

Chronic urticaria and infections

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Purpose of review

The pathogenesis of chronic urticaria is multifactorial and a specific treatment is lacking. In acute urticaria there is no doubt of a causal relationship with infections and all chronic urticaria must start as the acute form. However, in the chronic form a primary role for infection is controversial, although it is undeniable that concurrent infections exacerbate the condition. This is the first English language review based on a detailed analysis of current peer-reviewed publications dealing with infections and chronic urticaria.

Recent findings

In chronic urticaria there is a lot of evidence for different infections, but randomized controlled trials are missing. The prevalence of infections is not increased but in susceptible patients the immune response may lead to the development of chronic urticaria. Interestingly, there is evidence for an infection-associated autoreactive response at least in the subgroup with a positive autologous serum skin test. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry.

Summary

Actually the arguments for an important role of underlying causal infections in chronic urticaria are weak, from an evidence-based viewpoint, but there are data suggesting a link. Moreover, an association with underlying or precipitating infectious causes is difficult to establish because there is no possibility for challenge and the number of other urticarial triggers is vast. For the future it will be necessary to reveal the link between urticaria, autoreactivity, non-immunoglobulin E-mediated hypersensitivity reactions and infections to find attractive and specific therapeutic interventions for urticarial symptomatology.

Keywords

acute urticaria, chronic urticaria, autoimmune urticaria, infection, *Helicobacter pylori*, molecular mimicry, autoreactivity, hypersensitivity

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Abbreviations

ASST	autologous serum skin test
CagA	cytotoxin-associated gene
ELISA	enzyme-linked immunosorbent assay
HCV	hepatitis C virus
NSAID	non-steroidal antiinflammatory drug

Introduction

Urticaria affects 15–25% of the population once in their lifetime [1]. Chronic urticaria is defined as a period of almost daily whealing often associated with angioedema lasting for at least 6 weeks with a profound impact on the quality of life [2]. After 10 years not even half of the patients are symptom free [3]. Physical urticarias are different and should be excluded by appropriate physical tests [4]. The annoying symptoms of chronic urticaria are suggested to be mediated by mast cell and basophil mediator release. Interestingly, basopenia can be found in chronic urticaria, particularly in autoimmune urticaria [5,6].

Some patients with chronic urticaria demonstrate a peculiar susceptibility to develop (transient) non-allergic hypersensitivity to non-steroidal antiinflammatory drugs (NSAIDs), particularly aspirin, or food additives [7–9]. There is no increased incidence of atopy in patients with chronic urticaria but emerging data provide evidence that about 13% have autoantibodies to thyroid [10], and about 30% histamine releasing antibodies to the high affinity immunoglobulin E receptor, FcεRI, or to immunoglobulin E [11,12]. A positive autologous serum skin test (ASST) is found in a subgroup but is not clearly correlated to the functional serum activity or the presence of autoantibodies [13–15], which may be natural rather than disease-specific [16]. Very recently, a positive ASST was found in most children and adults (particularly women) with ‘allergy-like’ respiratory difficulties suggesting that the ASST might reflect unspecific minimal persistent inflammation [17]. Of note, only in one third of patients with chronic urticaria does the condition have an autoimmune basis [18*] and anti-FcεRI antibodies and a positive ASST can still be found in patients who have entered remission [19,20], suggesting that the autoreactivity may be of a secondary nature.

Infections are the most documented cause of acute urticaria and by definition all chronic urticaria must start as the acute form. In addition, for a long time focal infections have been suggested to trigger chronic urticaria symptomatology. Recently there has been renewed interest in the role of infections on the susceptibility to autoimmune and allergic diseases [21].

In this review, we will largely present the current peer-reviewed literature about infections and chronic urticaria. Cases with physical urticaria were excluded in addition to articles without English abstracts. Searching review

databases (*Cochrane Database of Systematic Reviews* and the *Database of Abstracts of Reviews of Effectiveness*) no entries addressing chronic urticaria and infections were found.

