Autoimmune chronic spontaneous urticaria: what we know and what we don’t know

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Abstract
Chronic spontaneous urticaria (CSU) is a mast-cell driven skin disease, characterized by the recurrence of transient wheals, angioedema, or both for more than 6 weeks. Autoimmunity is thought to be one of the most frequent causes of CSU. Type I and type II autoimmunity, i.e. IgE to autoallergens and IgG autoantibodies to IgE or its receptor, respectively, have been implicated in the etiology and pathogenesis of CSU. We analyzed the relevant literature and assessed the existing evidence in support of a role for type I and II autoimmunity in CSU with the help of Hill’s criteria of causality. For each of these criteria, i.e. strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy, we categorized the strength of evidence as “insufficient”, “low”, “moderate” or “high” and then assigned levels of causality for type I and II autoimmunity in CSU, from level 1 (causal relationship) to level 5 (causality not likely). Based on the evidence in support of Hill’s criteria, type I autoimmunity in CSU has level 3 causality (causal relationship suggested) and type II autoimmunity has level 2 causality (causal relationship likely). There are still many aspects of the pathologic mechanisms of CSU that need to be resolved, but it is becoming clear that there are at least two distinct pathways, type I and type II autoimmunity, that contribute to the pathogenesis of this complex disease.

Keywords: chronic spontaneous urticaria; autoimmunity; IgE-anti-self; IgG-anti-FcεRI/IgE; causality; Hill’s criteria of causality
Abbreviations:

AAbs: autoantibodies
ASST: autologous serum skin test
BAT: basophil activation test
BP: bullous pemphigoid
CSU: chronic spontaneous urticaria
dsDNA: double stranded DNA
FcεR: receptor of IgE Fragment c
IgE: immunoglobulin E
IgG: immunoglobulin G
IgM: immunoglobulin M
SLE: systemic lupus erythematosus
TPO: thyroperoxidase
Introduction

Chronic spontaneous urticaria (CSU) is a mast cell driven skin disease, characterized by the recurrence of transient wheals (hives), angioedema, or both for more than 6 weeks. Several mechanisms have been investigated as possibly contributing to the pathogenesis of CSU including infections, food intolerance, coagulation cascade, genetic factors and autoimmunity. Autoimmunity, i.e. autoimmune mechanisms of skin mast cell activation, is held to be a frequent underlying cause of CSU. Two types of Gell and Coombs hypersensitivity reactions have been postulated to be relevant in autoimmune CSU.

A Type I hypersensitivity to self, also called autoallergy, in which antigens crosslink the IgE on mast cells and basophils to cause the release of vasoactive mediators (Figure 1), was first suggested by Rorsman in 1962 to explain urticaria-associated basopenia. A role of autoallergy in urticaria was also postulated from the finding in 1999 of IgE-autoantibodies (AAbs) against the thyroid microsomal antigen in the serum of a female CSU patient. This work has been confirmed and extended to propose autoallergy in the pathogenesis of both CSU and chronic inducible urticaria.

A Type II hypersensitivity reaction in which antibodies, usually IgG or IgM, bind to antigen on a target cell (Figure 1), was originally postulated following the identification of IgG-AAbs against IgE in 3 of 6 CSU patients. The presence of these AAbs was confirmed by Grattan and co-workers in 1991 in patients whose sera induced a wheal and flare response when injected
intradermally, the autologous serum skin test (ASST).\textsuperscript{12} The presence of AAbs to the high affinity receptor for IgE on mast cells and basophils (IgG-anti-FcεRI) in a subset of CSU patients was reported by the same group 2 years later.\textsuperscript{13} In theory, IgG-anti-FcεRII/CD23 autoantibodies that were identified in CSU sera may also elicit mast cell degranulation, via activation of eosinophils with the consequent release of major basic protein and other mast cell secretagogues (Figure 1).\textsuperscript{14}

We assessed the evidence for the role of these two forms of autoimmunity in CSU by the use of Hill’s nine criteria of causality, which were developed by Sir Austin Bradford Hill, an English epidemiologist and statistician as a research tool for the medical field (Table 1).\textsuperscript{15} These criteria should be viewed as guidelines rather than a checklist of definite causes.\textsuperscript{15, 16} Furthermore, Hill did not indicate how many of the nine criteria need to be fulfilled to define the relationship as causal. When we reviewed the data on autoimmunity and CSU we categorized the strength of evidence for each criterion as “insufficient”, “low”, “moderate” or “high” (Tables 2, 3) as previously described.\textsuperscript{17, 18} Finally, we assigned established levels of causality based on Hill’s criteria (Table 4, see Systematic review methodology in the Online Repository).\textsuperscript{19}

1: Strength of association and 2: Consistency

Type I autoimmunity

The strength of association between IgE-AAbs and CSU is currently unknown, and the relative risks have not been assessed. Six independent studies from different teams evaluated the link between CSU and IgE-AAbs such as IgE-
anti-dsDNA\textsuperscript{9} and IgE-anti-thyroidperoxidase (TPO)\textsuperscript{5, 6, 10, 20, 21} (Table 5). Three of these studies show that serum levels of IgE-AAbs (anti-dsDNA or anti-TPO) are significantly higher in CSU patients than in normal subjects.\textsuperscript{6, 9, 10}

Three studies failed to reproduce an association between IgE-AAbs and CSU.\textsuperscript{5, 9, 20} In the first of these studies, all of 23 CSU patients showed serum IgG-anti-TPO, but no patient was positive for IgE-anti-TPO.\textsuperscript{20} In the second study, only 2 of 20 CSU patients with IgG-anti-thyroid antibodies had detectable IgE-anti-thyroid antibodies.\textsuperscript{5} Hatada and colleagues, in the third study, failed to find differences in levels of IgE against thioredoxin, peroxiredoxin, or thyroglobulin between patients with CSU and healthy subjects.\textsuperscript{9} A radioimmunoassay or direct ELISA\textsuperscript{5, 9, 20} approach was used in all of these 3 studies, where IgG-AAbs to the antigen can mask the presence of IgE-AAbs due to competition.\textsuperscript{22} In contrast, Altrichter et al., who showed a high prevalence of IgE-anti-TPO in CSU, used a site-directed human IgE capture ELISA, in which IgE-anti-TPO does not compete with IgG-anti-TPO antibodies.\textsuperscript{6}

Strength of evidence: Low.

