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par
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TITRE

Intérêt des régimes dans l'urticaire chronique spontanée :
revue systématique de la littérature

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira
pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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I/ Présentation générale du travail

L'urticaire chronique spontanée est une maladie cutané-muqueuse, de mécanisme immuno-inflammatoire, de prévalence mal connue, pouvant être très invalidante. Le traitement de première intention repose sur les anti-histaminiques de type anti-H1. La prise en charge est difficile en cas de résistance à cette première ligne de traitement. La dernière conférence de consensus française, datant de 2003, avait permis une homogénéisation des pratiques, notamment concernant les explorations biologiques à visée étiologique et la prise en charge thérapeutique. Des recommandations européennes lui ont succédé, en 2006, 2009 puis 2017, permettant de positionner les nouvelles stratégies thérapeutiques de seconde et troisième intentions que sont la quadruple dose d'anti-H1 et les anticorps monoclonaux humanisés anti-IgE (omalizumab). L'efficacité et la tolérance de l'omalizumab ont été évalués au cours de plusieurs essais thérapeutiques randomisés promus par l'industrie, apportant un niveau de preuves élevé quant à son utilisation ; son coût est toutefois très élevé.

La prise en charge non médicamenteuse de l'urticaire chronique spontanée (psychothérapies, éducation thérapeutique, régimes d'éviction alimentaire...) n'apparaît quasiment pas dans les recommandations, et les pratiques, notamment sur la prescription des régimes alimentaires, sont très hétérogènes.

L'objectif de ce travail a été d'étudier les données disponibles dans la littérature sur les régimes d'éviction alimentaire dans l'urticaire chronique spontanée, par une revue systématique selon la méthodologie de la *Cochrane Collaboration*. Ce travail s'inscrit dans un travail plus large d'élaboration de recommandations nationales sur l'urticaire chronique spontanée pour les médecins libéraux et spécialistes, basées sur l'étude systématique de la littérature par un groupe de travail pluridisciplinaire dépourvu de tout conflit d'intérêt, et non plus sur l'avis seul des experts, comme cela avait été le cas pour les recommandations françaises de 2003. Ces recommandations sont menées par le Centre de Preuves en

Dermatologie, organe créé en 2015, reliant par une convention la SFD (Société Française de Dermatologie), le CEDEF (Collège des Enseignants en Dermatologie de France), la FFFCEDV (Fédération Française de Formation Continue et d'Evaluation en Dermatologie-Vénérologie) et la HAS (Haute Autorité de Santé).

II/ Résumé

Rationnel – L’urticaire chronique spontanée (UCS) est une maladie cutanéomuqueuse immuno-inflammatoire, qui résulte de l’activation des mastocytes provoquant une décharge histaminique. L’alimentation peut être responsable d’urticaire, en apportant un excès d’histamine ou en stimulant l’histamino-libération des mastocytes. Le traitement de l’UCS repose, en première intention, sur les anti-histaminiques H1 ; en cas d’UCS réfractaire aux anti-H1, des stratégies médicamenteuses comportant anti-H2, montelukast, immunosupresseurs ou omalizumab sont proposées. La place des régimes alimentaires est mal codifiée.

Objectif – L’objectif de ce travail a été d’évaluer l’intérêt des régimes d’éviction alimentaire dans le traitement de l’UCS en réalisant une revue systématique de la littérature.

Méthodes – La recherche documentaire a été faite sur MEDLINE, EMBASE et CENTRAL. Était éligible tout article original rapportant l’efficacité de régimes d’éviction alimentaire chez des patients atteints d’UCS, enfants ou adultes. Les articles concernant l’urticaire aiguë, l’urticaire physique et les vascularites urticariennes ont été exclus. La sélection des articles et l’extraction des données a été faite en doublon indépendant.

Résultats – Sur les 278 articles trouvés, 20 ont été inclus (7 cas cliniques et 13 études prospectives), impliquant au total 1734 patients ; 5 articles rapportaient des régimes d’exclusion alimentaire personnalisée, adaptés aux sensibilisations du patient, et 15 articles décrivaient 4 types de régimes d’éviction systématique : régime pauvre en pseudo-allergènes (n=1555 patients), régime pauvre en histamine (n=223), et régime sans poisson ou crustacé (n=47), régime sans gluten chez 3 patients atteints de maladie cœliaque. Ces régimes induisaient respectivement 4,8%, 11,7%, 10,6% et 100% de rémission complète. Une rémission complète était obtenue dans 74,6% des cas pour les 63 patients ayant suivi un régime d’éviction personnalisé.

III/ Article scientifique

Intérêt des régimes dans l'urticaire chronique spontanée : revue systématique de la littérature

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Mots clés : urticaire chronique spontanée, urticaire chronique, régime, tests allergologiques

Keywords: chronic spontaneous urticaria, chronic urticaria, diet, allergological tests

Abstract

Rationale - Chronic spontaneous urticaria (CSU) is a rare inflammatory skin dermatitis that results from mast cell activation. Certain foods rich in histamines or that induce histamine release may be responsible for urticaria. CSU treatment includes H1-antihistamine drugs as first-line therapy and H2-antihistamines, montelukast, immunosuppressants or omalizumab for refractory disease. Strategies for diet are less well codified.

Objective - This systematic review assessed the interest of diet in managing CSU.

Methods - In MEDLINE, EMBASE, CENTRAL and LILACS, we searched for original reports of diets followed by children and adults with CSU. Articles were selected and data were extracted in duplicate.

Results: Among the 278 reports screened (1 734 patients), 20 were included (7 case reports, 13 non-randomized prospective studies); 5 reports described personalized exclusion diets (n=63), adapted to allergological tests, and 15 described 4 types of systematic diets: pseudoallergen-free diet (n=1 555 patients), low-histamine diet (n=223), diet without fish products (n=47) and gluten-free diet in 3 patients with celiac disease. These diets induced complete remission in 4.8%, 11.7%, 10.6% and 100% of patients, respectively. Complete remission was achieved in 47/63 patients (74.6%) following a personalized diet. In these reports, the population and outcomes were heterogeneous. No randomized controlled trials were found.

Conclusion - There is no high-level evidence for the benefit of systematic diets in CSU.

Introduction

Rationale

Chronic urticaria is a rare inflammatory skin and mucosa dermatitis defined as the occurrence of spontaneous wheals, angioedema or both for more than 6 weeks. The guidelines of the European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum and World Allergy Organization divide chronic urticaria into 2 groups: chronic inducible urticaria and chronic spontaneous urticaria (CSU). Chronic inducible urticaria includes symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar and heat urticaria, vibratory angiodema, cholinergic urticaria, contact urticaria and aquagenic urticaria (1). The causes of CSU are frequently unknown. CSU might occur at any age but is more frequent in young adults and has a female predominance.

