garvey C, Singer JP, Bruun AM, Soong A, Rigler J, Hays S (2018) Moving pulmonary rehabilitation into the home: a clinical review. J Cardiopulm Rehabil Prev 38:8–16. https://doi.org/10.1097/HCR.0000000000000287

Gatheral TL et al (2017) Personalised asthma action plans for adults with asthma. Cochrane Database Syst Rev 4:CD011859. https://doi.org/10.1002/14651858.CD011859.pub2

Gibson PG, Powell H (2004) Written action plans for asthma: an evidence-based review of the key components. Thorax 59:94–99

Gibson PG et al (2003) Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev:CD001117. https://doi.org/10.1002/14651858.CD001117

Goldstein RS, Gort EH, Guyatt GH, Feeny D (1997) Economic analysis of respiratory rehabilitation. Chest 112:370–379

Gotzsche PC, Johansen HK (2008) House dust mite control measures for asthma: systematic review. Allergy 63:646–659. https://doi.org/10.1111/j.1398-9995.2008.01690.x

Grafetstatter C et al (2016) No concentration decrease of house dust mite allergens with rising altitude in alpine regions. Allergy Asthma Immunol Res 8:312–318. https://doi.org/10.4168/aair.2016.8.4.312

Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA (2001) Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 56:779–784

Halken S et al (2017) EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 28:728–745. https://doi.org/10.1111/pai.12807

Harari M, Shani J, Seidl V, Hristakieva E (2000) Climatotherapy of atopic dermatitis at the Dead Sea: demographic evaluation and cost-effectiveness. Int J Dermatol 39:59–69

Heratizadeh A et al (2017) Effects of structured patient education in adults with atopic dermatitis: multicenter randomized controlled trial. J Allergy Clin Immunol 140:845–853 e843. https://doi.org/10.1016/j.jaci.2017.01.029

Holm L, Bengtsson A, van Hage-Hamsten M, Ohman S, Scheynius A (2001) Effectiveness of occlusive bedding in the treatment of atopic dermatitis – a placebo-controlled trial of 12 months' duration. Allergy 56:152–158

Ibler KS et al (2012) Skin care education and individual counselling versus treatment as usual in healthcare workers with hand eczema: randomised clinical trial. BMJ 345:e7822. https://doi.org/10.1136/bmj.e7822

Karagiannidis C et al (2006) High-altitude climate therapy reduces local airway inflammation and modulates lymphocyte activation. Scand J Immunol:63

Karppinen TT, Ylianttila L, Kautiainen H, Reunala T, Snellman E (2015) Empowering heliotherapy improves clinical outcome and quality of life of psoriasis and atopic dermatitis patients. Acta Derm Venereol 95:579–582. https://doi.org/10.2340/00015555-2028

Karppinen T, Laine JP, Kautiainen H, Pasternack R, Reunala T, Snellman E (2017) Empowering heliotherapy in psoriasis and atopic dermatitis: an observational study of 186 subjects. Acta Derm Venereol 97:255–257. https://doi.org/10.2340/00015555-2506

Kim J, Kim EH, Oh I, Jung K, Han Y, Cheong HK, Ahn K (2013) Symptoms of atopic dermatitis are influenced by outdoor air pollution. J Allergy Clin Immunol 132:495–498.e491. https://doi.org/10.1016/j.jaci.2013.04.019. Epub 2013 Jun 12

LeBovidge JS, Elverson W, Timmons KG, Hawryluk EB, Rea C, Lee M, Schneider LC (2016) Multidisciplinary interventions in the management of atopic dermatitis. J Allergy Clin Immunol 138:325–334. https://doi.org/10.1016/j.jaci.2016.04.003

Lee YL, Su HJ, Sheu HM, Yu HS, Guo YL (2008) Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. J Invest Dermatol 128:2412–2420. https://doi.org/10.1038/jid.2008.110. Epub 2008 May 1

Lingner H, Ernst S, Grobetahennig A, Djahangiri N, Scheub D, Wittmann M, Schultz K (2015) Asthma control and health-related quality of life one year after inpatient pulmonary rehabilitation: the ProKAR Study. J Asthma 52:614–621. https://doi.org/10.3109/02770903.2014.996650. Epub 2015 Jul 7

Mahler V et al (2017) Occupational skin diseases: actual state analysis of patient management pathways in 28 European countries. J Eur Acad Dermatol Venereol 31(Suppl 4):12–30. https://doi.org/10.1111/jdv.14316

Mancuso CA, Rincon M (2006) Impact of health literacy on longitudinal asthma outcomes. J Gen Intern Med 21:813–817. https://doi.org/10.1111/j.1525-1497.2006.00528.x

Marsakova A, Kudish A, Gkalpakiotis S, Jahn I, Arenberger P, Harari M (2019) Dead Sea climatotherapy versus topical steroid treatment for atopic dermatitis children: long-term follow-up study. J Dermatolog Treat:1–19. https://doi.org/10.1080/09546634.2019.1605138

Menger W (1989) Indications and successes of climate therapy of children. Paper presented at the Das Offentliche Gesundheitswesen Indikationen und Erfolge der Klimatherapie bei Kindern

MeteoSchweiz (2019) Pollen-prognose. https://www.meteoschweiz.admin.ch/home.html?tab=pollenprediction

Moldovan HR et al (2017) The eastern European experience on occupational skin diseases. Make underreporting an issue? J Eur Acad Dermatol Venereol 31(Suppl 4):5–11. https://doi.org/10.1111/jdv.14315

Myers L, Murray RK (2019) Overcoming health literacy barriers to improve asthma inhaler therapy adherence. Ann Am Thorac Soc 16:182–186. https://doi.org/10.1513/AnnalsATS.201805-338PS

Nathell L (2005) Effects on sick leave of an inpatient rehabilitation programme for asthmatics in a randomized trial. Scand J Public Health 33:57–64. https://doi.org/10.1080/14034940410028343

Nici L, ZuWallack RL (2014) Pulmonary rehabilitation: definition, concept, and history. Clin Chest Med 35:279–282. https://doi.org/10.1016/j.ccm.2014.02.008. Epub 2014 Apr 12

Nowak E, Schaub B (2018) Prevention of allergies. In: Implementing precision medicine in best practices of chronic airway disease, Elsevier S&T Books

Ochmann U, Kotschy-Lang N, Raab W, Kellberger J, Nowak D, Jorres RA (2012) Long-term efficacy of pulmonary rehabilitation in patients with occupational respiratory diseases. Respiration 84:396–405. https://doi.org/10.1159/000337271. Epub 2012 May 31

O'Connor GT et al (2008) Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 121:1133–1139.e1131. https://doi.org/10.1016/j.jaci.2008.02.020

Oosting AJ et al (2002) Effect of mattress encasings on atopic dermatitis outcome measures in a double-blind, placebo-controlled study: the Dutch mite avoidance study. J Allergy Clin Immunol 110:500–506

Platts-Mills TAE (2008) Allergen avoidance in the treatment of asthma: problems with the meta-analyses. J Allergy Clin Immunol 122:694–696. https://doi.org/10.1016/j.jaci.2008.07.045

Price DB et al (2017) Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. J Allergy Clin Immunol Pract 5:1071–1081.e1079. https://doi.org/10.1016/j.jaip.2017.01.004. Epub 2017 Mar 9

Purschel W (1973) Dermatological climatotherapy on the North Sea. Clinical-analytical studies of constitutional eczematoid with-without bronchial asthma and-or atopic rhinitis. Dermatologica 146(Suppl 1):1–98

Pürschel W (1987) Neurodermitis atopica–Klimabehandlung am Meer. Allergologie 10:526–530

Purschel W, Pahl O (1985) Behavior of eosinophilic granulocytes, total IgE and allergen-specific IgE antibodies in atopic neurodermatitis during hospital treatment in the North Sea climate. Z Hautkr 60:661–670

Renolleau-Courtois D et al (2014) Home-based respiratory rehabilitation in adult patients with moderate or severe persistent asthma. J Asthma 51:552–558. https://doi.org/10.3109/02770903.2014.885039. Epub 2014 Feb 19

Renzetti G et al (2009) Less air pollution leads to rapid reduction of airway inflammation and improved airway function in asthmatic children. Pediatrics 123:1051–1058. https://doi.org/10.1542/peds.2008-1153

Ricci G, Patrizi A, Specchia F, Menna L, Bottau P, D'Angelo V, Masi M (2000) Effect of house dust mite avoidance measures in children with atopic dermatitis. Br J Dermatol 143:379–384

Ricci G, Bendandi B, Aiazzi R, Patrizi A, Masi M (2009) Three years of Italian experience of an educational program for parents of young children affected by atopic dermatitis: improving knowledge produces lower anxiety levels in parents of children with atopic dermatitis. Pediatr Dermatol 26:1–5. PDE813 [pii]. https://doi.org/10.1111/j.1525-1470.2008.00813.x

Ries AL et al (2007) Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 131:4S–42S. https://doi.org/10.1378/chest.06-2418

Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Bel EH, Weersink EJ (2012) High-altitude treatment in atopic and nonatopic patients with severe asthma. Eur Respir J 40:1374–1380. 09031936.00195211 [pii]. https://doi.org/10.1183/09031936.00195211

Salt BH, Boguniewicz M, Leung DY (2007) Severe refractory atopic dermatitis in adults is highly atopic. J Allergy Clin Immunol 119:508–509. S0091-6749(06)02341-4 [pii]. https://doi.org/10.1016/j.jaci.2006.11.006

Sargen MR, Hoffstad O, Margolis DJ (2014) Warm, humid, and high sun exposure climates are associated with poorly controlled eczema: PEER (Pediatric Eczema Elective Registry) cohort, 2004-2012. J Invest Dermatol 134:51–57. https://doi.org/10.1038/jid.2013.274. Epub 2013 Jun 17

Sauder MB, McEvoy A, Sampson M, Kanigsberg N, Vaillancourt R, Ramien ML, Zemek R (2016) The effectiveness of written action plans in atopic dermatitis. Pediatr Dermatol 33:e151–e153. https://doi.org/10.1111/pde.12774. Epub 2016 Jan 17

Schuh A (1995) Angewandte medizinische Klimatologie: Grundlagen und Praxis. Sonntag Stuttgart

Schuh A (2009) Evidence of the efficacy of climatotherapy and thalassotherapy – a review. Paper presented at the Schweizerische Zeitschrift fur GanzheitsMedizin Die Evidenz der Klima- und Thalassotherapie. Ein Review

Schultz K et al (2017) Effectiveness of pulmonary rehabilitation for patients with asthma: study protocol of a randomized controlled trial (EPRA). BMC Pulm Med 17:49. https://doi.org/10.1186/s12890-017-0389-3

Schultz K et al. (2019) Asthmakontrolle 3, 6 und 12 Monate nach stationärer pneumologischer rehabilitation (EPRA-Studie). Paper presented at the 28. Rehabilitationswissenschaftliches Kolloquium/15th Congress of EFRR 2019, Berlin

Selzler AM et al (2018) Telehealth pulmonary rehabilitation: a review of the literature and an example of a nationwide initiative to improve the accessibility of pulmonary rehabilitation. Chron Respir Dis 15:41–47. https://doi.org/10.1177/1479972317724570. Epub 2017 Aug 8

Silverberg JI, Hanifin J, Simpson EL (2013) Climatic factors are associated with childhood eczema prevalence in the United States. J Invest Dermatol 133:1752–1759. https://doi.org/10.1038/jid.2013.19. Epub 2013 Jan 18

Silverman RA, Ito K (2010) Age-related association of fine particles and ozone with severe acute asthma in New York City. J Allergy Clin Immunol 125:367–373.e365. https://doi.org/10.1016/j.jaci.2009.10.061

