

## REVIEW ARTICLE

**When is an oral food challenge positive?**

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**Abstract**

Oral food challenges still remain the gold standard in the diagnosis of food related symptoms and are performed to obtain a clear 'yes or no' response. However, this is often difficult to achieve, and so proposals may be appropriate for criteria on when to stop oral food challenges. In daily practice it makes sense to challenge until clear objective symptoms occur without harming the patient. Clinical symptoms should be objective and/or: (a) severe or (b) reproducible or (c) persisting. A sensitive parameter for a beginning clinical reaction is a general change of mood. The sooner symptoms appear, the more likely they are to represent a 'true' positive reaction and the more organ systems are involved the easier it is to assess an oral food challenge as positive. In the case of subjective symptoms, the number of placebo doses should be increased. In unclear situations, the observation time until the next dose should be prolonged or the same dose repeated. Transient objective clinical symptoms usually end up in a positive challenge result. There are a number of causes for false positive and false negative challenge results, which should be considered. The aim of all oral challenge testing should be to hold the balance between two conflicting aspects: on the one hand the need to achieve clear and justified results from oral food challenges in order to avoid unnecessary diets, and on the other hand to protect patients from any harm caused by high doses of a potentially dangerous food.

Food related clinical symptoms are much more often suspected than proven (1, 2). Since there is no laboratory parameter, which can ensure the clinical relevance of a given food in most cases, oral food challenges remain the gold standard in the diagnosis of food related symptoms (3, 14). Oral food challenges are performed to obtain a 'yes or no' answer as to a certain food has to be eliminated from the diet of an individual patient or not. Since unnecessary diets may harm patients, only thorough and well-justified results from oral food challenges should be used.

However, in many cases the responsible physician is tempted to assess an oral food challenge as 'questionable positive' or 'questionable negative'. This may derive from the following dilemma: If one continues oral food challenges very far, the patient may be in danger because of severe or even life-threatening clinical symptoms. On the other hand, if one stops an oral food challenge very early, unnecessary dietary restrictions may result. Furthermore, the patient may develop more severe unpredictable symptoms if a higher dose of the corresponding food is eaten afterwards. Therefore, proposals for criteria when to stop oral food challenges and declare a challenge as positive or negative may be meaningful.

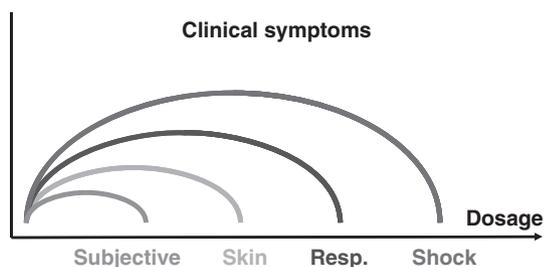
**When should an oral food challenge be stopped?**

An oral food challenge should be stopped if a clear 'yes or no' answer is obtained for an outcome. However, there is a wide range of criteria, which can be used to reach this aim (Fig. 1).

Firstly, one could stop at 'subjective symptoms' in order not to bring harm to the patient if higher doses may lead to severe or potentially life-threatening symptoms. Subjective symptoms are symptoms not observed by the responsible physician and may include e.g. nausea, tongue burning, heart palpitations or itch. However, they may reflect psychological factors but may not justify a long-term elimination diet.

Secondly, a food challenge could be stopped at 'mild or intermittent objective symptoms', e.g. occurrence of flush, local urticaria, or a slight worsening of an underlying eczema. These are objective signs, but the potential severity of the reactions may be under-assessed.

Thirdly, an oral food challenge could be performed until 'moderate to severe objective clinical reactions' occur, such as respiratory symptoms of upper or lower airway dyspnoea.



**Figure 1** Hypothetical situations how far to proceed with the oral food challenge.

Fourthly, a challenge could be continued until the 'individual maximum clinical reaction' is reached, which may also include the risk of full-blown anaphylaxis. This procedure would allow assessing the maximal risk of the patient but would certainly comprise unjustified risk behaviour.