Type II autoimmunity

Although the presence of IgG-AAbs to IgE and FcεRI has been repeatedly observed in CSU (Table 6), the strength of association and relative risks have not been formally assessed. However, many independent studies have reported higher rates of IgG-anti-IgE and/or IgG-anti-FcεRI in immunoassays in CSU patients in comparison with healthy controls,\textsuperscript{23-26} atopic patients,\textsuperscript{27, 28}
patients with inducible urticaria\textsuperscript{24} and patients with psoriasis.\textsuperscript{28} However, this was not the case in all studies.\textsuperscript{29-33}

The rates of IgG-anti-FcεRI positivity in CSU were investigated by 16 studies, and the prevalence of these autoantibodies ranged from 0 to 64%. In healthy controls, the prevalence of IgG-anti-FcεRI ranged from 0 to 57% as reported by 11 studies (Table 6). The rates of IgG-anti-IgE positivity in CSU ranged from 0 to 69% (7 studies) as compared to 0 to 30% in healthy controls (6 studies, Table 6). In all studies, IgG-AAbs were detected by Western blot and/or ELISA or immunoenzymetric assays.

Strength of evidence: Moderate.

3: Biological plausibility and 4: Coherence

Type I autoimmunity

Several independent findings support the plausibility and coherence of type I autoimmunity as a relevant cause of CSU (Table 7). IgE-AAbs in the blood of CSU patients, such as IgE-anti-TPO and IgE-anti-dsDNA, have been shown to bind to basophils and to induce degranulation after interaction with their specific antigen.\textsuperscript{9, 10}

A second reason why it is plausible that IgE-anti-self can induce the signs and symptoms of CSU is the analogy with acute urticaria due to IgE-mediated immediate hypersensitivity. IgE against a wide range of environmental allergens is known to cause acute urticaria.\textsuperscript{34} Also, IgE-AAbs in some CSU
patients may contribute to higher levels of total IgE\(^1\), which was proposed to be a potential marker for severe CSU.\(^3\)\(^5\) One study reported significantly higher levels of total IgE in CSU patients with IgE-anti-TPO compared with those without autoantibodies.\(^1\)\(^0\) Additional evidence-based arguments for the coherence of type I autoimmunity as a cause of CSU are that other autoimmune diseases are common comorbidities of CSU patients\(^6\)\(^,\)\(^3\)\(^6\), and that wheals in CSU patients show features of IgE/allergen-induced late-phase cutaneous reactions including T cell infiltrates\(^3\)\(^7^-\)\(^3\)\(^9\) (Table 7).

Strength of evidence: Moderate for biological plausibility and high for coherence.

**Type II autoimmunity**

Direct evidence that type II autoimmune CSU, according to the revisited Witebsky’s postulates \(^4\)\(^0\), is plausible comes from studies that show that IgG-AAbs from the serum of CSU patients are able to release histamine from healthy donor mast cells \(^4\)\(^1\) and basophils.\(^1\)\(^2\) IgG-mediated basophil activation *in vitro* has also been demonstrated repeatedly with the serum of CSU patients.\(^4\)\(^2\) Moreover, these IgG-AAbs can activate complement and generate C5a, a potent inducer of human skin mast cell degranulation.\(^4\)\(^3\), \(^4\)\(^4\)

Significant circumstantial evidence for the coherence of autoimmunity type II as a cause of CSU includes the fact that IgG-AAbs-positive CSU patients often have other autoimmune comorbidities such as autoimmune thyroiditis, \(^3\)\(^6\), \(^4\)\(^5\) can show T lymphocytic infiltration of wheals,\(^3\)\(^7^-\)\(^3\)\(^9\) exhibit decreased
numbers of regulatory T cells, appear to have a HLA-associated genetic predisposition for autoimmune diseases (class I and II alleles), exhibit cytokine profiles indicative of autoimmunity.

Strength of evidence: High.

5: Temporality

Type I autoimmunity

The temporal relationship between IgE-AAbs and CSU development has not yet been investigated. However, the efficacy of anti-IgE (omalizumab) and the relapse of the disease after withdrawal of drug may be seen as indirect evidence for temporality.

Strength of evidence: Insufficient.

Type II autoimmunity

Currently, there are no published data on the temporal relationship between IgG-AAbs and CSU development. Positive ASSTs reportedly persist after CSU remission in some studies, whereas in other studies the ASST became negative after remission of CSU in most patients. Grattan and colleagues demonstrated that ASSTs are positive in CSU patients in remission when done with stored sera, but not fresh sera. These findings suggest that IgG-anti-FcεRI and IgG-anti-IgE antibodies may decrease during remission in some patients.
Strength of evidence: Insufficient.

6: Dose–response relationship (biological gradient)

Type I autoimmunity

There have been no studies that assessed the link between the incidence or severity of CSU and levels of IgE-AAbs.

Strength of evidence: Insufficient.

Type II autoimmunity

The link between the risk to develop CSU and levels of IgG-AAbs against FcεRI or IgE has not been studied. However, it has been shown that serum levels of histamine-releasing IgG-anti-FcεRI-AAbs, but not of non histamine-releasing IgG-anti-FcεRI-AAbs, correlate with disease severity, and their removal by plasmapheresis may lead to CSU remission. Additional indirect evidence appears to support this: Disease activity in CSU is correlated with blood basopenia, which, in turn, is reportedly linked to serum basophil histamine releasing activity and to high levels of IgG-anti-FcεRI and IgG-anti-IgE.

Strength of evidence: Low – Moderate.
7: Experiment

**Type I autoimmunity**

Omalizumab, a humanized monoclonal anti-IgE antibody, has been shown in a randomized placebo-controlled clinical trial to be effective in CSU patients with high levels of IgE-anti-TPO.\(^7\) This suggests that omalizumab may protect from urticarial symptoms by reducing IgE-AAbs such as IgE-anti-TPO (Figure 2).