Acute urticaria and chronic urticaria

By definition, chronic urticaria begins as acute urticaria and infections are the most frequently documented cause of the acute form [22•,23–29]. A recent review [30•] summarized five studies and, taken together, upper respiratory viral infections were found in 47% of patients with acute urticaria. However, bacterial infections such as cystitis and tonsillitis can be also found (Wedi *et al.*, unpublished data) [22•]. In addition, it has been demonstrated that about 20–30% of children with acute urticaria, of which about 91% were considered to have disease caused by infection, progressed to the chronic form [22•]. Therefore, it is conclusive that chronic urticaria is also triggered by infections, but thus far, the role of infections in chronic urticaria is still controversial.

Interestingly, it was demonstrated quite recently that there is a link between acute urticaria, NSAIDs and later development of chronic urticaria [31•]. Moreover, adults with a history of acute NSAID-induced urticaria or with multiple drug allergy syndrome demonstrated autoreactivity in terms of a positive ASST [32,33]. Given the fact, that in most cases antibiotics and NSAID are consumed due to infections, the role of the drugs might have been overestimated and that of the infections underestimated [23]. Vice versa it is a well-known fact that chronic urticaria is exacerbated by acute infections and by NSAIDs.

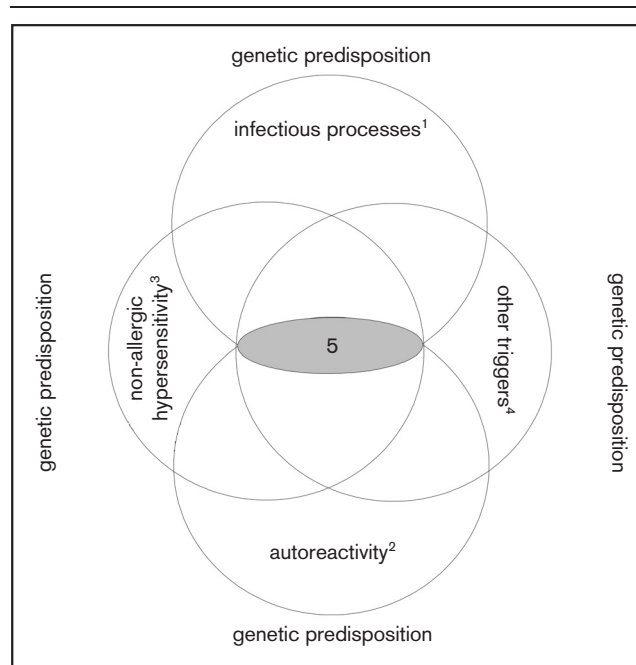
Taken together, these data point to a link between infection/inflammation, drug hypersensitivity and the development of urticaria. Furthermore, there may be an underlying genetic predisposition. Major histocompatibility complex II associations have been shown for both, NSAID-induced anaphylactoid reactions [34] and chronic urticaria [35].

Prevalence of infections in chronic urticaria

Intrinsically, there are several flaws in summarizing studies that address this issue. The studies and their results differ substantially with respect to such factors as the study population, the diagnostic tests, the evaluation procedure and follow-ups, assessment of treatment and the interpretation. Moreover, all the studies oversimplify the multitude of triggering factors in chronic urticaria (Fig. 1). It is often not considered that in several cases two or more different causes, such as non-allergic hypersensitivity, infection, autoreactivity and also several infections, can be identified [36].

A recent systematic review [37•] tried to explain the variation in the reported percentages of identified causes

Figure 1. Chronic urticaria is triggered by multiple factors



¹Bacterial (e.g. *Helicobacter pylori*), viral, parasitic, (fungal). ²For example, autoantibodies to the high affinity immunoglobulin E receptor FcεRIα, to immunoglobulin E, or to thyroid. ³To drugs (e.g. aspirin) or food additives. ⁴For example malignant processes. ⁵This set represents a combination of all triggering factors (e.g. a genetically predisposed individual with *H. pylori*-gastritis, positive autologous serum skin test, autoantibodies against FcεRIα, non-allergic hypersensitivity to aspirin and breast cancer). Urticaria may resolve after adequate treatment of one of these triggers, or persist until all have been removed.

of chronic urticaria by the variation in the geographic region, the kind of setting, different diagnostic assessment, personal prejudices and preconceived opinions of the investigators. With respect to infections the authors summarized that using their inclusion criteria a total of eight studies reported infections in 11–31% whereas in 11 other studies infections were designated as the cause in 0–6% of the patients.