Skudlik C, John SM (2020) Prevention and rehabilitation. In: John SM, Johansen JD, Rustemeyer T, Elsner P, Maibach HI (eds) Kanerva's occupational dermatology. Springer, Cham, pp 1617–1629. https://doi.org/10.1007/978-3-319-68617-2_108

Skudlik C et al (2012) First results from the multicentre study rehabilitation of occupational skin diseases – optimization and quality assurance of inpatient management (ROQ). Contact Dermatitis 66:140–147. https://doi.org/10.1111/j.1600-0536.2011.01991.x

Smith HE, Jones CJ (2015) Psychological interventions in asthma current treatment options in allergy. Curr Treat Options Allergy 2:155–168. https://doi.org/10.1007/s40521-015-0051-3
Smith JR, Mugford M, Holland R, Noble MJ, Harrison BD (2007) Psycho-educational interventions for adults with severe or difficult asthma: a systematic review. J Asthma 44:219–241. https://doi.org/10.1080/02770900601182012
Sokolova A, Smith SD (2015) Factors contributing to poor treatment outcomes in childhood atopic dermatitis. Australas J Dermatol. https://doi.org/10.1111/ajd.12331
Spieksma FT, Zuidema P, Leupen MJ (1971) High altitude and house-dust mites. Br Med J 1:82–84
Spielman SC, LeBovidge JS, Timmons KG, Schneider LC (2015) A review of multidisciplinary interventions in atopic dermatitis. J Clin Med 4:1156–1170. https://doi.org/10.3390/jcm4051156
Spruit MA et al (2013) An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 188:e13–e64. https://doi.org/10.1164/rccm.201309-1634ST
Spruit MA et al (2014) Differences in content and organisational aspects of pulmonary rehabilitation programmes. Eur Respir J 43:1326–1337. https://doi.org/10.1183/09031936.00145613
Staab D, von Rueden U, Kehrt R, Erhart M, Wenninger K, Kamtsiuris P, Wahn U (2002) Evaluation of a parental training program for the management of childhood atopic dermatitis. Pediatr Allergy Immunol 13:84–90
Staab D et al (2006) Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. BMJ 332:933–938 :332/7547/933 [pii]. https://doi.org/10.1136/bmj.332.7547.933
Stalder JF et al (2013) Therapeutic patient education in atopic dermatitis: worldwide experiences. Pediatr Dermatol 30:329–334. https://doi.org/10.1111/pde.12024
Sunyer J, Basagana X, Belmonte J, Anto JM (2002) Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma. Thorax 57:687–693
Trevor JL, Bhatt SP, Wells JM, Kirkpatrick D, Schumann C, Hitchcock J, Dransfield MT (2015) Benefits of completing pulmonary rehabilitation in patients with asthma. J Asthma 52:969–973. https://doi.org/10.3109/02770903.2015.1025410. Epub 2015 Aug 18
Vervloet D, Penaud A, Razzouk H, Senft M, Arnaud A, Boutin C, Charpin J (1982) Altitude and house dust mites. J Allergy Clin Immunol 69:290–296
Vocks E (2006) Climatotherapy in atopic eczema. In: Ring J, Przybilla B, Ruzicka T (eds) Handbook of atopic eczema, 2nd edn. Springer, Berlin, pp 507–523
Vocks E, Borelli S, Rakoski J (1994) Climatotherapy (in atopic dermatitis). Paper presented at the Allergologie Klimatherapie (Bei Neurodermitis)
Weinstein AG, McKee L, Stapleford J, Faust D (1996) An economic evaluation of short-term inpatient rehabilitation for children with severe asthma. J Allergy Clin Immunol 98:264–273
Wilfinger D, Aberer W (2017) Curriculum Berufsdermatologie – Neues Praventionsmodell in Osterreich. J Dtsch Dermatol Ges 15:591–593. https://doi.org/10.1111/ddg.13204
Zemp E et al (1999) Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. Am J Respir Crit Care Med 159:1257–1266. https://doi.org/10.1164/ajrccm.159.4.9807052

Nutritional Interventions to Prevent the Development of Atopic Diseases: A Focus on Cow's Milk Allergy

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Abstract

In the western world the prevalence of atopic diseases such as food allergies is increasing highly significantly. One of the earliest and most prevalent food allergies occurring in the first year of life is cow's milk allergy. No treatment is available and only avoidance of the cow's milk allergens prevents the occurrence of an allergic reaction. Since cow's milk allergic children have an increased risk of developing other allergies later in life, investigating nutritional strategies to prevent the development of cow's milk allergy by developing oral tolerance is of high interest. Nutritional components such as prebiotics, probiotics, synbiotics and long-chain polyunsaturated fatty acids possess potential to support the maturation of the immune system early in life that might prevent the development of cow's milk allergy. The available research, so far, shows promising results particularly on the development of eczema. However, the preventive effects of the nutritional interventions on the development of food allergy are inconclusive. Future research may benefit from the combination of various dietary components. To clarify the preventive effects of the nutritional components in food allergy more randomized clinical trials are needed.

Keywords

Atopic disease · Cow's milk allergy · Food allergy · Long-chain polyunsaturated fatty acids · Nutritional prevention · Oral tolerance · Prebiotics · Probiotics · Synbiotics

1 Introduction

In the western world the prevalence of atopic diseases is increasing – with the first manifestations occurring early in childhood. Atopic diseases develop in a characteristic sequential pattern, starting early in life with atopic dermatitis, followed by food allergy, allergic rhinitis, and allergic asthma. This sequential process is known as the allergic march, which is also supported by the discovery that these atopic diseases are linked as infants diagnosed with one atopic disease are more predisposed to develop other allergies later in life (Czarnowicki et al. 2017).

Being the second manifestation of the allergic march, food allergies are potential disorders, which may clearly benefit (and have a need) for therapeutic interventions. One of the earliest and most prevalent food allergies occurring in the first year of life is cow's milk allergy (CMA) affecting around 2–5% of infants in some countries (Schoemaker et al. 2015; Fiocchi et al. 2010). Symptoms of CMA include skin rash, gastro-intestinal discomfort like diarrhoea, vomiting, respiratory problems and in severe circumstances anaphylactic shock. Although CMA is spontaneously remitted at the age of 3 in 79–90% of diagnosed children (Host and Halken 1990; Skripak et al. 2007), currently, no treatment is available and only avoidance of the cow's milk allergens prevents the occurrence of an allergic reaction. Since cow's milk allergic children have an increased risk of developing other allergies later in life,

investigating nutritional strategies to prevent the development of cow's milk allergy is of high interest. Here we review the preventive capacities of nutritional components in the development of allergic diseases with a focus on cow's milk allergy.

2 Development of Oral Tolerance Towards Food Allergens

At birth the baby's immune system is skewed towards a T helper 2 cell (Th2)-mediated response to prevent fatal immunological reactions between mother and child during pregnancy. If this Th2-skewed immune response is not adequately counterbalanced in a timely manner, Th2-mediated immunological disorders such as food allergy may arise. Environmental factors progressively educate the immune system towards a more balanced immune system, reflecting in appropriate regulatory T cell (Treg), T helper 17, T helper 1 (Th1) and Th2 responses, thereby preventing the development of diseases like autoimmunity and allergies (Gollwitzer and Marsland 2015).

An important environmental factor is exposure to food antigens, which is essential for the maturation of the immune system and the development of oral tolerance towards food allergens. The exact mechanism of immunological oral tolerance induction is unknown, but the differentiation into Tregs plays an important role. The differentiation into Tregs, involved in oral tolerance, takes place in the periphery, and more specifically in the gut-associated lymphoid tissue (GALT). Dendritic cells (DCs) sample antigens in the gut from where they migrate to the GALT. In the GALT the DCs instruct naïve T cells to differentiate into antigen-specific Tregs under the influence of anti-inflammatory and regulatory factors, like transforming growth factor-β (TGF-β) and interleukin (IL)-10 (Pabst and Mowat 2012).

Next to the exposure to food antigens, the development of the immune system is also dependent on the composition of the intestinal microbiota. It has been suggested that the microbiota plays a role in the development of mucosal immunological tolerance (Pabst and Mowat 2012). Indeed, the composition of the intestinal microbiota between atopic and healthy children is different, and reduced bacterial diversity and dysbiosis is associated with development of atopic diseases (Wopereis et al. 2014, 2018). A dysbiosis in allergic infants is characterized by low levels of genera Bifidobacteria and Lactobacilli compared to healthy infants (Cukrowska et al. 2020). Furthermore, it has been demonstrated that certain commensal intestinal bacteria, such as *Bacteroides fragilis* and several clostridial species through their ligands and metabolites, can stimulate macrophages and DCs to produce high amounts of TGF-beta and IL-10, thereby promoting the increase of Tregs (Hill and Artis 2010; Lehmann et al. 2015; Round and Mazmanian 2010; Smith et al. 2013). In addition, early life antibiotic exposure that has a major effect on the intestinal microbes increases the risk of developing allergic problems later in life (Ahmadizar et al. 2017a, 2018). Therefore, a dysbiosis in the intestinal microbiota might lead to an inadequately developed immune system associated with reduced

number of Tregs, reduced oral tolerance and possibly to the development of food allergy.

The development of the intestinal microbiota can be influenced by several factors during infancy. Some of these factors include the delivery mode (vaginal vs caesarean section), antibiotics usage during early life and most importantly early life diet (breast milk vs formula milk) will have a major impact on the intestinal microbiota. In conclusion, early life food allergies, such as cow's milk allergy, may be the result of intestinal dysbiosis and related derailed mucosal immune system not handling cow's milk proteins in a proper way.

3 Dietary Interventions for the Prevention of Cow's Milk Allergy

During the first years of life, diet affects the composition of the intestinal microbiota and has a major influence on the development of the immune system. We here review the allergy-preventive effects of several nutritional components that modulate the intestinal microbiota and/or the immune system early in life.

3.1 Human Milk

Breast milk is the recommended dietary source from the day of birth. It contains dietary nutrients important for the growth and development of the new-born as well as growth factors, antigens and immunomodulatory components like immunoglobulins, long-chain polyunsaturated fatty acids (LCPUFAs), bacteria, non-digestible oligosaccharides and vitamins, all derived from the maternal diet or maternal immune system. These components are essential for shaping the intestinal microbiota composition and for the maturation of the immune system, i.e. to develop oral tolerance in the new-born (van den Elsen et al. 2019; Verhasselt 2010). The 2011 guideline from the WHO recommends exclusively breast milk as nutrition for infants during the first 6 months of life (Exclusive breastfeeding for 6 months best for babies everywhere, https://www.who.int/mediacentre/news/statements/2011/breastfeeding_20110115/en/). Already after 3-4 months of consumption of breast milk the risk of wheeze, asthma and eczema development is decreased; however, the evidence is insufficient to form a conclusion regarding food allergy (Greer et al. 2019; Gungor et al. 2019; Ahmadizar et al. 2017b).

However, breastfeeding is not always possible and the best available alternative for infants is infant milk formula. To ensure optimal development of the intestinal microbiota and (mucosal) immune system, it is of great importance to identify all beneficial components in breast milk to enable full deployment of their potential when added to infant formula. Therefore, more information on the composition of breast milk and the function of the breast milk components might lead to new strategies to prevent allergy development.

