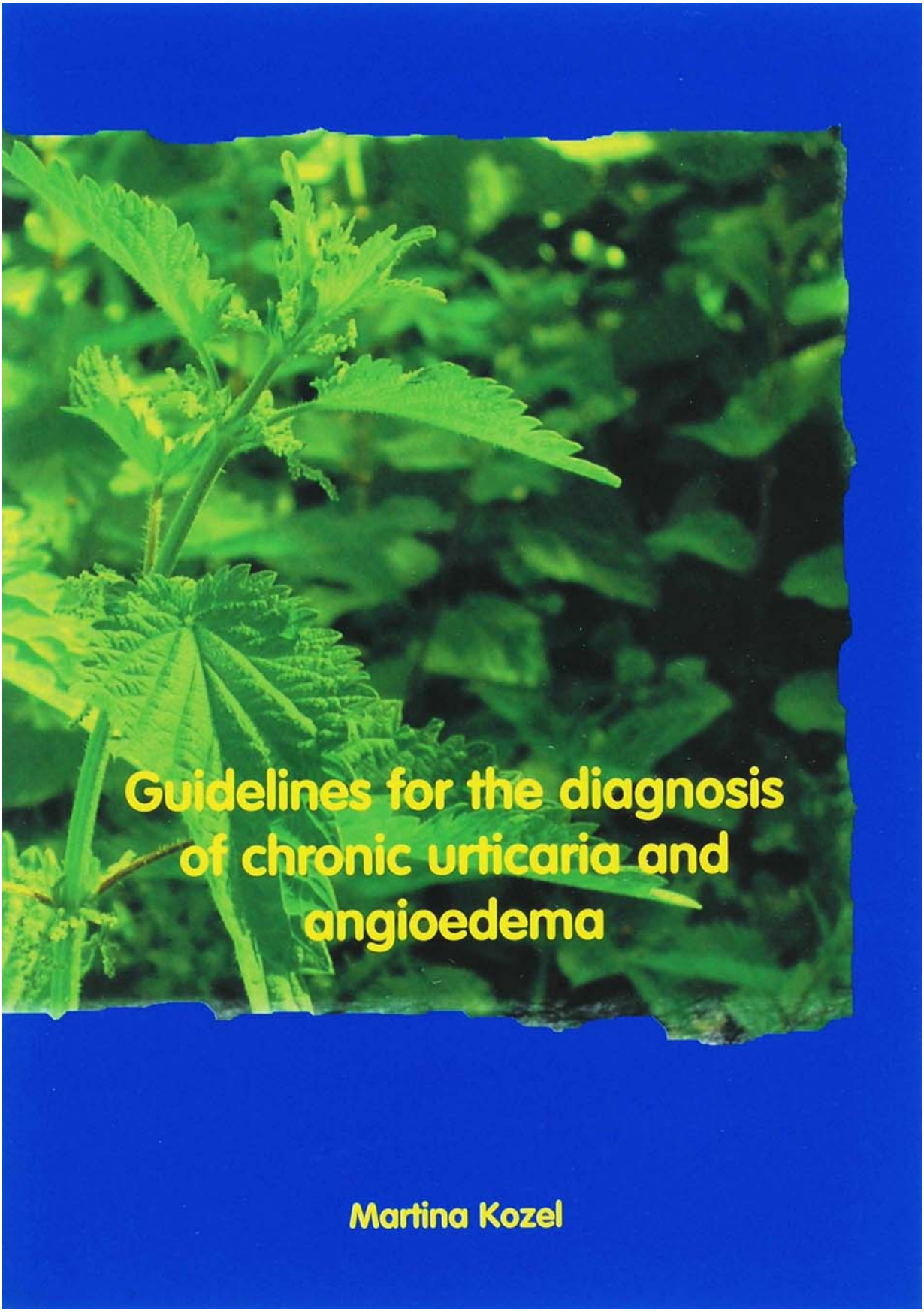

Guidelines for the diagnosis of chronic urticaria and angioedema

Martina Kozel

GUIDELINES FOR THE DIAGNOSIS OF CHRONIC URTICARIA AND ANGIO-EDEMA

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To my parents

CONTENTS:

