

*Review*

# Histamine intolerance in children

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**Abstract:** Histamine intolerance is defined as disequilibrium of accumulated histamine and the capacity for histamine degradation. This clinical term addresses a non-immunologically mediated pathology when histamine ingested with food is not particularly high, but its degradation is decreased. Clinical picture of histamine intolerance in children is similar to that observed in adults apart from male predominance found in paediatric patients. Both in children and adults, histamine-free diet seems to be the treatment of choice. Diamine oxidase supplementation offers another treatment option. There is no symptom and/or test pathognomonic for histamine intolerance. Nevertheless, manifestations of chronic gastrointestinal symptoms, measurement of diamine oxidase deficits, positive results of histamine provocation tests and improvement of symptoms with histamine-free diet greatly increase the probability of histamine intolerance diagnosis. These factors have been included in the proposed in this paper diagnostic algorithm for histamine intolerance. In children histamine intolerance probably co-occur with allergies and bowel diseases, which creates an additional diagnostic challenge. As the evidence for children is weak, further research is needed to establish epidemiology, validate diagnostic algorithms and establish possible treatment options regarding histamine intolerance.

**Keywords:** Children; histamine intolerance; nutrition; diagnostic algorithm; epidemiology

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## Aim

The aim of this review is to provide a current update on etiopathology, epidemiology, possible diagnostic algorithms as well as diagnostic challenges of histamine intolerance in children. The differences between children and adult population are also highlighted.

## Histamine intolerance pathophysiology

Histamine intolerance, HIT, is defined as disequilibrium of accumulated histamine and the capacity for histamine degradation [1]. This clinical term addresses a non-immunologically mediated pathology when histamine ingested with food is not particularly high, but its degradation is decreased [1, 2]. This should be differentiated from the situation when individuals presenting with normal histamine degradation enzyme activity ingest too much histamine rich products (mainly fish) and develop histamine-induced symptoms, which is classified as histamine intoxication [3].

Histamine is metabolised by two enzymes: diamine oxidase, DAO, and histamine-N-methyltransferase, HNMT [3]. HNMT is responsible for intracellular histamine metabolism, while DAO is a secretory protein which metabolises histamine extracellularly [4]. DAO has higher expression than HNMT [3], being the primary barrier for the intestinal histamine absorption [4]. As the degradation in the intestine is decreased due to low DAO concentration, histamine enters the blood flow. Additionally, tissue HNMT is inhibited

by histamine metabolites [5]. This causes histamine accumulation in intestinal mucosa and blood plasma. Histamine starts to act on its H<sub>1</sub> - H<sub>4</sub> receptors [6], which results in the appearance of histamine-mediated symptoms [3].

### Histamine intolerance aetiologies

#### Food

Ingested food may cause abnormal histamine accumulation in several ways (Figure 1):

Fish, sauerkraut, smoked meat products or cheeses are foods that contain large amounts of histamine and may trigger HIT symptoms due to over-availability of histamine [1, 3, 5, 7–9] (Table 1, Figure 1). Histamine's presence in these foods is a result of histidine decarboxylation by microorganisms that exhibit histidine decarboxylase activity. This process occurs during food production [4]. To diagnose HIT, ingestion of histamine-rich food must be accompanied with DAO deficit. If not, then histamine intoxication should be diagnosed.

It is very likely that some products can trigger histamine release. Examples are citrus fruits, chocolate, some types of nuts, fish, pork, spices or additives [1].

Food rich in other biogenic amines, like tyramine or putrescine, usually accompanied by histamine, may cause competitive DAO inhibition and in combination with usually tolerable histamine amounts cause HIT [1, 3].

Putrescine most probably promotes histamine liberation from the intestinal mucosa [1]. Examples include cheese, fermented sausages, fish sauces or citrus fruits [10, 11].

One should also keep in mind that some foods can cause acquired DAO deficit via several mechanisms simultaneously. For example, fish is a histamine-rich, histamine-releasing and DAO-inhibitory food product.