3.2 Human Milk Oligosaccharides: Prebiotics

Human milk oligosaccharides (HMOs) are one of the major components of breast milk (Xiao et al. 2017). They stimulate the development of the immune system either directly via modulation of immune cells or indirectly by influencing the gut microbiota as a substrate for fermentation (Triantis et al. 2018). Indicative for the importance of HMOs is the finding that the profiles of HMOs in breast milk are associated with food sensitization early in life (Miliku et al. 2018; Ayechu-Muruzabal et al. 2018). Since the alternative for breast milk, infant formula, is based on cow's milk, the composition of oligosaccharides in infant formula is very different (low abundance) compared to human milk (Boehm and Stahl 2007). Therefore, to mimic the composition of human milk, it is favourable to supplement infant formulas with non-digestible oligosaccharides, which show beneficial (prebiotic) properties. The definition of a prebiotic according to the International Scientific Association for Probiotics and Prebiotics (ISAPP) is 'a substrate that is selectively utilized by host micro-organisms conferring a health benefit' (Gibson et al. 2017). Prebiotics stimulate the growth and activity of beneficial commensal intestinal bacteria (Gibson and Roberfroid 1995). Studies have shown that prebiotic supplementation of infant formula with a specific mixture of short-chain galacto-oligosaccharide (scGOS) and long-chain fructo-oligosaccharide (lcFOS) results in an intestinal microbiota composition similar to breastfed infants (Wopereis et al. 2018; Oozeer et al. 2013) indicating that supplementation of infant formula with certain prebiotics will beneficially affect the intestinal microbiota development. In a randomized double-blind placebo-controlled study with formula fed infants at risk of developing atopic manifestations it was shown that scGOS/lcFOS supplementation for 6 months reduced the development of atopic manifestations and infections during the first 6 months of life compared to the control group (Moro et al. 2006). This protective effect was still observed 2 and 5 years after the prebiotic intervention indicating that next to beneficial effects on microbiota composition and the shown health benefits, immune programming by prebiotics in early life can have a long-term protective effect (Arslanoglu et al. 2008, 2012).

The mechanisms by which these prebiotics exert their effects are diverse and not completely clear. Prebiotics stimulate the growth and activity of beneficial commensal intestinal bacteria like Bifidobacteria and Lactobacilli (Gibson and Roberfroid 1995). Increase in number and activity of the beneficial bacteria has antimicrobial effects since they compete with pathogenic bacteria to bind on intestinal epithelium (Ayechu-Muruzabal et al. 2018). In addition, it is known that HMOs and scGOS/lcFOS are able to cross the intestinal epithelial barrier either through receptor-mediated transcytosis or through paracellular transfer (Eiwegger et al. 2010; Gnoth et al. 2001). This indicates that these compounds may also have a systemic effect. This is in line with the fact that at least 1% of HMOs is detected systemically (Goehring et al. 2014). In addition to the microbial modulatory capacities of prebiotics, scGOS/lcFOS have been shown to have direct immunomodulatory effects on the immune system. In vitro assays showed that scGOS/lcFOS promotes IL-10 release by DC and these DC can upregulate the number of functional

suppressive Foxp3 positive T cells (Lehmann et al. 2015). In co-culture assays with intestinal epithelial cells and activated peripheral blood mononuclear cells (PBMCs), it is demonstrated that scGOS/lcFOS induces an epithelial cell-dependent development of tolerogenic Treg and Th1 responses (de Kivit et al. 2013; Hayen et al. 2018). Using a murine model of CMA it is demonstrated that the acute allergic response was significantly decreased in mice receiving scGOS/lcFOS during sensitization (Schouten et al. 2009). Moreover, the mixture of scGOS/lcFOS enhanced mucosal IL-10 and TGF-β transcription and induced Tregs response which were essential in allergy prevention since neutralizing TGF-β or IL-10 in vivo abrogated the protective effects (Schouten et al. 2010; Kerperien et al. 2014, 2018).

Despite the documented promising health benefit of prebiotics in several preclinical and clinical studies, some clinical studies show no differences (Ranucci et al. 2018; Boyle et al. 2016). One of these studies, a double-blind, randomized controlled trial comparing prebiotic containing formula with standard formula and breastfeeding, shows no differences in the incidence of allergic manifestations. The lack of difference may be due to the prebiotic mixture used in this trial, as this consisted of GOS and polydextrose (PDX) (Ranucci et al. 2018). These results indicate that a careful consideration of which type of prebiotic to use is important. So far, evidence from randomized trials that prebiotics (FOS, GOS and PDX) have a preventive effect on development of allergies is limited (Cuello-Garcia et al. 2017). More clinical studies are essential to learn more about the possible preventive effects on allergies of specific prebiotics, including HMOs. However, prebiotics are safe to use and the World Allergy Organization (WAO) guideline panel suggests prebiotic supplementation in not-exclusively breastfed infants, both at high and at low risk for developing allergy (conditional recommendation, very low certainty of evidence) (Cuello-Garcia et al. 2016).

3.3 Live Micro-Organisms: Probiotics

The intestinal microbiota play an essential role in the development of the (mucosal) immune system and also in the process of oral tolerance development. Modulation of the microbiota composition via nutrition is an appealing strategy. As discussed in the preceding paragraph, prebiotics are one strategy. Another strategy is to directly supplement diets with live micro-organisms. As live micro-organisms have been isolated from human milk (Martin et al. 2009; Jeurink et al. 2013), addition of selective bacterial strains to infant formula might further potentiate the beneficial healthy effects of infant formula. The category currently used to refer to these live micro-organisms is probiotics. The definition of a probiotic according to ISAPP is ‘live microorganism that, when administered in adequate amounts, confer a health benefit on the host’ (Hill et al. 2014).

There have been multiple clinical studies in which potential health benefits of probiotics were investigated. In a recently published double-blind placebo-controlled study, children receiving a daily mixture of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. *lactis* for 6 months (at the age of 8–14 months)

developed less eczema compared to the control group. The number of sensitized children was not significantly different between the 2 groups (Schmidt et al. 2019). In another randomized placebo-controlled trial, a positive effect on eczema prevalence was only demonstrated for *Lactobacillus rhamnosus* and not for *Bifidobacteria animalis* subsp. *lactis*. The supplementation was given daily to mothers from gestational week 35 until 6 months after birth (if they were lactating) and to the infants from birth up to 2 years of age. At 6 years of age the incidence of sensitization in *L. Rhamnosus* group was reduced (Wickens et al. 2013); however, this reduction in sensitization was not further specified into the tested allergens, either food (egg, cow's milk and peanut) or aeroallergens (cat, grass pollen or house dust mite). At 11 years of age a significant lower prevalence of eczema was observed in the group receiving *L. Rhamnosus* whereas supplementation of the *Bifidobacteria* had no effects (Wickens et al. 2018). These data are in line with the meta-analyses (Cuello-Garcia et al. 2015; Zuccotti et al. 2015) which conclude that probiotic supplementation is beneficial in the prevention of eczema and that there is no proven effect on development of other allergies. It is important to realize that the preventive effect of probiotic supplementation is optimal when supplemented during both the pre- and postnatal period (Cuello-Garcia et al. 2015). This suggests that a combined strategy (pre- and postnatal) is most effective in prevention of eczema, and also to reduce sensitization. However, timing and duration of the intervention need more investigation and also food challenges are needed as an outcome in clinical trials to achieve more solid evidence of the preventive probiotic effects in food allergies (West et al. 2016; Zhang et al. 2016). Furthermore, a combination of probiotic strains seemed to lead to a more pronounced effect in the prevention of eczema compared with the use of single strains (Zuccotti et al. 2015). However, strain-specific differences should be taken into account. The WAO states the following: although the recommendations are supported by weak evidence, there can be a beneficial effect of probiotics in certain cases, i.e. pregnant women having a child at high risk, women who breastfeed children at high risk for developing allergies and infants at high risk for developing allergies (Fiocchi et al. 2015).

3.4 Synbiotics

As probiotics and prebiotics show some promising effects in allergy management, it is tempting to speculate that a combination of the so-called synbiotics might lead to synergistic effects. Synergy may be achieved by an optimal combination of prebiotics with probiotics, in which the prebiotics selectively promote the growth and activity of the probiotics. A few (pre)clinical studies have evaluated the synbiotic strategy on the development of (food) allergies.

In a mouse model of CMA, a synbiotic diet comprised of a mixture of prebiotics (scGOS/lcFOS, 9:1) in combination with the probiotic strain, *Bifidobacterium breve M-16 V*, significantly reduced the allergic response, and was shown to be more effective in symptom resolution than either the pre- or probiotics singularly (Schouten et al. 2009). Interestingly, next to alleviation of the allergic response, a

synbiotic diet (comprised of scFOS/lcFOS and *B. breve M16V*) was shown to increase tolerance development in a murine CMA preventive model. (Kostadinova et al. 2017). The beneficial effects of the synbiotics in these allergy models can be partly explained by their effects on the intestinal epithelial cells.

The synbiotic intervention increases epithelial-cell-derived galectin-9 (gal-9) levels in the intestine and mesenteric lymph nodes of mice in the CMA model. Moreover, it is demonstrated that in human PBMC assays gal-9 can induce the development of Th1 and Treg responses, which will contribute to amelioration of the allergic (Th2) response (de Kivit et al. 2012). Gal-9 is a soluble-type lectin and possesses sugar-binding motifs by which they bind to adaptive immune cells. Gal-9 also binds to IgE, which might prevent IgE cross-linking and consequently prevent degranulation of mast cells and/or basophils (Niki et al. 2009). In line with these results, the serum level of gal-9 in atopic dermatitis patients and in CMA mice was significantly increased after a synbiotic intervention and associated with amelioration of symptoms (de Kivit et al. 2012).

To the best of our knowledge, the preventive effects of a synbiotic strategy on the development of food allergies in clinical studies have not been evaluated. However, several studies investigated the synbiotic effect on the prevention of eczema and they all report significant improvements (Kukkonen et al. 2007; Roze et al. 2012; van der Aa et al. 2010). In one of the studies, infants diagnosed with atopic dermatitis (age < 7 months) received a synbiotic supplemented infant formula or a formula without synbiotic for 12 weeks. The synbiotic supplement significantly reduced the severity of eczema, in the infants with IgE-associated eczema (van der Aa et al. 2010). After 1 year, asthma-like symptoms and medication use were less in the infants who had received the synbiotic formula (van der Aa et al. 2011). In line with the preclinical data, systemic gal-9 levels in children with eczema were increased in the group receiving synbiotic supplementation (de Kivit et al. 2012).

In conclusion, limited studies have evaluated the synbiotic intervention as treatment of atopic diseases and the knowledge about the preventive capacities of synbiotics is still limited. Promising results from preclinical studies suggest synbiotics to be of considerable interest in the prevention of allergies.

3.5 Long-Chain Polyunsaturated Fatty Acids

Dietary long-chain polyunsaturated fatty acids (LCPUFAs) are important as they are incorporated in the cell membrane and facilitate a favourable environment for immune development and maturation. LCPUFAs can be divided into omega-3 (ω-3 PUFAs) and omega-6 (ω-6 PUFAs) fatty acids. The ω-6 PUFAs arachidonic acid (AA), also found in meat, can be converted into the pro-inflammatory eicosanoids 2 and 4 series like prostaglandin E_2. In contrast, the ω-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are incorporated in the cell membrane on the expense of AA, which leads to less available AA and therefore less conversion into pro-inflammatory prostaglandins and leukotrienes (Calder et al. 1994). DHA and EPA also compete with AA as substrates for

cyclooxygenase and lipoxygenase by which EPA and DHA can be metabolized into the less pro-inflammatory prostaglandin and thromboxanes 3 and 5 series (van den Elsen et al. 2012). In addition, cyclooxygenase can also convert DHA and EPA into resolvins, which are suggested to be anti-inflammatory through activation of the resolvins E1 receptor (Miles and Calder 2017).