Chapter 1

Introduction and aims of the thesis

Chapter 1

HISTORY

Hippocrates (460-377 BC) mentioned in his 'About Diseases' the occurrence of elevated lesions, resembling the lesions caused by nettles and mosquitoes, but less itching, in patients with gastrointestinal disorders.[1] He called the disorder *knidosis*, which is the Greek word for nettle (*Urtica dioica*), the well known stinging plant from which the term urticaria is derived.

DEFINITION AND CLASSIFICATION

Urticaria (nettle rash, hives, wheals) is a transient eruption of erythematous swellings of the dermis, usually associated with itching.[2] Angioedema (angioneurotic oedema, giant oedema, Quinke's oedema) consists of transient swellings in the deeper dermal, subcutaneous and submucosal tissues.[2] Urticaria and angioedema often occur together. For convenience, both complaints are often summarized as urticaria. Urticaria and angioedema can be subdivided into different subgroups of disorders based on duration and underlying cause. The disease duration allows for distinction between acute and chronic urticaria. By arbitrary definition, acute urticaria lasts for maximal six weeks. Acute urticaria is the most common form of urticaria. Chronic urticaria is defined as hives lasting longer than six weeks.[3] In approximately 10% of the patients with urticaria or angioedema the symptoms will maintain for more than six weeks.

EPIDEMIOLOGY

Urticaria and angioedema are common disorders: about 12-22% of the population will have urticaria or angioedema at least once in their lifetime.[4,5] The incidence of urticaria was 1.85% per year in a study performed during 10 years in a dermatology department in Sweden.[6] Prevalence percentages reported in the literature varied between 0.05-35% depending on the age of the included patients, the geographic region and the preselection of the patients.[7] Low values (less than 1%) were obtained from field studies of the general population, percentages between 0.27-2.1% were calculated in family practices,[7,8] percentages between 1-4% were found in patients consulting dermatological

outpatient departments, and percentages higher than 10% were identified in preselected patients in allergy or dermatology clinics.[7] In the Netherlands 1.4-2.4% of the patients visiting Dermatology outpatient departments had urticaria or angioedema as a major complaint.[9,10] In a Dutch study in patients visiting general practitioners, an incidence of acute and chronic urticaria of 4.3 per 1000 patients/year and a prevalence of 5.0 per 1000 patients/year was reported; 5.1% had urticaria longer than 4 weeks, and 4.1% were referred to a dermatologist.[11] The incidence of urticaria in a general practice, with ± 4000 patients, in 1953 was 1.8%.[12] 53 of the 72 patients with urticaria had symptoms for longer than four weeks.[12] In another study 79 patients with urticaria were seen in a university family practice center during 1976 to 1983. In 70% of the patients the urticaria lasted less than six weeks.[8] The distribution of gender varies between different studies, 31% to 53% were male patients.[7] Urticaria is a disease of the middle-aged, with a peak in frequency between the second and the third decade. While acute urticaria is mainly a disease with a peak of frequency between the ages of 10 to 40 years, chronic urticaria occurs more often between the ages of 20 to 60 years, and physical urticarias were most frequent seen in the age groups of 10 to 40 years.[7] An increased incidence of urticaria has not been recorded during the past years.[13]