**Table 1.** Foods likely to cause histamine intolerance and foods allowed in histamine-free diet.

Histamine-rich food	Fish, cheese, fermented sausages, fermented ham, salami, sauerkraut, spinach, tomatoes, alcohol (also strong DAO inhibitor)
Food containing histamine-releasers	Fish, pork, egg white, citrus fruits, papaya, strawberries, nuts, chocolate, food additives, spices
Putrescine-rich food	Fish, sauces, cheese, fermented sausage, citrus fruits, green pepper, wheatgerm, soybean sprouts
Tyramine-rich food	Cheese, fermented sausage, fermented ham, sauerkraut
Foods allowed on histamine-free diet in children, adopted from Rosell et al. [5]	Water, coffee, tea
	Potatoes, rice, pasta, cereals
	Yoghurt and unaged cheese (milk should be avoided though)
	Vegetables: lettuce, cauliflower, broccoli, chicory, corn salad, cucumber, carrot, garlic, pumpkin, pepper, mushroom, radish, rhubarb, asparagus, courgette, onion
	Fruits: apple, pear, peach, plum, cherry, melon, blueberry
	Herbs and spices
	Vegetable oil, vinegar, olives
Drugs excluded on histamine-free diet in children, adopted from Rosell et al. [5].	Meat, poultry, fish (hake, cod, angler), raw sausages
	Cold meat: boiled ham
	Contrast media
	Muscle relaxants: pancurorium, alcuronium, D-tubocurarine

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Anaesthetics: thiopental  
 Analgesics: morphine, pethidine, NSAIDs, ASA, metamizole  
 Local anaesthetics: prilocaine  
 Cardiotonics: dobutamine, dopamine  
 Antihypertensives: verapamil, alprenolol, dihydrazine  
 Antiarrhythmics: propafenone  
 Diuretics: amiloride  
 Antibiotics: cefuroxime, isoniazid, pentamidine, clavulanate, chloroquine  
 Mucolytics: ambroxol, acetylcysteine  
 Bronchodilators: aminophylline  
 Cytostatics: cyclophosphamide  
 Antidepressants: amitriptyline  
 Prokinetics: metoclopramide  
 Antihistamines: cimetidine

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### Breastfeeding

Exclusive breastfeeding is recommended for about 6 months and should be followed by the introduction of complementary foods until [weaning when] the child is 12 months old or older [12]. There is no direct evidence on whether histamine present in mother's food may trigger histamine intolerance in children. Perez et al. report that sometimes breast milk histamine concentration as well as other biogenic amines like putrescine increase when breastfeeding women are diagnosed with mastitis [13]. This molecule may act as a DAO inhibitor increasing the risk of decreased histamine metabolism [1]. To date, the earliest reported symptom onset of HIT was reported in a 6-month old child [5], which most probably coincided with the introduction of complementary foods [12]. Thus, the question arises whether increased concentrations of biogenic amines transferred in breast milk are high enough to cause histamine intoxication or induce histamine intolerance in an infant.

### Drugs

Certain drugs have been claimed to inhibit DAO activity and contribute to HIT pathogenesis. This list includes morphine, non-steroidal anti-inflammatory drugs, acetylcysteine, acetylsalicylic acid, clavulanic acid, isoniazid or cimetidine [1]. As many of these drugs are used in paediatric diseases [14, 15], iatrogenic DAO inhibition in children should also be considered, especially if the drugs are used for long term treatment or chronic conditions. However, there is no evidence on this issue yet. Nevertheless, some drugs are excluded on histamine-free diets for children (Table 1) [5].