CSU is the consequence of mast cell activation. Activated mast cells release histamine first, then other mediators such as platelet-activating factor, leukotrienes and prostaglandins that induce sensory nerve activation, vasodilatation, and plasma extravasation. These effects are responsible for dermal oedema, whose clinical features are urticarial characteristic lesions. In CSU, mast cells are pre-activated in the immunologic pathway (IgE, IgG, complement) or non-immunologic pathway by transmembrane receptors or intracellular signals (2). The complete mast cell activation is triggered by other multiple signals, including infections, drugs, stress and others.

Certain foods might be responsible for urticaria because they are rich in histamine or are able to activate mast cells via the non-immunologic pathway and induce histamine release. Many foods that might be involved include cheese, fish, vegetables, fruits, chocolate or alcohol (non-exhaustive list). Contrary to acute urticaria being linked to food allergy, the mechanism is not an IgE-mediated type I reaction but is rather dose-dependent, usually

delayed pseudoallergic reaction to food coloring, artificial flavouring or preservatives. CSU is usually considered due to intolerance when clinical manifestations have improved after 3 weeks of strict adherence to a low-pseudoallergen diet or if provocative testing with food additives aggravates symptoms (3).

CSU treatment frequently includes H1-antihistamine drugs as first-line treatment; second-line treatments are H2, antihistamine drugs, antileukotrienes, immunosuppressive drugs, and anti-IgE antibody (omalizumab). Many other treatments have been anecdotally reported. Regarding diet, the European (1), British (4), US (5), Australian and World Allergy Organization guidelines (6) do not recommend diet for managing CSU, but Asian guidelines (7–9) recommend an exclusion diet in specific cases (Supplemental File 1).

Objective

We aimed to perform a systematic review to assess the interest of systematic and personalized diets in managing CSU.

Methods

We systematically searched for original articles referring to diet in CSU. The PRISMA guidelines were followed for reporting.

Eligibility criteria

We included all original reports (randomized control trials [RCTs], observational reports, case series, case reports and items of correspondence) describing the effect of diet on CSU with or without angioedema in children and adults. Reports of acute urticaria, inducible urticaria and urticaria vasculitis were excluded.

Information sources and search

The search was performed by an information specialist (GF) in November 2016. We searched in the electronic databases MEDLINE via Pubmed, EMBASE, CENTRAL and LILACS, for

articles published in common European languages (English, French, Spanish and German) from 1995 to November 2016. Search equations are in Supplemental File 2.

Study selection

According to the pre-defined criteria, 2 authors (HC, AM) independently and in duplicate selected reports on the basis of the title, then the abstract. Then the 2 authors examined the full texts of the selected reports. Duplicate publications were identified by several criteria such as authors, location, title and intervention characteristics. Any discrepancies were resolved by consensus.

Data collection process and data items

For each selected report, 2 authors (HC, AM) independently extracted information on the first author, publication year, journal, country/site, study design, characteristics of patients, type of urticaria, severity and duration of urticaria and comorbidities. Data collected on diet included tests performed before the diet, type and duration of the diet, efficacy, side effects, co-interventions and follow-up. We classified diets as systematic diets with the food elimination not based on allergological tests and personalized diets with the food elimination specific to positive results of allergological tests before the diet. To evaluate the quality of RCT reports, the risk of bias tool from the Cochrane Collaboration would be used. Any disagreements were resolved by consensus.

Statistical analysis

We planned to perform a meta-analysis in case combining results of RCTs was possible. Otherwise the analysis was descriptive, reporting data as n (%).

Results

Among 278 publications screened, 20 full-text articles (1 734 patients) were included (Figure 1). The reasons for exclusion are in Supplemental File 3. Seven of the 20 articles were

case reports and 13 were prospective studies. We found no RCT. Characteristics of included publications are in Table 1.

Reports of 4 systematic diets (including 1 671 patients) were identified: pseudoallergen-free diet (PFD; n=1 555 patients), low-histamine diet (LHD; n=223), diet without fish products (n=47), and gluten free diet (GFD; n=3). Personalized diets involved 63 patients. Details on the diets are in Supplemental file 4.

For the PFD, the median duration of the diet was 3 weeks; 74 patients (4.8%) were in complete remission (CR) and 575 (37.0%) in partial remission (PR) at the end of the diet. Pseudoallergens were reintroduced in 1 171 patients and recurrence was observed in 240 (20.5%). For the LHD, the median duration of the diet was 3 weeks and led to CR in 26 patients (11.7%) and PR in 98 (43.9%). Histamine triggers were reintroduced in 157 patients, independent of the response to the diet, and CSU recurrence occurred in 66 (42.0%). The diet without fish products involved 47 patients, 25 of whom were sensitized to *Anisakis simplex*, without clinical history of food allergy. The duration of the diet ranged from 3 to 16 months and led to CR in 5 patients (10.6%), PR in 2 (4.3%) and no improvement in 40 (85.1%). Fish products were reintroduced in 6 patients with a no-fish diet and induced CSU recurrence in 1 patient. A GFD was tested in 3 patients in 3 case reports. All had coeliac disease. The duration of the diet lasted 3 months, and all patients were in CR after avoiding gluten. In one case, the allergens were reintroduced and led to CSU recurrence. No data on observance to diet was reported. In total, with systematic diets, 85/1 671 patients (5.1%) were in CR after the diet and 626 were in PR (37.5%).

In the 5 publications (63 patients) evaluating personalized diets, 47 patients (74.6%) were in CR after the diet: 53 underwent reintroduction of specific allergens, which led to CSU recurrence in 11 (20.8%).

In 16 publications (3 of GFD, 2 of diet without fish products, 5 of PFD, 1 of LHD and 5 of personalized diets), allergological tests were performed before the diet. These were always performed for personalized diets and were inconsistently performed for systematic diets. Allergological tests consisted of skin prick tests (SPTs), specific IgE testing or both, and diets were introduced to patients with positive allergological test results in 8 publications, patients with negative test results in 6 publications and all patients in 2 publications. For PFD, 604/1 306 (46.2%) patients reported a history of food allergy. With negative allergological test results, CR was achieved at the end of the diet in 2.7% and PR in 39.4%; 20.7% showed recurrence after reintroduction. Data were not extractable for positive allergological test results. For LHD, in one publication, 10 patients had a negative SPT result without knowledge of clinical history of food allergy: 3 patients showed CR and 7 PR at the end of LHD. For the GFD, no history of food allergy was reported in the 3 publications. Two patients with negative SPT results to food allergens were in CR at the end of the GFD, with no reintroduction. One patient with a positive SPT result to gliadin was in CR after elimination and showed recurrence of urticarial symptoms after reintroduction of gluten. For personalized diets, 32.3% of patients related a history of food allergy; 17.9% had a positive allergological test result. CR was achieved in 100% with a negative SPT result and 75% with a positive SPT result, with 33% recurrence after reintroduction. Data are in Table 2.