PATHOPHYSIOLOGY

The primary process of urtication is vasodilation followed by edema resulting from plasma transudation due to increased subdermal capillary and venular permeability. Hives are the result of mast cell degranulation and release of potent mediators from storage granules, predominantly histamine.[14] The clinical improvement on treatment with H1 antihistamines underlines the role of histamine as a major mediator in urticaria. Other vasoactive and chemoattractant mast-cell mediators, and secondary release of non-mast cell mediators from inflammatory cells, may amplify and prolong the wheal.[2] Mast cells react to several immunologic, non-immunologic, chemical and physical stimuli, cytokines, and complement activation. In the classical type I immunoglobulin E (IgE) mediated immune reaction, mast cell degranulation is caused by allergen-induced crosslinking of at least two IgE molecules bound to their high affinity IgE-receptor on the mast cells, the FcεRIα receptor. Examples of this mechanism are: penicillin and

other antibiotics, venoms, insulin, allergen extracts, and some foods such as crustaceans, peanuts, and many others. Several recent studies in patients with chronic idiopathic urticaria have revealed the presence of circulating autoantibodies against the α-subunit of the high affinity IgE receptor on mast cells (FcεRIα), which can cause crosslinking and mast cell degranulation.[15-18] These autoantibodies, which are predominantly of the IgG subtype (IgG1, IgG3),[19] may be present in 30-60% of the patients with chronic idiopathic urticaria.[15,20,21] This finding may be relevant for the ethiopathogenesis of chronic urticaria, and may have implications for future treatment.[17,22] Complement activation is often provoked by immune complexes (e.g., in leukocytoclastic vasculitis, serum sickness, and transfusion reactions), and can also result in mast cell activation. Non-allergic mast cell activation can occur by a variety of stimuli such as radiocontrast media; neuropeptides such as substance P; drugs such as opiates, aspirin, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors; and some foods, for instance strawberries.

HISTOPATHOLOGY

The histopathology of urticarial wheals usually show the following characteristics: edema of the papillary and reticular dermis, dilated lymphatic vessels and small venules of the upper dermis, and a variable perivascular cellular infiltrate in the dermis consisting of lymphocytes, monocytes, neutrophils, and eosinophils.[23] Electron microscopy shows mast cell degranulation. The number of mast cells seems to be increased in both lesional and uninvolved skin of acute, chronic, and physical urticarias.[24] Urticarial vasculitis is a disease which presents clinically with hives, but because of the histopathological changes (leukocytoclastic vasculitis) it differs from urticaria. Characteristic histopathological changes include endothelial swelling, an intra- and perivascular cellular infiltrate with neutrophils and leukocytoclasia, erythrocyte extravasation, and fibrinoid deposits in and around blood vessels.[2,25] Immunopathological changes are IgM, IgG, IgA, C1q, C4, C3, and fibrinogen deposits in the upper dermal vessels and at the dermoepidermal junction.[25]

CLINICAL ASPECTS

Urticaria lesions are well-demarcated eruptions of transitory, usually itchy, erythematous skin swellings that can recur for months or years. The lesions can occur everywhere on the body, including the palms and the soles. The size can vary from a few millimeters to large body areas. The shape can vary from round, annular, to irregular patterns. Urticaria affects the superficial dermis and bouts of urticaria can last for 30 minutes to 24 hours. Most patients experience urticaria as intense pruritic and sometimes even painful. In general, patients rub rather than scratch their lesions and many patients experience the itch more intensively in the evening.[26] Urticaria and angioedema occur simultaneously in about 50% of the patients.[2] Angioedema affects the deep dermis, the subcutaneous or submucosa tissues. Bouts of angioedema can last for 24 to 72 hours. The lesions in angioedema are pale and sometimes painful. Preferential areas are the lips, eyelids, tongue, hands, feet, genitals, pharynx and larynx. In both urticaria and angioedema, especially in severe bouts, extra-cutaneous symptoms can occur, like malaise, headache, vomiting, abdominal pain, diarrhoea, hoarseness, stridor, dizziness, arthralgia, and syncope.