### Genetics

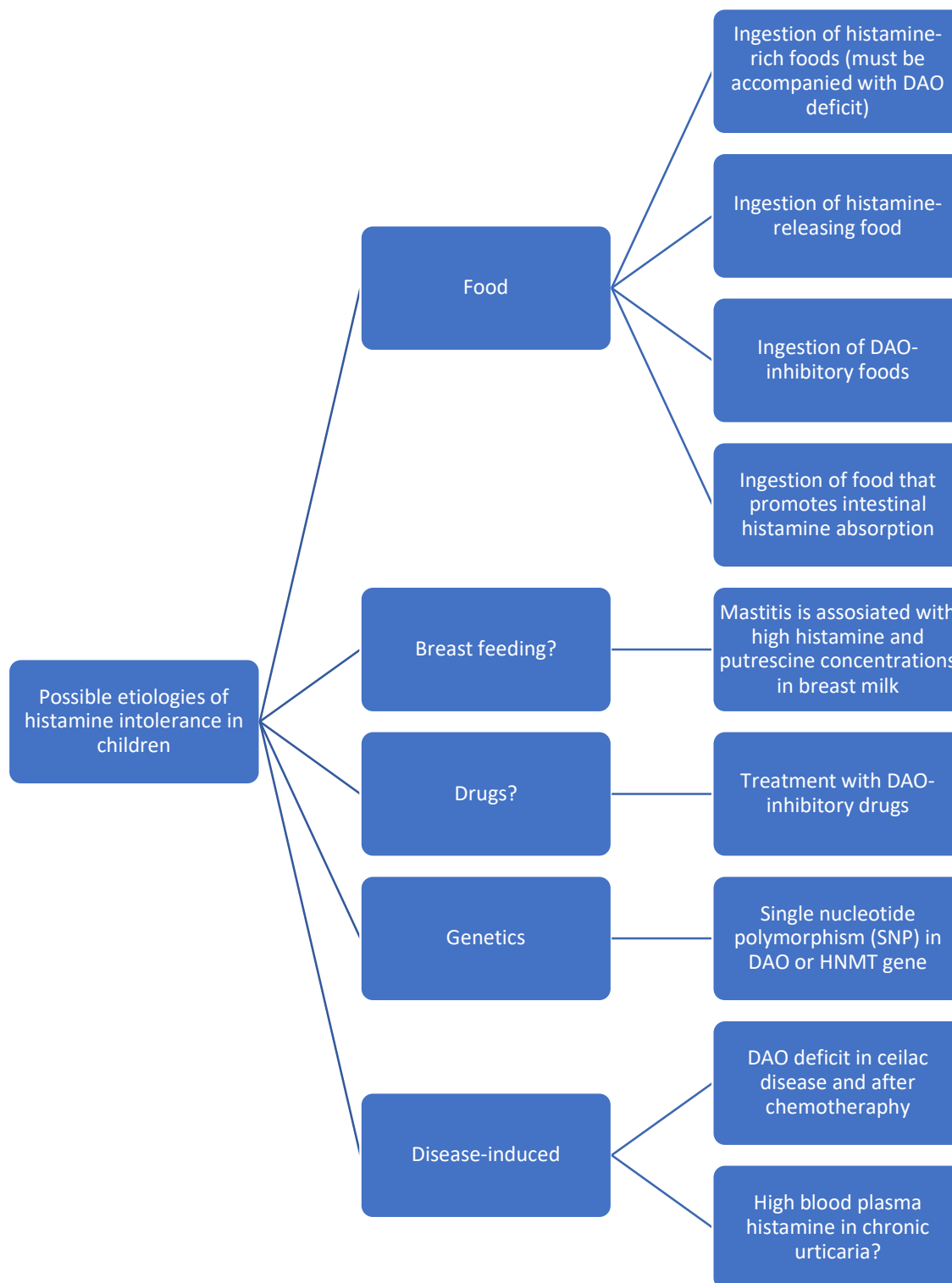
HIT can be also a genetic condition. In this case it is caused by single nucleotide polymorphisms, SNPs, in the DAO gene. Expression of this gene results in altered protein production with lower enzymatic activity than usual. In the adult population, the most important SNPs in the DAO gene causing its deficit are rs10156191, rs1049742, rs2268999 and rs1049793 [3, 16, 17]. SNPs in the promoter region which decrease the DAO gene expression (rs2052129) are also reported [16]. Similarly to the adult population, in children the DAO SNP rs1049793 is associated with lower DAO activity and leads to higher serum histamine levels in paediatric patients with allergic rhinitis [18].

Similarly to the adult population [17], in children the relation between SNPs of HNMT gene (N-methyltransferase C314T allele) and allergic diseases was also investigated. It looks like HNMT SNPs are associated with more severe courses of atopic

dermatitis and allergic rhinitis but for asthma and bronchial hyperresponsiveness the results are contradictory [18–22].

#### **Disease-induced histamine intolerance**

DAO deficit was found in children undergoing cyclophosphamide administration in neuroblastoma paediatric patients [23], in celiac disease [24] as well as during protracted diarrhoea [25]. Last but not least, decreased DAO excretion was noticed in other diseases like chronic urticaria, viral hepatitis [1] or inflammatory bowel diseases [3] in adult cohorts. These pathologies also occur in childhood [26–28] but the DAO deficit issue has not been evidenced for them yet, although in one report, histamine intolerance was diagnosed in a child with a viral intestinal infection [29].