The skewing towards a high consumption of ω-6 PUFAs in the western world has been associated with an increasing prevalence of allergies (Blumer and Renz 2007). This was also indicated in a preclinical model of CMA, where CMA mice exposed to ω-6 PUFAs containing diet demonstrated more severe allergic symptoms (van den Elsen et al. 2015; Thang et al. 2013). In contrast, a ω-3 PUFAs diet prevented the development of the acute allergic response as well as the IgE response and concomitantly increased the number of intestinal Tregs (van den Elsen et al. 2013, 2014). In a rat model of food allergy, it was shown that during two critical periods of immune development (pregnancy and weaning) extra supplementation with ω-3 PUFAs was able to steer the immune system towards oral tolerance. Perinatal supplementation (during pregnancy & lactation) of ω-3 PUFAs stimulated the maturation of the immune system of the offspring towards a Th1 (IFNγ) and Treg (IL-10) response (Richard et al. 2016). The data from these preclinical studies suggest a promising role for ω-3 PUFAs in the prevention of allergies.

Several clinical trials investigated the effect of fish oil, EPA and/or DHA supplementation during pregnancy and/or lactation on atopic disease development (Lumia et al. 2011; Furuhjelm et al. 2009, 2011; Bisgaard et al. 2016; Palmer et al. 2012; Best et al. 2016). However, there are differences between studies; which atopic diseases they evaluate, the timing of the intervention and the age of the children at the time of reporting the data. Some report beneficial effects on the development of food allergies and sensitization to allergens (e.g. sensitization to egg) whilst others report no effects on these atopic diseases (Furuhjelm et al. 2009; Palmer et al. 2012; Best et al. 2016, 2018; Noakes et al. 2012). According to a meta-analysis of maternal fish oil supplementation during pregnancy, the infants were at lower risk of developing eczema and a significant reduction in sensitization to egg was demonstrated in the first 12 months. This meta-analysis suggests maternal ω-3 PUFAs to have positive effects regarding the prevention of infant allergy development; however, the authors conclude that the link between maternal intake of ω-3 PUFAs and allergic disease development in the infants can be neither rejected nor confirmed due to inconsistency in results from the consulted studies (Best et al. 2016). Based on current studies there is no clear evidence whether maternal consumption of ω-3 PUFAs and/or fish oil prevents development of allergies in offspring, more adequate-designed randomized clinical trials are needed to establish adequate evidence.

The evidence that supplementation of ω-3 PUFAs after birth and/or during infancy influences allergy development is limited. In infants receiving fish oil or ω-3 PUFAs after birth a lower incidence of diagnosed food sensitization was reported and also a delayed time to first allergic illness (Clausen et al. 2018; Foiles et al. 2016; D'Vaz et al. 2012a). Mechanistic insights showed that immune cells from infants receiving fish oil displayed a decreased IL-13 production and increased

IFNγ and tumour necrosis factor α (TNFα) production indicating a favourable shift towards Th1 in the Th1/Th2 balance (D'Vaz et al. 2012a). In contrast, in another study no effect was observed on allergic outcomes in infants receiving ω-3 PUFAs supplementation after birth (D'Vaz et al. 2012b). A meta-analysis from 2016 concluded that LCPUFAs supplementation during infancy has no effect on the development of food allergy, asthma and eczema (Schindler et al. 2016).

4 Avoidance or Early Life Introduction of Cow's Milk Proteins

Historically, allergen avoidance during pregnancy and lactation has been the recommendation to mothers with children at high risk for allergic diseases. Avoidance of food allergens such as cow's milk, fish, and egg from the maternal diet was hypothesized to prevent and reduce the risk of food allergic reactions in the infants (American Academy of Pediatrics 2000). As the ingested allergens have been shown to pass through the placenta and are present in breast milk, this may lead to sensitization of the baby. However, the evidence that avoidance decreases the risk of food allergy is insufficient (Agostoni et al. 2008). Moreover, it has been demonstrated that early introduction of peanut could actually prevent peanut allergy in infants at risk (Du Toit et al. 2015, 2016, 2018; Perkin et al. 2016). The increased risk for allergy in infants avoiding allergens, can be explained by the lack of allergen-specific oral tolerance induction due to the absence of the allergen and/or by sensitization towards the allergen via other routes (like the skin or airways) (Nowak-Wegrzyn and Chatchatee 2017; Fox et al. 2009).

For infants at risk of developing cow's milk allergy, consumption of infant formulas exposes these infants to the major cow's milk allergens, casein and whey, which may lead to sensitization. To reduce the sensitizing potential of infant formulas, the allergenic load of the formula can be reduced by processes such as hydrolysation, heat-treatment and/or ultra-filtration (Hays and Wood 2005). This leads to reduction in the molecular weight of the cow's milk protein and is expected to reduce sensitization capacities of casein and whey (von Berg 2009). Hydrolysates exist as partial and extensive hydrolysates. Partial hydrolysates are used in the prevention of CMA in high risk infants and extensive hydrolysates are used for infants already diagnosed with CMA (Fiocchi et al. 2010). The preventive property of the hydrolysates is mainly tested in children at risk, only a few studies were conducted in healthy infants. According to a systematic review, hydrolysates have no effect on the prevention of allergic diseases in non-allergic infants; however, the quality of evidence was very low (Osborn et al. 2017). In infants at risk only limited studies have been performed with contradictory results. A recently published systematic review concluded that the use of partial hydrolysates in high risk infants reduces the risk of development of any allergic disease and in particular of eczema (Szajewska and Horvath 2017). The effect of hydrolysed cow's milk formula on allergy prevention has been shown in a cohort of infants at risk of atopic diseases (von Berg et al. 2003). The preventive effect of hydrolysates was particularly shown to reduce the risk of developing atopic dermatitis, which even persisted after 10 years

(von Berg et al. 2013). Further investigation into the exact composition of hydrolysates might further contribute to identifying specific tolerizing capacity of the various hydrolysates. It has recently been demonstrated that certain peptides within whey-based hydrolysates can contribute to the development of oral tolerance to whey (Gouw et al. 2018). Moreover, it is tempting to speculate that less processed milk, which is proven to be less allergenic, may have tolerance-promoting capacities (Abbring et al. 2019a, b). Further research is necessary to investigate the role of processing of milk in cow's milk allergy-preventive strategies.

5 Conclusion

The incidence of food allergies is increasing and there is a need for preventive strategies. Several nutritional components with intestinal microbiota and immune modulatory properties are suggested to have a potential role in the prevention of development of allergies. Next to the components reviewed in this chapter other important nutritional components like vitamins, postbiotics, ferments, short-chain fatty acids are also known to have potential beneficial effects but could not all be discussed in this overview. The available research, so far, shows promising results particularly on the development of eczema. However, the preventive effects of the nutritional interventions on the development of food allergy are not conclusive. A reason for this can be inconsistency (e.g. differences in prebiotic mixtures, differences in probiotic strains, differences in timing of intervention) in the used dietary components and the timing of intervention. Future research may benefit from the combination of various dietary components. To clarify the preventive effects of the nutritional components in food allergy more randomized clinical trials are needed.

References

Abbring S, Kusche D, Roos TC et al (2019a) Milk processing increases the allergenicity of cow's milk-preclinical evidence supported by a human proof-of-concept provocation pilot. Clin Exp Allergy 49:1013–1025

Abbring S, Ryan JT, Diks MAP et al (2019b) Suppression of food allergic symptoms by raw cow's milk in mice is retained after skimming but abolished after heating the milk-a promising contribution of alkaline phosphatase. Nutrients 11:1499

Agostoni C, Decsi T, Fewtrell M et al (2008) Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 46:99–110

Ahmadizar F, Vijverberg SJH, Arets HGM et al (2017a) Early life antibiotic use and the risk of asthma and asthma exacerbations in children. Pediatr Allergy Immunol 28:430–437

Ahmadizar F, Vijverberg SJH, Arets HGM et al (2017b) Breastfeeding is associated with a decreased risk of childhood asthma exacerbations later in life. Pediatr Allergy Immunol 28:649–654

Ahmadizar F, Vijverberg SJH, Arets HGM et al (2018) Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: a meta-analysis. Allergy 73:971–986

American Academy of Pediatrics (2000) Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 106:346–349

Arslanoglu S, Moro GE, Schmitt J et al (2008) Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 138:1091–1095

Arslanoglu S, Moro GE, Boehm G et al (2012) Early neutral prebiotic oligosaccharide supplementation reduces the incidence of some allergic manifestations in the first 5 years of life. J Biol Regul Homeost Agents 26:49–59

Ayechu-Muruzabal V, van Stigt AH, Mank M et al (2018) Diversity of human milk oligosaccharides and effects on early life immune development. Front Pediatr 6:239

Best KP, Gold M, Kennedy D et al (2016) Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. Am J Clin Nutr 103:128–143

Best KP, Sullivan TR, Palmer DJ et al (2018) Prenatal omega-3 LCPUFA and symptoms of allergic disease and sensitization throughout early childhood – a longitudinal analysis of long-term follow-up of a randomized controlled trial. World Allergy Organ J 11:10

Bisgaard H, Stokholm J, Chawes BL et al (2016) Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med 375:2530–2539

Blumer N, Renz H (2007) Consumption of omega3-fatty acids during perinatal life: role in immuno-modulation and allergy prevention. J Perinat Med 35(Suppl 1):S12–S18

Boehm G, Stahl B (2007) Oligosaccharides from milk. J Nutr 137:847s–849s

Boyle RJ, Tang ML, Chiang WC et al (2016) Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. Allergy 71:701–710

Calder PC, Yaqoob P, Harvey DJ et al (1994) Incorporation of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty acid composition and membrane fluidity. Biochem J 300(Pt 2):509–518

Clausen M, Jonasson K, Keil T et al (2018) Fish oil in infancy protects against food allergy in Iceland-results from a birth cohort study. Allergy 73:1305–1312

Cuello-Garcia CA, Brozek JL, Fiocchi A et al (2015) Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 136:952–961

Cuello-Garcia CA, Fiocchi A, Pawankar R et al (2016) World allergy organization-McMaster University guidelines for allergic disease prevention (GLAD-P): prebiotics. World Allergy Organ J 9:10

Cuello-Garcia C, Fiocchi A, Pawankar R et al (2017) Prebiotics for the prevention of allergies: a systematic review and meta-analysis of randomized controlled trials. Clin Exp Allergy 47:1468–1477

Cukrowska B, Bierła JB, Zakrzewska M, Klukowski M, Maciorkowska E (2020) The relationship between the infant gut microbiota and allergy. The role of bifidobacterium breve and prebiotic oligosaccharides in the activation of anti-allergic mechanisms in early life. Nutrients 12(4)

Czarnowicki T, Krueger JG, Guttman-Yassky E (2017) Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. J Allergy Clin Immunol 139:1723–1734

D'Vaz N, Meldrum SJ, Dunstan JA et al (2012a) Fish oil supplementation in early infancy modulates developing infant immune responses. Clin Exp Allergy 42:1206–1216

D'Vaz N, Meldrum SJ, Dunstan JA et al (2012b) Postnatal fish oil supplementation in high-risk infants to prevent allergy: randomized controlled trial. Pediatrics 130:674–682

de Kivit S, Saeland E, Kraneveld AD et al (2012) Galectin-9 induced by dietary synbiotics is involved in suppression of allergic symptoms in mice and humans. Allergy 67:343–352

de Kivit S, Kraneveld AD, Knippels LM et al (2013) Intestinal epithelium-derived galectin-9 is involved in the immunomodulating effects of nondigestible oligosaccharides. J Innate Immun 5:625–638