Chapter 1

CAUSES OF URTICARIA AND ANGIOEDEMA

Physical urticarias

In this subgroup of urticaria specific physical stimuli elicit reproducible hives. Physical urticaria was identified in 12-57% of the patients as the cause of urticaria in different studies in the literature performed from 1937 to 1985, depending on the selected cohort and the referral pattern.[27] These studies included 120 to 500 patients. The most common types of physical urticaria and their characteristics are summarized in the following table.[28-30]

Table 1. Characteristics of physical urticarias

Type of urticaria	Eliciting stimulus	Time of onset	Duration
dermographism	firm stroking of the skin	within 5 min	1 - 3 hrs
pressure urticaria	locally applied weight for 20 min	½ to 10 hrs	8 - 72 hrs
cholinergic urticaria	physical exercise, hot shower or bath	within 20 min	½ - 1 hrs
cold urticaria	cold contact for 20 min, cold air or wind	within 5 min	1 - 3 hrs
solar urticaria	UV-light induces hives in exposed areas	within 15 min	¼ - 3 hrs
heat contact urticaria	contact with heat object or water	within 15 min	½ - 1 hrs
aquagenic urticaria	contact with water of any temperature	within 20 min	½ - 1 hrs
exercise anaphylaxis	supervised exercise (shortly after meal)	within 5 min	½ - 1 hrs

Dermographic urticaria

Literally, dermography means skin writing.[28] Synonyms are factitious urticaria and dermographism. In dermographic urticaria the skin is responding to stroking, friction, rubbing, or scratching with a rapidly appearing and itchy, often linear wheal formation. The prevalence of dermographism in the healthy population ranges from 1.4 to 5%.[29] This condition can occur in all age groups, with a peak prevalence in young adults.[29] It may last for many years.

Delayed pressure urticaria

In delayed pressure urticaria often tender and painful swellings develop on sites were pressure was applied at an earlier point in time. This condition may be associated with malaise, fever, arthralgia, leukocytosis and a moderate raised erythrocyte sedimentation rate.[29,30] The condition may last for many years and in most patients, unfortunately, anti-histamines are of little value. Oral corticosteroids (prednisone 10 to 30

mg) are helpful, but have adverse side effects when used for a long period of time.[31] Potent topically applied corticosteroids (clobetazol propionate 0.05%) can reduce the clinical response to pressure on the skin.[32] Other therapies have been used and presented in case reports: dapsone (50 to 100 mg/day),[29] sulfasalazine (500 to 2000 mg/day),[33] and danazol (600 mg/day; lectures at the international clinically orientated ESDR symposium Urticaria 2000 in Berlin, Germany, 20 - 21 september 2000). Nonsteroidal anti-inflammatory drugs (NSAIDs) can suppress the painful sensation,[31] but can aggravate coexisting ordinary urticaria.

Cholinergic urticaria

Stimuli which raise the core temperature of the body, like exercise, warmth, or emotional stress can elucidate 1 to 5 mm pruritic pinpoint wheals on an erythematous base, in most patients on the upper part of the body. This condition is mild but common. An overall prevalence of 11% was identified in high school and university students (15 - 35 years of age).[34] Antihistamines are helpful in suppressing the itching and whealing. After provoking the urticaria some patients experience a refractory period of 8 to 24 hours. These patients can use physical exercise to suppress the symptoms for a special event.[2,29]

Cold urticaria

Itching and whealing of the skin may occur after exposure to cold, especially cold wind, cold rain, or swimming in cold water. A few patients experience edema of the oral cavity and pharynx after consuming cold beverages or ice-cream. Total body exposure to cold can cause generalized anaphylaxis, and drowning is a potential hazard for patients who swim in cold waters.[30] 96% of the patients with cold urticaria have idiopathic cold urticaria.[35] Cold urticaria syndromes are rarely associated with underlying diseases, such as malignancies, systemic leuko-cytoclastic vasculitis, and infectious diseases.[36]

Solar urticaria

Solar urticaria can be provoked by ultraviolet waves (UV) ranging between 280 to 760 nm (UVB, UVA, and visible light).[29] It is a very rare condition. Similar skin lesions can occur in systemic lupus erythematodes, porphyria, drug-induced photoallergic reactions, and polymorphous light eruption.[30] The hives are limited to the sun exposed area. They can be small, but they can as well cover large parts of the to light exposed body surface. Induction of tolerance by UVB, UVA, or

