is, gastritis and esophagitis is healed.[69] However, similar to infections, it is not easily possible to discern whether any of these are relevant causes of CSU but should be treated as many of them may be also associated with development of malignancies.

5.2.4 | Stress

Although the mechanisms of stress-induced exacerbation are not well investigated, some evidence indicates that disease activity in patients with CSU can be linked to stress.[70] Further studies are needed to characterize the prevalence and relevance of CSU exacerbation by stress as well as the underlying mechanisms.

5.2.5 | Reduction of functional autoantibodies

Direct reduction of functional autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients.[61] Due to limited experience and high costs, this therapy is suggested for autoantibody-positive CSU patients who are unresponsive to all other forms of treatment. Autoantibodies and potentially activated T cells may also be reduced by immunosuppressive medication, such as cicloporin.[71]

5.2.6 | Food

IgE-mediated food allergy is extremely rarely the underlying cause of CSU.[72,73] If identified, the specific food allergens need to be omitted as far as possible, which leads to a remission within less than 24 h. In some CSU patients, pseudoallergic reactions (non–IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been observed.[72-77] A pseudoallergen-free diet, containing only low levels of natural and artificial food pseudoallergens, has been tested in different countries,[78] and also, a low histamine diet may improve symptoms in some patients.[79] Those diets are controversial and as yet unproven in well-designed double-blinded placebo-controlled studies. When used they must usually be maintained for a minimum of 2–3 weeks before beneficial effects are observed. This kind of treatment requires cooperative patients, and success rates may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effects of natural and artificial ingredients of food on urticaria.

5.3 | Inducing tolerance

Inducing tolerance can be useful in some subtypes of CIndU. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where a rush therapy with UV-A has been reported to be effective within 3 days.[80] However, tolerance induction is only lasting for a few days; thus, a consistent daily exposure to the stimulus just at threshold level is required. Tolerance induction and maintenance are often not accepted by patients, for example, in the case of cold urticaria where daily cold baths/showers are needed to achieve this.

5.4 | Symptomatic pharmacological treatment

5.4.1 | The targets and aims of pharmacological therapies and the need for continued treatment

Current recommended treatment options for urticaria aim to target mast cell mediators such as histamine, or activators, such as autoantibodies. Novel treatments currently under development aim to silence mast cells via inhibitory receptors or to reduce mast cell numbers. The overall goal of all of these symptomatic treatments is to help patients to be free of signs and symptoms until their urticaria shows spontaneous remission. To achieve this, pharmacological treatment should be continuous, until no longer needed. Non-sedating 2nd generation H_1-antihistamines, for example, should be used daily, to prevent the occurrence of wheals and angioedema, rather than on demand. This is supported by their safety profile (safety data are available for several years of continuous use), the results of randomized controlled trials and real-life studies,[81,82] and their mechanism of action, that is, their inverse agonist effects on the H_1 receptor, stabilizing its inactive state. Some patients with CIndU can benefit from short-term prophylactic antihistamine treatment before relevant trigger exposure.

5.4.2 | H_1-antihistamine treatment

H_1-antihistamines have been available for the treatment of urticaria since the 1950s. The older 1st generation H_1-antihistamines have pronounced anticholinergic and sedative effects, and many interactions with alcohol and other drugs, such as analgesics, hypnotics, sedatives, and mood-elevating drugs, have been described. They can also interfere with rapid eye movement (REM) sleep and impact on learning and performance. Impairment is particularly prominent during multi-tasking and performance of complex sensorimotor tasks such as driving. In a GA²LEN position paper,[83] it is strongly recommended not to use 1st generation H_1-antihistamines any longer in allergy both for adults and especially in children. This view is shared by the WHO guideline ARIA.[84] Based on strong evidence regarding potentially serious side effects of 1st generation H_1-antihistamines (lethal overdoses have been reported), we recommend against their use for the routine management of CU as first-line agents.

Modern 2nd generation H_1-antihistamines are minimally or non-sedating and free of anticholinergic effects.[85] However, two 2nd generation H_1-antihistamines, astemizole and terfenadine, are shown to have cardiotoxic effects in patients treated with inhibitors of the cytochrome P450 (CYP) 3A4 isoenzyme, such as ketoconazole or erythromycin. Astemizole and terfenadine are no longer available in most countries, and we recommend that they are not used.