

Guideline

Allergy prevention

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Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) in cooperation with the Society of German Allergologists (ÅDA), the German Society for Pediatric and Adolescent Medicine (DGKJ), the German Society of Dermatology (DDG) and the German Society of Pediatric Allergology (GPA)

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Summary

The further increase of allergies in industrialized countries demands evidence-based measures of primary prevention. The recommendations as published in the guideline of 2004 were updated and consented on the basis of a systematic literature search. Evidence from the period February 2003–May 2008 was searched in the electronic databases Cochrane and MEDLINE as well as in reference lists of recent reviews and by contacting experts. The retrieved citations were screened for relevance first by title and abstract and in a second step as full paper. Levels of evidence were assigned to each included study and the methodological quality of the studies was assessed as high or low. Finally the revised recommendations were formally consented (nominal group process) by representatives of relevant societies and organizations including a self-help group.

Of originally 4556 hits, 217 studies (4 Cochrane Reviews, 14 meta-analyses, 19 randomized controlled trials, 135 cohort and 45 case-control studies) were included and critically appraised. Grossly unchanged remained the recommendations on avoiding environmental tobacco smoke, breast-feeding over 4 months (alternatively hypoallergenic formulas for children at risk), avoiding a mold-promoting

indoor climate, vaccination according to current recommendations, and avoidance of furry pets (especially cats) in children at risk. The recommendation on reducing the house dust mite allergen exposure as a measure of primary prevention was omitted and the impact of a delayed introduction of supplementary food was reduced. New recommendations were adopted concerning fish consumption (during pregnancy / breast-feeding and as supplementary food in the first year), avoidance of overweight, and reducing the exposure to indoor and outdoor air pollutants. The revision of this guideline on a profound evidence basis led to (1) a confirmation of existing recommendations, (2) substantial revisions, and (3) new recommendations. Thereby it is possible to give evidence-based and up-to-date recommendations on primary prevention of allergies.

Keywords

allergy – evidence-based and consented guideline – primary prevention – update

Introduction

Allergic disorders such as allergic asthma, hay fever and atopic dermatitis have continued to increase in recent years in western industrialized nations [1]. The causes of this development and increase are still largely unclear. As causal therapy approaches are limited, prevention is of special significance in counteracting this rising trend [5]. With the support of the Federal Ministry of Health and Social Security the first S3 guideline on allergy prevention was published in 2004 within the framework of the Allergy Prevention Action Alliance (Aktionsbündnis Allergieprävention, abap) [8]. Using the methodology of evidence-based and consented guidelines this has now been revised. The revised guideline and the methodology which it is based on are presented here.

Results

Using the search strategy described above a total of 4556 hits were found in the Medline data bank for the time period from 2003 to 2008. In the first selection process based on title and abstract 4228 publications could be excluded and 328 references included in the second selection process. The second selection process was performed using the full paper. Additional papers were included that were named by the members of the consensus group. In the end 217 original publications were considered in the analysis. These included four Cochrane

reviews (CR), 14 meta-analyses (MA), 19 randomized controlled trials (RCT), 135 cohort studies (CS) and 45 case-control studies (CCS) (Figure 1). The entire evidence base classified according to subject and with statement of study number and study types, evidence levels and grades of recommendation is shown in Table 1 and 2.

The consented recommendations on primary prevention of asthma, hay fever and atopic dermatitis are valid for persons at risk and not at risk, if not explicitly differentiated or stated and are as follows:

On the subject of diet the consensus group unanimously supports the recommendation of the medical societies and organizations (www.fke-do.de, www.dge.de) (external links) on a balanced and nutritionally sufficient diet for infants, toddlers, pregnant women and nursing mothers.