Du Toit G, Roberts G, Sayre PH et al (2015) Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 372:803–813
Du Toit G, Sayre PH, Roberts G et al (2016) Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med 374:1435–1443
du Toit G, Sayre PH, Roberts G et al (2018) Allergen specificity of early peanut consumption and effect on development of allergic disease in the learning early about peanut allergy study cohort. J Allergy Clin Immunol 141:1343–1353
Eiwegger T, Stahl B, Haidl P et al (2010) Prebiotic oligosaccharides: in vitro evidence for gastrointestinal epithelial transfer and immunomodulatory properties. Pediatr Allergy Immunol 21:1179–1188
Fiocchi A, Brozek J, Schunemann H et al (2010) World allergy organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. World Allergy Organ J 3:57–161
Fiocchi A, Pawankar R, Cuello-Garcia C et al (2015) World allergy organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. World Allergy Organ J 8:4
Foiles AM, Kerling EH, Wick JA et al (2016) Formula with long-chain polyunsaturated fatty acids reduces incidence of allergy in early childhood. Pediatr Allergy Immunol 27:156–161
Fox AT, Sasieni P, du Toit G et al (2009) Household peanut consumption as a risk factor for the development of peanut allergy. J Allergy Clin Immunol 123:417–423
Furuhjelm C, Warstedt K, Larsson J et al (2009) Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr 98:1461–1467
Furuhjelm C, Warstedt K, Fageras M et al (2011) Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. Pediatr Allergy Immunol 22:505–514
Gibson GR, Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 125:1401–1412
Gibson GR, Hutkins R, Sanders ME et al (2017) Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14:491–502
Gnoth MJ, Rudloff S, Kunz C et al (2001) Investigations of the in vitro transport of human milk oligosaccharides by a Caco-2 monolayer using a novel high performance liquid chromatography-mass spectrometry technique. J Biol Chem 276:34363–34370
Goehring KC, Kennedy AD, Prieto PA et al (2014) Direct evidence for the presence of human milk oligosaccharides in the circulation of breastfed infants. PLoS One 9:e101692
Gollwitzer ES, Marsland BJ (2015) Impact of early-life exposures on immune maturation and susceptibility to disease. Trends Immunol 36:684–696
Gouw JW, Jo J, Meulenbroek L et al (2018) Identification of peptides with tolerogenic potential in a hydrolysed whey-based infant formula. Clin Exp Allergy 48:1345–1353
Greer FR, Sicherer SH, Burks AW (2019) The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. Pediatrics 143:e20190281
Gungor D, Nadaud P, LaPergola CC et al (2019) Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. Am J Clin Nutr 109:772s–799s
Hayen SM, Otten HG, Overbeek SA et al (2018) Exposure of intestinal epithelial cells to short- and long-chain fructo-oligosaccharides and CpG oligodeoxynucleotides enhances peanut-specific T helper 1 polarization. Front Immunol 9:923
Hays T, Wood RA (2005) A systematic review of the role of hydrolyzed infant formulas in allergy prevention. Arch Pediatr Adolesc Med 159:810–816
Hill DA, Artis D (2010) Intestinal bacteria and the regulation of immune cell homeostasis. Annu Rev Immunol 28:623–667

Hill C, Guarner F, Reid G et al (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11:506–514

Host A, Halken S (1990) A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 45:587–596

Jeurink PV, van Bergenhenegouwen J, Jimenez E et al (2013) Human milk: a source of more life than we imagine. Benef Microbes 4:17–30

Kerperien J, Jeurink PV, Wehkamp T et al (2014) Non-digestible oligosaccharides modulate intestinal immune activation and suppress cow's milk allergic symptoms. Pediatr Allergy Immunol 25:747–754

Kerperien J, Veening-Griffioen D, Wehkamp T et al (2018) IL-10 receptor or TGF-beta neutralization abrogates the protective effect of a specific nondigestible oligosaccharide mixture in cow-milk-allergic mice. J Nutr 148:1372–1379

Kostadinova AI, Pablos-Tanarro A, Diks MAP et al (2017) Dietary intervention with beta-lactoglobulin-derived peptides and a specific mixture of fructo-oligosaccharides and bifidobacterium breve M-16V facilitates the prevention of whey-induced allergy in mice by supporting a tolerance-prone immune environment. Front Immunol 8:1303

Kukkonen K, Savilahti E, Haahtela T et al (2007) Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 119:192–198

Lehmann S, Hiller J, van Bergenhenegouwen J et al (2015) In vitro evidence for immune-modulatory properties of non-digestible oligosaccharides: direct effect on human monocyte derived dendritic cells. PLoS One 10:e0132304

Lumia M, Luukkainen P, Tapanainen H et al (2011) Dietary fatty acid composition during pregnancy and the risk of asthma in the offspring. Pediatr Allergy Immunol 22:827–835

Martin R, Jimenez E, Heilig H et al (2009) Isolation of bifidobacteria from breast milk and assessment of the bifidobacterial population by PCR-denaturing gradient gel electrophoresis and quantitative real-time PCR. Appl Environ Microbiol 75:965–969

Miles EA, Calder PC (2017) Can early omega-3 fatty acid exposure reduce risk of childhood allergic disease? Nutrients 9:784

Miliku K, Robertson B, Sharma AK et al (2018) Human milk oligosaccharide profiles and food sensitization among infants in the CHILD study. Allergy 73:2070–2073

Moro G, Arslanoglu S, Stahl B et al (2006) A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 91:814–819

Niki T, Tsutsui S, Hirose S et al (2009) Galectin-9 is a high affinity IgE-binding lectin with anti-allergic effect by blocking IgE-antigen complex formation. J Biol Chem 284:32344–32352

Noakes PS, Vlachava M, Kremmyda LS et al (2012) Increased intake of oily fish in pregnancy: effects on neonatal immune responses and on clinical outcomes in infants at 6 mo. Am J Clin Nutr 95:395–404

Nowak-Wegrzyn A, Chatchatee P (2017) Mechanisms of tolerance induction. Ann Nutr Metab 70 (Suppl 2):7–24

Oozeer R, van Limpt K, Ludwig T et al (2013) Intestinal microbiology in early life: specific prebiotics can have similar functionalities as human-milk oligosaccharides. Am J Clin Nutr 98:S561–S571

Osborn DA, Sinn JK, Jones LJ (2017) Infant formulas containing hydrolysed protein for prevention of allergic disease and food allergy. Cochrane Database Syst Rev 3:Cd003664

Pabst O, Mowat AM (2012) Oral tolerance to food protein. Mucosal Immunol 5:232–239

Palmer DJ, Sullivan T, Gold MS et al (2012) Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. BMJ 344:e184

Perkin MR, Logan K, Marrs T et al (2016) Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol 137:1477–1486.e1478

Ranucci G, Buccigrossi V, Borgia E et al (2018) Galacto-oligosaccharide/polidextrose enriched formula protects against respiratory infections in infants at high risk of atopy: a randomized clinical trial. Nutrients 10:286

Richard C, Lewis ED, Goruk S et al (2016) A dietary supply of docosahexaenoic acid early in life is essential for immune development and the establishment of oral tolerance in female rat offspring. J Nutr 146:2398–2406

Round JL, Mazmanian SK (2010) Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci U S A 107:12204–12209

Roze JC, Barbarot S, Butel MJ et al (2012) An alpha-lactalbumin-enriched and symbiotic-supplemented v. a standard infant formula: a multicentre, double-blind, randomised trial. Br J Nutr 107:1616–1622

Schindler T, Sinn JK, Osborn DA (2016) Polyunsaturated fatty acid supplementation in infancy for the prevention of allergy. Cochrane Database Syst Rev 10:Cd010112

Schmidt RM, Pilmann Laursen R, Bruun S et al (2019) Probiotics in late infancy reduce the incidence of eczema: a randomized controlled trial. Pediatr Allergy Immunol 30:335–340

Schoemaker AA, Sprikkelman AB, Grimshaw KE et al (2015) Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. Allergy 70:963–972

Schouten B, van Esch BC, Hofman GA et al (2009) Cow milk allergy symptoms are reduced in mice fed dietary synbiotics during oral sensitization with whey. J Nutr 139:1398–1403

Schouten B, van Esch BC, Hofman GA et al (2010) Oligosaccharide-induced whey-specific CD25 (+) regulatory T-cells are involved in the suppression of cow milk allergy in mice. J Nutr 140:835–841

Skripak JM, Matsui EC, Mudd K et al (2007) The natural history of IgE-mediated cow's milk allergy. J Allergy Clin Immunol 120:1172–1177

Smith PM, Howitt MR, Panikov N et al (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341:569–573

Szajewska H, Horvath A (2017) A partially hydrolyzed 100% whey formula and the risk of eczema and any allergy: an updated meta-analysis. World Allergy Organ J 10:27

Thang CL, Boye JI, Shi HN et al (2013) Effects of supplementing different ratios of omega-3 and omega-6 fatty acids in western-style diets on cow's milk protein allergy in a mouse model. Mol Nutr Food Res 57:2029–2038

Triantis V, Bode L, van Neerven RJJ (2018) Immunological effects of human milk oligosaccharides. Front Pediatr 6:190

van den Elsen L, Garssen J, Willemsen L (2012) Long chain N-3 polyunsaturated fatty acids in the prevention of allergic and cardiovascular disease. Curr Pharm Des 18:2375–2392

van den Elsen LW, van Esch BC, Hofman GA et al (2013) Dietary long chain n-3 polyunsaturated fatty acids prevent allergic sensitization to cow's milk protein in mice. Clin Exp Allergy 43:798–810

van den Elsen LW, Bol-Schoenmakers M, van Esch BC et al (2014) DHA-rich tuna oil effectively suppresses allergic symptoms in mice allergic to whey or peanut. J Nutr 144:1970–1976

van den Elsen LW, van Esch BC, Dingjan GM et al (2015) Increased intake of vegetable oil rich in n-6 PUFA enhances allergic symptoms and prevents oral tolerance induction in whey-allergic mice. Br J Nutr 114:577–585

van den Elsen LWJ, Garssen J, Burcelin R et al (2019) Shaping the gut microbiota by breastfeeding: the gateway to allergy prevention? Front Pediatr 7:47

van der Aa LB, Heymans HS, van Aalderen WM et al (2010) Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. Clin Exp Allergy 40:795–804

van der Aa LB, van Aalderen WM, Heymans HS et al (2011) Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. Allergy 66:170–177

Verhasselt V (2010) Oral tolerance in neonates: from basics to potential prevention of allergic disease. Mucosal Immunol 3:326–333

von Berg A (2009) Modified proteins in allergy prevention. Nestle Nutr Workshop Ser Pediatr Program 64:239–247; discussion 247–257

von Berg A, Koletzko S, Grubl A et al (2003) The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 111:533–540

von Berg A, Filipiak-Pittroff B, Kramer U et al (2013) Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 131:1565–1573

West CE, Jenmalm MC, Kozyrskyj AL et al (2016) Probiotics for treatment and primary prevention of allergic diseases and asthma: looking back and moving forward. Expert Rev Clin Immunol 12:625–639

Wickens K, Stanley TV, Mitchell EA et al (2013) Early supplementation with *Lactobacillus rhamnosus* HN001 reduces eczema prevalence to 6 years: does it also reduce atopic sensitization? Clin Exp Allergy 43:1048–1057

Wickens K, Barthow C, Mitchell EA et al (2018) Effects *of Lactobacillus rhamnosus* HN001 in early life on the cumulative prevalence of allergic disease to 11 years. Pediatr Allergy Immunol 29:808–814

Wopereis H, Oozeer R, Knipping K et al (2014) The first thousand days – intestinal microbiology of early life: establishing a symbiosis. Pediatr Allergy Immunol 25:428–438

Wopereis H, Sim K, Shaw A et al (2018) Intestinal microbiota in infants at high risk for allergy: effects of prebiotics and role in eczema development. J Allergy Clin Immunol 141:1334–1342. e1335

Xiao L, Stahl B, Folkerts G et al (2017) The immunological benefits for complex oligosaccharides in human milk. In: Calder PC, Kulkarni AD (eds) Nutrition, immunity, and infection, 1st edn. CRC Press, Boca Raton

Zhang GQ, Hu HJ, Liu CY et al (2016) Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine 95:e2562

Zuccotti G, Meneghin F, Aceti A et al (2015) Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy 70:1356–1371

Comprehensive Approach: Current Status on Patient Education in Atopic Dermatitis and Other Allergic Diseases

Stephan Traidl, Claudia Lang, Peter Schmid-Grendelmeier, Thomas Werfel, and Annice Heratizadeh

Contents

Abstract

Allergic diseases are characterized by a complex complex chronic pathophysiology. Therapeutic patient education (TPE) programs are an important part of health care for allergic patients. These programs aim to increase the patient's adherence to evidence-based treatment and improve their ability to cope with the disease. TPE led by a multiprofessional team covers the complex pathogenesis of the disease, trigger factors, nursing and dietary issues, and the broad variety of treatment options available including psychological and behavioral aspects.