Viruses

A recent review published in French concluded that no viral cause has ever been clearly documented in chronic urticaria and that the screening of viral markers does not yield significant results, compared with the general population (hepatitis B and C, HIV) [38].

Hepatitis viruses

Urticaria is classically considered to be a symptom of hepatitis A and hepatitis B infections [39,40] and is suggested to be mediated by circulating immune complexes [41]. However, in the literature there is scant evidence for a link between hepatitis A or B virus infections and chronic urticaria. A recent case report

found neutrophilic urticaria associated with hepatitis-B-associated adult-onset Still's disease in which an infectious cause has been suggested [42]. Positive hepatitis B virus serology has been demonstrated in 9% ($n=100$; France) and 18% (only two with hepatitis B surface antigen; $n=85$; USA) of patients with chronic urticaria [43,44].

Infection with hepatitis C virus (HCV) may present with dermatologic manifestations such as urticaria [45,46] and at least two studies [47,48] correlated neutrophilic urticaria with underlying HCV infection.

A study from Japan [49] investigated 21 patients with acute and 58 patients with chronic urticaria and found anti-HCV antibodies in 24% and HCV RNA in 22%. The control group consisted of 1692 healthy blood donors in whom the rate of antibody carriage was 1.1%. Several subsequent studies from France, the UK and Italy, however, did not confirm such an association. They found HCV antibodies in 0–2% of patients ($n=50$ –135) [48,50–53]. A case–control study [54] of 53 patients with urticaria in Iran did not find any relationship using an anti-HCV-enzyme-linked immunosorbent assay (ELISA) system [54]. In addition, systematic HCV screening of 110 patients with chronic urticaria and 110 sex- and age-matched controls identified HCV antibodies in one patient with urticaria and in one of the control group [51]. HCV-RNA could not be detected, excluding the concept that urticaria may occur in an early phase of HCV infection [51]. These authors reviewed the literature for urticaria and HCV infection (patients with urticarial vasculitis were excluded) including their own study and found a total of 30 described cases [51]. Moreover, on assessing skin diseases in 96 patients with chronic HCV infection only one case of urticaria was found [55]. In contrast, Jackson [56] concluded in his review that HCV antibody assessment by ELISA should be ordered in patients with chronic urticaria. A French group also investigated HGV by ELISA and polymerase chain reaction detecting a low positivity of 2% ($n=110$) in chronic urticaria [51].

Other viruses

Cases of viral infections with Epstein-Barr virus and cytomegalovirus (CMV) have been described in children and adults with chronic urticaria [57–59], but a systematic study is lacking. The same is true for influenza and parainfluenza viruses [57] and for HIV. Among 147 patients infected with HIV 3.1% suffered from chronic urticaria [60].

A neonate with angioedema due to intrauterine parvovirus B19 infection has been described [61]. However, on looking for parvovirus B19 in skin biopsies, DNA was found in 50% of chronic urticaria patients ($n=35$) and

64% of controls ($n=22$) [62]. Moreover, no differences in serum anti-parvovirus B19 immunoglobulin G and immunoglobulin M were found [62].

Bacteria

Infections with several bacterial pathogens have been described in chronic urticaria. Most of them were silent and persistent.

Helicobacter pylori

There is no matter of debate that the prevalence of *Helicobacter pylori* infection in chronic urticaria is similar to that found in the general population. This issue was recently reviewed [20]. However, the immune response to *H. pylori* may be different in chronic urticaria. Several pathogen–host interactions have been described in the pathogenesis of *H. pylori* infection [63]. In chronic urticaria it was demonstrated that *H. pylori*-infected patients demonstrate a higher prevalence of immunoglobulin G and in part also immunoglobulin A antibodies to the *H. pylori*-associated lipoprotein lpp20 than *H. pylori*-infected patients without chronic urticaria [64]. In addition, peripheral blood mononuclear cells of patients with chronic urticaria showed a significantly higher proliferation rate to heat-inactivated *H. pylori* antigens than healthy controls [65]. Recently evidence for an impaired clearance of immune complexes was found in *H. pylori*-infected patients with chronic urticaria [66]. Serum eosinophil cationic protein was significantly higher in chronic urticaria patients than in controls regardless of infectious status. In addition, gastric juice eosinophil cationic protein and gastric eosinophil infiltration were significantly higher in *H. pylori*-infected chronic urticaria patients than in non-infected patients [67].