Breastfeeding
Existing data largely support the recommendation of exclusive breastfeeding for

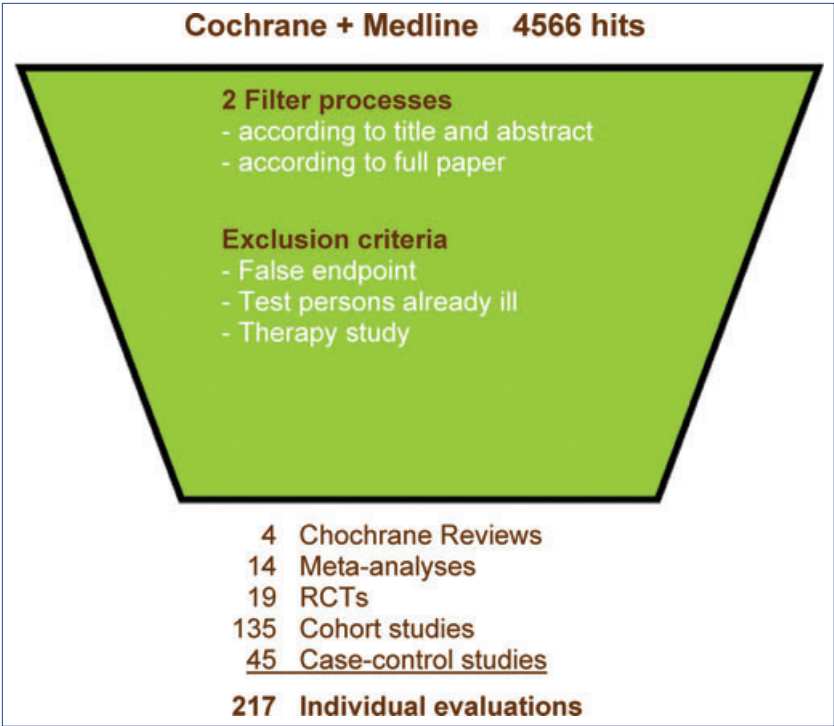


Figure 1: Graphic depiction of the results of the evidence search.

Table 1: Total depiction of evaluated studies with number and study types, derived evidence levels and consented grades of recommendation according to subject.

Subject	Study types and number	Evidence levels	Grades of recommendation
Breastfeeding	0 CR, 1 MA, 3 RCT, 13 CS, 1 CCS	3×1b, 1×2a, 13×2b, 1×3b,	A
Maternal diet during pregnancy and/or nursing	1 CR, 0 MA, 2 RCT, 13 CS, 1 CCS	1×1a, 2×1b, 13×2b, 1×3b	A and B
Infant formula for children at risk	2 CR, 0 MA, 3 RCT, 2 CS, 0 CCS	2×1a, 3×1b, 2×2b	A
Introduction of supplemental food and child's diet in the 1 st year of life	0 CR, 1 MA, 3 RCT, 12 CS, 3 CCS	1×1a, 3×1b, 12×2b, 3×3b	A and B
Diet after the 1 st year of life	0 CR, 0 MA, 0 RCT, 3 CS, 6 CCS	3×2b, 6×3b	A
Pets	0 CR, 2 MA, 0 RCT, 13 CS, 0 CCS	2×2a, 13×2b	B
House dust mites	0 CR, 0 MA, 2 RCT, 6 CS, 1 CCS	2×1b, 6×2b, 1×3b	B
Molds and humidity	0 CR, 1 MA, 0 RCT, 4 CS, 2 CCS	4×2b, 1×3a, 2×3b	B
Exposure to tobacco smoke	0 CR, 1 MA, 0 RCT, 7 CS, 2 CCS	1×2a, 7×2b, 2×3b	A
Interior pollutants	0 CR, 1 MA, 0 RCT, 4 CS, 7 CCS	4×2b, 1×3a, 7×3b	B
Vaccination	0 CR, 1 MA, 1 RCT, 9 CS, 3 CCS	1×1a, 1×1b, 9×2b, 3×3b	A
Body weight	0 CR, 3 MA, 0 RCT, 11 CS, 1 CCS	3×2a, 11×2b, 1×3b	A
Automobile emission	0 CR, 0 MA, 0 RCT, 4 CS, 2 CCS	4×2b, 2×3b	B
Effects of probiotics	1 CR, 1 MA, 5 RCT, 1 CS, 0 CCS	2×1a, 5×1b, 1×2b	-
Unspecific immunomodulation	0 CR, 1 MA, 0 RCT, 10 CS, 5 CCS	10×2b, 1×3a, 5×3b	-
Antibiotics	0 CR, 1 MA, 0 RCT, 3 CS, 1 CCS	1×2a, 3×2b, 1×3b	-
Total: 4 CR, 14 MA, 19 RCT, 115 CS, 35 CCS		7×1a, 19×1b, 8×2a, 115×2b, 2×3a, 35×3b	

Table 2: Evidence levels (Oxford Centre for Evidence-based Medicine, March 2009 www.cebm.net).