**Figure 1.** Possible histamine intolerance aetiologies in children.

### **Epidemiology of histamine intolerance in the paediatric population**

It is estimated that prevalence of HIT is approximately 1% in the world population and that about 80% of those patients are adults [1]. In children, a lower diagnosis rate is possible, as children most probably do not consume as much fish, cheese, fermented sausages and/or alcohol as adults and the symptoms may not be displayed clearly enough to diagnose HIT. Nevertheless, the true prevalence of HIT in children may be the same as in adult population. It is also claimed that due to multifaced symptoms and many organs involved, HIT prevalence is most likely underestimated [1].

In one study involving children, about 8% of children who report chronic abdominal pain and have a history of histamine-rich foods consumption have decreased serum DAO concentration [30]. Also, males seem to predominate in the paediatric population which is different to the adult population [5, 30, 31]. However, all these hypotheses need to be verified in larger cohorts. Also, the question arises about the minimum age at which HIT diagnosis can be made. For now, a 15 months old child is the youngest diagnosed patient with HIT [29]. However, another study claims that the symptoms of HIT were noticed in a 6 months old patient [5].

### **Histamine intolerance diagnosis in children**

As of now, two publications proposing a diagnostic scheme for paediatric HIT are available. Hoffman et al. propose the following diagnostic criteria: 1) patient has chronic abdominal pain; 2) patient has serum DAO concentration  $\leq 10$  IU/mL; 3) the suspected HIT symptoms improve after histamine-free diet; 4) positive result of histamine provocation test [30].

On the other hand, Rosell-Camps et al. recruited 1) patients with chronic abdominal pain; 2) whose symptoms improve on histamine-free diet; 3) who may have serum DAO concentration  $\leq 10$  U/mL [5].

The first stage of diagnosis is consistent between studies. Gastrointestinal symptoms seem to be the most common among paediatric patients with HIT. This includes chronic, diffuse abdominal pain, diarrhoea, vomiting or flatulence [5, 30]. The same observation was made in the adult population, where symptoms like abdominal distension (92%), postprandial fullness (73%), diarrhoea (71%), abdominal pain (68%) and constipation (55%) were observed in the majority of the studied population [31].

However, when the second stage is considered, only about 50% of children who have decreased DAO activity report improvement of symptoms in histamine-free diet [30] (Table 2). On the other hand, Rosell-Camps et al. reported that all patients with decreased DAO activity responded well to histamine-free diet [5]. Therefore, it seems that the DAO activity measurement should follow the histamine-free diet trial, not the other way round. Additionally, this scheme is consistent with the ones proposed by Maintz et al. or Comas-Basté et al. for the adult population [1, 3]. However, researchers suggest that the patient should be presenting at least two symptoms of histamine intolerance. It is unknown if this criterion was fulfilled by patients enrolled by Hoffman et al. [30], while in the study carried out by Rosell-Camps et al. all patients met this criterion [5].

**Table 2.** Comparison of recent studies on histamine intolerance in children.

Clinical outcome	Number of patients	
	Rosell et al. [5]	Hoffman et al. [30]
Abdominal pain	16 (100%)	394 (100%)
DAO deficit	14 (87.5%)	31 (7.9%)
Males	11 (68.8%)	17 (54.8%)
DAO deficit and positive response to histamine-free diet	14 (100%)	16 (43.2%)
High serum histamine level	1 out of 8 measured (12.5%)	22 (71.0%)
High urine histamine level	1 out of 8 measured (12.5%)	13 (41.2%)

As histamine-free diet helps to improve symptoms in paediatric patients without DAO deficit [5], while not all patients with DAO deficit respond to histamine-free diet [30], it seems that in the paediatric population decreased DAO concentration is not pathognomonic for HIT. The same issue as well as high variations in prevalence of DAO deficit in the studied populations were observed in adults [32, 33].