Discussion

In this systematic review of publications related to diet treatment of CSU, among the 1 734 patients with CSU from the 20 included reports, 1 671 had a systematic diet and 63 a personalized diet. Systematic diets led to CR in 5.1% of cases and PR in 37.5%. Altogether, personalized diets led to a CR rate of 74.6%. Systematic diets consisted of 4 different types:

PFD (4.8% CR and 37.0% PR), LHD (11.7% CR, 43.9% PR), diet without fish products (10.6% CR, 4.3% PR), and GFD (3 patients, all with CR).

Regarding pseudoallergens, hypersensitivity, a suggested cause of CSU (3,10), is a non-immunological reaction. The clinical history is not sufficient to diagnose hypersensitivity to pseudoallergens and these cases account for only 1% to 3% of CSU (11). As a diagnostic help, a recommendation was to follow a therapeutic test by a pseudoallergen-free diet for 3 weeks with daily or almost daily CSU (1). In our review, the rate of CR after 3 weeks was overall low (4.8%), but criteria to define CR or PR were not standardized. Moreover, inclusion criteria were limited to non-inducible CSU, without distinction on severity or duration of symptoms that are important known negative prognostic factors. In CSU, natural remission is estimated to occur in 32% of patients at 3 years, 34% at 5 years and 49% at 10 years (12,13). In the absence of a control arm in the studies of included publications and with missing data on CSU duration and severity, the remission rate linked to the diet is difficult to analyze. The duration of diet in our included publications was also heterogeneous. Because of the absence of a regular measurement of outcome during and after the diet period as well as the lack of follow-up in most publications, we cannot evaluate an optimal diet duration and its effectiveness in the short and long term. The use of antihistamines if needed was also permitted in some publications and not in others and may interfere with regime efficiency data.

Comparing the efficiency of the LHD (CR 11.7% in our review) is difficult because of the assessment of few patients, and because part of them followed both LHD and PFD. Histamine intolerance has been suggested as cause of CSU, with some patients reporting exacerbation with histamine-rich foods. Siebenhaar showed that CSU patients may or may not benefit from avoiding histamine in their diet, but this benefit cannot be predicted from patients' previous experience of tolerating or not histamine-rich foods (14). In most patients

who respond, determining whether the response is due to the absence of histamine in these diets, the natural evolution of CSU or due to avoidance of pseudoallergens is difficult. Currently, we have few studies with one group following a LHD and another following a PFD. The EAACI/GA2LEN/EDF/WAO urticaria guidelines (1) do not recommend any PFD or LHD. Results from our review do not help identifying subgroups of patients who could benefit from diet; indeed performing allergological tests concerning food allergens in CSU does not seem to predict clinical response to LHD or PFD.

Although no data on observance was reported, PFD and LHD seem to be complicated to follow in everyday life because many common foods are excluded. In the long-term, the diets would be unhealthy by creating a risk of malnutrition, but data on safety with a long follow-up study are lacking. Moreover, we do not know whether PFD or LHD improve the global quality of life even with remission.

Other diets apply to only specific cases. A GFD is mandatory for coeliac disease. It seemed to be effective for treating CSU in the 3 case reports found. These data are consistent with the case reports previously described (15,16). An increased permeability of intestinal mucosa may facilitate the absorption of antigens, which may induce urticaria symptoms by the formation of circulating immunocomplexes. Pathophysiology data are controversial (16–18).

Conflicting data exist concerning the association of sensitization to the fish parasite *A. simplex* and CSU (19–22). Two studies including 47 patients who followed a diet without fish products because of sensitization to *A. simplex* yielded contradictory results. This diet is simple to follow but excludes the dietary benefits of fish, particularly for patients with hyperlipemia.

By extension, multiple studies highlighted the interest of eliminating specific allergens in previously sensitized patients. Many patients believe that “food allergies” are the cause of

their CSU (23,24). This research can be guided by interrogation during the clinical examination of the patient. If the clinical story is in favor, allergological tests such as SPT, serum-specific IgE testing or oral food challenge can be performed (25). In our systematic review, with allergological test results positive for a food allergen, in most cases, CR occurred after elimination of these specific allergenic foods. However, the performance of allergological tests and the indications to perform the tests were heterogeneous. Allergological tests are sometimes performed systematically or oriented by interrogation. The question arises of performing allergological tests systematically because cases of remission are reported after specific food elimination despite a clinical history not evoking food allergy, but prevalence of real food allergies remains low (25). Personalized diets are simpler to follow than broad-spectrum diets such as an LHD or PFD. The diet is recommended case-by-case and cannot constitute a recommendation for care. Moreover, regarding the specific trigger and the good response with a specific simple elimination diet, we wonder about their classification in CSU because the pathophysiology and the management seem different (allergological tests, personalized elimination diet) with CSU of an unknown cause.

Limitations

The main limitation of the study is that we found no RCT of diets and no study comparing diets. The level of evidence is thus low. Second, because of the heterogeneity of durations of diets, mode of outcomes and comorbidities, comparison of included population is difficult. We also found a high level of heterogeneity regarding allergological tests. Third, diets do not take into account the dietary habits and regional differences in food, which may affect the success rate. Finally, diagnosis of CSU in cases of patients undergoing personalized diets is questionable.

Conclusion

There is no high-level evidence for the benefit of allergological tests and systematic diets in CSU.

Acknowledgments

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References

1. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA² LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–87.
2. Augey F, Gunera-Saad N, Bensaid B, Nosbaum A, Berard F, Nicolas J-F. Chronic spontaneous urticaria is not an allergic disease. *Eur J Dermatol EJD*. 2011;21:349–53.
3. Zuberbier T. The role of allergens and pseudoallergens in urticaria. *J Investig Dermatol Symp Proc*. 2001;6:132–4.
4. Powell RJ, Leech SC, Till S, Huber PAJ, Nasser SM, Clark AT. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2015;45:547–65.
5. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270–7.e66.
6. Sánchez-Borges M, Asero R, Ansotegui IJ, Baiardini I, Bernstein JA, Canonica GW, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J*. 2012;5:125–47.