Provocation testing is another way to assess the effects of altered autoantibody/autoantigen levels. Successful passive transfer of serum from a patient with symptomatic dermographism, a form of chronic inducible urticaria, to monkey was shown.\(^58\) In 1942, Rajka described the successful passive transfer of solar urticaria from a patient to a healthy subject after intradermal injection of patient’s serum with subsequent light exposure of injected skin.\(^59\) These data were later confirmed by Kojima and colleagues.\(^60\) These types of passive transfer approaches are based on the Prausnitz-Küstner test, a test for the presence of IgE-associated immediate hypersensitivity reactions.\(^61\) However, serum transfer studies do not necessarily confirm presence of IgE-AAbs. In some cases, transfer of other histamine-releasing serum factors such as IgG-AAbs or thrombin may also take place.

Strength of evidence: Moderate.

**Type II autoimmunity**
Experimental evidence for a pathogenic role of IgG-AAbs come from the demonstration that heterologous and autologous injections of IgG-anti-FcεRI-positive serum can induce wheal and flare reactions. Grattan and Francis reported the development of wheals in vivo after the intradermal injection of plasma from a CSU patient into the skin of a healthy volunteer with previously negative ASST. However, the attempts to perform a cross-species passive transfer of sera from ASST-positive CSU patients to guinea pigs or macaque monkeys did not bring any success.

The ASST is considered to be a screening test for autoimmune CSU due to IgG-anti-IgE and/or anti-FcεRI AAbs. The rates of ASST positivity were higher in CSU patients compared to healthy control subjects, atopic patients and patients with inducible urticaria in some studies but not by others. A positive ASST is significantly associated with CSU and with female gender. A negative ASST has a high predictive value for the absence of circulating functional AAbs. Direct evidence of mast cell degranulation in wheals of ASST-positive responses of CSU patient has been provided by electron microscopy.

Autoimmune CSU in ASST-positive patients requires in vitro demonstration of IgG-AAbs against FcεRI or IgE by ELISA or Western Blot and testing of these IgG-AAbs for functional activity, e.g. by use of a basophil activation test (BAT). IgG autoreactivity measured by BAT was observed more frequently in CSU patients than in healthy controls in many studies. Approximately 25% of CSU patients have both, a positive ASST and BAT.
Furthermore, ASST and BAT positivity in CSU are associated with longer duration of the disease in some studies but not in all, higher disease severity and a poor response to antihistamine treatment.

The efficacy of omalizumab also supports a type II autoimmune pathomechanism in CSU. In CSU patients with IgG-AAbs against IgE or FcεRI, the effect of omalizumab may be associated with the decrease of mast cell–bound IgE with the subsequent downregulation of FcεRI on mast cells and basophils (Figure 2). Thus, CSU patients with type II autoimmunity can be expected to show a slow response to omalizumab treatment, although this has not yet been confirmed experimentally.

Finally, the effectiveness of immunosuppressive treatments, e.g. with cyclosporine A, intravenous immunoglobulins, rituximab, methotrexate, mycophenolate mofetil, and the removal of autoantibodies by plasmapheresis provide experimental evidence for a role of IgG-AAbs in the pathogenesis of CSU. Treatment with cyclosporine A reduces the level of histamine-releasing IgG-AAbs, decreases ASST response rates and leads to the inhibition of dose-dependent histamine release from mast cells and basophils. BAT-positive CSU patients respond better to cyclosporine A treatment than BAT-negative ones.

Arguments that challenge the concept of type II autoimmunity include the reported ASST positivity in some CSU patients during remission and the lack of a clear correlation between immunoassays and functional assays.
Strength of evidence: High.

8: Specificity

Type I autoimmunity

It is still unknown whether or not IgE-AAbs, by themselves, can induce CSU. CSU patients who express IgE against one autoantigen are likely to exhibit IgE against other autoantigens.\textsuperscript{6, 9}

Strength of evidence: Insufficient.

Type II autoimmunity

It is still not known whether or not IgG-AAbs alone are able to induce CSU. It is thought that an IgG-anti-FcεRI/IgE-mediated activation of mast cells and basophils may be dependent on or augmented by other factors such as complement C5a, which can activate skin mast cells via its CD88/C5aR receptor (Figure 1).\textsuperscript{43, 44, 85} However, there is evidence that complement is not necessary for CSU serum-induced basophil activation.\textsuperscript{12, 28} Functionality of these IgG-AAbs also depends on IgG\textsubscript{1,3} subclasses.\textsuperscript{86}

IgG-AAbs against the low affinity IgE receptor (FceRII) can activate eosinophils, and their release of major basic protein and other mast cell secretagogues may contribute to the induction of CSU signs and symptoms (Figure 1).\textsuperscript{14}
9: Analogy

_Type I autoimmunity_

IgE against environmental allergens is responsible for the activation of mast cells in allergic diseases including anaphylaxis.\(^3^4\) IgE-AAbs (directed to skin antigens) and autoallergic mast cell activation have been observed and described in other chronic inflammatory skin diseases such as bullous pemphigoid (BP)\(^8^7,8^8\) and atopic dermatitis.\(^8^9\) IgE-anti-BP180 has been described to occur in up to 90% of untreated BP patients, and mast cell degranulation by BP180 has been suggested to be a key trigger for the development of BP skin lesions, which often first manifest as wheals.\(^8^8\) Recently, elevated levels of IgE-AAbs against nuclear antigens, dsDNA or TPO were described in other autoimmune diseases such as systemic lupus erythematosus (SLE)\(^8^9,9^0\) and autoimmune thyroiditis.\(^9^1\) Levels of autoreactive antinuclear IgE were found to be significantly higher in patients with SLE and rheumatoid arthritis than in healthy controls.\(^9^2\)

Strength of evidence: Moderate.