PUVA (psoralens plus UVA-light) is a possible treatment. Topical sunscreens, antimalarials, and/or antihistamines are other treatment options.[29]

Adverse drug reactions

Adverse reactions to drugs or diagnostic reagents complicate the course of approximately 2 to 5% of hospitalized patients.[37] Adverse drug reactions are mostly maculopapular or urticarial rashes. Antimicrobial agents are the most frequent cause of adverse drug reactions, but every drug can provoke a cutaneous reaction. Drug-related risk factors for an adverse drug reaction, in general, are the propensity of the specific drug to activate an immune response, the route of administration (topical treatment is more sensitizing than oral or parenteral treatment), dose and duration of therapy (low doses of drugs and single doses or short courses appear to be less likely to sensitize than high-dose, prolonged therapy).[38] Patient-related risk factors are the multiple drug allergy syndrome (a patient who had an adverse drug reaction once will have a 10-fold increased risk of reacting to different classes of drugs in the future), and genetic factors (children of parents with an adverse drug reaction have a 15-fold increase risk of an adverse drug reaction compared to children of parents without an adverse drug reaction).[38] Drugs frequently responsible for urticaria and/or angioedema are: antimicrobial agents, antiphlogistic and analgetic drugs, sedatives and hypnotics, anti-epileptics, angiotensin-converting enzyme inhibitors, blood products and blood substitutes, contraceptives, monoclonal antibodies, and antihistamines.[38,39]

Adverse food reactions

The role of adverse food reactions is controversial, reported frequencies range from 5 to 73%, probably depending on patient selection and the variation in the way of testing (history, elimination diet, oral provocation, laboratory tests, double-blind placebo-controlled challenge).[40,41] Extra cutaneous clinical manifestations of food allergy are gastrointestinal complaints such as oral allergy syndrome, vomiting, and diarrhoea. The mechanisms involved in adverse food reactions are: IgE-mediated reactions (e.g. fish, crustaceans, milk, nuts), vasoactive amines (e.g. cheese, bear, wine, fish), and pseudoallergic mechanisms (e.g. food additives, natural salicylates and benzoates in food).[39]

Inhalants
Urticaria due to inhalant allergens is rare. It can occur in sensitized patients, especially if they work in a surrounding were these aeroallergens are produced or are present (e.g., flour, pharmaceutical- or chemical industry; latex production or utilization). The most common clinical manifestation of an allergy to inhalants is asthma and rhinitis.[39]

Contact urticaria
Itch and hives confined to the contact area or generalized urticaria, combined with angioedema or anaphylaxis can occur following skin contact with a specific allergen in sensitized individuals. The eliciting agents may cause whealing by different mechanisms, e.g. IgE-mediated mechanisms (latex, foods, plants, drugs, cosmetics, animal products, and industrial products), non-immunological mechanisms (plants and animals with nettle hairs), histamine liberators (spices, fragrances, drugs, preservatives, and metals),[2] and yet not identified mechanisms. The reaction occurs mostly within 30 minutes. Contact allergy to natural rubber (latex) is an increasing problem in health care workers. 3 to 17% of health care workers have specific IgE antibodies.[42-46] In 48% of patients with a spina bifida a sensitization to latex was identified.[47] The prevalence of an allergy for latex in the general population is less than 1%.[48,49] Therefore, routine testing for specific IgE in patients undergoing surgery is not (yet) performed.

Infections and infestations
Bacterial infections are a very rare cause of urticaria.[50] More recently, an infection with Helicobacter pylori has been suggested as a possible cause for chronic urticaria; in most controlled prospective studies no relationship could be identified.[51-53] Viral infections are associated with acute or chronic urticaria. In one study upper respiratory tract infections were responsible for 40% of acute urticaria in adults.[54]
Mononucleosis infectiosa, hepatitis B and C, especially in the prodromal phase are associated with urticaria or angioedema.[39] The role of fungal infections, especially candida infections is controversial. Intestinal parasites as a cause of urticaria is very rare in both developed and developing countries, and only observed in patients traveling in or living in the (sub)-tropics.