Moreover, Hoffman et al. claims that during double-blind placebo-controlled trial only one out of seven patients developed symptoms of HIT and thus the test result was interpreted as positive [30]. This is consistent with other study based on the adult population. It shows that the histamine provocation test results are not reproducible and its use to diagnose HIT maybe inappropriate [34].

In addition to that, it was found that children's serum DAO concentration does not correlate with serum or urine histamine concentrations ( $R^2=0.38$  and  $0.28$ , respectively) [30]. A similar outcome was observed by Rosell-Camps et al. as in eight patients who had undergone measurements, only one child had urine and blood histamine concentrations above physiological level [5].

Kacik et al. implement a completely different diagnostic scheme, where patients are divided into allergy and pseudoallergy groups based on their serum IgE concentration [2]. It was found that low serum DAO is associated with low total and specific IgE concentration, thus no allergy, and it was concluded that the most probable diagnosis is histamine intolerance [2]. However, the DAO concentration in the pseudoallergy group ( $n=8$ ) was still very high ( $46.40 \pm 7.19$  IU/ml) in comparison to  $\leq 10$  IU/mL which is claimed to be a cut-off value to diagnose DAO deficit [30]. Moreover, contrary to two previous studies [5, 30], the most common symptoms in the pseudoallergy group were respiratory (75%), skin (50%) and symptoms appearing after food ingestion (50%). However, the digestive system symptoms were present in only 25% of the non-allergic children, compared to 100% or nearly 100% in other studies [5, 30, 31]. IgE concentration, both total and specific, can be helpful in the diagnosis of allergy. Lower DAO is also noticed for example in celiac disease [24]. Moreover, there is no mention if patients were treated with histamine-free diet and if symptoms improved [2]. Also, the symptoms appearing after food ingestion can be attributed to many other diseases, for example lactose intolerance [35]. Thus, HIT diagnosis in these patients cannot be straightforward based solely on low IgE concentration and lower DAO activity. Nevertheless, testing for total and specific IgE concentration may be useful in differential diagnosis between allergy and histamine intolerance.

To sum up, the HIT diagnosis scheme remains unclear, both for children and adults. Variety of displayed symptoms [2, 5, 31] as well as lack of strong, zero-one correlations between biochemical markers of HIT, HIT symptoms and HIT treatment methods makes HIT diagnosis very challenging.

### Proposed diagnostic algorithm for histamine intolerance

Based on current evidence, instead of flow chart method proposed by Maintz et al. [1], supported by Comas-Basté et al. [3] or the diet-provocation algorithm developed by Reese et al. [36], authors would like to propose and discuss a new approach to HIT diagnosis based on major and minor criterion fulfilment. As it is based on research regarding children and adults, a proposal for patients of all ages may be established.

**Table 3.** Proposed algorithm for histamine intolerance diagnosis.

<b>Must-have criteria</b>
Presenting $\geq 3$ symptoms of histamine intolerance in total or $\geq 2$ gastrointestinal symptoms
<b><math>\geq 2</math> Major criterion</b>
Positive histamine oral provocation test
OR
positive 50-skin-prick test when other possible pathologies giving positive result are excluded
serum DAO deficit ( $\leq 10$ IU/mL)
OR
symptoms improvement after DAO supplementation (4-8 weeks)
OR
symptoms improvement after DAO inhibitory drugs dismissal
OR
identification of single nucleotide polymorphism responsible for DAO/HNMT deficit
OR
decreased DAO activity in colon biopsy
Symptoms improvement after histamine-free diet (4-8 weeks)
<b>Additional criteria that increase the probability of histamine intolerance diagnosis.</b>
Correlation between specific food consumption and symptomatology based on diet diary
High concentration biomarkers of histamine metabolism in urine, blood or stool samples
Exclusion of mastocytosis (tryptase)
Exclusion of food allergies (skin prick test)
Exclusion of other underlying diseases relevant to presented symptoms (for example endoscopy for gastrointestinal symptoms)

### Symptoms of histamine intolerance

In our proposed diagnostic scheme, two gastrointestinal or three overall symptoms of histamine intolerance is the necessary condition for HIT diagnosis and the starting point of the diagnostic path (Table 3). This is different to Maintz et al, as in this study authors indicate possible HIT diagnosis when patient presents at least 2 symptoms of histamine intolerance [1]. Rosell et al. noticed that paediatric patients with HIT intolerance display symptoms from other systems than just digestive system like pruritus, rash, bronchospasm, cough, headache, nausea, or tachycardia [5]. This is consistent with adult population, in which such symptoms are less common than gastrointestinal ones, but definitely not rare [31]. Also, there is no symptom that would be reported by 100% of the patients [31]. Nevertheless, an adult patient usually displays many symptoms at once, ranging from 2 to 21, most frequently about 8-12. For children, it is on average 3 symptoms [5]. Also, the gastrointestinal symptoms are the most frequent and their occurrence is more indicative for HIT than symptoms from other organ systems [5, 31].