1a	Systematic review of RCTs
1b	Individual RCTs
1c	(All or none)
2a	Systematic review of cohort studies
2b	Individual cohort studies and RTCs of lower quality
2c	("Outcomes" research, ecological studies)
3a	Systematic review of case-control studies
3b	Individual case-control studies
4	(Case series and) poor quality case-control studies or cohort studies

four months for the prevention of atopic disorders. (A)

Diet of the mother during pregnancy and/or breastfeeding

A balanced and nutritionally sufficient diet during pregnancy and breastfeeding is recommended.

There is no evidence for recommending dietary restrictions (avoidance of potent food allergens) during pregnancy or breastfeeding. (A)

There are some indications that fish in the mother's diet during pregnancy or breastfeeding has a protective effect on the development of atopic disorders in the child. (B)

Infant formulas for children at risk

When breastfeeding is not or not adequately possible partially or extensively hydrolyzed infant formulas¹ are recommended for children at risk up to the end of the 4th month of life. (A) soy-based infant formulas are not recommended for the purpose of allergy prevention. (A)^{2, 3}

¹ Not all the infant formulas tested in the studies included are available in Germany.

² Further, the indication for soy-based infant starter formulas is viewed as very limited by scientific nutritional societies (Nutritional Commission of the German Society for Pediatric and Adolescent Medicine and Nutritional Commission of the Swiss Society for Pediatrics: Position Paper on the Use of Infant Formulas Based on Soy Protein. Monatsschr. Kinderheilkd. 2006; 154 (9): 913–916; ESPGHAN Committee on Nutrition (Agostoni C, Axelsson I, Goulet O,

Koletzko B, Michaelsen KF, Puntis J, Rieu D, Rigo J, Shamir R, Szajewska H, Turck). Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. J. Pediatr. Gastroenterol. Nutr. 2006; 42: 352–361).

³ To date there is no evidence for allergy preventive effects of milk from other animals such as goat's, sheep's or mare's milk.

Introduction of solid food and child's diet in the 1st year of life

There is no secure evidence of a preventive effect of prolonged introduction of solid food until after the completion of the 4th month of life. It is therefore not recommended. (A).

There is no evidence of a preventive effect of dietary restriction by avoidance of potent food allergens in the first year of life. It is therefore not recommended. (B) Indications exist that fish consumption by the child in the 1st year of life has a protective effect on the development of atopic disorders. (B)

The recommendation made at present in Germany not to introduce solid food before the completion of the 4th month of life is sensible from the viewpoint of nutritional science.

Diet after the 1st year of life

A general diet for allergy prevention cannot be recommended. (A)

Pets

There is no reason for people without an increased allergy risk to avoid pets on preventive grounds.

For children at risk:

The effects of pets on the development of allergy in children at risk cannot definitively be evaluated at the present time. Procuring a furry pet as a preventive measure is not recommended.

With regard to cats, studies that view cats as a risk factor predominate, so that cats should be avoided for children at risk.

Dogs are probably not associated with an increased allergy risk. (B)

House dust mites

As a measure of primary prevention⁴ the reduction of exposure to house dust mite allergens cannot be recommended. (B).

⁴ This does not apply to measures of secondary and tertiary prevention.

Molds and humidity

An interior environment that favors the growth of molds (high humidity, inadequate ventilation) should be avoided for the sake of allergy prevention. (B)

Exposure to tobacco smoke

Active and passive exposure to tobacco smoke increases the allergy risk (especially the risk of asthma) and should be avoided. This is especially true during pregnancy. (A)

Interior pollutants

There are indications that interior pollutants increase the risk of atopic disorders and especially asthma (volatile organic compounds, e. g. formaldehyde, as can be released by new furniture, painting and renovation work, among others). It is recommended to minimize exposure to interior pollutants. (B)

Vaccinations

There is no proof that vaccinations increase the allergy risk, but indications that vaccinations can decrease the allergy risk.

