

Guideline

Diagnostic approach for suspected pseudoallergic reaction to food ingredients

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Summary

Chronic urticaria, recurrent angioedema and non-allergic asthma have all been associated with pseudoallergic reactions to food ingredients. For atopic dermatitis and diseases of the gastrointestinal tract, this association is controversial. Pseudoallergic reactions can be elicited by additives as well as by natural food ingredients. An altered histamine metabolism may be associated with pseudoallergy.

Acute urticaria or a short episode of angioedema is not an indication for exhaustive evaluation. If basic diagnostic screening is negative in chronic urticaria, a low-pseudoallergen diet can be considered. Skin and serological tests are not objective diagnostic parameters for pseudoallergic reactions. The severity of symptoms should be documented while the patient is on a low-pseudoallergen diet.

Oral provocation with additives leads to reproducible symptoms only in a few cases. Therefore, if a low-pseudoallergen diet brings improvement, the patient is then exposed to a pseudoallergen-rich "super meal". After a positive reaction to the "super meal" the challenge with additives takes place in the form of collective group exposition. When the patient has asthma or a history of anaphylactoid reactions, testing with individual substances in carefully increasing dosages is required.

The suspicion of adverse reactions against histamine can be confirmed by a challenge with histamine dihydrochloride. In the case of respiratory symptoms, provocation by inhalation should be considered. Objectifying symptoms especially in gastrointestinal diseases is mandatory and should include double-blind placebo-controlled food challenge, if possible.

Introduction

Pseudoallergic reactions are defined as clinical reactions whose symptoms resemble allergic reactions without identifiable immunologic sensitization. In addition to non-steroidal antiphlogistic drugs, muscle relaxants and x-ray contrast media, food ingredients can act as pseudoallergens that can cause difficulties in sensitive individuals [4]. Pseudoallergic reactions to food ingredients have been described in the following diseases: chronic urticaria, recurrent angioedema and non-allergic bronchial asthma (intrinsic asthma). There are also indications that pseudoallergens can worsen the symptoms of individual patients with atopic dermatitis. It is controversial if these observations always reflect a pseudoallergic pathomechanism (Werfel et al., 2002; Worm et al., 2000a) [20, 24, 28]. As a consequence no general recommendations for the diagnostic approach to this disorder can yet be made, as there is still a great need for research. In addition, case reports and studies with a small number of patients have been published on other diseases, among others of the gastrointestinal tract (e. g. Crohn disease) with regard to pseudoallergic reactions (Pearson et al., 1993; Raithel et al., 2005; Worm et al., 2000b).

Chronic urticaria, recurrent angioedema and non-allergic asthma have been associated with pseudoallergic reactions to food ingredients. For atopic dermatitis and diseases of the gastrointestinal tract, this association is controversial.

The following position paper focuses primarily on the approach when pseudoallergic reactions to food ingredients are suspected in chronic urticaria. In this disease pseudoallergy is often suspected as a trigger factor. As no results from large controlled studies in the sense of evidence-based medicine exist, non-standardized and often time-consuming diagnostic procedures are performed on an individual basis. The present guideline proposes a simplified approach that has become established in several institutions. Primarily practical reasons employing this scheme, as controlled clinical studies supporting the approach are not available.

Statements on the frequency of relevant pseudoallergic reactions to food ingredients are rare. Even for chronic urticaria, which is most commonly associated with these reactions, the prevalence varies considerably from under 1 % to over 50 % (Czech et al., 1995; Henz et al., 1996; Metcalfe et al., 1996; Simon and Stevenson, 1993; Wedi and Kapp, 1998; Zuberbier et al., 1995). Provocation with additives that have long been viewed as major causes leads to pseudoallergic reactions only in a minority of patients whose symptoms improve during an elimination diet (Ehlers et al., 1996; Metcalfe et al., 1996; Simon and Stevenson, 1993). Even a pseudoallergen-rich challenge diet (see below), that includes natural foods in addition to additives as triggers, elicits symptoms only in a proportion of responders to diet. This observation suggests healing may be initiated by a diet that avoids known triggers for a limited period of time. The justification for a low-pseudoallergen diet is supported by observations in patients with chronic urticaria; especially patients with increased gastroduodenal permeability profit from the diet. The permeability of the gastric mucosa normalizes in patients who profit from the diet over 3–4 weeks (Bühner et al., 2004).