#### Conclusion

In daily practice it makes sense to challenge until clear objective symptoms occur without doing harm to the patient by continuing to the maximum response.

#### What can be used as criteria for objective symptoms?

- Simply 'visible, observable clinical reactions'? But what about vomiting once or an intermittent flush, which can be seen by the observing physician, but still may be due to subjective, psychological factors.
- Only 'measurable, quantifiable symptoms'? But what about the subjective Part C of the SCORAD-Score (pruritus and sleeplessness) (5–7), which can be quantified, but certainly includes subjective, nonreliable aspects. Furthermore, objective symptoms may also be influenced by psychological factors.
- Only 'reproducible or persistent symptoms'? Not all symptoms are reproducible anyway and single reactions even of one organ may be clear (e.g. short-term stridor).

#### Conclusion

Clinical symptoms should be objective and/or: (a) severe or (b) reproducible or (c) persisting.

#### General change of demeanour

It may seem surprising that a very important criterion for the onset of a positive reaction is an unspecific general change of mood of children, who stop playing, become more quiet and inactive, move to the mother's fold, etc. A child, who runs along the corridor, is not likely to be assessed as positive – even with one or two hives. In nonverbal children, clues to the onset of a reaction may be subtle such as ear picking, tongue rubbing, putting a hand in the mouth, or neck scratching (8).

#### Conclusion

A sensitive parameter for a beginning clinical reaction is a general change of demeanour.

#### Factor 'time'

The time interval between administering the food and observing a clinical reaction is an ambivalent factor. If the time interval between ingestion of a challenge portion and the clinical reaction during an oral food challenge is short, it may be easy to assess an oral food challenge as positive. The longer the reaction takes, the more difficult it is to allocate the observed symptoms to the food challenge. Clinical symptoms more than 48 h after the challenge should usually not be attributed to the suspected food.

#### Conclusion

The sooner symptoms appear or are observed, the more likely a 'true' positive reaction is.

#### What are objective symptoms of the different organ systems?

##### Gastro-intestinal tract

What about vomiting? Vomiting is a clear and visible sign, but of course it may be of psychological origin, e.g. if the patient has an aversion to the administered food or remembers clinical reactions in the past. This may be the case even if the oral food challenge is performed in a double-blind, placebo-controlled fashion (DBPCFC). For these reasons, vomiting once should usually not lead to stopping an oral food challenge; for this, vomiting should be severe and/or repetitive. Repeated vomiting, especially if severe, is more likely to be a positive response to a given food.

A more predictive clinical symptom is a crampy-like abdominal pain, which may be a warning sign of beginning anaphylaxis. This should be taken seriously and is different to the unspecific and subjective symptoms of nausea and diarrhoea, which may derive from aversion or excitement.

##### Respiratory tract

Usually, respiratory symptoms from the upper or lower airways usually are objective and clear positive reactions – not only if dyspnoea is observed. Symptoms from the respiratory tract should always be taken seriously – even if only the nose is affected. For instance reddening of the eyes, tears, and a watery rhinitis may be clear objective symptoms, especially if occurring in combination. Stridor deriving from upper airway obstruction or wheezing as a sign of peripheral airway obstruction are always clear and objective symptoms.

##### Skin symptoms

Another ambiguous situation is the occurrence of urticaria. While one or two wheals around the mouth may simply

reflect contact urticaria, and the food may be tolerated if orally administered, generalized urticaria or wheals away from the location of contact on the skin may be a clear and objective positive reaction (in the absence of chronic urticaria or factitious urticaria).

On the other hand, many authors do not look for clinical reactions after more than 2 h (a generally accepted threshold for a late phase reaction), which would not allow the diagnosis of an eczematous exacerbation as a food-related symptom. Since eczematous exacerbation is especially difficult to quantify, a severity scoring system should be used such as the SCORAD index (5–7). It seems realistic to require a difference of at least 15 points for a positive eczematous reaction.