It is recommended that all children, even children at risk, be vaccinated according to the STIKO (Standing vaccination commission) recommendations. (A)

Body weight

There is evidence that an increased Body Mass Index (BMI) is associated positively especially with asthma.

The avoidance of overweight, especially in children, is recommended also on the grounds of allergy prevention. (A)

Automobile emissions

The exposure to nitrogen oxides and fine particles (PM_{2.5}) particularly by living on a busy street is associated with an increased risk especially for asthma.

It is recommended to minimize exposure to automobile emissions. (B)

On the following subjects positions were taken (evidence level in brackets), but no recommendations passed.

Effects of probiotics

The data on the effects of probiotics on the development of allergy are contradictory. Only one Scandinavian study indicates that the administration of probiotics has preventive effects and this only with regard to atopic dermatitis. Therefore no recommendation can be made. (1a–b)

Nonspecific immunomodulation

There are indications that an early nonspecific immunostimulation can protect from the development of atopic disorders. Growing up on a farm, visiting a day-care center in the first two years of life and a larger number of older siblings are, among others, considered unspecific immunostimulation. Worm infections, especially hookworm infections, have a negative association with asthma. (2b–3b)

Antibiotics

There is no proof of a causal relationship between the administration of antibiotics and the development of asthma, allergic rhinitis and atopic dermatitis. (2a–3b)

Discussion

In the course of revision of the S3 guideline "Allergy Prevention" existing recommendations were further supported, previous recommendations revised and new recommendations passed.

The recommendations on breastfeeding, on pets, on the subject molds and humidity and on tobacco smoke exposure were further supported by recent studies. Revised or newly adopted recommendations are discussed in the following.

Revisions were made with regard to the mother's diet and the diet of the child, as many studies show a preventive effect of fish consumption and the respective recommendations were newly adopted.

Revisions were also made with respect to infant formulas. It must be taken into consideration that hydrolyzed infant formulas tested in the studies are in part

no longer available in Germany. For soy-based infant formulas not only is evidence of a preventive effect lacking, there are also concerns of health hazards.

It is not recommended to delay the introduction of solid food beyond the completion of the 4th month of life. In fact, current German cohort studies no longer demonstrate an effect of prolonged introduction of solid food.

As far as measures to reduce house dust mite allergens were studied as a single measure for primary prevention, no effect could be shown. Thus this recommendation was removed, which does not affect these measures for secondary and tertiary prevention, for which evidence of effectiveness exists.

Current research into the subject of interior pollutants suggests that volatile organic compounds increase the risk especially of development of asthma.

A further development occurred with regard to outdoor pollution (automobile emissions). Particularly the risk of development of asthma is increased e. g. by living on a busy street.

The recommendation to vaccinate all children according to the STIKO recommendations was retained and strengthened by the fact that indications exist that immunization might even reduce the risk of allergy.

While in 2004 several indications existed that an increased Body Mass Index was associated positively with asthma, recent studies provide proof. Reduction of overweight is thus recommended on the grounds of primary prevention.

The recommendation formerly passed on dietary restrictions for the mother during pregnancy and/or breastfeeding and for the child in the first year of life was not retained in this form but included in the chapter on supplementary food. The statements on specific immunotherapy were no longer included due to the limitation here to measures of primary prevention.

The evidence base for the revision of the guideline can be considered comprehensive with 217 included and evaluated single studies. A prevention guideline has methodological peculiarities that make it different especially with regard to therapy guidelines. First, multiple targets such as asthma, allergic rhinitis and atopic dermatitis are examined. Second, multiple influencing factors are observed. A limitation to a particular type of

study (e. g. RCT) is not possible, as many of the prevention measures to be evaluated cannot be studied in a randomized design (e. g. breastfeeding, smoking). Therefore cohort and case-control studies must also be considered and preventive recommendations must be derived indirectly from the described associations.