Internal diseases

The following autoimmune diseases are associated with chronic urticaria: systemic lupus erythematodes (SLE), Still's disease, Sjögren's syndrome, rheumatic fever, and polymyositis.[39,55] The following clinical manifestations may point to an underlying connective tissue disease: lesions persist for longer than 24 hours; lesions are painful rather than itchy; lesions leave residual purpura, bruising, or staining; lesions are combined with other complaints such as joint pain, or malaise; elevated ESR; lesions with histopathological changes characteristic for a leukocytoclastic vasculitis; and a poor response to antihistamines.[26,55] The same clinical manifestations can be seen in urticarial vasculitis syndromes. Extra cutaneous symptoms of urticarial vasculitis are arthralgias in 50 to 75%. In 20 to 50% of these patients hypocomplementaemia can be identified.[2,25] Patients with hypo-complementaemia more often have involvement of the kidneys, lungs, and eyes than patients with normocomplementaemia.[25] Another rare internal cause is IgM-paraproteinemia, like in Schnitzler' syndrome (urticarial vasculitis with monoclonal gammopathy), which presents with bone pain, hyperostosis, intermittent fever, and malaise.[55]

Hereditary angioedema is a very rare disorder which is transmitted in an autosomal dominant way, but may occur spontaneously. In hereditary angioedema the synthesis (in 85% of the patients) or the function (in 15% of the patients) of the C1 esterase inhibitor (C1-INH) is abnormal.[56] Consequently, the level of the complement C4 is decreased. The onset is usually in early childhood with recurrent swelling of the skin and mucous membranes, especially in the oral cavity, the larynx, and the intestine. The swellings can occur spontaneously or after local trauma.[57] Acute attacks can be treated with C1-INH concentrate, available from the Red Cross Blood Transfusion Service in Amsterdam. Tranexamic acid can be used in children and during pregnancy as prophylaxis. Prophylactic treatment can best be achieved by danazol and stanazol, both are equally effective. The side-effects of these androgens are hepatic dysfunction, hirsutism, and menstrual irregularities.[58] These drugs can not be used during pregnancy. In hereditary angioedema adrenaline, corticosteroids, and antihistamines are ineffective.

Malignancies

In a large epidemiological study no association between chronic urticaria and malignancies could be found.[59] Of 1155 patients with chronic urticaria, a malignancy was diagnosed in 36, while the expected number was 41. Acquired C1-INH deficiency is associated with lympho-

proliferative disorders. In patients with lymphoproliferative disorders a prevalence of 0.5% of symptomatic acquired C1 inhibitor deficiency, presenting as angioedema, was observed.[60] In another study, the relationship between urticaria and malignancies was evaluated in a prospective 10 year follow-up study including 6913 allergic adults. The relative risk of developing leukemia, lymphoma, or myeloma for patients with a history of hives was 7.89 (95% confidence interval, 3.13 to 19.89), but the frequency was very low.[61]

Combination of physical urticarias and idiopathic urticaria
The combination of physical urticaria and chronic idiopathic urticaria is described in the literature.[50] For instance patients may have ordinary urticaria and dermographism simultaneously. Another example is the combination of delayed pressure urticaria and idiopathic urticaria.[62-65]

Idiopathic urticaria
In the past extensive and costly routine laboratory investigations were performed (provocation tests, blood chemistry, allergy tests, screening for infections, complement profile, screening for autoimmune diseases and malignancies) to exclude an underlying disease. Despite these extensive laboratory investigations, 70-90% of chronic urticaria and/or angioedema remained idiopathic.[11,50,62,66-68]