Regarding atopic dermatitis (AD), randomized, controlled studies have demonstrated the beneficial effects of delivering structured group training to children, their caregivers, and adult patients with AD. Such intervention achieved substantial improvements in quality of life and objective clinical disease parameters. Besides AD, training programs have also been developed and evaluated for patients with anaphylaxis and asthma. This article provides an

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overview of the multitude of TPE concepts and their impact on subjective and objective outcomes. It focuses on AD but also sheds light on other allergic diseases such as anaphylaxis and asthma.

Keywords

Anaphylaxis · Atopic dermatitis · Patient care · Therapeutic patient education programs

1 Introduction

Since the proposal of the biopsychosocial model of illness by George Engel in 1977, the understanding has risen that diseases are a complex interaction between biological pathologies, personal and behavioral contributions, and the social environment (Engel 1977). Patients with chronic diseases in particular require multimodal approaches for sufficient treatment (Wade and Halligan 2017). To satisfy this, the patients should be educated about the disease, the influence it has on daily life, the impact and the handling of treatment, and taught coping mechanisms to help live with the disease.

Nowadays evidence-based patient education programs are provided for several allergic disease. These programs vary in different countries, mainly regarding the age and number of patients, content of the interventions, teaching techniques, frequency, and the duration of the sessions (Stalder et al. 2013). Concerning atopic dermatitis (AD), programs can be classified according to the "European guidelines for treatment of atopic eczema" in four groups: age-related multidisciplinary structured group training (eczema school), eczema workshops, nurse-led eczema workshop, and structured lay-led self-management education training programs (Wollenberg et al. 2018a, b). Due to the diverse settings, comparison between the different interventions can be challenging.

2 The Need of Patient Education for Atopic Dermatitis

Atopic dermatitis, one of the most common inflammatory skin diseases, is characterized by erythematous lesions and distinct pruritus. It is accompanied by an intense burden on the quality of life (QoL) due to the disease symptoms – not just for the patients but also for the caregivers of children with AD. Nighttime pruritus disrupts sleep which leads to a reduced performance in school. Indeed, 30% of children require medication to sleep during disease exacerbations (Paller et al. 2002). Furthermore, AD affects interpersonal relationships and self-esteem as well as daily life activity (Paller et al. 2002). The ailment can lead to sexual problems and difficulties finding jobs. The importance of this impaired QoL by influencing the somatic and psychological health is underlined by the fact that the SCORAD (Scoring atopic dermatitis), one of the most common used tools to rate AD severity, contains the subjective markers "itch" and "insomnia" alongside objective markers.

Interestingly, in comparison with other skin disease, e.g. psoriasis, AD patients report more severe limitations of QoL (Beikert et al. 2014).

In order to carry out sufficient disease therapy, a trustful patient–doctor relationship and strict adherence is necessary to manage the chronic relapsing character of the AD. For example, topical steroids are recommended as a first-line anti-inflammatory treatment and are necessary for an adequate disease control (Wollenberg et al. 2018b). Indeed, proactive usage of topical steroids reduces the frequency of AD exacerbations (Wollenberg and Ehmann 2012). However, an interview study of 2000 patients revealed that nearly the half are concerned about using topical steroids. This restraint leads to insufficient treatment (Zuberbier et al. 2006). In a French study as many as four out of five AD patients reported to be afraid of using steroids and one in three admitted nonadherence to the treatment (Aubert-Wastiaux et al. 2011). Interestingly, this incompliance was largely due to a lack of solid information about usage, effects, and adverse events of the cream. This inadequate therapy and the consequently insufficiently controlled disease can provide impetus to attempt complementary medicine. Around one in five children treated by homeopaths are AD patients. However, a systematic review of controlled trials of homeopathic therapies revealed no evidence for a beneficial effect of those treatments (Simonart et al. 2011). Furthermore, the complementary treatments were shown to involve higher costs (Roll et al. 2013), thereby, contributing it contributes to unsatisfactory control of the disease and a higher socioeconomic burden.

Concerning socioeconomic burden, a report published by Zuberbier et al. estimated the insufficient treatment of allergic disease costs 55–151 billion euros in indirect costs (Zuberbier et al. 2014). A recent cross-sectional European study revealed mean extra, out-of-pocket spending of €927 per patient per year (Arents et al. 2019). The highest monthly costs of €27.63 are due to emollients and moisturizers. These investigations emphasize the benefit of adequate therapy not just for the patient but also for the society.

The need of patient education is further underlined by the fact that most AD patients have sparse or false knowledge about their disease. In 2004, a French study of 103 adult patients who participated in a 2.5 h seminar about AD and its treatment revealed that 48% of adult AD patients previously believed that asthma could be worsened by successful AD treatment (Dagregorio and Guillet 2005).

Interestingly, concerning the psychological influence of AD, recent studies revealed a potential connection between AD and an increased risk of psychological diseases. A questionnaire health register study of around 9,500 patients revealed moderately to severely affected patients had elevated rates of intake of antidepressant and anxiolytic drugs (Thyssen et al. 2018). Moreover, children suffering from AD exhibit higher level of attention-deficit/hyperactivity disorder symptoms which may underline the psychological impact of the disease (Schmitt et al. 2018).

It becomes clear that improving QoL is one of the main aims when treating chronic disease. For this purpose it is important that the patients implement the therapy in their daily routine and, additionally, develop coping strategies to live with the ailment. However, due to the multifarious pathophysiology, explaining and understanding the disease can be challenging in routine clinical consultation, as

physicians feel exposed to permanent time and economic pressure. It can lead to the feeling of patients to be left alone with their disease. Therefore, patient education depicts a tool to fulfill the patients need for coping and treating the disease.

3 Patient Education for Adult AD Patients

The aim of patient education is to provide information about the complex pathophysiology of the disease, so that the patients gain a better understanding of their illness. This can build a basis for an improved acceptance of treatment, as such as daily moisturizing and the benefit of topical steroids when treating AD. Furthermore, education facilitates the awareness of disease trigger factors and provides an opportunity to correct misinformation. Patient education is therefore not just for improving the adherence for the treatment and the reduction of the disease severity but also the perception of the disease and the pruritus as the cardinal symptom of AD. Additionally, referring to the socioeconomic burden of the disease, patient education should reduce the need for consultations and other utilization of the medical system such as non-evidence-based diagnostics and treatment as well as a reduction of the disease-related costs incurred by the patients themselves.

The first reports of the beneficial effect of psychological intervention in AD patients are dated at the end of the 1940s and in the 1950s (Klein 1949; Shoemaker et al. 1955). However, the first randomized controlled trial was performed by Ehlers et al. in 1995. 124 adult patients were grouped into four groups. Each group received a different intervention: (1) dermatological educational program (DE), (2) autogenic training as a form of relaxation therapy (AT), (3) cognitive-behavioral treatment (BT), and (4) the combined DE and BT treatments (DEBT) (Ehlers et al. 1995). The behavioral treatment focused on self-control of scratching, stress management, and relaxation. The interventions were performed in groups of five to seven patients for 12 weeks (weekly 1.5–2 h). The 1-year follow-up showed the severity of skin lesions from patients of the AT, BT, and DEBT group were significantly lower compared to the standard medical treatment. Furthermore, the catastrophizing of itching and the feeling of helplessness were reduced in those intervention groups. However, no differences were seen for the severity of itching and scratching. In further studies it became apparent that group interventions are more successful than individual therapy (Gieler 1993; Stangier and Ehlers 1993).

Based on these positive experiences and data, Coenraads et al. evaluated their program of group education of five to six patients over 2 weeks in Groningen, Netherlands. The 31 patients who were part of the intervention group used their daily moisturizer more frequently, required less of information and scores lower in the "Marburger Neurodermitis Fragebogen," a questionnaire tool measuring disease coping, compared to a waiting control group (Coenraads et al. 2001).

In 2009, a study performed in the Netherlands analyzed the effect of a multidisciplinary itch-coping training (Evers et al. 2009). 61 patients of the age 16 years or above participated in four weekly group sessions and one session a month after this period. The training was conducted by a psychologist and a dermatology nurse

specialist. After 1 year, the intervention group exhibited significant differences in disease severity measured by the eczema area and severity index (EASI) score, itch, conscious of scratching, itch catastrophizing, itch self-efficacy, and the acceptance of the disease compared to a waiting control group. Additionally, intervention led to a reduced use of dermatological care.

However, most AD educational program studies in the last decade were focused on children, adolescents, and caregivers (see Sect. 4 below). Given the success of educating children and adolescents with AD in Germany, and the fact that there were deficits in the care of adult patients, a multidisciplinary expert group in Germany established the "Arbeitsgemeinschaft Neurodermitisschulung für Erwachsene (ARNE)". In a large nationwide, multicenter, randomized controlled trial the ARNE aimed to evaluate effects of structured patient education on the health care situation of adult outpatients with AD (Heratizadeh et al. 2017).

315 adult patients with moderate to severe AD were recruited at 15 sites across Germany; 168 became part of the intervention group and 147 formed the control population (Heratizadeh et al. 2017). The training program was developed and consented by a multidisciplinary group of professionals in dermatology, psychology, psychosomatics and psychotherapy, medical sociology, nutrition, and health services research. Small groups of five to eight patients were delivered standardized training according to a training manual over six two-hour sessions. Each meeting covered basic information about the disease, e.g. trigger factors, the itch-scratch cycle and the broad variety of evidence-based therapeutic options, psychological aspects, such as relaxation exercises and coping strategies, and nutritional aspects, such as allergy prevention, adverse food reactions, and diets. These aspects were carried out by professionals in the field of psychology and psychotherapy, respectively, dermatology and nutrition. Change in catastrophizing cognitions with respect to itching, measured by the Juckreiz-Kognitions-Fragebogen (JKF) (Leung and Guttman-Yassky 2014), social anxiety, detected by the Marburger Hautfragebogen (MHF) (Werfel 2009), the subjective burden (assessed by Skindex-29) (Wollenberg et al. 2016) and disease severity (SCORAD) (Schmitt et al. 2007) were determined as the primary endpoints. After 1 year, the catastrophizing cognitions with respect to itch were significantly lower in the patient education program group compared to the waiting control group. Interestingly, not just the SCORAD but also the objective SCORAD and the patient-oriented SCORAD (PO-SCORAD defined as one of the secondary endpoints) were lower in the education group compared to the control group even though in adulthood most AD patients show a long history of chronic AD.

This study was the first to evaluate patient education in adults in a multicenter, controlled randomized study concept. However, more studies are required to analyze and compare the variety of education programs and to better define and understand the corresponding effects.

In the digital era, video-based education provides an opportunity to reach many patients, further acting as an option for patients that cannot attend multiple intervention sessions over several weeks. A randomized controlled trial investigating video-based education was performed by Amstrong et al. (2011). The videos

contained information about AD and different treatments and had to be watched by the 40 patients at least once in 12 weeks. 40 other patients received the same information via a written pamphlet. After 12 weeks, the video-based education group had significant reductions in disease severity measured by the patient-oriented eczema measure (POEM).

In summary, there is increasing evidence for the beneficial effect of structured group training for adult patients with AD. However, further investigation is needed to elucidate which training concepts are most effective.