Pseudoallergic reactions are elicited by additives but also by natural food ingredients. The list of pseudoallergens used diagnostically in clinical practice is to an extent based on case reports of documented hypersensitivity reactions (Simon and Stevenson, 1993). Since the spectrum of additives has changed considerably in recent years, clinically relevant food components may be missing in common diagnostic protocols or irrelevant additives

may still be tested. Because of these uncertainties, the evaluation of the clinical relevance of pseudoallergens requires a uniform and regularly updated approach for investigating reactions to food ingredients. In the following guideline of the Task Force on Food Allergy of DGAKI (German Society of Allergology and Clinical Immunology, Deutsche Gesellschaft für Allergologie und klinische Immunologie) and the above mentioned institutions, the diagnostic guidelines for suspected pseudoallergy are updated, and will be regularly re-evaluated with respect to the spectrum of pseudoallergens

Role of *in vitro* and *in vivo* tests

In contrast to IgE-mediated reactions to food, where *in vitro* tests and skin tests have an established role in diagnostics before oral provocation tests are performed (Kleine-Tebbe et al., 2001; Niggemann et al., 2005), no reliable laboratory or skin tests are available for pseudoallergic reactions at this time.

The proportion of patients with altered histamine metabolism appears elevated in the diseases described above (Kanny et al., 1993 and 1996; Lessof et al., 1990; Götz, 1996). These observations might explain why a diet poor in biogenic amines helps some patients.

Skin tests (rub tests, prick tests, perhaps intracutaneous tests) can indicate an IgE-mediated reaction. Such reactions are extremely rare, e. g. to parabens (Nagel et al., 1977) or sulfites (Ring et al., 1987; Simon, 1993 and 1986). With a history of threatening symptoms (i. e. severe airway obstruction, severe angioedema, anaphylactic reactions) skin tests should be considered for the sake of safety. They usually are negative in the case of pseudoallergic reactions and are thus not of aid in diagnostics in a strict sense, so that identification of possible triggers always demands an elimination diet and oral challenge.

There are no reliable skin or laboratory tests as objective diagnostic parameters.

In principle, targeted testing of one or few ingredients when specific suspicion of an intolerance e. g. tartrazine intolerance in association with an already known intolerance to acetylsalicylic acid (idiosyncrasy) (Simon and Stevenson, 1993) or targeted provocation following a positive skin test must be differentiated from an untargeted search in the face of chronic complaints (usually chronic

urticaria or chronic recurrent angioedema) which is covered first in the following text.

Elimination diets for chronic urticaria and recurrent angioedema

Acute urticaria (i. e. signs and symptoms < 6 weeks) or a short episode of angioedema does not constitute an indication for extensive diagnostic efforts. With chronic urticaria or angioedema recurring in a time period longer than 6 weeks, other causes or trigger factors should be excluded by the diagnostic approach summarized in the DDG Guideline Urticaria (Zuberbier et al., 2003) or in the European EAACI/GA²LEN/EDF guidelines (Zuberbier et al., 2006a and b). Physical urticaria including urticaria factitia, immediate-type allergies and infectious triggers should be excluded.

Acute urticaria or a short episode of angioedema does not constitute an indication for an expensive and time-consuming diagnostic approach. If the basic diagnostic evaluation of chronic urticaria is negative, a low-pseudoallergen diet can be considered. If no infectious cause is identified, a low-pseudoallergen diet (Table 1) four at least four weeks is recommended. If no improvement of symptoms occurs, perhaps a stricter oligoallergenic basic diet (compare Table 3) over further 5 to 7 days, as recommended for IgE-mediated reactions, should be followed (Niggemann et al., 2006). Further, in individual cases symptom-oriented special tests at specialized centers (including hypoallergenic liquid diet [Pearson et al., 1993]) might be necessary.

The Task Force Food Allergy of the DGAKI concurs in the evaluation of low-pseudoallergen diet as a diagnostic tool with the position paper of the Working Group "Diet in Allergology" of the German Society of Nutrition (DGE AG "Diätetik in der Allergologie", 2004).