URTICARIA IN CHILDREN

Urticaria in children can be acute or chronic. Acute urticaria is more common in childhood. In table 2 we present the percentages of chronic urticaria in the different study populations, which included children with both acute and chronic urticaria.[69-78] An explanation for the differences in the proportion of chronic urticaria may be the variation in geographical region, the kind of setting (secondary or tertiary care center), or the referral pattern.
The identified causes of acute and chronic urticaria reported in the above mentioned studies are shown in percentages in table 3.[69-78]
In two studies data were available on the percentage of identified causes in children with chronic urticaria only. Harris et al. performed a retrospective study including outpatients in the USA; Volonakis et al. prospectively investigated outpatients in Greece. The percentages of identified causes in these two studies are presented in table 4.[79,80]

Table 2. Proportion of chronic urticaria in children with urticaria.

Author(s)	n*	% Chronic urticaria	Study design**	Setting ■	Country
Sehgal (1975)	44	9	pros.	outp.	India
Bonifazi (1977)#	62	30	pros.	outp.	Italy
Kauppinen (1984)	163	34	retros.	inp.	Finland
Tuchinda (1986)	142	13	pros.	outp.	Thailand
Sörensen (1987)	79	42	retros.	outp.	Denmark
Moreno (1988)	161	7	pros.	outp.	Spain
Legrain (1990)##	40	5	retros.	inp.	France
Ghosh (1993)	44	80	retros.	outp.	India
Mortureux (1998)###	57	5	pros.	inp.	France

Explanation of the symbols and notes:
- * number of patients included in the study
- ** study design: prospective (pros.) or retrospective (retros.)
- ■ setting: out-patients (outp.) or in-patients (inp.) included
- # study was performed to analyze immunological parameters
- ## included children were younger than 2 years
- ### included children were younger than 3 years.

Table 3. Identified causes of urticaria (acute and chronic) in children

Author(s)	Physical urticaria	Adverse food reaction	Adverse drug reaction		Infection & infestations	Atopy	Unknown
Sehgal	7	20	5		16	-	48 #
Kauppinen	14	25	1		14	-	46
Tuchinda	1	10	17		2	-	68 #
Sörensen	3	18	1		-	4	71 #
Moreno	-	30	28		-	3	39
Legrain	2	25	10	18 ##	10	-	35
Ghosh	34	4	4		-	-	58
Mortureux	-	11	-	81 ###	-	-	8

Explanation of the symbols and notes:
- # a small number of patients (2-4) had papular urticaria or contact urticaria
- ## in 18% of the included patients a combination of an infection and an adverse drug reaction was identified as the cause of the urticaria (additionally to the 10% of the patients with an adverse drug reaction and the 10% with an infection as the identified cause of the urticaria)
- ### in 81% of the included children an infection either associated or not associated with drug intake was identified as the cause of the urticaria.

Table 4. Identified causes of chronic urticaria in children

Author(s)	n*	Adverse food reaction	Adverse drug reaction	Physical urticaria	Infection & infestations	Unknown
Harris#	94	2	-	9	2	84
Volonakis##	226	7	2	6	4	79

Explanation of the symbols and notes:
* number of patients included in the study
\# in 3% of the children a connective tissue disease was identified as the cause
\## in 2% of the children aeroallergens were identified as the cause.

In general, the number of identified causes seems to be higher in acute urticaria than in chronic urticaria in children, but is it easier to assign a diagnosis to an already cleared condition than to prove a relationship in a chronic condition.