Other data showed that *H. pylori* gastritis may lead to increased immunoglobulin E production, although there was no difference in mean densities of immunoglobulin E-containing gastric cells between *H. pylori*-infected and non-infected patients with chronic urticaria [68]. Moreover, there is additional evidence for the induction of an immunoglobulin E response by *H. pylori* [69–74].

A recent study [75••] addressed the effect of antibiotic therapy for chronic urticaria patients infected with *H. pylori*. Systematically reviewing existing studies with this topic revealed that resolution of urticaria was more likely when antibiotic therapy was successful in eradication of *H. pylori* than when patients were infected and did not achieve eradication [75••]. Ten studies met the inclusion criteria and when data from these studies were combined, eradication of *H. pylori* was both quantitatively and statistically associated with remission of urticaria, with an odds ratio of 2.9 (95% confidence interval 1.4–6.8; $P=0.005$). The authors concluded that

Table 1. Double-blind placebo controlled studies of *Helicobacter pylori* eradication in chronic urticaria patients

Verum treatment	Benefit ^a in <i>H. pylori</i> -eradicated patients	Benefit ^a in untreated <i>H. pylori</i> -infected patients	Study, country
Amoxicillin, Lansoprazole	1/3 (33%)	4/14 (29%)	[76], Switzerland
Amoxicillin, Metronidazole	8/11 (73%) ^b	9/13 (69%) ^b	[77], Austria
Omeprazole, Amoxicillin, Clarithromycine	4/9 (44%) ^c	1/7 (12%)	[78], Spain

^aComplete or partial remission of urticarial symptomatology. ^bPatients had chronic recidivant urticaria, i.e. symptom free intervals of several weeks.

^cComplete remission; significant improvement was found in more than 70%.

clinicians, after considering other causes of urticaria, should constitute (1) testing for *H. pylori*; (2) treating with appropriate antibiotics if *H. pylori* is present; and (3) confirming successful eradication of infection. The rate of remission of urticaria when *H. pylori* was eradicated was 30.9% (59/191) compared with 21.7% (18/83) when *H. pylori* was not eradicated, whereas the background remission rate among control subjects without *H. pylori* infection was 13.5% (10/74) [75**].

Looking at double-blind placebo controlled studies, only three have been published so far. In all of these studies only a few patients with proven *H. pylori* eradication could be evaluated (Table 1) [76–78]. *H. pylori* non-infected patients were not included. Moreover, only one study used the recommended triple treatment. Why this is important has been discussed in detail elsewhere [20].

A recent prospective, but non-comparative study from Japan [79] demonstrated remission of chronic urticaria in 73% of patients treated with triple therapy consisting of omeprazole, amoxicillin and clarithromycin. These patients were followed monthly for at least 1 year after cure of *H. pylori* infection.

In one of our own studies, patients were treated until *H. pylori* was eradicated, and frequently, patients needed two or more triple treatment courses [58]. Remission or improvement of chronic urticaria after *H. pylori* eradication (proven by histopathologic reexamination) was seen in 91% of *H. pylori*-positive patients. In contrast, symptoms decreased or disappeared in only 50% of untreated *H. pylori*-positive individuals, in 43% of *H. pylori*-negative individuals with urticaria of idiopathic origin and in 69% of patients in whom another trigger (e.g. chronic sinusitis) was successfully treated [58]. We found three patients in whom *H. pylori* was eradicated and subsequently chronic urticaria disappeared who demonstrated recurrence of chronic urticaria after intervals of 2, 2.5 and 3 years [20,36]. Of interest, we found recolonization with *H. pylori* by gastroscopy in all of them, and again their urticaria disappeared within 8–12 weeks after *H. pylori* eradication. Similarly, other authors found remission of chronic urticaria after elimination of *H. pylori* and a relapse with a reinfection, which again cleared after elimination [7].