Here it is stated that "an elimination diet consisting of unprocessed self-prepared food is a cost-effective diagnostic tool to rule out natural pseudoallergens and food additives as cause or trigger factors in chronic urticaria...For the duration of four weeks no nutritional deficiencies must be feared as the low-pseudoallergen diet contains all macro- and micro-nutrients in sufficient amounts, as long as the missing fruits are compensated by a significantly higher consumption of vegetables".

In severe cases a potato-rice diet can be followed for a limited time period of several days. In chronic urticaria possible success with diet usually can only be expected after a longer period of time, i. e. one to three weeks. A short-term potato-rice diet does not harm an otherwise healthy person, but a week-long diet lowers compliance significantly.

With outpatient diets, the danger of dietary errors is large. Ideally, but not always possible in day-to-day practice, detailed counseling by a nutritional expert should be performed. In any case, the foods eaten should be noted by the patient daily in a food diary. As far as possible, suppression of symptoms with drugs should be avoided during the diet. In order to increase the patient's compliance, one can consider antihistamines for the first 10–14 days, when no improvement due to the diet can be expected. After this the drugs should be discontinued in order to evaluate the response to the diet. During the diet the severity of chronic urticaria should be assessed with an urticaria score (see Table 2) daily (usually by the patient) and documented in a diary. The urticaria score takes into account an objective (number of wheals) and a subjective (evaluation of pruritus) parameter. Angioedema is similarly evaluated (score from 0–3). The low-pseudoallergen diet (as shown in Table 1) leads to an improvement of symptoms with regard to pruritus and extent of wheals in many patients with urticaria (Zuberbier et al. 1995 and 2002). If no improvement of clinical symptoms occurs under this regimen and perhaps an oligoallergenic diet over 5 to 7 days (see Table 3), triggering of symptoms by food is improbable and provocation tests are not sensible.

Oral provocation without indication of specific causes

If there is a significant improvement or complete remission of symptoms (total score 0) during the low-pseudoallergen diet, inpatient admission for the sake of safety for oral challenge testing should occur. There should be no angioedema at the time point of provocation. Drugs that could influence the provocation such as antihistamines and corticosteroids should be discontinued sufficiently long before testing (i. e. 1 week for antihistamines, 3 weeks for systemic steroids).

Table 1: Example of a low-pseudoallergen diet (modified according to Zuberbier, 1995).

Prohibited in general: All foods containing aromas, preservatives, dyes and antioxidants. This is suspected for all industrially processed foods.		
	Allowed	Prohibited
Basic food stuffs	Bread and rolls without preservatives, semolina, millet, potatoes, rice, durum wheat noodles (without egg), rice waffles (only containing rice and salt!)	All other foods (e. g. noodle products, egg noodles, cakes, French fries)
Fats	Butter, vegetable oils	All other fats (margarine, mayonnaise etc.)
Milk products	Fresh milk, fresh cream (without carrageen), curd, natural yogurt, cream cheese (unseasoned), small amount of young gouda	All other milk products
Animal foods	Fresh meat, fresh ground meat (unseasoned), cold meat (self-made)	All processed animal food stuffs, eggs, fish, crustaceans
Vegetables	All vegetables except the prohibited; allowed are e. g. salad (well-washed), carrots, zucchini, Brussels sprouts, white cabbage, Chinese cabbage, broccoli, asparagus	Artichokes, peas, mushrooms, rhubarb, spinach, tomatoes and tomato products, olives, peppers
Fruits	None	All fruits and fruit products (including dried fruits such as raisins)
Spices	Salt, sugar, chives, onions	All other spices, garlic, herbs
Sweets	None	All sweets including chewing gum and artificial sweetener
Beverages	Milk, mineral water, coffee, black tea (non-aromatic)	All other beverages including herbal teas and alcoholic beverages
Bread fillings	Honey and the products previously mentioned	All bread fillings not mentioned

Table 2: Urticaria score.