### Cardiovascular symptoms

Pulse oximetry should be established to monitor a child if potentially dangerous foods are administered or a more severe reaction is suspected. If cardiovascular symptoms are observed, which cannot be attributed to vegetative symptoms, especially in the presence of a lowered blood pressure plus tachycardia, it seems easy to immediately assess an oral food challenge as positive.

### Number of involved organs

There is less room for doubt if two or more organ systems are involved, e.g. skin plus the gastro-intestinal tract or skin plus respiratory symptoms.

### Conclusion

The more organ systems are involved the easier it is to assess an oral food challenge as positive.

### Subjective symptoms

The following causes may lead to subjective symptoms:

- Aversion (e.g. the food is disliked by patient);
- Nocebo-effect (anticipation of side-effects or negative symptoms);
- Excitement (e.g. special features in the situation of provocation).

A practical consequence of suspected subjective symptoms is to increase the number of placebo doses, e.g. to a ratio of at least two placebos to one food.

Although subjective symptoms may be reproducible, they do not represent a true causal relationship. Certainly, highly subjective symptoms such as palpitations, tongue burning or abdominal discomfort are not sufficient to assess an oral food challenge as positive. The situation is more difficult if itching is reported without visible symptoms. Although this may represent the beginning of an allergic reaction, a clearer, more objective reaction should be induced, e.g. by administering a higher dose. In our example, one should continue challenging until swelling in the mouth or pharynx is observed.

If a decision is not possible on the basis of a mild or unclear clinical reaction, but one is afraid of harming the patient if the next higher dose is administered, there are two possibilities (Fig. 2): waiting for another 15 min, or repeating the same dose. The latter increases the cumulative dose but may 'avoid the next highest single dose'.

### Conclusion

In the event of suspected subjective symptoms the number of placebo doses should be increased. In unclear situations during an oral provocation, the observation time until the next dose should be prolonged or the same dose is repeated.

### How to handle intermittent, transient objective clinical symptoms?

From time to time, during the titrated procedure, transient objective symptoms such as wheals are observed, which disappear despite administering the next higher dose. Sometimes even the maximum planned dose can afterwards be reached. However, in our experience, transient, but objective symptoms, usually lead to assessing an oral food challenge as positive. This is also true if symptoms are only around the mouth, which may simply reflect contact urticaria to the corresponding food, which is tolerated when eaten. This is a realistic point of view, since patients will not accept a food when regularly symptoms occur. Finally, in doubt, a potentially dangerous food should be eliminated for some time. A consequence from such a situation should be that the time period until re-provocation should be shortened from 12/18 months to 6 months (in the case of cow's milk or hen's egg).

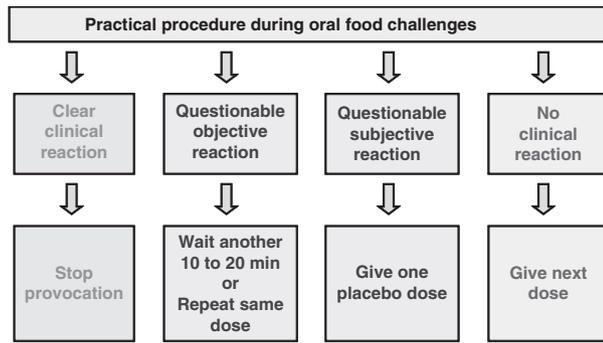
### Conclusion

Transient objective clinical symptoms usually lead to a positive challenge result.

### False negative and false positive oral food challenges

1. Possible reasons for 'false negative' assessments:

- Inadvertent drug use during or before oral challenges by physicians (e.g. not withdrawing a potentially interfering drug in good time before the challenge) or by parents (e.g. a mother is unaware of interfering effects and administers an antihistamine without the knowledge of the physician). Therefore, taking a thorough history before starting an oral food challenge is mandatory.
- A short-term specific oral tolerance (SOTI) may be induced as increasing amounts of the offended food are administered during a titrated oral food challenge, leading to clinical tolerance (9). This is the reason why a cumulative dosage of the corresponding food is administered on another day.
- The observation period is too short and possible late phase reactions are not considered when planning an oral food challenge. The length of observation should be chosen



**Figure 2** Proposal for the differential procedure in different situations during the oral food challenge.

according to the type of expected clinical symptoms. Clinical symptoms beyond 48 h do not seem to be an important factor; in cases of doubt, another day may be added for an extended observation period.