Table 2. Abnormal serology for streptococci or staphylococci in chronic urticaria

Abnormal serology	Positive	Study
Antistreptolysin	37% (n = 504)	[85]
Antistreptolysin	19% (n = 220)	[86]
Antistreptolysin	10% (n = 99)	[58]
Antistreptolysin	37% (n = 325)	[36,59]
Antistreptolysin or antideoxyribonuclease B or antistreptokinase	42% (n = 145) ^a	[83]
Antistreptolysin or antideoxyribonuclease B or antistaphylolysin	35% (n = 20) ^b	[24]
Antistaphylolysin	1% (n = 504)	[85]
Antistaphylolysin	10% (n = 145)	[83]

^aAntistreptolysin (22%); antideoxyribonuclease B (28%); antistreptokinase (77%). ^bChildren.

H. pylori infection has also been described to trigger chronic urticaria in children [24] and a recent article described a significant higher prevalence of the extra-digestive symptom of chronic urticaria in *H. pylori*-positive children than *H. pylori*-negative children [80]. Hereditary and acquired angioedema may also be exacerbated by infection with *H. pylori* and, interestingly, *H. pylori* eradication resulted in an increase of complement factors [81,82].

Streptococci/staphylococci

Group A streptococci are known as triggers of post-infective syndromes. They produce exocellular toxins (streptolysine) and enzymes (jaluronidase, deoxyribonuclease) and possess a special cell wall component (antigen M) that is able to elicit a specific antibody response. Antibodies to streptococcal and staphylococcal antigens have been found in chronic urticaria (Table 2) [36,58,59,83–86], but a comparative and systematic treatment study is lacking.

Among 13 patients with antibodies to streptococci, four showed remission of chronic urticaria after erythromycin [87]. Others found abnormally high antistreptococcal antibodies in nine patients with chronic urticaria and treatment with amoxicillin, plus colloidal bismuth if they were also *H. pylori* positive, resulted in benefit in eight of the nine (six asymptomatic, two significantly improved) [88]. We found complete remission of urticaria in all infected children after cefuroxim or amoxicillin [24].

Other microbial processes

There are several case reports of dental infections associated with chronic urticaria [89–92]. For example, a 45-year-old woman had severe antihistamine resistant chronic urticaria and a high C-reactive protein level [90]. Dental radiographs showed seven periapical abscesses (culture, *Veillonella parvula* and *Streptococcus oralis*). During teeth extraction severe general fatigue, high fever, severe and generalized urticarial eruptions occurred. After treatment of all abscesses and root canal therapy anti-urticarial medication could be stopped and urticaria was absent [90]. Investigating unselected patients with chronic urticaria, abnormal dental radiographs were found in 2–22% [58,59,83,93–96].

Improvement of urticaria after dental treatment was found in five of seven cases [95], three of 10 cases [94], and four out of eight cases [96], respectively. However, a comparison of six untreated and five treated patients showed no difference with respect to urticaria [97]. Moreover, a very recent study investigating 66 patients suffering from acute urticaria or chronic urticaria versus 65 age- and sex-matched healthy controls did not find a correlation between chronic dental infections (caries, periapical lesions, non-vital and missing teeth) and urticaria [98].

Radiographs identifying sinusitis have been described in 2–9% of unselected patients with chronic urticaria [58,94–96]. Two other studies [36,83] regarded ear, nose and throat infections as a triggering cause in 17 and 28%, respectively [36,83]. Another study [96] did not separate ear, nose and throat and dental focal infections that were found in 15% ($n=107$). However, the role of treatment on the course of the urticaria is still ill defined. Single cases resulting in an improvement have been described [58,96]. In contrast, in a randomized study urticarial symptomatology was similar in patients with chronic urticaria who received surgery for sinusitis compared with untreated patients [97]. In contrast, in nine of nine patients with acquired angioedema and chronic sinusitis symptoms improved after antibiotic treatment and in six of nine patients sinusitis was silent and only diagnosed by computed tomography [99].

In addition, urogenital tract infections have been described to trigger chronic urticaria. Among 220 patients 12% suffered from vaginitis and 8% from cystitis although treatment did not result in urticaria improvement (not specified) [86,100]. Furthermore, there is recent evidence for persistent yersiniosis. A strikingly high prevalence of abnormal yersinia immunoglobulin A and immunoglobulin G antibodies with several bands in immunoblots has been described in chronic urticaria (31% of 145 patients [83]; 39% of 93 patients [36,59,84]). In several cases treatment with chinolones resulted in

partial or complete remission of urticaria although a controlled systematic study is missing.