Severity of wheals
0 : No wheals
1 : Few wheals (less than 10)
2 : Moderate severity (10 and more standing alone)
3 : Many wheals (multiple densely aggregated or confluent)
Pruritus
0 : No pruritus
1 : Little pruritus
2 : Moderate pruritus
3 : Severe pruritus

Table 3: Example of an oligoallergenic basis diet (The individual components must be determined on an individual basis and can be combined freely).

Grain: rice
Meat: lamb, turkey
Vegetable: cauliflower, broccoli, cucumber
Oil: refined vegetable oil, non-dairy margarine
Beverages: mineral water, black tea
Spices: salt, sugar

Table 4: Exposition protocol for provocation without indication of specific triggers for example in urticaria.

1st Day of provocation Pseudoallergen-rich provocation diet, day 1 (see Table 5)*	For collective exposition the following (additive) ingredients are tested in the listed amounts in gelatin capsules: <ul style="list-style-type: none"> • Color mix (E100 Curcumin, E120 Carmines, E132 Indigo carmine, E141 Copper complexes of chlorophylls and chlorophyllins, E172 Iron oxides and hydroxides, E102 Tartrazine, E104 Quinoline yellow, E110 Sunset yellow, E122 Azorubine, E123 Amaranth, E124 Cochineal red, E127 Erythrosine, E129 Allura red, E131 Patent blue, E133 Brilliant blue FCF, E142 Greens S, E151 Brilliant black) 5 mg each • Sorbic acid 1000 mg • Sodium benzoate, p-hydroxybenzoic acid 1000 mg each • Potassium disulfide 300 mg • Sodium nitrate 100 mg • Sodium salicylate 1000 mg • Antioxidants (butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, tocopherol, caffeic acid) 50 mg each • Artificial sweeteners (200 mg aspartame, 100 mg acesulfame K, 40 mg Na salt of saccharin, 400 mg cyclamate)
2nd Day of provocation Pseudoallergen-rich provocation diet, day 2 (see Table 5)	
3rd Day of provocation Collective exposition with the following ingredients (in capsules)	
4th Day of provocation Identical number of placebo capsules (or in reverse order)	
* Illustrated is the temporal course in the optimal case. In case of a positive reaction after an exposition step a further exposition can only be performed after reduction of the urticaria score < 3 and absence of angioedema. Adaptation of the provocation protocol is necessary in case of proven or known food pseudoallergies, In case of known bronchial asthma or anaphylactoid reactions slowly incremental dosage necessary.	

As oral provocation testing with food additives, especially coloring agents, benzoates, sulfites and antioxidants only rarely result in reproducible positive reactions, routine successive provocation with the individual substances is no longer recommended.

Oral provocation with additives only leads to reproducible symptoms in individual

cases in chronic urticaria. Therefore, after a positive course of a low-pseudoallergen diet first exposition to a "super meal" is performed, as long as there is no targeted suspicion of a specific intolerance.

In order to exclude a role for all possible food ingredients reported as trigger factors of chronic urticaria in the literature (Czech et al., 1996; Metcalfe et al. 1996;

Simon and Stevenson, 1993; Wedi et al., 1996; Zuberbier et al., 2002) provocation should first be performed in form of a pseudoallergen-rich challenge diet under observation with the availability of emergency medical care. If no reaction occurs after one day a second day of a pseudoallergen-rich challenge diet is recommended due to the possibility of a dose-dependent effect (Table 4). Table 5 is an example of such a "super meal" which is high on additives as well as biogenic amines and natural aromas. This provocation diet can be employed as a "search test". Of course, individual foods can be replaced by other additive-rich foods. This is particularly necessary when an IgE-mediated allergy towards a food is already known. The pseudoallergen-rich provocation test is **not** free of allergens!

The patient should give informed consent after being informed about the nature of the testing and the likelihood of gaining information. Correct planning and execution of the testing is the physician's responsibility.

Beware: Oral challenge tests with pseudoallergens can cause systemic reactions and require close observation over a time period of 16 to 24 hours.