_Type II autoimmunity_

The causal association between IgG autoantibodies and different autoimmune diseases such as pemphigus vulgaris, dermatomyositis, SLE, and bullous pemphigoid, is well established.\(^9^3\)
Strength of evidence: High

**Overall evidence and conclusion**

Taken together, the evidence in support of Hill’s criteria is suggestive of a causal relationship (level 3 causality) for type I autoimmunity in CSU and a likely cause of CSU (level 2 causality) for type II autoimmunity. In both cases, activation of dermal mast cells to release histamine appears critical to the development of symptoms. Type I and type II autoimmunity are likely to be relevant in CSU subpopulations rather than the same patients (although some patients may exhibit IgE-AAbs and IgG-anti-IgE/FcεRI). Arguments in support of this theory include the identification of 2 distinct subgroups of CSU patients – one IgE-anti-TPO-low and the other IgE-anti-TPO-high\(^6\), the absence of a correlation between IgE-AAbs and ASST response\(^6,\,9\), the correlation of IgG-AAbs with disease activity/severity\(^{24,\,54}\) and the absence of such correlation in the case of IgE-AAbs\(^6,\,9\), and different speeds of onset of action of omalizumab.\(^7,\,49,\,76,\,94,\,95\) More than half of all omalizumab-treated CSU patients become symptom free within one week of their first injection. This would be consistent with type I autoimmunity in which omalizumab rapidly binds free IgE-AAbs and omalizumab-IgE complexes bind autoallergens and thus reduce mast cell activation (Figure 2).\(^{49}\) The remainder of patients responds more slowly to omalizumab. This would be consistent with type II autoimmunity in which the slow loss of membrane-bound IgE and subsequently FcεRI from skin mast cells\(^{95}\) renders them less susceptible to activation by IgG-anti-IgE and IgG-anti-FcεRI, respectively.
On the one hand, the existence of natural anti-FcεRIα autoantibodies found in healthy people as confirmed by ASST and BAT results might be explained by the concept of “conditional autoimmunity”. It is suggested that these autoantibodies can cause CSU only under certain conditions and they become pathogenic over time, depending on the state of occupancy of the FcεRI by its natural IgE ligand. On the other hand, autoantibodies do not lead to clinical manifestations in many rheumatologic and allergic diseases, and may be nonfunctional.

Future studies should be aimed at closing the gaps of knowledge on the role and relevance of type I and I autoimmunity in CSU (Tables 2 and 3). For type I autoimmune CSU, standardized diagnostic tests need to be developed, the associations of IgE-AAbs and the risk for CSU development and CSU severity need to be characterized, the temporal relationship of IgE-AAbs and CSU development needs to be determined and IgE-AAbs transfer and depletion studies need to be performed. For type II autoimmune CSU, the use of tests for functional IgG-anti-IgE and IgG-anti-FcεRI needs to be harmonized to assess if these IgG-AAbs are risk factors for CSU, the link between these AAbs and disease severity should be determined, and the temporal relationship between IgG-anti-IgE/FcεRI expression and CSU development and remission must be clarified. Finally, autoimmune type I and II CSU patients should be compared for clinical differences and therapeutic responses, to facilitate optimal treatment of both subpopulations of CSU patients.
Thus, there are still many aspects of the pathologic mechanisms of CSU that need to be resolved, but it is becoming clear that there are at least two distinct pathways, type I and type II autoimmunity, that contribute to the pathogenesis of this complex disease.
Figure 1. **Mechanisms of mast cell activation in chronic spontaneous autoimmune urticaria. Type I autoimmunity:** Type I autoantigens (“autoallergens”) can activate mast cells and basophils by crosslinking IgE-AAbs. **Type II autoimmunity:** IgG-AAbs can do the same by binding to IgE or to the high affinity receptor for IgE (FcεRI), which may involve complement C5a and the CD88/C5aR receptor. IgG-AAbs against the low affinity IgE receptor (FcεRII) may activate eosinophils and induce subsequent mast cell degranulation. AAbs: autoantibodies; MBP: major basic protein; ECP: eosinophil cationic protein; LTs: leukotrienes; PAF: platelet-activating factor; SCF: stem cell factor; VEGF: vascular endothelial growth factor
Figure 2. **Possible actions of omalizumab in CSU patients with type I or II autoimmunity.** *Type I autoimmunity (rapid response to treatment):* In patients with type I autoimmune (“autoallergic”) CSU, omalizumab neutralizes IgE autoantibodies and forms omalizumab-IgE immune complexes that may bind type I autoantigens (“autoallergens”). *Type II autoimmunity (slower response to treatment):* The downregulation of free IgE results in a downregulation of FcεRI expression on mast cells, which reduces their activation by IgG-anti-IgE and IgG-anti-FcεRI.
Table 1. Hill’s criteria of causality\textsuperscript{15, 16}