7. Chow SKW. Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. *Asia Pac Allergy*. 2012;2:149.
8. Chung W-H, Chu C-Y, Huang Y-H, Wang W-M, Yang C-H, Tsai T-F. Taiwanese Dermatological Association consensus for the definition, classification, diagnosis, and management of urticaria. *J Formos Med Assoc*. 2016;115:968–80.
9. Hide M, Hiragun T. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. *Allergol Int*. 2012;61:517–27.
10. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki B. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. *Acta Derm Venereol*. 1995;75:484–7.
11. Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, Lo Bianco C, et al. Food-Additive-Induced Urticaria: A Survey of 838 Patients with Recurrent Chronic Idiopathic Urticaria. *Int Arch Allergy Immunol*. 2005;138:235–42.
12. Van der Valk PG, Moret G, Kiemeny LM. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol*. 2002;146:110–3.
13. Quaranta JH, Rohr AS, Rachelefsky GS, Siegel SC, Katz RM, Spector SL, et al. The natural history and response to therapy of chronic urticaria and angioedema. *Ann Allergy*. 1989;62:421–4.
14. Siebenhaar F, Melde A, Magerl M, Zuberbier T, Church MK, Maurer M. Histamine intolerance in patients with chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol*. 2016;30:1774–7.
15. Haussmann J, Sekar A. Chronic urticaria: a cutaneous manifestation of celiac disease. *Can J Gastroenterol J Can Gastroenterol*. 2006;20:291–3.

16. Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol*. 2005;16:428–32.
17. Candelli M, Nista EC, Gabrielli M, Santarelli L, Pignataro G, Cammarota G, et al. CASE REPORT: Celiac Disease and Chronic Urticaria Resolution: A Case Report. *Dig Dis Sci*. 2004;49:1489–90.
18. Levine A, Dalal I, Bujanover Y. Celiac disease associated with familial chronic urticaria and thyroid autoimmunity in a child. *Pediatrics*. 1999;104:e25.
19. Frezzolini A, Cadoni S, De Pità O. Usefulness of the CD63 basophil activation test in detecting Anisakis hypersensitivity in patients with chronic urticaria: diagnosis and follow-up. *Clin Exp Dermatol*. 2010;35:765–70.
20. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites--a systematic review. *Allergy*. 2016;71:308–22.
21. López-Sáez MP, Zubeldia JM, Caloto M, Olalde S, Pelta R, Rubio M, et al. Is Anisakis simplex responsible for chronic urticaria? *Allergy Asthma Proc*. 2003;24:339–45.
22. Daschner A, Pascual C-Y. Anisakis simplex: sensitization and clinical allergy. *Curr Opin Allergy Clin Immunol*. 2005;5:281–5.
23. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol*. 1981;104:369–81.
24. Hsu M-L, Li L-F. Prevalence of food avoidance and food allergy in Chinese patients with chronic urticaria: Food avoidance and food allergy in chronic urticaria. *Br J Dermatol*. 2012;166:747–52.

25. Cianferoni A, Spergel JM. Food allergy: review, classification and diagnosis. *Allergol Int Off J Jpn Soc Allergol.* 2009;58:457–66.

Table 1. Review of the literature related to diets in chronic spontaneous urticaria (CSU)