Guidelines of the highest level (S3) must, among others, fulfill the following five demands:

1. *Logic.* „Clinical Practice Guidelines“ should in the form of a logical analysis provide a decision-making and action process to solve a specific problem (clinical algorithm) [9]. Even if this point is targeted more at therapy guidelines, the prevention recommendations were transferred into an algorithm differentiated for children at risk and children not at risk (Figure 2).
2. *Consensus.* Formal consensus procedures should avoid a lack of transparency and distortion of the adopted recommendations due to group dynamic processes but also status or personality variables of the participants as well as their political or economic interests. The participation of all potential users of the guideline is important for its implementation (acceptance and use in practice) [4]. A formal consensus (nominal group process) took place with members of the consensus group with participation of representatives of patient groups with external moderation. The advantages of a nominal group process versus e. g. the Delphi method are more group dynamics, greater group interaction, more feeling of belonging and more possibilities for clarification. Disadvantages are less anonymity of the contributions, a possibly longer duration and the possibility of being able to give a response only once.
3. *“Evidence-based medicine”, that is the problem of the methodological viewpoint versus clinical relevance (Spitzer).* The adopted recommendations were formulated using the criteria of evidence-based medicine by way of a systematic literature search and critical methodological evaluation.
4. *The decision-making process analyzes the expected benefit in relation to the resulting costs. It is a quantitative comparison of available alternatives [3].* It can be anticipated that the

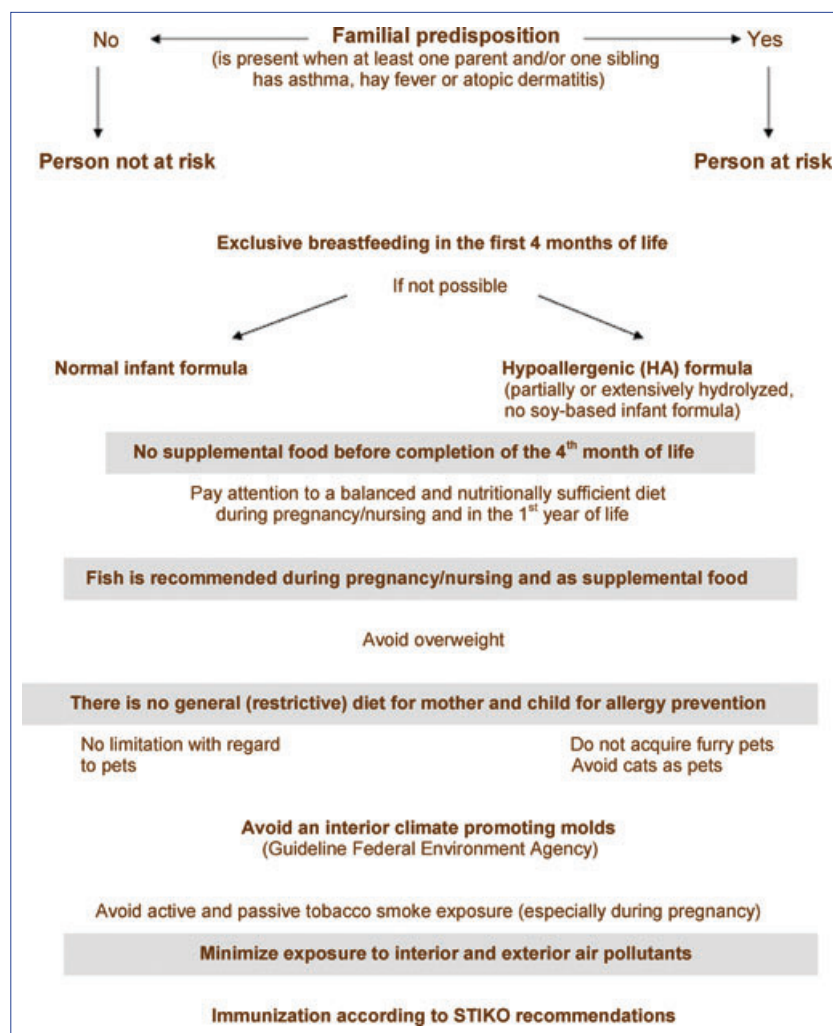


Figure 2: Algorithm for primary prevention of asthma, hay fever and atopic dermatitis in persons at risk and not at risk.

expected benefit of the recommended measures are always higher than the resulting costs even in an economic view. In some cases, for example in avoiding smoking, following the prevention recommendation leads to a double win situation (saved costs of smoking + saved costs of treatment). Feeding a hypoallergenic infant formula leads to a onetime cost of 400 Euro in a half year. By comparison treatment of a patient with asthma costs on average over 650 Euro per year in Germany. Indirect and intangible costs or benefit are not yet considered here.