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Strength of association</td>
<td>The strength of association between exposure and outcome is defined as the size of the risk and measured in odds ratios, risk ratios or rate ratios.</td>
</tr>
<tr>
<td>2 Consistency (Reproducibility)</td>
<td>Different persons in different places with different samples should find the same association. It is usually evaluated to rule out other explanations for an outcome. A lack of consistency does not exclude a causal association.</td>
</tr>
<tr>
<td>3 Biological plausibility</td>
<td>Biological mechanisms through which the exposure leads to the outcome. The evidence generally comes from basic laboratory research.</td>
</tr>
<tr>
<td>4 Coherence</td>
<td>Cause-outcome association does not conflict with what is known about the natural history and the biology of the disease.</td>
</tr>
<tr>
<td>5 Temporality</td>
<td>Criterion is thought to be essential and is fulfilled when exposure precedes the outcome.</td>
</tr>
<tr>
<td>6 Biological gradient</td>
<td>Greater exposure leads to an increased risk of the development or stronger expression of the outcome.</td>
</tr>
<tr>
<td>7 Experiment</td>
<td>Evidence from epidemiological, clinical and/or laboratory studies demonstrates that altering the cause alters the outcome. Randomized clinical trials are thought to be the most persuasive studies.</td>
</tr>
<tr>
<td>8 Specificity</td>
<td>A single cause leads to a specific outcome. Some researchers feel that specificity is the weakest of all the criteria and the lack of specificity does not exclude a causal association.</td>
</tr>
<tr>
<td>9 Analogy</td>
<td>Evidence for similar exposure-disease relationships. It is one of the weakest criteria because it is dependent upon the subjective opinion of the researcher.</td>
</tr>
</tbody>
</table>
Table 2. Evidence for a causal relationship between type I autoimmunity and CSU according to Hill’s criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Questions to the literature</th>
<th>Answers</th>
<th>Evidence</th>
<th>Unmet needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of association</td>
<td>1. What are the risk ratios for the association of IgE-AAbs and CSU? 2. Are IgE-AAbs increased in CSU patients vs HCs?</td>
<td>1. Unknown 2. Yes, in some studies, but not in all</td>
<td>Low</td>
<td>➔ Evaluate if functional IgE-AAbs are risk factors for CSU development ➔ Develop and standardize screening tests for type I autoimmunity</td>
</tr>
<tr>
<td>Consistency (reproducibility)</td>
<td>1. Have the risk ratios of IgE-AAbs been reproduced by others? 2. Are increased IgE-AAbs levels reproducibly detected in CSU?</td>
<td>1. No 2. Yes, in some studies, but not in all</td>
<td>Low</td>
<td>➔ Harmonize the global use of IgE-AAbs tests ➔ Study the association between IgE-AAbs and a risk for CSU development and CSU severity in different centers worldwide</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Are there mechanisms that connect IgE-AAbs with CSU?</td>
<td>Yes (See Table 7)</td>
<td>Moderate</td>
<td>➔ Characterize the role and relevance of IgE-AAbs in CSU pathogenesis ➔ Test if some IgE-AAbs are more likely than others to cause CSU?</td>
</tr>
<tr>
<td>Coherence</td>
<td>Is the link of IgE-AAbs and CSU coherent?</td>
<td>Yes</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Temporality</td>
<td>Does the appearance of IgE-AAbs precede the development of CSU?</td>
<td>Unknown</td>
<td>Insufficient</td>
<td>➔ Study temporal relationship between IgE-AAbs and CSU</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Do higher levels of IgE-AAbs increase the risk or severity of CSU?</td>
<td>Unknown</td>
<td>Insufficient</td>
<td>➔ Assess the link between IgE-AAbs levels and CSU development and severity/activity</td>
</tr>
<tr>
<td>Experimental evidence</td>
<td>Are there epidemiological, clinical and/or laboratory data that show that changes in IgE-AAbs can alter CSU?</td>
<td>Indirect evidence only</td>
<td>Moderate</td>
<td>➔ Develop type I autoimmune CSU animal model ➔ Test IgE-AAbs+ CSU patients for response to AAs provocation and IgE-AAbs depleting therapies</td>
</tr>
<tr>
<td>Specificity</td>
<td>1. Can IgE-AAbs induce CSU? 2. In patients who have them, are IgE-AAbs responsible for their CSU?</td>
<td>1. Unknown 2. Unknown</td>
<td>Insufficient</td>
<td>➔ Perform IgE-AAbs transfer studies ➔ Test IgE-AAbs+ CSU patients for response to AAs provocation and IgE-AAbs depleting therapies</td>
</tr>
<tr>
<td>Analogy</td>
<td>Is there evidence for pathogenic functions of IgE-AAbs?</td>
<td>Yes, in BP, RA, and SLE</td>
<td>Moderate</td>
<td>➔ To better understand pathogenic relevance of IgE-AAbs in other diseases</td>
</tr>
</tbody>
</table>

Overall, how strong is the strength of evidence for a causal relationship between IgE-AAbs and CSU? | Low |

What is the level of causality for type I autoimmunity in CSU? | Level 3 (of 5) |

Abbreviations: IgE-AAbs = IgE-Autoantibodies; AAs = autoantigens; HCs = healthy controls; BP = bullous pemphigoid, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.
Table 3. Evidence for a causal relationship between type II autoimmunity and CSU according to Hill’s criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Questions to the literature</th>
<th>Answers</th>
<th>Evidence</th>
<th>Unmet needs</th>
</tr>
</thead>
</table>
| Strength of association                      | 1. What are the CSU risk ratios for IgG-anti-FcɛRI/IgE? 2. Are IgG-anti-FcɛRI/IgE increased in CSU patients vs HCs? | 1. Unknown 2. Yes, in many studies, but not in all | Moderate  | → Evaluate if functional IgG-anti-FcɛRI/IgE are risks factors for CSU development  
→ Standardize and harmonize the use of tests for IgG-anti-FcɛRI/IgE                                                                 |
| Consistency (reproducibility)                | 1. Have the risk ratios of IgG-anti-FcɛRI/IgE been reproduced? 2. Are increased IgG-anti-FcɛRI/IgE levels reproducibly detected in CSU? | 1. No 2. Yes, in many studies, but not in all | Moderate  | → Multi-center use of IgG-anti-FcɛRI/IgE tests  
→ Study the association IgG-anti-FcɛRI/IgE and CSU risk and CSU severity in different centers worldwide |
| Biological plausibility                      | Are there mechanisms that connect IgG-anti-FcɛRI/IgE with CSU? | Yes (see Table 7)                            | High      | → Characterize the role and relevance of IgG-anti-FcɛRI/IgE in CSU pathogenesis  
→ Determine why IgG-anti-FcɛRI/IgE in some but not all CSU patients activate mast cells |
| Coherence                                    | Is the link of IgG-anti-FcɛRI/IgE and CSU coherent? | Yes                                           |           | → Study temporal relationship between IgG-anti-FcɛRI/IgE and CSU                                                                         |
| Temporality                                  | Does the appearance of IgG-anti-FcɛRI/IgE precede CSU? | Unknown                                      | Insufficient | → Assess the link between IgG-anti-FcɛRI/IgE levels and CSU development and severity/activity                                    |
| Biological gradient                         | Do IgG-anti-FcɛRI/IgE levels correlate with CSU risk/severity? | Indirect evidence only                       | Low - Moderate | → Study type II autoimmune CSU animal models  
→ Test responses to provocation with or neutralization of IgG-anti-FcɛRI/IgE                                                   |
| Experimental evidence                        | Are there epidemiological, clinical and/or laboratory data that show that changes in IgG-anti-FcɛRI/IgE can alter CSU? | Yes                                           | High      | → Assess the link between IgG-anti-FcɛRI/IgE levels and CSU development and severity/activity                                    |
| Specificity                                  | 1. Can IgG-anti-FcɛRI/IgE induce CSU? 2. Is CSU due to IgG-anti-FcɛRI/IgE in patients who have them? | Unknown                                      | Insufficient | → Perform IgG-anti-FcɛRI/IgE transfer studies  
→ Test IgG-anti-FcɛRI/IgE+ CSU patients for response to depleting therapies                                                   |
| Analogy                                      | Is there evidence for pathogenic functions of IgG autoantibodies? | Yes, e.g. in PV, DM, SLE, BP                  | High      | → To better understand pathogenic relevance of IgG-anti-FcɛRI/IgE in other diseases                                                      |