4 Patient Education for Children, Adolescents, and Caregivers in AD

For pediatric patients, particularly infants and young children, it is of great importance that the caregivers are educated about the disease of their children. However, it is also important to integrate the children in this educational process, due to the chronic nature of the disease and the importance of adherence. In an Australian study it was shown that a lack of adherence is a frequent cause for treatment failure (Fischer 1996). Being afraid to use topical corticosteroids and not understanding the chronic relapsing character of the disease are exemplary explanations for inadequate compliance.

In contrast to the relatively scarce evidence of patient education in adult AD patients, the intervention for children, adolescents, or their parents is evaluated decidedly better due to the fact that AD is more prevalent at a younger age.

In 2002, Chinn et al. published a parallel group study on a 30-min intervention carried out by a primary care nurse (Chinn et al. 2002). The study recruited 115 families of children aged below 4 and 120 children and adolescents aged 4–16 years for the patient education group. In the follow-up 4 and 12 weeks after the instruction, no significant improvement of the QoL was detected when compared to a control group. The authors hypothesized that the non-significance may have been rooted in the patient selection suggesting to recruit more patients, participants suffering from a more severe AD and to investigate different outcomes.

Following the two latter suggestions, a randomized controlled study delivered a 15-min individual education session by an AD educator to 50 patients with a mean SCORAD of 34 (Shaw et al. 2008). However, no significant effects on the SCORAD or the QoL were apparent compared to a control group. The authors argued that this may have been due to the high dropout rate of 30% and the fact that the control group participants were instructed by dermatologists and pediatricians during their routine consultation. Furthermore, they included several caregivers who were not mainly responsible for the child's skin care.

In 2006, Grillo et al. published a study assessing a two-hour workshop group intervention program delivered to children alongside their parents (Grillo et al. 2006). Information on the personnel leading the workshop was not given. When compared to a control group of 29 patients, the 32 children educated alongside their parents showed a significant decline of the SCORAD after 4 and 12 weeks. The

study population was formed largely by moderate to severely affected patients, as at baseline the mean SCORAD was 50 in the intervention group. Due to the fact that AD is a burden of care for the families, the authors expected to see a reduction of the Dermatitis Family Impact (DFI) score. However, no differences concerning the DFI were seen in this study (O'Connell 2004; Su et al. 1997). Furthermore, the intervention had no significant impact on the QoL. Regarding workshop educational programs, the United Kingdom is particularly well established in nurse-led care (Courtenay and Carey 2007). Therefore, Moore et al. performed a 90-min eczema workshop led by nurses of children aged 16 years or less (Moore et al. 2009). These patients showed a significant reduction in SCORAD at the 4-week follow-up when compared to those attending a dermatologist-led clinic, and adhered to disease management more successfully. Comparing the care of a nurse practitioner and dermatologist, Schuttelaar et al. randomized 160 patients aged 16 years or less to either a nurse care or the care by a dermatologist (Schuttelaar et al. 2010). No differences were observed concerning the improvement of the disease severity (SCORAD) or the QoL at 4, 8, and 12 months.

Focusing on the QoL and the impact on the family, Weber et al. analyzed the effect of support groups in a small study. The 90 minute meetings for the children took part fortnightly, were organized by a child psychiatrist together with a volunteer medical student, and included activities such as playing und simulations. The parent meetings were led by dermatologists. A 6 month follow up revealed a significant improvement of the QoL of the 16 patients between 2 and 16 years. However, as in the study of Grillo et al. (2006) no differences were seen concerning the FDI.

A German multicenter, randomized, controlled study, called German Atopic Dermatitis Intervention Study (GADIS), consisting of 823 participants, represents one of the milestones concerning the evidence of the beneficial effects of educational programs for children and adolescents (Staab et al. 2006). The study was conducted with the aim of developing standardized educational interventions. 274 young (3 months–7 years), 102 middle-aged (8–12 years), and 70 older (13–18 years) children with moderate to severe AD and their families were part of the educational program group after randomization. Compared to the studies previously mentioned, participants of this trial received six 2-h sessions in small groups over 6 weeks. The content was stipulated by a standardized training manual and provided by professionals in the field of pediatrics, dermatology, psychology, and nutrition who had to complete a specific training before starting the training program. The change in the disease severity after 12 months measured by the SCORAD was determined as the primary endpoint. In all three age-groups the SCORAD was significantly reduced compared to the control groups. Additionally, the parents' handling of their affected children and the children's coping behavior improved. The latter was seen by an effect on the itching-scratching cognition scales (Kupfer et al. 2010). The itch intensity correlated in negative manner with the QoL in middle-aged children and adolescents (Weisshaar et al. 2008).

In summary, these studies elucidated the benefits of empowering and educating patients through standardized group interventions. In 2007, 1 year after the GADIS trial was published, a refunding for this educational program was recommended by the head associations of German insurance companies. Interestingly, this situation is

quite unique, as is shown by a recent overview by Stalder et al. (2013). In contrast to health insurance companies covering the costs in Germany, funding is baed on donations in the United States, pharmaceutical firms in Japan and Italy and by regional health authorities in France (Heratizadeh 2014).

In 2016, Pustišek et al. published a randomized controlled trial analyzing an educational program of children (3 month to 7 years) and their caregivers in Croatia (Pustisek et al. 2016). In Dermatologists gave a two-hour lecture along with written material to groups of five to eight participants. Significant differences were apparent regarding the SCORAD, pruritus, sleep disturbance, and quality of family life between the intervention group ($n = 64$) and control group ($n = 64$).

Focusing on the characteristics of parents interested in educational programs, a questionnaire-based study elucidated that caregivers with low social support, high active problem-solving behavior and dissatisfaction with medical care are more interested participating in these interventions (Schut et al. 2012). Based on the GADIS data of the 3-month to 7-year-old children, Breuer et al. evaluated predictors of positive effects by an education program (Breuer et al. 2014). It was shown that psychological factors had greater impact on the outcome than somatic variables. Negative treatment experiences in the past and limited coping abilities concerning scratch control were identified as positive predictors for capitalizing from an educational program. It is worth noting that the, severity of AD at baseline and patient socioeconomic status had no influence on the long-term outcome. Strangier et al. analyzed the same topic finding a correlation between a low serum IgE level, a high frequency of coping-related cognition regarding itching, and an increased level of scratching at baseline as positive predictors for the long-term outcome (Stangier et al. 2004).

In a study performed in the Netherlands, von Os-Medendrop sought to determine the effect of e-health compared with face-to-face care as follow-up for children and adults with moderate AD (van Os-Medendorp et al. 2012). Disease severity measured by affected body surface, QoL, and intensity of the pruritus no differences were present between the study groups at the baseline, 3-month and 12-month time point. However, e-health saved 594€ per patients in indirect costs mainly due to a reduction in work absenteeism.

In 2014, a Cochrane review on the psychological and educational interventions for AD in children published a meta-analysis of ten randomized controlled trials (Ersser et al. 2014). The review concluded there is a significant influence on the disease severity and the QoL in nurse- and dermatologist-led interventions, but criticized the lack of rigorously designed trials and comparisons to stand-alone psychosocial self-help. In a position paper of "The Oriented Patient-Education Network in Dermatology," it was recommended that patient education "[. . .] should be offered to patients and parents with a history of therapeutic failures, with or without efficient and credible treatment, and to families who feel they have poor social support" and should be delivered by multidisciplinary teams (Barbarot et al. 2013).

In conclusion, patient educational programs for children and caregivers depict a central aspect of AD management, as they influence the disease severity, QoL, and treatment costs.

5 Patient Education for Other Allergic Diseases

Besides AD, there are patients with other chronic allergic diseases that benefit from training programs. The Global Initiative for Asthma (GINA) emphasizes the importance of structured asthma training for controlling and managing the disease (Horak et al. 2016). Training on inhaler usage, self-management regarding monitoring the peak flow, asthma action plans, and the reaction to an asthma exacerbation are particularly important. Notably, 70–80% of patients practice a wrong inhaling technique. It has been shown by Melani et al. that mishandling of inhalers is related with impaired disease control (Melani et al. 2011). Teaching inhaling skills can be provided effectively by pharmacists and nurses.

Concerning adherence, to disease management, around 50% of asthma patients are inconsistent in taking medication. Parallel to AD patients, asthma patients also tend to be concerned about medication side effects. Therefore, providing information about the treatment can influence the medication-taking behavior (Partridge et al. 2011). Furthermore, a shared decision concept improves patient adherence, as do home visits by an asthma nurse and inhaler reminder (Chan et al. 2015; Morton et al. 2017; Otsuki et al. 2009; Williams et al. 2010).

There are several controlled trials and meta-analyses revealing the positive influences of patient education. A Cochrane review of 38 studies with 7,843 children demonstrated there is a reduced risk of emergency department visits follwing an educational intervention (Boyd et al. 2009). No statistically significant difference was seen concerning QoL and symptoms, however, the authors justify this by a lack of data. In the P2AET trial, 338 children accompanied by their parents were included in either an instruction group, an education group, or a waiting group (Szczepanski et al. 2010). After 6 months the education group trained by a multiprofessional team had a reduced risk of emergency visits.

Due to this solid evidence, education programs have been integrated in the German national care guidelines for asthma underlining the importance of interventional methods.

Concerning patient education to prevent adverse events, the training of anaphylaxis patients represents an important aspect to avoid life-threatening systemic hypersensitivity reactions.

In 2013, the World Allergy Organization published an anaphylaxis guideline emphasizing the importance of educational programs for patients with a history of anaphylaxis, particularly how use of epinephrine auto-injectors can save a patient's life during an anaphylactic shock (Simons et al. 2013). Topal et al. revealed that around 39% of anaphylaxis patients do not carry their auto-injectors 1 year after prescription (Topal et al. 2013). Half of them justified this by a lack of need. Only 40% were able to use the injector correctly. Bock et al. investigated fatalities due to

anaphylactic reactions to foods eliciting that 90% of those patients either received no epinephrine or had a significant time delay before its administration (Bock et al. 2001). In a review by Kaster et al. the importance of educational programs was underlined referring to the lack of information available to anaphylaxis patients (Kastner et al. 2010). Notably, regular allergy visits correlated with the possession of an auto-injector and believing that it is necessary. Furthermore, Sicherer et al. conducted a study including 60 parents of children recently diagnosed with food allergy providing information materials in print and via the internet utilizing video formats (Sicherer et al. 2012). Interestingly, the correct number of auto-injector activation steps improved from 3.4 to 5.95 (of 6) after the intervention and remained at 5.47 after 1 year. Most solid evidence for educational programs in anaphylaxis was provided by the working group on anaphylaxis training and education (AGATE) in 2015 (Brockow et al. 2015). In this trial 95 caregivers of diagnosed children and 98 patients with previous anaphylactic reactions were randomized to either a control or intervention group. The latter received two 3-h training, sessions measuring the knowledge of anaphylaxis and emergency management competence in an anaphylaxis training situation conducted 3 months after the training seesions. Both primary endpoints were significantly improved compared to the control group.

In both our centers patient education is offered for all these diseases and has proved to become a very useful instrument to improve both patient knowledge and adherence to treatment schedules. Additionally, due to a better understanding of their disease, and better disease management tools, patients are able to improbe their QoL. Besides regular courses, small patient-tailored education sessions of a few minutes repeatedly offered to the patients can be a very useful additional tool of patient education. Such “microeducation” is easy to apply and, despite its minimal time needs, has a high impact on the patients (Bieber et al. 2016).

An important aspect of efficient patient education is also an interprofessional assortment among the faculty, as different professions offer not only a diverse knowledge but also variable approaches to the patient. Thus, the involvement of psychologists, nutrition specialists, nurses, and other allied health care providers is of great importance, for patient care, prevention, and finally behavior change (Madan et al. 2020).