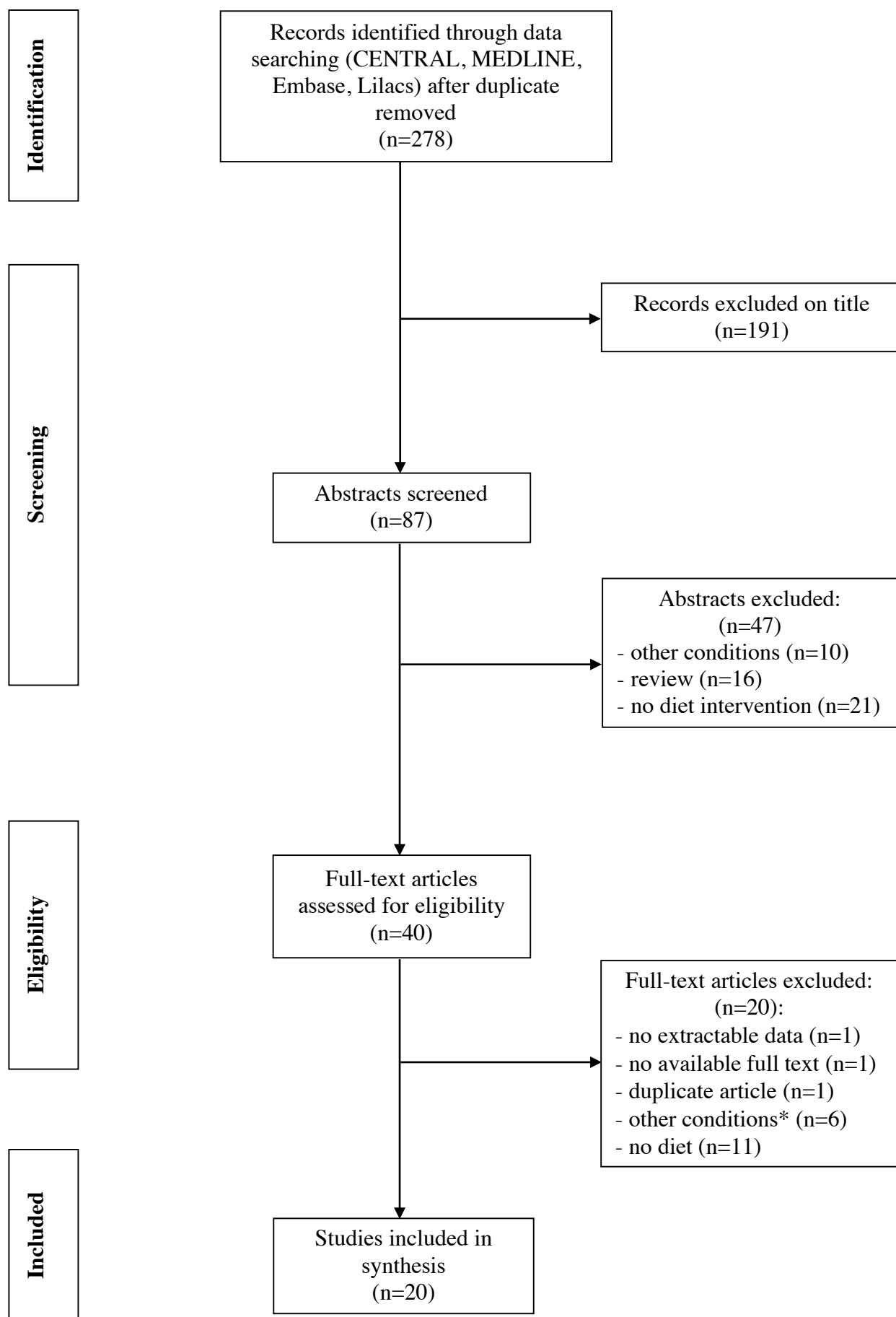
Reference (author, year)	Associated diseases (%)	Patients receiving diet (N/total)	Diet duration (weeks)	Positive reactions to food allergens (%)	Improvement after diet (%)	Methodology for treatment reintroduction	Recurrence after treatment reintroduction (N/total, %)
Gluten free diet							
Candelli, 2004	Celiac disease	1/1	12	(-) (0) ^(a)	CR (100)	—	—
Scala, 1999	Celiac disease, allergic rhinitis	1/1	12	(-) (0) ^(a+b)	CR (100)	—	—
Mingomataj, 2011	NSAID intolerance	1/1	—	Alpha gliadin (+) ^(a)	CR (100)	No control, No blinding	1/1 (100)
Diet without fishery products							
Dashner, 2013	Atopy (79%)	38/38	21	Anisakis simplex ^(a+b) (+) 16/38 (42)	No positive effect	—	—
Gracia-Bara, 2000	None	9/17	24 to 64	Anisakis simplex ^(a+b) (+) 9/9 (100)	CR (55) PR (22) Lost to follow up (22)	No control, No blinding	1/6 (16)
Pseudoallergen-free diet							
Siebenhaar, 2016	—	157	3	—	CR (14.6) PR (31.2)	DBPC	66/157 (42)
Akoglu, 2011	None	34/68	4	—	41.2	—	—
Bunselmeyer, 2009	Asthma (5.2%) Allergic rhinitis (9.8%) Atopic dermatitis (3.3%)	104/153	5	No extractable data ^(a)	CR (17.3) PR (51)	No control, No blinding	29/31 (93.6)
Magerl, 2009	—	140/140	3	—	CR (14.3) PR (13.5)	—	—
Di Lorenzo, 2005	—	838/838	4	0/402 (0) ^(a)	31.5	DBPC	116/838 (13.8)
Pigatto, 2000	—	202/348	3	No extractable data	62.4	DBPC	15/75 (20)
Ehlers, 1998	—	16/16	3	0/16 (0) ^(a+b)	CR (81) PR (19)	DBPC	5/6 (84)
Zuberbier, 1995	Atopy (10%)	64/67	3	0/64 (0) ^(a)	73.4	DBPC	9/64 (19)
Low-histamine diet							
Siebenhaar, 2016	—	157/157	3	—	CR (14.6) PR (31.2)	DBPC	66/157 (42)
Wagner, 2016	—	56/66	3	—	75	—	—
Guida, 2000	—	10/10	3	0/10 (0) ^(a)	CR (30) PR (70)	—	—
Personalized diets							
Heffler, 2014	Celiac disease	1/1	2	Buckwheat flour (+) ^(a+b)	CR (100 after buckwheat elimination)	No control, No blinding	1/1 (100)
Asero, 2013	NSAID intolerance	1/1	4	Birch pollen and peach (+) ^(a)	CR (100 after peach elimination)	No control, No blinding	1/1 (100)
Hsu, 2012	—	59/494	2	75/341 (22) ^(b)	CR (73)	No control, No blinding	9/51 (18)
Ozturk, 2005	—	1/1	—	(-) (0) ^(a)	CR (100 after home-made canned tomato elimination)	—	—
Kanny, 2000	Asthma	1/1	4	Wheat flour (+) ^(b) and (-) ^(a)	CR (100 after wheat flour elimination)	—	—

NSAID: non-steroidal anti-inflammatory drugs, DBPC: Double-blind, placebo-controlled study, CR: complete remission, PR: partial remission, (a) skin prick test, (b) specific IgE, (+) positive test, (-) negative test

Table 2. Data about allergological tests

Reference (author, year)	Patients receiving diet (N/total)	Patients with clinical history of food allergy (n/N, %)	Positive reactions to food allergens in patient with clinical history of food allergy, (n/N, %)	Improvement after diet in patients with positive test (%)	Recurrence after reintroduction in tested patients (N/total, %)	Improvement after diet in patients with negative test (%)	Recurrence after reintroduction with negative test (N/total, %)
Gluten free diet							
Candelli, 2004	1/1	0/1 (0)	(-) (0) ^(a)	—	—	100	—
Scala, 1999	1/1	0/1 (0)	(-) (0) ^(a+b)	—	—	100	—
Mingomataj, 2011	1/1	0/1 (0)	Alpha gliadin (+) ^(a)	100	1/1 (100)	—	—
Diet without fishery products							
Dashner, 2013	38/38	0/38 (0)	Anisakis simplex ^(a+b) (+) 16/38 (42)	No positive effect	—	—	—
Gracia-Bara, 2000	9/17	0/17 (0)	Anisakis simplex ^(a+b) (+) 9/9 (100)	CR (55) PR (22) Lost to follow up (22)	1/6 (16)	—	—
Pseudoallergen-free diet							
Bunselmeyer, 2009	104/153	0/104 (0)	No extractable data ^(a)	No extractable data	No extractable data	No extractable data	No extractable data
Di Lorenzo, 2005	838/838	402/838 (48)	0/402 (0) ^(a)	—	—	CR (0) PR (34.8)	84/402 (20.9)
Pigatto, 2000	202/348	202/348 (58)	No extractable data ^(a+b)	No extractable data	No extractable data	No extractable data	No extractable data
Ehlers, 1998	16/16	0/16 (0)	0/16 (0) ^(a+b)	—	—	CR (81) PR (19)	5/6 (84)
Zuberbier, 1995	64/67	No mentioned	0/64 (0) ^(a)	—	—	73.4	9/64 (19)
Low-histamine diet							
Guida, 2000	10/10	No mentioned	0/10 (0) ^(a)	—	—	CR (30) PR (70)	—
Personalized diets							
Heffler, 2014	1/1	1/1 (100)	Buckwheat flour (+) ^(a+b)	CR (100 after buckwheat elimination)	1/1 (100)	—	—
Asero, 2013	1/1	0/1 (0)	Birch pollen and peach (+) ^(a)	CR (100 after peach elimination)	1/1 (100)	—	—
Hsu, 2012	59/494	158/494 (32)	17/108 (16) ^(b)	CR (70.6)	7/17 (41.2)	—	—
Ozturk, 2005	1/1	1/1 (100)	(-) (0) ^(a)	—	—	CR (100 after home-made canned tomato elimination)	—
Kanny, 2000	1/1	1/1 (100)	Wheat flour (+) ^(b) and (-) ^(a)	CR (100 after wheat flour elimination)	—	—	—