5. "Outcome" analysis denotes the evaluation of the total result that can be achieved by a diagnostic and therapeutic complex. This includes the objective state of health as determined by the physician (e. g. mortality, complication rates) and the self-evaluation of quality of life by

the patient. In order to determine which targets are truly capable of demonstrating the effectiveness of a process in clinical routine, qualitative empirical processes are needed (analysis of clinical relevance from the viewpoint of the physician and patient [6]). The outcome analysis of this prevention guideline deals with other concepts than those described above. Outcomes represent among others the approaches and knowledge about existence and content of the guideline, which can be ascertained by a member survey of the medical societies. A part of the outcome analysis is the in the meantime completed survey of the state of knowledge about allergies in the general population. After implementation corresponding changes in the state of knowledge will be measurable. The clinically relevant target is the expected decrease in disease burden (incidence).

Dissemination and implementation

The guideline will be published in the national journals of the participating societies and organizations and in the internet. Further, pamphlets as short information will be produced for the lay and professional public.

Procedure in creating consensus

Methods

The methods used in the revision of the guideline follow national and international standards for the development of evidence-based and consented guidelines [2] [4] [7].

Goal and target group

The primary targets of the guideline are the important atopic disorders: atopic dermatitis, allergic rhinoconjunctivitis and allergic asthma.

The guideline is concerned exclusively with measures of primary prevention according to the modified definition for the field of allergy in abap: *Primary prevention* encompasses the elimination or reduction of (partial) causes of significance to the development of disease including changing causative or predisposing environmental and occupational factors as well as increasing the tolerance of individuals. Primary prevention is particularly effective in groups at risk (genetic predisposition) but is aimed in an unrestricted form at the total population and includes allergy-specific promotion of health.

The target groups of *secondary prevention* are persons with early signs of disease (e. g. bronchial or nasal hyperreactivity with known sensitization) and sensitized persons still without symptoms. The goals of secondary prevention are the avoidance of manifest disease as well as a change of symptoms. Its measures include the avoidance of clinically relevant allergens and toxic irritant substances, counseling and in cases of persons with early signs of disease perhaps pharmacoprophylaxis and specific immunotherapy (hyposensitization).

While in the algorithm of the first issue of this guideline measures pertaining to children at risk were termed secondary prevention, now following the definition above only the term primary prevention is used and measures are differentiated with respect to persons with or without genetic predisposition. Studies on

persons already ill, even those with the goal of preventing a second disease, were thus no longer considered.

The *target population* are persons, especially children, with and without genetic predisposition for atopic disorders. Children with genetic predisposition (children at risk) are defined as having at least one parent or sibling with one of the atopic disorders mentioned.

Users of the guideline are all medical and non-medical organizations and person groups concerned with prevention, especially allergy prevention.

Members of the guideline development group are: C. Muche-Borowski, M. Kopp (DGKJ), I. Reese (Working Group Diet in Allergology), H. Sitter (Association of the Scientific Medical Societies in Germany, AWMF), T. Werfel (DGAKI) and T. Schäfer (coordinator, DDG)

„Evidence“ search

The electronic literature search was done in the data banks MEDLINE and CHOCHRANE for the time period February 2003 to May 2008.

For the search strategy three categories of key terms were defined: the group of diseases (asthma, allergy, allergic, atopic, hay fever, dermatitis, eczema, rhinitis, the measures (prevention risk factor, epidemiology) and the block of study types (randomized controlled trials, clinical trials, controlled study, case-control study, cohort study, systematic review, meta-analysis). The connection within the groups was made with “or” and between the groups with “and”.

Included were studies on humans published in German or English. Studies that did not have allergic disorders as target as well as therapy or drug studies were excluded.

Further, the reference lists of recent reviews were scanned for relevant literature and all members of the consensus were requested to provide relevant citations. In a first screening step title and abstract of all found citations were viewed. Studies that did not have one of the defined atopic disorders as target as well as therapy of drug studies were excluded. The remaining papers were obtained as full papers in a second screening step analyzed in a similar fashion for suitability of content.