If the nutritional history shows that the diet of the patient contains no or only certain additives, an individual provocation adapted to the particular patient is desirable. This should then be limited to the natural foods as triggers and only suspected additives should be tested in a targeted fashion. When clinical reactions fail to occur, extension of the challenge with the pseudoallergen-rich provocation diet for further 2 days is recommended. After positive reactions, characterized by objective symptoms such as urticaria and angioedema, symptomatic therapy should be followed by a renewed diet phase until improvement is observed. To rule out additives as trigger of the observed reactions, a subsequent collective group exposition with additives listed in Table 4 is suggested. This list must continually be updated as to new, but also as to no longer or not relevant triggers. When collective exposition leads to a positive reaction, step-by-step exposition of individual components follows. In case of severe past reactions (e. g. urticaria with extensive angioedema) a titrated provocation of individual components instead of collective exposition is recommended (see below).

Table 5: Example of a pseudoallergen-rich provocation diet (Bunselmeyer et al., 2005) (If known sensitization to one of the listed foods exists, it is waived).

<p>Day 1</p> <p>Breakfast: Coffee or tea, artificial sweetener tablets (with cyclamate and saccharin), condensed milk or coffee cream, diet yogurt with fruit with cereal mix (corn flakes, almonds, hazelnuts, walnuts, cashew nuts, peanuts, sunflower seeds, sesame, linseed, pumpkin seeds, raisins, plums (with sorbic acid) sulfurized fruits (apricots, peas, peaches, apple rings), orange juice</p> <p>Snacks during the day: 6 strawberry-flavored sugar foam candies (with aroma and coloring), 2 “ice” candies (with aroma), 2 caramel candies (with aroma) 1 peanut butter cereal bar, 2 chewing gums (with artificial sweetener and antioxidant), 30 g paprika-flavored potato chips, 1 chocolate bar, 1 sports beverage (with color and perhaps preservative), 1 Cola light, 1 apple, 1 banana</p> <p>Lunch: Spicy pizza: yeast dough, tomato sauce. Oregano, pepper, salt, garlic, paprika, spinach, tuna fish in oil, salmon, shrimps (with preservatives and artificial color), olives (colored black), Emmental cheese, parsley, 0.5 l beer (adults), 0.33 l Cola light (children)</p> <p>In-between meal: Coffee or tea, artificial sweetener tablets (cyclamate and saccharin), condensed milk or coffee cream, 3 sugar foam waffles (with artificial color and aroma)</p> <p>Supper: Tea, artificial sweetener, 2 slices whole grain bread (with sesame), 2 slices cheese, 2 portions low-fat margarine (with preservatives), 2 portions diet marmalade, 1 tuna fish salad (with thickening agent and aroma)</p>
<p>Day 2</p> <p>Breakfast: Coffee or tea, artificial sweetener tablets, condensed milk or coffee cream, 2 multigrain rolls, low-fat margarine, 1 portion peanut butter, Maasdam cheese</p> <p>Snacks during the day: 1 Kinder® Chocolate snack bar, 2 spearmint chewing gums (with artificial sweetener and antioxidant), 10 chewy fruit candies (with aroma and artificial color), “Studentenfutter” (mixture of nuts and raisins), 1 coconut bar, Cola light, multivitamin juice, kiwi fruit, orange</p> <p>Lunch: Waldorf salad (with mayonnaise, celery, pineapple and walnuts), sulfurized potatoes, jello red/green (with artificial color), vanilla dessert sauce and colored sugar sprinklings (with artificial color), 250 ml red wine (adults), 200 ml apple juice (children)</p> <p>In-between meal: Coffee or tea</p> <p>Supper: Salads of the season, leaf salad, tomatoes, field salad, carrots, cucumber, peppers, “Thousand Islands” dressing, herring salad (with potassium sorbate, sodium benzoate and stabilizers), sunflower seed bread, cheese slices, cooked ham, low-fat margarine (with preservative), tea</p>

When in addition to or independent of urticaria or angioedema other signs or symptoms occur (respiratory, anaphylactoid symptoms) further provocation tests should be performed with defined pseudoallergens in incremental dosages with the availability of emergency care.

When adverse reactions against histamine are suspected, challenge with histamine dihydrochloride (0.75 mg/kg body weight and 1.5 mg/kg body weight) (Fiedler et al., 2005) – after exclusion of medical contraindications and with availability of emergency care – can be considered. Glutamate (4 g) can also be employed in an isolated manner when indicated.