- Only repeated doses over several days lead to clinical symptoms. This may be relevant in rare cases of children with atopic eczema and no concomitant early type clinical symptoms. If suspected, the provocation procedure should be adapted accordingly, e.g. by administering a cumulative dose the next day.

#### 2. Possible reasons for 'false positive' assessments:

- It may be practically difficult to maintain an appropriate strict diet throughout the oral challenge procedure, e.g. if the staff in a hospital kitchen fail to appreciate the requirements, or simply make a mistake.
- There are often many other children on the ward and visitors, and they may inadvertently give the child food, which leads to a positive clinical reaction. This may then be attributed to one of other foods in question or to the placebo phase, resulting in a false assessment of the oral challenge as positive.
- Subjective symptoms mentioned by the patient were misleading. It should be aimed at achieving objective symptoms.
- The elimination diet implemented before the oral food challenge in children with atopic eczema and suspected food related symptoms may actually be responsible for immediate type clinical symptoms, which had not been reported by the parents before (10). Therefore, the elimination phase should be kept as short as possible.

#### 3. Possible reasons for 'both false negative and false positive' assessments:

- Augmentation factors are among the most plausible explanations for the inadequate reproducibility of an oral food challenge. The best-known augmentation factor is physical exercise (11, 12), other augmentation factors include drugs (13, 14), alcohol, a warm bath or sauna, hormonal factors (e.g. menstruation), respiratory or gastro-intestinal infections, systemic mastocytosis as an underlying disease, or psychogenic factors (e.g. stress). These factors may have been present in the daily life situation and may impair reproduc-

**Table 1** Procedure after "de-blinding" of double-blind, Placebo-controlled food challenges (adapted from (15))

ALLERGEN	PLACEBO	Procedere
+	–	Elimination diet
+	+	Repeat challenge
–	–	No diet
–	+	Nodiet

ibility under clinic conditions. Conversely, augmentation factors may lead to positive reactions during challenge testing which may not have been present in the past.

#### Possible consequences of the decision to stop an oral food challenge

- The time-point when an oral food challenge is terminated may influence the kind of symptoms reported. It may be that immediate type symptoms are seen more often during oral food challenges because authors do not go on to administer sufficiently large amounts of food to elicit eczematous symptoms – even if they are ready to observe late phase reactions.
- The same may be true for the occurrence of anaphylaxis. Usually, oral food challenges do not involve risking a severe anaphylactic reaction, but are designed to establish the minimum dosage which provides a clear 'yes or no' answer as an argument for deciding on a diet. Therefore only minor symptoms are seen and reported, and the danger emanating from the food may be underestimated.
- Table 1 offers a procedure after 'de-blinding' a double-blind, placebo-controlled oral food challenge.

#### A note of caution

Results from oral food challenges can hardly ever be used as an estimation of the risk for the patient. The main reason is the presence or absence of augmentation factors. There is no absolute safety after oral food challenges.

#### Conclusions

The aim of all oral challenge testing should be to maintain a balance between two conflicting aspects: on the one hand, the need to achieve clear and justified results from oral food challenges in order to avoid unnecessary diets, which may be annoying or even harmful to the patient, and on the other hand, the ethical necessity to protect patients from any risk or harm deriving from giving high doses of a potentially dangerous on purpose.

Therefore, challenges should be continued until objective and/or (a) severe or (b) reproducible or (c) persisting symptoms occur. The sooner symptoms appear, the more organ systems are involved, and the more a child changes its general mood, the easier an oral food challenge can be assessed as positive.

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