However, at this stage of developing the diagnostic scheme the severity and frequency of symptoms required to consider the possibility of HIT diagnosis is has not yet been determined and further research is required.

### Major criteria

Histamine-free diet is easy and cheap to administer as well as widely available, compared to experimental serum DAO measurements, colon biopsy or SNPs investigation that are rather expensive, invasive, require trained personnel and cannot be performed in all laboratories. Also, patients who find histamine-free diet improves their symptoms adhere to it after four weeks [30], which indicates well if the therapy is successful or not.



Moreover, the diagnostic value of histamine-free diet is well evidenced [3]. On the other hand, histamine-free diet is not helpful for some patients with DAO deficit [30] and it sometimes helps patients who do not have DAO deficit [5]. What is more, "histamine-free" tends to be also "-free" of other substances. For example, histamine-free diets seem to be also biogenic amine-free, or at least contain reduced amounts of biogenic amines [1, 3]. Nevertheless, histamine-free diet seems to be the most useful test, although biochemical confirmation of DAO deficit is a valuable diagnostic clue, too.

DAO supplementation is also claimed to be a valuable diagnostic marker. However, there are no studies regarding its use in children although it seems to be effective way of HIT treatment in adults [3] and can be also considered as the first-step histamine-specific test for the paediatric population, too.

Interpretation of histamine oral provocation test is sometimes confusing and lacks reproducibility [30, 34]. Also, the test has serious side-effects. Nevertheless, it can be a useful indicator of problems with histamine digestion, as it shows direct causative effect of a large histamine dose on patients' bodies.

Some authors [3, 36–38] also propose a 50-skin-prick test. Indeed, a positive result can be indicative for HIT, however, any other possible diseases such as systemic mastocytosis or allergies have to be excluded and DAO inhibitory drugs must be discontinued before the test is performed. Thus, it can be useful when HIT is an isolated, primary disease only. When HIT is a comorbidity, the 50-skin-prick test becomes inconclusive [38].

Thus, even the fulfilment of at least two major criteria cannot be used for conclusive HIT diagnosis. Nevertheless, if patient meets at least two of the criteria, HIT becomes a highly probable diagnosis. Finally, if three major criteria are fulfilled, the diagnosis of HIT can be made, as all possible histamine-specific diagnostic tests groups indicate histamine intolerance.

### **Minor criteria**

There are also factors that make HIT diagnosis even more probable, but are less indicative for problems related to histamine-mediated symptoms specifically. Again, their fulfilment just increases the probability of HIT and does not allow for unequivocal diagnosis.

A food diary can help to diagnose HIT intolerance. However, if it is the patient who asks for diagnosis of HIT based on their own reports, its usefulness can vary greatly, depending on its content. Some patients may report time between given food ingestion and symptoms or provide an hour-by-hour diary while some will just report foods eaten and symptoms experienced in a given day. On the other hand, a physician can advise the patient to complete a 24- or 48-hour thorough diet-to-symptoms diary. It is important to provide detailed instructions and make the patient aware that the temporal relation between ingested food and symptoms is the key. However, one has to remember that 24 or 48 hours maybe too short a period of time and patients might not be fully compliant, leading to only partial notes and resulting in an incorrect diagnosis. Also, to date there is no established protocol for such a diary. Thus, the diagnostic value of diary data is case-dependent.