If a positive reaction occurs only to the pseudoallergen-rich provocation test, a slow build-up of the diet is performed, where every three days a formerly prohibited food is added, until ideally an individual “therapeutic diet” can be recommended. The detailed diagnostic approach is outlined in a flow diagram (Figure 1).

The proposed pseudoallergen-rich challenge diet is designed to reflect the day-to-day situation of the patient better than the provocation with individual substances. Nevertheless, only rarely are clinically reactions (urticaria) observed in patients whose chronic urticaria had previously improved under a low-pseudoallergen diet. By means of the uniform approach further focusing on previously unsuspected pseudoallergens, e. g. fragrances (Zuberbier et al., 2002), is possible.

Oral provocation with individual components

For reactions to collective group exposition, for severe clinical reactions or for the relatively rare clinical suspicion of a defined pseudoallergen as trigger of clinical symptoms (e. g. sulfites in causing respiratory tract obstruction) a double-blind oral provocation with individual substances is suggested. For severe clinical reactions, in departure from the above mentioned dosages (Table 4), a titrated exposition to defined substances is recommended (for examples see Table 6). Due to the possibility of delayed onset of symptoms, in most cases only one substance group should be provoked per day. *With known bronchial asthma or anaphylactoid reactions, slow increase in l dosage is an absolute necessity.*