Overall, how strong is the strength of evidence for a causal relationship between IgG-anti-FcɛRI/IgE and CSU? Moderate

What is the level of causality for type II autoimmunity in CSU? Level 2 (of 5)

Abbreviations: HCs = healthy controls; PV = pemphigus vulgaris; DM = dermatomyositis; SLE = systemic lupus erythematosus; BP = bullous pemphigoid
Table 4. Definitions of strength of evidence and Levels of causality for Hill's criteria\textsuperscript{17-19}

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low</td>
<td>Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence either is unavailable or does not permit a conclusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Levels of causality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Causal relationship; well-conducted studies using realistic exposures have been replicated, and chance, bias, and confounding can be ruled out with reasonable confidence</td>
</tr>
<tr>
<td>Level 2</td>
<td>Causal relationship is likely, similar evidence to that for a causal relationship but important uncertainties remain</td>
</tr>
<tr>
<td>Level 3</td>
<td>Causal relationship is suggested by the evidence, but chance, bias, and confounding cannot be ruled out</td>
</tr>
<tr>
<td>Level 4</td>
<td>Causal relationship cannot be adequately inferred, the available studies lack the quantity, quality, consistency, or statistical power on which to base a decision</td>
</tr>
<tr>
<td>Level 5</td>
<td>Causal relationship is not likely, the evidence from several studies suggests that a causal relationship is unlikely</td>
</tr>
</tbody>
</table>
Table 5. Serum IgE autoantibody reactivity in CSU patients and controls (HCs) measured by immunoassays

<table>
<thead>
<tr>
<th>Study</th>
<th>IgE-AAbs</th>
<th>Method</th>
<th>CSU patients with high levels of IgE-AAbs, % (n/total)</th>
<th>HCs with high levels of IgE-AAbs, % (n/total)</th>
<th>IgE-AAbs is higher in CSU patients vs HCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin et al.¹¹</td>
<td>anti-TPO</td>
<td>dELISA</td>
<td>8.3 (8/96)</td>
<td>0 (0/69)</td>
<td>Yes</td>
</tr>
<tr>
<td>Hatada et al.⁹</td>
<td>anti-dsDNA, anti-Th, anti-Pe, anti-TG</td>
<td>dELISA</td>
<td>–* (–*/85)</td>
<td>–* (–*/67)</td>
<td>Yes²</td>
</tr>
<tr>
<td>Altrichter et al.⁶</td>
<td>anti-TPO</td>
<td>sELISA</td>
<td>54.2 (259/478)</td>
<td>–* (–*/127)</td>
<td>Yes</td>
</tr>
<tr>
<td>Concha et al.⁵</td>
<td>anti-TPO, anti-TG</td>
<td>dELISA</td>
<td>10 (2³/20)</td>
<td>0 (0/12)</td>
<td>–</td>
</tr>
<tr>
<td>Tedeschi et al.²⁰</td>
<td>anti-TPO</td>
<td>RIA</td>
<td>0 (0/38)</td>
<td>0 (0/11)</td>
<td>No</td>
</tr>
<tr>
<td>Gimenez-Arnau et al.²⁰</td>
<td>anti-TPO</td>
<td>ELISA</td>
<td>16.7 (2/12)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