Parasites

Only anecdotal series of cases documented a link between chronic urticaria and parasites such as *Toxocara canis*, *Giardia lamblia*, *Strongyloides stercoralis*, *Trichuris trichiura* and *Blastocystis hominis*. A controlled study published in Spain [101] found a statistical correlation between *B. hominis* infection and the symptom urticaria (OR=3.19). In addition an interesting case has been described in which hypersensitivity to NSAIDs and chronic urticaria was cured by treatment of *B. hominis* infection [102]. Among 220 patients with chronic urticaria 10 showed parasites (not specified) and six of them eosinophilia [86]. In four of these cases urticaria cleared after antiparasitic treatment [86].

After an initial study [103] demonstrating *T. canis* antibodies in 65% of patients with chronic urticaria ($n=51$), compared with 21% in controls ($n=81$), others found a seroprevalence of 20% in chronic urticaria ($n=128$) versus 13% in controls ($n=236$) [104] and of 8% in chronic urticaria ($n=110$) and of 13% in children with the condition and of 30% in controls [105]. Using home-made ELISAs fasciolosis but not toxocariasis seropositivity was significantly higher in chronic urticaria patients than in healthy controls ($P<0.05$) [106].

Giardia lamblia has been found by serology in 2–12% of patients with chronic urticaria [107–110], sometimes with and sometimes without benefit after treatment. Successful treatment for strongyloides has been described in one case [111].

Sometimes improvement of urticaria has been described after antiparasitic treatment, but the data are not very convincing.

Fungi

Mucocutaneous candidosis has been associated with chronic urticaria [112–118] but randomized controlled trials are missing. In addition, there is a little, but unconfirmed, evidence for dermatophytosis [119,120]. It is generally accepted that massive candidosis should be treated adequately, but that in the past the role of fungi may have been overestimated as causative in chronic urticaria [7].

Infection and urticaria: summary

At present, there is international consensus that infections (viral, bacterial, fungal and parasitic) are potential pathomechanisms of urticaria and that the following diagnostic tools are possible but not obligatory in chronic urticaria: search for *H. pylori* and stool for ova or parasites [121]. Other guidelines have only recommended the

search for parasites [122]. However, looking at the literature, there are no arguments over why the search for parasites but not for other infectious processes is recommended.

From the literature it can be seen that the prevalence of infections, whether bacterial, viral, parasitic or fungal, appears not to differ from the general population (for yersinia this has to be demonstrated). However, there is a very large number of reports demonstrating benefit after eradication of infectious processes and it is hard to believe that all of these are due to spontaneous remissions. Nevertheless, available studies have common flaws and cannot be reviewed as a meta-analysis or according to evidence-based medicine rules. The best evidence exists for *H. pylori* but well designed randomized controlled treatment studies are lacking. This may be due to a lot of confounding factors that have to be considered, such as (1) the frequency and relevance of infectious diseases varies between different patient groups and in different regions; (2) patients may have not only multiple infectious processes, but also multiple other triggering factors (e.g. non-allergic hypersensitivity reactions, autoreactivity, malignancy (Fig. 1); (3) spontaneous remission of chronic urticaria is possible; (4) placebo treatment is a problem in heavily affected patients; (5) the eradication of the infectious process has to be proven; (6) objective evaluation of urticarial symptomatology is a problem; and (7) as yet the pathophysiological link between infection and urticaria is unclear.

Infection and autoimmunity

Certain subgroups in chronic urticaria demonstrate autoimmunity. About 14% of patients have autoantibodies to thyroid [10] and 30–50% histamine releasing antibodies to the high affinity immunoglobulin E receptor (FcεRI) or to immunoglobulin E [12,123]. Moreover, the serum of patients with positive ASST contains undefined immunoglobulin-independent stimulators of mast cell/basophil activation resulting not only in histamine release, but also in cysteinyl leukotriene production and basophil activation (CD63 surface expression) [15]. In this regard, complement activation may play a major role but does not explain all the functional effects [14]. In addition the association of certain human leukocyte antigen class II alleles supports an autoimmune pathogenesis in a subset of patients with chronic urticaria [35].