In conclusion, patient education depicts an indispensable part of the management and treatment of allergic disease, not just for the improvement of the disease control and the patients’ quality of life but also with a beneficial socioeconomic effect.

References

Arents B, Fink-Wagner A, Seitz IA, Mensing U, Wettemann N et al (2019) Out-of-pocket costs for individuals with atopic eczema: a cross-sectional study in nine European countries. Acta Derm Venereol 99:263–267

Armstrong AW, Kim RH, Idriss NZ, Larsen LN, Lio PA (2011) Online video improves clinical outcomes in adults with atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol 64(3):502–507

Aubert-Wastiaux H, Moret L, Le Rhun A, Fontenoy AM, Nguyen JM, Leux C et al (2011) Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. Br J Dermatol 165(4):808–814

Barbarot S, Bernier C, Deleuran M, De Raeve L, Eichenfield L, El Hachem M et al (2013) Therapeutic patient education in children with atopic dermatitis: position paper on objectives and recommendations. Pediatr Dermatol 30(2):199–206

Beikert FC, Langenbruch AK, Radtke MA, Kornek T, Purwins S, Augustin M (2014) Willingness to pay and quality of life in patients with atopic dermatitis. Arch Dermatol Res 306(3):279–286

Bieber T, Akdis C, Lauener R, Traidl-Hoffmann C, Schmid-Grendelmeier P, Schappi G et al (2016) Global allergy forum and 3rd Davos declaration 2015: atopic dermatitis/eczema: challenges and opportunities toward precision medicine. Allergy 71(5):588–592

Bock SA, Munoz-Furlong A, Sampson HA (2001) Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 107(1):191–193

Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M (2009) Interventions for educating children who are at risk of asthma-related emergency department attendance. Cochrane Database Syst Rev 2009(2):Cd001290

Breuer K, Matterne U, Diepgen TL, Fartasch M, Gieler U, Kupfer J et al (2014) Predictors of benefit from an atopic dermatitis education programme. Pediatr Allergy Immunol 25(5):489–495

Brockow K, Schallmayer S, Beyer K, Biedermann T, Fischer J, Gebert N et al (2015) Effects of a structured educational intervention on knowledge and emergency management in patients at risk for anaphylaxis. Allergy 70(2):227–235

Chan AH, Stewart AW, Harrison J, Camargo CA Jr, Black PN, Mitchell EA (2015) The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. Lancet Respir Med 3(3):210–219

Chinn DJ, Poyner T, Sibley G (2002) Randomized controlled trial of a single dermatology nurse consultation in primary care on the quality of life of children with atopic eczema. Br J Dermatol 146(3):432–439

Coenraads PJ, Span L, Jaspers JP, Fidler V (2001) Intensive patient education and treatment program for young adults with atopic eczema. Hautarzt 52(5):428–433

Courtenay M, Carey N (2007) A review of the impact and effectiveness of nurse-led care in dermatology. J Clin Nurs 16(1):122–128

Dagregorio G, Guillet G (2005) Educational seminars for adults with atopic dermatitis: preliminary report about 103 patients. Allergy 60(4):540–541

Ehlers A, Stangier U, Gieler U (1995) Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. J Consult Clin Psychol 63(4):624–635

Engel GL (1977) The need for a new medical model: a challenge for biomedicine. Science 196 (4286):129–136

Ersser SJ, Cowdell F, Latter S, Gardiner E, Flohr C, Thompson AR et al (2014) Psychological and educational interventions for atopic eczema in children. Cochrane Database Syst Rev 2014(1): Cd004054

Evers AW, Duller P, de Jong EM, Otero ME, Verhaak CM, van der Valk PG et al (2009) Effectiveness of a multidisciplinary itch-coping training programme in adults with atopic dermatitis. Acta Derm Venereol 89(1):57–63

Fischer G (1996) Compliance problems in paediatric atopic eczema. Australas J Dermatol 37(Suppl 1):S10–S13

Gieler U (1993) Atopisches Ekzem – Psychische Bedingungen als Auslösefactor. Dermatologische Mantsschrift 79:2

Grillo M, Gassner L, Marshman G, Dunn S, Hudson P (2006) Pediatric atopic eczema: the impact of an educational intervention. Pediatr Dermatol 23(5):428–436

Heratizadeh A (2014) Therapeutic patient education. Curr Treat Options Allergy 1(4):358–364

Heratizadeh A, Werfel T, Wollenberg A, Abraham S, Plank-Habibi S, Schnopp C et al (2017) Effects of structured patient education in adults with atopic dermatitis: Multicenter randomized controlled trial. J Allergy Clin Immunol 140(3):845–53.e3

Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J et al (2016) Diagnosis and management of asthma – statement on the 2015 GINA guidelines. Wien Klin Wochenschr 128(15–16):541–554

Kastner M, Harada L, Waserman S (2010) Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. Allergy 65 (4):435–444

Klein HS (1949) Psychogenic factors in dermatitis and their treatment by group therapy. Br J Med Psychol 22:13

Kupfer J, Gieler U, Diepgen TL, Fartasch M, Lob-Corzilius T, Ring J et al (2010) Structured education program improves the coping with atopic dermatitis in children and their parents-a multicenter, randomized controlled trial. J Psychosom Res 68(4):353–358

Leung DY, Guttman-Yassky E (2014) Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. J Allergy Clin Immunol 134(4):769–779

Madan I, Parsons V, Ntani G, Coggon D, Wright A, English J et al (2020) A behaviour change package to prevent hand dermatitis in nurses working in the National Health Service: results of a cluster randomized controlled trial. Br J Dermatol 27

Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P et al (2011) Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 105 (6):930–938

Moore EJ, Williams A, Manias E, Varigos G, Donath S (2009) Eczema workshops reduce severity of childhood atopic eczema. Australas J Dermatol 50(2):100–106

Morton RW, Elphick HE, Rigby AS, Daw WJ, King DA, Smith LJ et al (2017) STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax 72(4):347–354

O'Connell EJ (2004) The burden of atopy and asthma in children. Allergy 59(Suppl 78):7–11

Otsuki M, Eakin MN, Rand CS, Butz AM, Hsu VD, Zuckerman IH et al (2009) Adherence feedback to improve asthma outcomes among inner-city children: a randomized trial. Pediatrics 124(6):1513–1521

Paller AS, McAlister RO, Doyle JJ, Jackson A (2002) Perceptions of physicians and pediatric patients about atopic dermatitis, its impact, and its treatment. Clin Pediatr 41(5):323–332

Partridge MR, Dal Negro RW, Olivieri D (2011) Understanding patients with asthma and COPD: insights from a European study. Prim Care Respir J 20(3):315–323. 17 p following 23

Pustisek N, Situm M, Vurnek Zivkovic M, Ljubojevic Hadzavdic S, Vurnek M, Niseteo T (2016) The significance of structured parental educational intervention on childhood atopic dermatitis: a randomized controlled trial. J Eur Acad Dermatol Venereol 30(5):806–812

Roll S, Reinhold T, Pach D, Brinkhaus B, Icke K, Staab D et al (2013) Comparative effectiveness of homoeopathic vs. conventional therapy in usual care of atopic eczema in children: long-term medical and economic outcomes. PLoS One 8(1):e54973

Schmitt J, Langan S, Williams HC (2007) What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol 120(6):1389–1398

Schmitt J, Buske-Kirschbaum A, Tesch F, Trikojat K, Stephan V, Abraham S et al (2018) Increased attention-deficit/hyperactivity symptoms in atopic dermatitis are associated with history of antihistamine use. Allergy 73(3):615–626

Schut C, Mahmutovic V, Gieler U, Kupfer J (2012) Patient education programs for childhood atopic dermatitis: who is interested? J Dtsch Dermatol Ges 10(9):657–661

Schuttelaar ML, Vermeulen KM, Drukker N, Coenraads PJ (2010) A randomized controlled trial in children with eczema: nurse practitioner vs. dermatologist. Br J Dermatol 162(1):162–170

Shaw M, Morrell DS, Goldsmith LA (2008) A study of targeted enhanced patient care for pediatric atopic dermatitis (STEP PAD). Pediatr Dermatol 25(1):19–24

Shoemaker RJ, Guy WB, McLaughlin JT (1955) The usefulness of group therapy in the treatment of atopic eczema. Pa Med J 58(6):603–609

Sicherer SH, Vargas PA, Groetch ME, Christie L, Carlisle SK, Noone S et al (2012) Development and validation of educational materials for food allergy. J Pediatr 160(4):651–656

Simonart T, Kabagabo C, De Maertelaer V (2011) Homoeopathic remedies in dermatology: a systematic review of controlled clinical trials. Br J Dermatol 165(4):897–905

Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF et al (2013) World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 162(3):193–204

Staab D, Diepgen TL, Fartasch M, Kupfer J, Lob-Corzilius T, Ring J et al (2006) Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. BMJ 332(7547):933–938

Stalder JF, Bernier C, Ball A, De Raeve L, Gieler U, Deleuran M et al (2013) Therapeutic patient education in atopic dermatitis: worldwide experiences. Pediatr Dermatol 30(3):329–334

Stangier U, Ehlers A (1993) Ein ambulantes psychologisches Gruppenprogramm bei Neurodermitis. Prax Klin Verhaltensmed Rehab 22(10):103

Stangier U, Ehlers A, Gieler U (2004) Predicting long-term outcome in group treatment of atopic dermatitis. Psychother Psychosom 73(5):293–301

Su JC, Kemp AS, Varigos GA, Nolan TM (1997) Atopic eczema: its impact on the family and financial cost. Arch Dis Child 76(2):159–162

Szczepanski R, Jaeschke R, Spindler T, Ihorst G, Forster J (2010) Preschoolers' and parents' asthma education trial (P2AET) – a randomized controlled study. Eur J Pediatr 169(9):1051–1060

Thyssen JP, Hamann CR, Linneberg A, Dantoft TM, Skov L, Gislason GH et al (2018) Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy 73(1):214–220

Topal E, Bakirtas A, Yilmaz O, Ertoy IH, Arga M, Demirsoy MS et al (2013) A real-life study on acquired skills from using an adrenaline autoinjector. Int Arch Allergy Immunol 160 (3):301–306

van Os-Medendorp H, Koffijberg H, Eland-de Kok PC, van der Zalm A, de Bruin-Weller MS, Pasmans SG et al (2012) E-health in caring for patients with atopic dermatitis: a randomized controlled cost-effectiveness study of internet-guided monitoring and online self-management training. Br J Dermatol 166(5):1060–1068

Wade DT, Halligan PW (2017) The biopsychosocial model of illness: a model whose time has come. Clin Rehabil 31(8):995–1004

Weisshaar E, Diepgen TL, Bruckner T, Fartasch M, Kupfer J, Lob-Corzilius T et al (2008) Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. Acta Derm Venereol 88(3):234–239

Werfel T (2009) The role of leukocytes, keratinocytes, and allergen-specific IgE in the development of atopic dermatitis. J Invest Dermatol 129(8):1878–1891

Williams LK, Peterson EL, Wells K, Campbell J, Wang M, Chowdhry VK et al (2010) A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. J Allergy Clin Immunol 126(2):225–231. 31.e1–4

Wollenberg A, Ehmann LM (2012) Long term treatment concepts and proactive therapy for atopic eczema. Ann Dermatol 24(3):253–260

Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B et al (2016) ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. J Eur Acad Dermatol Venereol 30(5):729–747

Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A et al (2018a) Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol 32(6):850–878

Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A et al (2018b) Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol 32(5):657–682

Zuberbier T, Orlow SJ, Paller AS, Taieb A, Allen R, Hernanz-Hermosa JM et al (2006) Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol 118(1):226–232

Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK (2014) Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy 69(10):1275–1279