¹Patients with aspirin intolerant chronic urticaria were included; it was not defined whether patients with inducible urticaria were excluded; ²the anti-dsDNA IgE levels were significantly higher in patients with CSU than in normal subjects, but no differences in the levels of thioredoxin-, peroxiredoxin- and thyroglobulin-reactive IgE were seen; ³one patient had anti-thyroid peroxidase IgE antibody and one patient had anti-thyroglobulin IgE; ⁴one of control subjects had autoimmune thyroiditis and two others had allergic rhinitis; ⁵patients with known Hashimoto’s thyroiditis but with no history of urticaria; *data were not shown in the paper; IgE-AAbs: IgE-autoantibodies; TPO: thyroid peroxidase; TG: thyroglobulin; dsDNA: double-stranded DNA; Th: thioredoxin; Pe: peroxiredoxin; BAT: basophil activation test; ELISA: enzyme-linked immunosorbent assay; HCs: healthy controls; RIA: radioimmunoassay; dELISA: direct ELISA; sELISA: site-directed human IgE capture ELISA; –: no data
Table 6. Prevalence of IgG-anti-FcεRI and IgG-anti-IgE in CSU patients and control subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>CSU patients with high levels of IgG-anti-FcεRI/IgE, % (n/total)</th>
<th>Controls with high levels of IgG-anti-FcεRI/IgE, % (n/total)</th>
<th>AAbs in CSU &gt; controls?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCs</td>
<td>Other</td>
</tr>
<tr>
<td>IgG-anti-FcεRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun et al.(^{26})</td>
<td>ELISA</td>
<td>−* (−*/100)</td>
<td>−* (−*/100)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee et al.(^{36})</td>
<td>ELISA</td>
<td>47 (19/40)</td>
<td>10 (2/20)</td>
<td>–</td>
</tr>
<tr>
<td>Mozena et al.(^{37})</td>
<td>ELISA</td>
<td>60 (12/20)</td>
<td>−</td>
<td>–</td>
</tr>
<tr>
<td>Eckman et al.(^{29})</td>
<td>IEMA</td>
<td>59 (43/73)</td>
<td>57 (13/23)</td>
<td>–</td>
</tr>
<tr>
<td>Vonakis et al.(^{39})</td>
<td>WB</td>
<td>21 (3/14)</td>
<td>0 (0/7)</td>
<td>25 (3/12)</td>
</tr>
<tr>
<td>Vasagar et al.(^{31})</td>
<td>WB</td>
<td>22 (2/9)</td>
<td>43 (3/7)</td>
<td>25 (2/8)</td>
</tr>
<tr>
<td>Staubach et al.(^{18})</td>
<td>ELISA, WB</td>
<td>18 (10/55)</td>
<td>−</td>
<td>–</td>
</tr>
<tr>
<td>Pachloupnik et al.(^{24})</td>
<td>ELISA</td>
<td>0* (0/19)</td>
<td>0* (0/3)</td>
<td>−</td>
</tr>
<tr>
<td>Hidvegi et al.(^{25})</td>
<td>WB</td>
<td>34 (17/50)</td>
<td>0 (0/9)</td>
<td>−</td>
</tr>
<tr>
<td>Sabroe et al.(^{26})</td>
<td>WB</td>
<td>41 (32/78)</td>
<td>0 (0/39)</td>
<td>0 (0/25)</td>
</tr>
<tr>
<td>Kikuchi and Kaplan(^{30})</td>
<td>WB</td>
<td>47 (122/260)</td>
<td>−</td>
<td>–</td>
</tr>
<tr>
<td>Zuberbier et al.(^{37})</td>
<td>ELISA</td>
<td>35 (17/48)</td>
<td>0 (0/5)</td>
<td>–</td>
</tr>
<tr>
<td>Fierz et al.(^{100})</td>
<td>WB</td>
<td>64 (34/53)</td>
<td>−* (−*/24)</td>
<td>–</td>
</tr>
<tr>
<td>Fiebiger et al.(^{28})</td>
<td>ELISA, WB</td>
<td>38 (106/281)</td>
<td>0 (0/41)</td>
<td>19 (33/173)</td>
</tr>
<tr>
<td>Fiebiger et al.(^{27})</td>
<td>WB</td>
<td>4 (2/50)</td>
<td>0 (0/20)</td>
<td>–</td>
</tr>
<tr>
<td>Fiebiger et al.(^{27})</td>
<td>WB</td>
<td>37 (12/32)</td>
<td>0 (0/15)</td>
<td>0 (0/15)</td>
</tr>
</tbody>
</table>

| IgG-anti-IgE                 |        |                                                               |                                                 |                         |                         |                         |
| Sun et al.\(^{26}\)         | ELISA  | −* (−*/100)                                                   | −* (−*/100)                                      | Yes                     | –                       | –                       |
| Cho et al.\(^{37}\)         | ELISA  | 0 (0/27)                                                      | 0 (0/20)                                       | 0 (0/53)                | No                      | No                      |
| Eckman et al.\(^{29}\)      | IEMA   | 47 (34/73)                                                    | 30 (7/23)                                      | –                       | No                      | –                       |
| Staubach et al.\(^{18}\)   | ELISA, WB | 4 (2/55)                                               | −                                          | –                       | −                       | −                       |
| Atta et al.\(^{36}\)        | ELISA  | −* (−*/46)                                                    | −* (−*/10)                                     | −                       | No                      | –                       |
| Sabroe et al.\(^{26}\)      | WB     | 9 (7/78)                                                      | 0 (0/39)                                       | 0 (0/25)                | Yes                     | Yes                     |
| Tong et al.\(^{37}\)        | WB     | 12 (6/50)                                                     | 5 (1/20)                                       | –                       | Yes                     | –                       |
| Fiebiger et al.\(^{27}\)    | WB     | 69 (22/32)                                                    | 26 (4/15)                                      | 73 (11/15)              | No                      | No                      |
| Gruber et al.\(^{11}\)      | ELISA  | 50 (3/6)                                                      | 0 (0/32)                                       | 52.9 (9*/17′*)          | Yes                     | No                      |