There is emerging evidence that infection-associated inflammation is a major contributor to autoimmune processes [124,125]. Interestingly, we and others showed a significant positive correlation between *H. pylori* infection and a positive ASST [83,126]. Indeed, in some patients ASST becomes negative after *Helicobacter*

eradication (Wedi *et al.*, unpublished observations). Moreover, recent data showed a significant difference in the prevalence of *H. pylori* infection between autoimmune urticaria with and without thyroid autoimmunity (90.9% versus 46.7%; $P=0.02$). Autoimmune thyroiditis was connected with cytotoxin-associated gene (*CagA*) positive *H. pylori* strains, as the *H. pylori*-specific immunoglobulin G antibodies revealed significant differences in the prevalence of 120 kDa immunoblot proteins ($P<0.05$). The results strengthen the possibility of cross-reactivity being triggered between *CagA*-positive *H. pylori* strains and some other organ-specific autoimmune diseases such as autoimmune urticaria and autoimmune thyroiditis. This indicates a possible role of *H. pylori* in triggering autoimmune urticaria in at least a subgroup of patients [127]. In immunologically predisposed individuals, *H. pylori* infection may result in the manifestation of a latent autoimmune pathomechanism.

There is no debate that autoimmune urticaria is associated with autoimmune thyroiditis [128,129]. In this aspect it may be of note that infection with yersinia is linked to autoimmune thyroiditis [130]. In addition, internalization of streptococci may lead to carriage and persistence of streptococcal infection [131], which has been associated with autoimmunity [132].

Molecular mimicry

Due to the apparent relationship of autoreactivity and associated infections in chronic urticaria several years ago we employed epitope mimicry as a possible mechanism for urticaria development [36,58,133]. This concept has also been discussed by others [134,135]. The link between cross-reactive antibodies produced during infection and the subsequent development of autoimmunity is well known and has been shown in several animal models for allergic encephalomyelitis, experimental myocarditis, experimental autoimmune uveitis, and keratitis. In addition, it has been shown that immunization of mice with peptides homologous to various microbial pathogens resulted in the induction of autoantibodies along with antiphospholipid syndrome manifestation [136]. In chronic urticaria *H. pylori* might contain chemical structures that mimic Lewis blood group antigens [36] or lpp20 might cross-react with a skin component [64]. *Yersinia enterocolitica* might cross-react with thyroid antigens [130] and streptococci with collagen-like structures [137].

Another mechanism with relevance to the influence of infection on urticaria may be antigenic competition, in which the immune response to an antigen is decreased by a concomitant immune response against an unrelated antigen [21]. Otherwise inflammation may cause an increase in the immunogenicity of autoantigens.

Conclusion

Although by definition all chronic urticaria cases must have started as acute urticaria and the acute form is mainly caused by infections, there are not enough clear-cut data to confirm a direct link, that fulfils Koch's postulations, between infections and chronic urticaria. Various correlations ranging from reasonably convincing to less so have been published. The best data come from bacteria: *H. pylori* infection. It is no matter of debate that the prevalence of infections in chronic urticaria is similar to control groups. However, patients with chronic urticaria may differ in their immune response to infections or may develop infection-induced autoreactivity/autoimmunity. This led to the employment of epitope mimicry as a possible mechanism for chronic urticaria development. The often (transient) susceptibility to developing non-immunologic hypersensitivity reactions, for example to aspirin or food additives, may also fit this concept. Clinical data support the involvement of infectious agents in the pathogenesis of urticaria, proving its existence can be quite a challenge. It should not be overlooked that chronic urticaria is a reaction pattern caused by several internal and external factors (Fig. 1). The pattern is uniform and identifiable, but the triggers are multiple and varied, some of them may be infectious. We clearly need randomized, double-blinded and placebo-controlled studies including the best characterized patients, adequate diagnostic schedules, sufficient treatment protocols, confirmation of healing, and adequate control groups to establish a role of infections in chronic urticaria. Despite the complexities involved in such studies, the possible reward of developing a still lacking specific and efficient treatment for the condition makes them well worth the effort.

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