CR: complete remission, PR: partial remission, (a) skin prick test, (b) specific IgE, (+) positive test, (-) negative test



* Concern acute urticaria

Figure 1. Flow of studies in the review

Supplemental File 1. Dietary management in guidelines

Guidelines	Dietary management
Europe	
<i>Europe</i> : (1)	No diet in the management of CSU.
<i>United Kingdom</i> : (4)	“No evidence to support the routine use of low salicylate diets.” “High-dose supplemental vitamin D3 has been reported to be beneficial irrespective of a patient’s vitamin D status.”
America	
<i>United states of America</i> : (5)	“The utility of a pseudoallergen-free diet for management of CU has not been convincingly demonstrated. Avoidance of pseudoallergens in the diet is not recommended.”
Asia	
<i>Asia</i> : (7)	“Dietary restrictions should only be recommended if allergens and pseudoallergens are proven to be causative by double-blind, provocation tests.” “In a subgroup of chronic urticaria patients, pseudoallergic reactions to naturally occurring food ingredients and in some cases to food additives are seen. In these cases a diet containing only low levels of natural as well as artificial food pseudoallergens could be instituted and maintained for a prolonged period of at least 3-6 months.”
<i>Japan</i> : (9)	No mentioned.
<i>Taiwan</i> : (8)	“Exclusion diet when indicated by history or blinded, placebo-controlled challenge. Low pseudoallergen diet: for 2-3 weeks trial in drug non responsive idiopathic urticaria.”
Oceania	
<i>Australia</i> : Prof Constance H Katelaris, Dr William Smith, Dr James Choi, Dr Katie Frith, Dr Wun Yee Lau, Dr Richard Nolan, Dr Katrina Randall, A/Prof Robert Stirling, Dr Brynn Wainstein., ASCIA Guidelines Chronic spontaneous urticaria	“The use of a pseudoallergen-restricted diet may provide additional benefit in chronic urticaria as an add-on to standard therapy. There is no clear guidance available however on the use of history or pseudoallergen challenges to identify likely responders. There is also significant uncertainty about the tolerability and nutritional sufficiency of stringent pseudoallergen-restricted diets. “ “Pseudoallergen-free diets are not recommended for routine use in children with CSU. “
Mondial	
<i>World allergy organization</i> : (6)	“The relation between food allergy/pseudoallergy and CU is controversial because some experts do not recommend elimination diets for such condition, whereas others have observed the improvement of symptoms by means of pseudoallergen-free diets in about one third of patients with chronic spontaneous urticaria.”

Supplemental File 2. Search equations (Medline)

Chronic spontaneous urticaria and diet:

MESH.EXACT("Urticaria") OR MJEMB.EXACT("chronic urticaria") OR TI(chronic spontaneous urticaria) OR AB(chronic spontaneous urticaria)
AND
(MESH.EXACT("Diet, Carbohydrate-Restricted") OR MESH.EXACT("Diet, Protein-Restricted") OR MESH.EXACT("Diet, Vegan") OR MESH.EXACT("Diet") OR MESH.EXACT("Diet, Vegetarian") OR MESH.EXACT("Diet Fads") OR MESH.EXACT("Diet, Macrobiotic") OR MESH.EXACT("Diet, Atherogenic") OR MESH.EXACT("Diet, Mediterranean") OR MESH.EXACT("Diet, Gluten-Free") OR MESH.EXACT("Diet, High-Fat") OR MESH.EXACT("Diet, Fat-Restricted") OR MESH.EXACT("Diet, Diabetic") OR MESH.EXACT("Diet, Cariogenic") OR MESH.EXACT("Diet, Reducing") OR MJEMB.EXACT("artificial diet") OR MJEMB.EXACT("elemental diet") OR MJEMB.EXACT("vegetarian diet") OR MJEMB.EXACT("raw food diet") OR MJEMB.EXACT("Mediterranean diet") OR MJEMB.EXACT("high fiber diet") OR MJEMB.EXACT("low calory diet") OR MJEMB.EXACT("gluten free diet") OR MJEMB.EXACT("Western diet") OR MJEMB.EXACT("cariogenic diet") OR MJEMB.EXACT("lipid diet") OR MJEMB.EXACT("macrobiotic diet") OR MJEMB.EXACT("low carbohydrate diet") OR MJEMB.EXACT("carbohydrate diet") OR MJEMB.EXACT("protein diet") OR MJEMB.EXACT("diet") OR MJEMB.EXACT("glycemic load") OR MJEMB.EXACT("fat content") OR MJEMB.EXACT("carbon source") OR MJEMB.EXACT("glycemic index") OR MJEMB.EXACT("nutrition") OR MESH.EXACT("Diet, Food, and Nutrition") OR MESH.EXACT("Nutritional Physiological Phenomena") OR TI(nutrition) OR TI(diet) OR MESH.EXACT("Food Hypersensitivity") OR TI(food intolerance) OR AB(food intolerance))