AAbs: autoantibodies; WB: Western blot; ELISA: enzyme-linked immunosorbent assay; IEMA: immunoenzymetric assays; HCs: healthy controls; AD: atopic dermatitis; SLE: systemic lupus erythematosus; BP: bullous pemphigoid;
DM: dermatomyositis; RA: rheumatoid arthritis; PV: pemphigus vulgaris; AC: atopic control; CoU: cold urticaria; DU: dermographic urticaria; ChU: cholinergic urticaria; Ps: psoriasis; UV: urticarial vasculitis; \(^1\)atopic and \(^{13}\)non-atopic controls; \(^2\)low levels of anti-Fc\(\varepsilon I\) autoantibodies in all tested blood samples; \(^3\)patients with immunoreactive histamine-releasing anti-Fc\(\varepsilon I\) autoantibodies \((n=20, 26\%)\) and immunoreactive anti-Fc\(\varepsilon I\) autoantibodies without histamine-releasing activity \((n=12, 15\%)\); \(^4\)some normal sera were positive and were considered to have insignificant titers; \(^5\)RA \((27),\) SLE \((26);\) \(^6\)AC \((8),\) CoU \((4);\) \(^7\)AC; \(^8\)DU \((15),\) ChU \((10);\) \(^9\)AD \((0),\) Ps \((0),\) SLE \((3),\) BP \((3),\) DM \((16),\) PV \((11);\) \(^{10}\)AD \((32),\) Ps \((30),\) SLE \((15),\) BP \((22),\) DM \((45),\) PV \((28);\) \(^{11}\)AD; \(^{12}\)CoU \((5),\) UV \((4)\); \(^{13}\)CoU \((9),\) UV \((8);\) \(^{14}\)AD, Ps/other; \(^*\)data were not shown in the paper; \(–\)no data.
<table>
<thead>
<tr>
<th>Argument</th>
<th>Type I (IgE-AAbs)</th>
<th>Type II (IgG-AAbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relevant?</td>
<td>Evidence</td>
</tr>
<tr>
<td><strong>Biological Plausibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAbs can activate mast cells / basophils</td>
<td>✓</td>
<td>+</td>
</tr>
<tr>
<td>AAbs can activate mast cells via complement activation</td>
<td>Ø</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute urticaria can be IgE/allergen-mediated</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td><strong>Coherence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAbs+ CSU patients have elevated total IgE levels</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Other autoimmune diseases are common comorbidities</td>
<td>✓</td>
<td>−</td>
</tr>
<tr>
<td>CSU wheals can show T cell infiltration</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Anti-autoimmune regulatory T cells are decreased in CSU</td>
<td>✓</td>
<td>NPR</td>
</tr>
<tr>
<td>Strong association with HLA alleles</td>
<td>✓</td>
<td>NPR</td>
</tr>
<tr>
<td>Cytokine profiles typical for autoimmunity</td>
<td>✓</td>
<td>NPR</td>
</tr>
<tr>
<td><strong>Biological Gradient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of AAbs correlates with disease activity/severity</td>
<td>✓</td>
<td>−</td>
</tr>
<tr>
<td><strong>Experiment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection of heterologous AAbs induces wheal</td>
<td>Ø</td>
<td>N/A</td>
</tr>
<tr>
<td>Injection of autologous AAbs+ serum induces wheal</td>
<td>Ø</td>
<td>N/A</td>
</tr>
<tr>
<td>Positive Prausnitz-Küstner test with AAbs or AAbs+ serum</td>
<td>✓</td>
<td>NPR</td>
</tr>
<tr>
<td>Omalizumab is an effective treatment</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Cyclosporine A is an effective treatment</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Corticosteroids can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Plasmapheresis can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Anti-CD20 (rituximab) treatment can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>IVIG treatment can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Methotrexate treatment can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
<tr>
<td>Mycophenolate treatment can be effective</td>
<td>✓</td>
<td>NPR*</td>
</tr>
</tbody>
</table>

AAbs = autoantibodies; ASST = autologous serum skin test; HLA = human leucocyte antigens; IVIG = intravenous immunoglobulin; ✓ = argument is relevant; Ø = argument is not relevant; + = there is evidence for argument; – = there is evidence against argument; NPR = no published results; N/A = data not analyzed; 1 Altrichter et
al. found significantly higher levels of IgG-anti-TPO levels in IgE-anti-TPO+ CSU patients as compared to IgE-anti-TPO- CSU patients; 3 T lymphocytes were found in the upper and mid-dermis with a perivascular distribution in CSU wheals and the ASST response; 4 Serum concentration of IL-17, IL-23 and TNF-α was significantly higher in CSU patients and ASST positive patients as compared to healthy control subjects and ASST negative patients, respectively; 5 The presence of functional IgE/IgG-AAbs was not assessed; 6 IgE-AAbs+ CSU patients had elevated total IgE levels in one study (Shin et al., 2015) but not in other (Althrichter et al., 2011, Hatada et al., 2013); * As of yet, no studies that compare the efficacy of treatment in AAbs-positive and AAbs-negative CSU patients have been published; ** Omalizumab has been shown to be an effective treatment option for CSU patients with IgE-anti-TPO who are refractory to conventional treatment; *** Only few case reports or case series on the efficacy of treatment in CSU patients with functional IgG-AAbs have been published; **** Cyclosporine A has been shown to be an effective treatment option in CSU patients with functional IgG-AAbs who are refractory to conventional treatment.
References


89. Sanjuan MA, Sagar D, Kolbeck R. The Role of IgE in Autoimmunity. Journal of Allergy and Clinical Immunology 2016; 137:1651–61.


Type I autoimmunity

- IgE-anti-self
- Autoantigen

- Release of mediators, e.g. histamine

Type II autoimmunity

- IgG-anti-FcεRI
- IgG-anti-FcεRII

- C5a
- Release of MBP, ECP, LTs, PAF, SCF, VEGF

DEGRANULATION

Wheals  Itch  Angioedema  Flare
Downregulation of FcεRI expression

Mast cell

Type I autoimmunity

Type II autoimmunity

Autoantigens

Omalizumab/IgE-AAbs complexes

IgE-AAbs

Omalizumab/IgE complexes

Omalizumab

IgG-anti-FcεRI/IgE

Skin

Blood

URTICARIA

IgG-anti-FcεRI

IgE/Abs

IgE/IgG-anti-IgE complexes
Online repository

Systematic review methodology

To find relevant trials, we performed a Medline and Google Scholar search of the literature published before March 2016 with the keywords “chronic urticaria” or “idiopathic urticaria” or “autoimmune urticaria” or “chronic spontaneous urticaria” or “autoreactive urticaria”. 3902 publications were found for “chronic urticaria”, 1145 for “idiopathic urticaria”, 770 for “autoimmune urticaria”, 401 for “chronic spontaneous urticaria” and 30 for “autoreactive urticaria”. After checking for doubles, titles and/or abstracts of 3950 reports were screened, and the remaining relevant 92 publications were included in the review. Full texts were obtained if available.

The identified literature was primarily evaluated by the first author and the last author. To be included in the review, studies had to meet the following inclusion criteria: 1) direct relevance to the specific issue (studies on IgE and/or IgG autoantibodies, studies that included comparison groups, studies that describe mechanisms of skin mast cells and/or basophils activation due to autoantibodies, etc); 2) no serious methodological limitations in the study with respect to the quality of the information for the selected outcome as determined by the assessors.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was chosen for the evaluation of the quality of evidence for Hill's criteria. The overall strength/quality of evidence for each criterion was categorized as “insufficient” (very low), “low”, “moderate” or “high”. Finally, we assigned established levels of causality based on Hill's criteria (Table 4).

The quality and strength of evidence were assessed independently by all authors for each criterion and then discussed in detail between the assessors, taking into consideration bias and limitations of studies. A consensus regarding the strength of evidence and levels of causality was finally achieved during discussion.
References