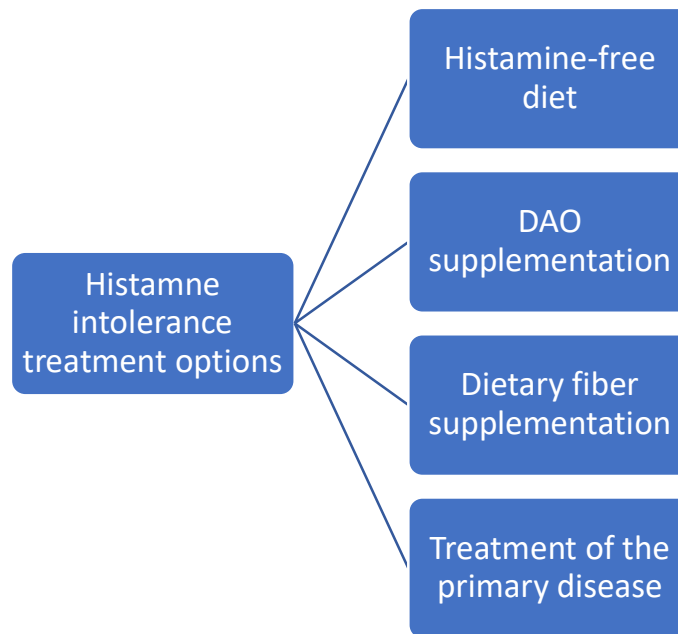
Biomarkers of histamine metabolism in urine or blood samples can also be helpful in diagnosis. However, the correlations with DAO concentration are weak [30] and their diagnostic usefulness is still being investigated [3, 39]. Moreover, it is difficult to provide clear guidance on when tests to exclude allergies or mastocytosis should be made, as it is indicated in the algorithm of Maintz et al. [1].

### **Comorbidities**

In the light of proposed diagnostic criteria, it is worth emphasizing that HIT may and in most cases probably is a comorbidity. This is supported by studies correlating DAO/HNMT deficit (measured by SNPs) or increases in blood serum histamine concentrations with the severity of allergic diseases like atopic dermatitis, allergic rhinitis or

asthma and bronchial hyperresponsiveness [18, 19, 21, 22]. Additionally, DAO deficit was noticed in bowel diseases, for example celiac disease in children [24] and in recurrent urticaria, colon adenoma as well as food allergies in adults [40–44]. Also, DAO activity level was proposed as a bowel integrity marker [23, 24]. As these are allergic and gastrointestinal diseases, the frequency and/or severity of histamine-mediated symptoms increases most probably due to the elevation of serum histamine concentration, leading to possible co-occurrence of histamine intolerance. However, this was not proven on the causative basis and HIT diagnosis was not the aim of these studies. Nevertheless, such possibility creates an additional diagnostic challenge.

### Treatment of histamine intolerance



**Figure 2.** Histamine intolerance treatment options.

According to recent studies, histamine-free diet is a treatment of choice for HIT [5, 30] (Figure 2). However, its effectiveness in symptom improvement in children varies. This choice of treatment is consistent with studies on adults with HIT [3]. Similarly, the effectiveness vary, but in general the response is rather good [3]. Additionally, Rosell et al. reports successful treatment of more severe cases of HIT in children with H<sub>1</sub> and H<sub>2</sub> antihistamines as well as oral zinc supplementation as a combination therapy along with histamine-free diet [5].

For adults, DAO supplementation is also proposed and the results are promising [1, 3]. However, there is no study on paediatric population that evaluates this treatment. There are companies that offer over-the-counter DAO supplements [45], even for children [46], but currently it is not possible to provide patients with evidence-based recommendation on this topic [47].

During cyclophosphamide administration in neuroblastoma paediatric patients the pre-administration of dietary fibre inhibited the influence of cyclophosphamide on DAO activity [23], which shows a potential treatment option of drug-induced HIT. Also, it might be helpful in other bowel disease-induced DAO deficits [41–43]. Nevertheless, this therapy has to be investigated more thoroughly to draw reliable conclusions.

## Conclusions

Histamine intolerance has to be regarded in children with non-specific gastrointestinal complaints and histamine related symptoms. Although decreased DAO activity seems to be the most relevant finding in the patients with HIT, its significance as a diagnostic marker needs to be verified in prospective, large cohort studies. Histamine-free diet is a treatment of choice for HIT, but other treatment options like DAO or dietary fibre supplementation might be proposed to patients who do not respond to elimination diet. Secondary HIT accompanying allergies and bowel pathologies could be responsible for worsening the symptoms of these conditions.

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