Supplemental File 3. Reasons for excluding full texts

References	Cause of exclusion
Ghiordanescu I-M, Ali S, Bumbacea RS, PD31-Pseudoallergic reactions to food and drugs in children with chronic idiopathic urticaria, Clinical and Translational Allergy 2014; 4	No extractable data
Daschner A, De Frutos C, Valls A, Vega De La Osada F, Blanco C, et al., Preliminary data of the effect of a temporary diet without fish in a randomised clinical trial of Anisakis simplex sensitisation-associated chronic urticaria patients, Allergy: European Journal of Allergy and Clinical Immunology 2011; 66 Pages: 33	Duplicate article
Thaiwat S, Nakakes A, Sangasapaviliya A, The Effect of Food Avoidance in Adult Patients with Chronic Idiopathic Urticaria, Journal of the Medical Association of Thailand = Chotmaihet thangphaet 2015; 98 Pages: 1162-1168	No available full text
Maurer M, Church MK, Metz M, Starkhammar M, Hamsten C, et al., Galactose- α -1,3-Galactose Allergy Is Not a Hitherto Unrecognized Cause of Chronic Spontaneous Urticaria, International archives of allergy and immunology 2015; 167 Pages: 250-252	No diet intervention
Rašković S, Matić IZ, Dordić M, Damjanović A, Kolundžija B, et al., Immunoreactivity to food antigens in patients with chronic urticaria, Immunological investigations 2014 ; 43 Pages : 504-516	No diet intervention
Heber G, Abraham S, Bauer A, Urticaria and angioedema after consumption of red meat, Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG 2013; 11	Other conditions (acute urticaria)
Asero R, Hypersensitivity to lipid transfer protein is frequently associated with chronic urticaria, European annals of allergy and clinical immunology 2011; 43 Pages: 19-21	No diet intervention
Antico A, Pagani M, Vescovi PP, Bonadonna P, Senna G, Food-specific IgG4 lack diagnostic value in adult patients with chronic urticaria and other suspected allergy skin symptoms, International archives of allergy and immunology 2011; 155 Pages: 52-56	No diet intervention
Mathelier-Fusade P, Boulinguez S, Everyday urticaria, Annales de dermatologie et de vénéréologie 2010 ; 137 Pages : 28-30	Other conditions
Daschner A, De Frutos C, Valls A, Vega de la Osada F, Different clinical presentation of Anisakis simplex associated urticaria is dependent on the frequency of raw fish intake, Allergologia et immunopathologia 2010; 38 Pages: 166-167	No diet intervention
Gutiérrez-Fernández D, Fuentes-Vallejo MS, Zavala BB, Foncubierta-Fernández A, Lucas-Velarde J, et al., Urticaria-angioedema due to limpet ingestion, Journal of investigational allergology & clinical immunology 2009; 19 Pages: 77-79	Other conditions (acute urticaria)
Piatt JD, Case report: Urticaria following intentional ingestion of cicadas, American family physician 2005; 71 Pages: 2048, 2050	Other conditions (acute urticaria)
Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, et al., The etiology of different forms of urticaria in childhood, Pediatric dermatology 2004; 21 Pages: 102-108	No diet intervention
Fernández-Nieto M, Sastre J, Quirce S, Urticaria caused by cola drink, Allergy 2002 ; 57 Pages: 967-968	Other conditions (acute urticaria)
Henz BM, Zuberbier T, Urticaria. New developments and perspectives, Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete 2000; 51 Pages: 302-308	No diet intervention
Henz BM, Zuberbier T, Most chronic urticaria is food-dependent, and not idiopathic, Experimental dermatology 1998; 7 Pages: 139-142	No diet intervention
Kim BK, Kang MG, Kim JY, Kang MK, Song WJ, et al., Hypersensitivity to monosodium glutamate, as a cause of chronic urticaria, Allergy: European Journal of Allergy and Clinical Immunology 2014; 69 Pages: 124	Other conditions
Kürzel R, Behr-Völtzer C, Zick C, Weißbecher R, Nutritional advice and dietetic measure in chronic urticaria, Allergologie 2006; 29 Pages: 221-230	No diet intervention
Mahadevan J, Ajtai SS, Vance G, Michaelis LJ, Vitamin D and iron deficiency; suboptimal nutrition, a trigger for chronic idiopathic urticaria (CIU) in children, Allergy: European Journal of Allergy and Clinical Immunology 2015; 70 Pages: 398	No diet intervention
Zuberbier T, Pfrommer C, Specht K, Vieths S, Bastl-Borrmann R, et al., Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria, The Journal of allergy and clinical immunology 2002; 109 Pages: 343-348	No diet intervention

Supplemental File 4. Indications for CSU diets and reintroduction of items

Diets

1. Pseudoallergen-free diet (based on the protocol described by Zuberbier et al.)

	<i>Permitted: pure, natural foods without artificial additives or flavours</i>	<i>Prohibited: all foods containing artificial additives, e.g. convenience food, sweets</i>
<i>Beverages</i>	Pure water, mineral water, coffee, black tea, milk, buttermilk	Herbal, rose hip or fruit teas, water and tea with aroma (e.g. citrus, bergamot, vanillin), flavoured instant coffee
<i>Basic foods</i>	Potatoes, noodles (without egg), rice, pure bread and rolls, flour (not self-raising), rice cakes and unprocessed cereals (e.g. pure corn flakes)	All others: e.g. bread or rolls with herbs, raisins, nuts or oil seeds (e.g. sun flower, pumpkin, flax seeds), potato chips, crisps, cakes, biscuits
<i>Fats</i>	Butter, refined plant oils	All others (e.g. margarine, cold pressed plant oils)
<i>Milk products</i>	Milk, pure cream, pure buttermilk, pure curd, cream cheese without additives, young gouda (mild)	All others (e.g. fruit yoghurt, cacao, herbal cheese, spread cheese and all other flavoured milk products)
<i>Meat, fish, eggs</i>	Fresh meat without any additives or seasonings (only prepared with salt and oil)	All others: fish, eggs and meat with seasonings or additives
<i>Vegetables</i>	All except those listed as forbidden (e.g. lettuce, carrots, zucchini, cabbage, broccoli)	Tomatoes and tomato products, sweet peppers, olives, spinach, rhubarb, mushrooms, peas, artichokes, onions
<i>Fruits</i>	None	All kind of fruits including fruit juices, puree, stewed and dried fruits (e.g. raisins)
<i>Herbs, spices</i>	Salt, sugar, pure vinegar to dilute with water (without herbs, balsamic, wine aromas)	All other including chives, pepper, chilli, herbs, garlic or other seasonings, sweeteners
<i>Sweets, spreads</i>	Honey, sugar beet molasses, (mild gouda)	All other

2. Low-histamine diet

List of allowed food:

Dairy products: milk, cream and sour cream, butter milk, cream cheese, soured milk, curd cheese	Meat and eggs: eggs, cooked ham, not cured beef, veal, pork, lamb, chicken
Fish (fresh or fresh frozen): plaice, coalfish, codfish, haddock, trout, hake, perch	Spread: butter, margarine, honey, homemade jam (permitted fruit only)
Sweets and Goodies: fruit drops, fruit gums, chewing gum, popcorn	Desserts: cold sweet soup, rice pudding, stewed fruit*, sorbet and ice cream, fruit yoghurt or curd cheese with fruit*, vanilla custard *(permitted fruit only)
Fruits: everything, except for strawberries, raspberries, citrus fruit, bananas, kiwis, plums, papaya	Vegetable: Any fresh or frozen vegetable, except for tomatoes, spinach, avocados, egg plant
Cereals/Potatoes/Noodles: bread and pastries, pasta, all kind of potatoes, cereals, grains (rice, corn, millet seed, buckwheat)	Beverages: Soda water, homemade fruit and vegetable juices* *(permitted fruit only)

Reintroduction tests

1. Double-blind, placebo-controlled oral histamine provocation (DBPCOH)

Verum [75 mg histamine (equivalent to 125 mg histamine dihydrochloride) plus 125 mg of sucrose] and placebo (125 mg of sucrose) were placed in identical gelatine capsules, which were swallowed by the patient. Verum and placebo were administered in a randomized fashion at the same time on alternate days, 6 h after the last meal and 6 h before the next meal. Patients avoided alcohol, non-steroidal anti-inflammatory drugs and strenuous exercise on challenge days. Both physicians and patients recorded the appearance of symptoms, e.g. weals, itching, redness, angioedema and diarrhoea, which occurred within 24 h of each challenge.