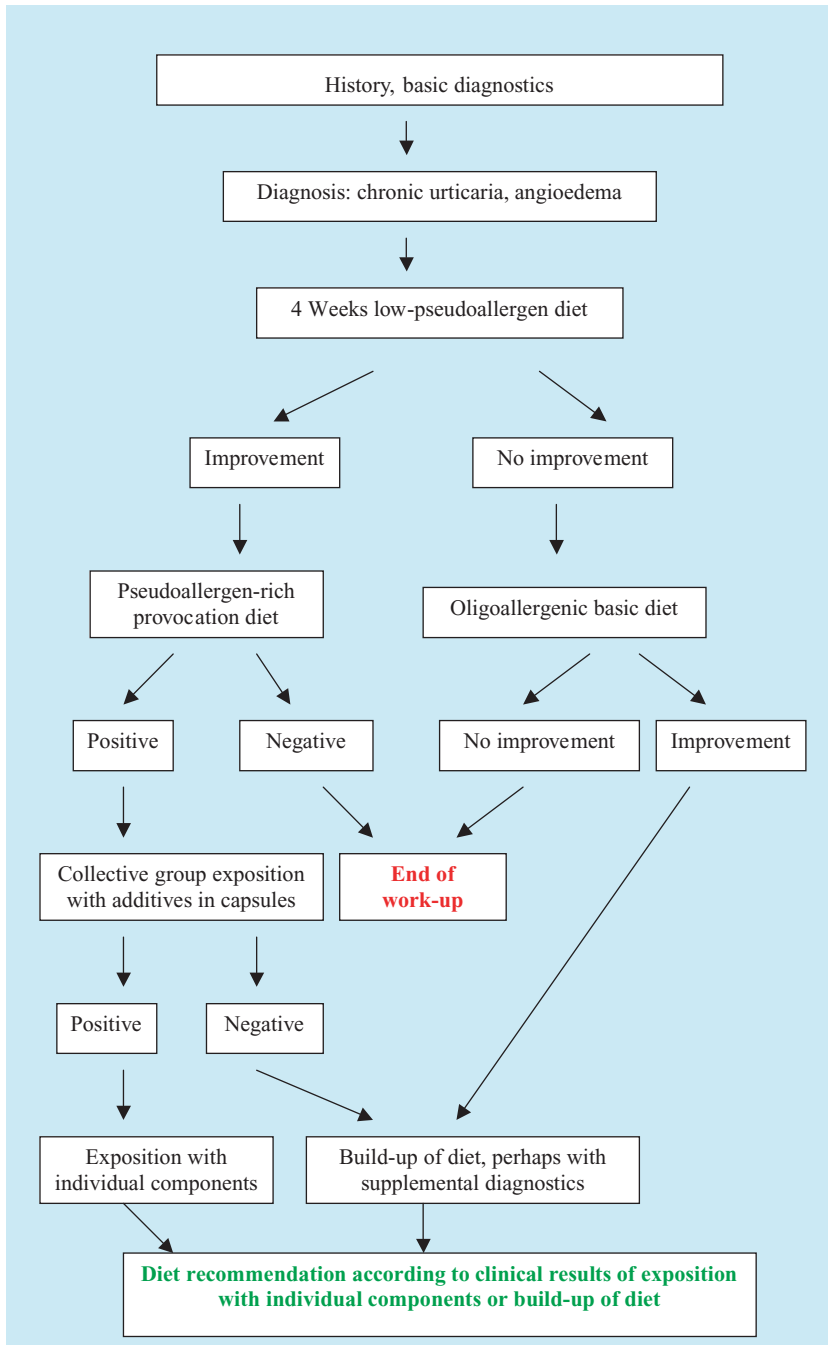


Figure 1: Diagnostic approach for non-specific suspicion of pseudoallergic food ingredients. Cave: Oral provocation with pseudoallergens are not without risk and its responsibility lies with the performing physician.

Table 6: Titration of individual substances (examples).

Substance name	Suggested dosage
Aspartame	50, 250 mg
Glutamate	0.5, 2, 5 g
Sodium benzoate	50, 250, 500 mg
Sodium nitrite	2, 10, 20 mg
Sodium salicylate	100, 250, 500, 1000 mg
Disulfite	10, 50, 100, 300, 500 mg
Tartrazine	10, 50 mg

Fundamental issues in oral provocation

For double-blind oral provocation the same rules as recently published for IgE-mediated reactions apply (Niggemann et al., 2006). The ratio verum: placebo should ideally be 1:1. For reasons of practicability and based on the low frequency of objective reactions in patients who are not overly fearful, a ratio of 4:1 can be justified.

Clinical evaluation should be done by the physician, at least for an entire provocation block. In the evaluation of reactions subjective and objective symptoms should be differentiated on a standardized documentation sheet. The evaluating physician must before each following step state in writing if the previous clinical reaction is to be judged positive or negative. De-blinding occurs only after completion of the planned challenge protocol. A positive placebo reaction draws possible positive verum challenges into question (Bahna, 1994). In such cases the previous tests must be repeated and more placebo challenges be planned. In patients with exercise-dependent pseudoallergic reactions, oral provocation should be followed by adequate exercise (e. g. treadmill) after 45 to 60 minutes.

Approach for extracutaneous symptoms

Pseudoallergic reactions that do not present as urticaria and/or angioedema are – with the exception of intolerance of analgesic drugs – not as well studied and possibly rarer, too. Reactions can occur in the upper respiratory tract (rhinitis, laryngeal edema), the lower airways (asthma), as well as lead to gastrointestinal symptoms and circulatory disorders including shock.

The approach with regard to drug-free intervals is identical to that for urticaria. In asthma with sulfite intolerance, direct SO₂ contact with the mucous membranes is apparently of importance and administration in capsule form can lead to false-negative results. Provocation with a soda beverage whose acid pH promotes SO₂ release (0.1 mg/ml) is better. Inhalation tests are also possible (Metcalf et al., 1996). Both should only be performed if emergency medical care is available, as threatening reactions are possible. For respiratory reactions regular peak flow measurements (supplemented by pulmonary function tests) are sensible.

When dealing with gastrointestinal complaints which are often not objective, double-blind conditions – as far as possible – are of special significance. For circulatory reactions control is by regular or continual blood pressure and pulse monitoring in a supine position. For challenges in signs and symptoms of the respiratory tract inhalation provocation should be considered.

Conclusions

Only very limited data exists for the diagnostic approach when pseudoallergic reactions to food ingredients are suspected, so that recommendations can be formulated only in the form of a S1 guideline. This implies that the recommended approach is not standardized and in part a time-consuming diagnostic approach that has to be performed on an individual basis. The present guideline is oriented on a simplified approach established on several institutions, with primarily practical reasons speaking for it. Controlled clinical studies are desirable to support these recommendations.

Procedure in creating consensus

Guideline commission "Diagnostic approach for suspected pseudoallergic reaction to food ingredients"; Chairperson: Prof. Dr. Thomas Werfel. The guideline was developed in three sessions of the commission.

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