„Evidence“ evaluation

In addition to the assignment of a formal evidence level (1a to 4), the studies were read in a methodologically critical manner according to pre-defined criteria (among others case number, temporal relationship between exposure and disease, considering other factors of influence) and corresponding extraction tables were filled out. The methodologically critical evaluation lead to a dichotomous estimation of the distortion potential of each individual study as either high (-) or low (+).

The entire evidence base was processed in the form of tables according to subject with study number, study types, evidence levels and grades of recommendation. For each subject evidence tables were prepared showing the number of studies found and evaluated according to study type, main result (protective, no effect, risk factor) and methodological quality (+ high, - low) (not shown here).

Guideline draft

On the basis of the studies found and evaluated a proposal for the revised prevention recommendation was drafted and circulated in the guideline and consensus group. Proposals for supplements and revisions were discussed and included when necessary.

Consensus

All persons involved in the development and consensus of the first version of the guideline were invited into the consensus group. In addition, representatives of other medical societies were named on the basis of suggestion.

The recommendations were passed by the consensus group constituted in this manner. As formal consensus procedure the nominal group process was employed, which requires a meeting of all participants. The procedure is strictly structured and can be divided into the following steps:

- 1 Presentation of the statements to be consented
- 2 Each participant prepares comments and wishes for discussion to each given statement.
- 3 The moderator asks each participant in order for comments and similar comments are summarized on a flipchart.
- 4 There is a vote on each noted point as to who wishes to discuss this point.

- 5 According to these votes the order of the subjects is determined.

- 6 The individual members in a mutual round make a statement one after another to each point of discussion.

- 7 After several rounds the participants finally agree to a specific wording by voting or ranking.

Steps 1–6 are repeated for each statement up for discussion.

The consensus meeting was held in January 2009 in Hannover and was moderated by Private Lecturer Dr. Sitter (University of Marburg and AWMF).

In the consented recommendations there is talk of proofs or indications. This terminology conforms to the methods formulated by IQWiG (Institute for Quality and Efficiency in Health Care). In “General Methods 3.0” it is stated:

For a “*proof*” it is usually demanded that a meta-analysis of studies with low insecurity of results with regard to endpoints demonstrates an appropriate statistically significant effect. If a meta-analysis cannot be conducted, at least two independent studies with low insecurity of results with regard to endpoints and appropriate statistically significant effect should exist, whose result is not called into question by further comparable studies with secure results with regard to endpoints (consistency of results). The two studies performed independently do not have to have the exactly identical design. Which deviations in design between two studies are still acceptable, depends on the question. A meta-analysis of studies with high insecurity of results with regard to endpoints of single study results can usually only provide an “indication” despite statistically significant effects. When as an exception a proof of benefit is to be derived from only one study, special demands must be made on such a study and its results.

The individual recommendations were passed by the consensus group with grades of recommendation (A, B, C) that appear in brackets after each recommendation. The grades of recommendation can be assigned on the basis of evidence level in a formalized form (see Table 3). In the course of the consensus process it is possible that in well-founded cases divergent grades of recommendation could be assigned. Subjects for which no prevention recommendation could be made were only assigned evidence levels.

Table 3: Grades of recommendation based on evidence levels.

Grade of recommendation	Evidence level	AHCPR (Agency for Health Care Policy and Research)
A	I	Conclusive literature of good quality with at least 1 RCT
B	II	Well-performed non-randomized clinical study
C	III	Reports/opinions of expert groups, consensus conferences, clinical experience of recognized authorities

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** In agreement with the recommendations (not able to attend the consensus meeting): Andreas Kleinheinz (Working Group Dermatological Prevention, ADP), Claudia Rudack (German Society of Oto-Rhino-Laryngology, Head and Neck Surgery, DGHNOKHC), Sylvia Schnitzer (Professional Association of ENT Physicians)

Support

The revision of the guideline was supported by the German Society for Allergology and Clinical Immunology (DGAKI) and the German Society for Pediatric and Adolescent Medicine (DGKJ).

Conflict of interest

Prof. Kopp is supported in his studies by the Infectopharm GmbH, Heppenheim, Germany. All other authors state, that there is no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

Validity

This guideline is valid until 2014 and will by then be revised by the corresponding authors.

Completed: April 2004

Last revision: March 2009

Next revision planned: 2014

Level: 3 + IDA

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