2. Incremental build up food

IBUF contained six 1-week steps with different cumulative food ingredients

Step I: It contained foods, which are not highly suspected to act as pseudoallergens [e.g. organic (bio) eggs, cold-pressed olive oil, fresh sea fish, pears], to increase the compliance for further intervention. These foods also reappear later in a processed manner.

Step II: It contained foods with high amounts of biogenic amines, e.g. tuna, well-maturated cheese, bananas and walnuts. We choose biogenic amines at this time-point, because there are foods containing biogenic amines but no other additives or seasonings: pure cheese without herbs, pure tuna in plant oil and salt without other additives. Betacarotene, nitrite and nitrate are permitted at this step, because these ingredients can be found in many pure natural foods, which have already been consumed within the PAD (e.g. vegetables).

Step III: Natural flavours, aromatic compounds, such as p-hydroxyl benzoic or salicylic acid were the main ingredients of this step, e.g. fruits, herbs, tomatoes and isolated spices. Up to step III, there are only pure foods with no considerable artificial food additives or flavours. For this reason, the nutritional consulting of the patients is highly important, not using convenience foods such as flavoured teas or broth (containing glutamate).

Step IV: It contained all foods supplemented with different additives (glutamate, sulphite, preservatives, anti-oxidants, flavours), with exception of food dyes. There are a lot of convenience foods without any artificial dyes, but containing other additives or seasonings. For this reason, step IV (food additives exceptionally dyes) must be given before step V (food dyes) and after step III (herbs, natural aromatic compounds).

Step V: All coloured food and beverages were permitted and patients were advised to choose preferential sweets and beverages containing different food dyes (E100–E199) [44, 45]. Furthermore, conventional [non-organic (non-bio)] eggs were now allowed, because hens feed can be supplemented with dyes (canthaxanthin), which can be found in the egg yolk.

Step VI: Alcohol was permitted only in the last step, because alcohol has been known to elicit urticaria directly and may lead to increased resorption of possible pseudoallergens.

Steps	Cumulative ingredients	Food selection
I	None	Whole flour bread, onions, garlic, organic (bio) eggs, cold-pressed olive oil, fresh sea fish, pears, watermelon, honey melon
II	Biogenic amines, nitrite, nitrate	Well-maturated cheese without herbs and other food additives such as nitrate, nitrite and beta-carotene: e.g. Emmentaler, Cheddar, Gouda, Camembert, Appenzeller, Edamer; Scombroidae: tuna, mackerel, herring, sardine; pickled cabbage, kohlrabi, spinach, beetroot, avocado, banana, walnut
III	Natural phenolic substances such as p-hydroxy benzoic acid, cumaric acid, salicylic acid, natural flavours, ethereal oils	All fruits, fruit juice, all vegetables (e.g. tomatoes), other nuts, isolated herbs and spices (no instant broth), natural herbal and fruit teas (without any flavouring)
IV	Food additives (without dyes), industrial aromas	Foods are permitted, if no dyes (E100–E199) are added (exception: betacarotene and riboflavin as natural dyes used for colouring cheese and butter) e.g. instant soup or broth, convenience food, sauces, chips, pizza, nut nougat cre`me, sweets, soft drinks, chocolate, cacao, all flavoured foods, e.g. teas
V	Food dyes (E100–E199)	Eggs, coloured foods with natural and artificial food dyes, e.g. coated chocolate lenses, bubble gums, drops, bonbons, soft drinks, ice creams, wine gums, custard, gelee dessert
VI	Alcohol	Beer, wine, liquor, spirits

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Résumé :

Rationnel – L'urticaire chronique spontanée (UCS) est une maladie cutanéomuqueuse immuno-inflammatoire, qui résulte de l'activation des mastocytes provoquant une décharge histaminique. L'alimentation peut être responsable d'urticaire, en apportant un excès d'histamine ou en stimulant l'histamino-libération des mastocytes. Le traitement de l'UCS repose, en première intention, sur les anti-histaminiques H1 ; en cas d'UCS réfractaire aux anti-H1, des stratégies médicamenteuses comportant anti-H2, montelukast, immunosupresseurs ou omalizumab sont proposées. La place des régimes alimentaires est mal codifiée.

Objectif – L'objectif de ce travail a été d'évaluer l'intérêt des régimes d'éviction alimentaire dans le traitement de l'UCS en réalisant une revue systématique de la littérature.

Méthodes – La recherche documentaire a été faite sur MEDLINE, EMBASE et CENTRAL. Était éligible tout article original rapportant l'efficacité de régimes d'éviction alimentaire chez des patients atteints d'UCS, enfants ou adultes. Les articles concernant l'urticaire aiguë, l'urticaire physique et les vascularites urticariennes ont été exclus. La sélection des articles et l'extraction des données a été faite en doublon indépendant.

Résultats – Sur les 278 articles trouvés, 20 ont été inclus (7 cas cliniques et 13 études prospectives), impliquant au total 1734 patients ; 5 articles rapportaient des régimes d'exclusion alimentaire personnalisée, adaptés aux sensibilisations du patient, et 15 articles décrivaient 4 types de régimes d'éviction systématique : régime pauvre en pseudo-allergènes (n=1555 patients), régime pauvre en histamine (n=223), et régime sans poisson ou crustacé (n=47), régime sans gluten chez 3 patients atteints de maladie cœliaque. Ces régimes induisaient respectivement 4,8%, 11,7%, 10,6% et 100% de rémission complète. Une rémission complète était obtenue dans 74,6% des cas pour les 63 patients ayant suivi un régime d'éviction personnalisé.

Mots clés : Urticaire chronique spontanée, urticaire chronique, régime, tests allergologiques

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