DIAGNOSIS

The importance of history taking and the statement that extensive laboratory work-up in patients with chronic urticaria is not necessary is explained in several diagnostic recommendations,[81-83] sometimes presented in flowcharts,[50,83-85] or in algorithms.[86-88] Studies including large numbers of patients with chronic urticaria have demonstrated that these diagnostic work-ups are of little value.[50,62,89] Current diagnostic recommendations limit the number of routine laboratory tests and recommend additional laboratory tests only if there is an indication in the history.[81-86] Most of these recommendations are based on opinions of experts in urticaria. Detailed information on the diagnosis of chronic urticaria is presented in chapter 7: a flow chart for the diagnosis of chronic urticaria. When physical urticarias are suspected, appropriate provocation tests can be performed. If there is an indication of an allergy in the history, laboratory tests (RAST, epi- or intracutaneous allergy tests) should be considered. If a systemic disease is suspected, appropriate laboratory investigations (hematology, chemistry, serum immunoglobulins, complement levels, serum proteins, and autoantibodies) are necessary. When urticarial vasculitis is suspected a skin biopsy should be performed for histopathological evaluation. In acute urticaria routine screening is also not indicated, and IgE tests should only be performed if a specific allergen is suspected.[28,88]

Differential diagnosis

In general, the diagnosis of urticaria or angioedema is rarely a problem, even when the hives are not visible at the moment of the consultation. Problems can arise only when the duration of individual hives cannot be clearly defined or when itching is absent.[88] The differential diagnosis of acute and chronic urticaria includes atopic dermatitis, erythema multiforme, maculopapular rashes (e.g. adverse drug reactions), papular urticaria (persisting reaction after insects biting or stings mainly on the lower legs of children), early phases of pemphigoid, Sweet's syndrome, and annular erythemas (erythema marginatum, erythema chronicum migrans, and erythema annulare centrifugum). The differential diagnosis of facial angioedema includes acute (allergic) contact dermatitis, erysipelas, and Melkersson-Rosenthal syndrome.

NATURAL COURSE

Studies on the natural course of urticaria are limited. In only three studies the natural course of *acute* urticaria in adults and children[90,91] and in children alone[78] was described. In one study 2 of 50 patients had symptoms for longer than one year.[90] In another study, in 72 patients having acute urticaria, the symptoms vanished spontaneously.[91] In the study including infants only, three infants still had hives after one year.[78] Data on the natural course of *chronic* urticaria are scarce as well. Two studies were performed in children. Harris et al followed 94 children, and 58% of them were free of symptoms after 1 year.[79] In a retrospective study 123 children were investigated and 47% were free of symptoms after the follow-up period. The worst prognosis was found in children with physical urticaria.[72] Three studies provided data on the natural course including mainly adult patients with having mostly chronic urticaria. Urbach found (in 500 patients with urticaria and/or angioedema) the following durations': 3 to 12 month (19%), 1 to 5 years (20%), 6 to 10 years (4%) and 11 to 20 years (1.5%).[92] Juhlin[89] found that the median duration of attacks of chronic urticaria and/or angioedema was between 2 to 4 years. Quaranta et al investigated 86 patients with chronic idiopathic urticaria over a 3-years period, in whom 27 (31%) resolved, 48 (56%) continued to have symptoms, and in 11 (13%) patients the natural cause was unknown.[93] Important information about the natural course of chronic urticaria in a large group of patient was presented by Champion et al in 1969.[66] In their study approximately 30 to 55% of patients with idiopathic urticaria and/or angioedema were free of symptoms after 1 year. In chapter 4 more recent data on the natural course of physical urticarias, and chronic urticaria and/or angioedema in a patient cohort of 220 patients are presented.

QUALITY OF LIFE

Different instruments to measure the quality of life in Dermatology have been developed. For example the dermatology quality of life scales (DQOLS), which is a quickly self-completed questionnaire for routine daily clinical practice, consisting of 10 items.[94] This questionnaire has been used in patients with different types of chronic urticaria.[95] The authors found that patients with delayed pressure or cholinergic urticaria endure the largest impairment of quality of life, more than patients with chronic idiopathic urticaria. The mean scores of quality of life impairment

(DQOLS) were comparable with scores seen in outpatients with severe atopic dermatitis, and higher than in outpatients with psoriasis and vitiligo.[95] In an earlier study, using the Nottingham health profile (NHP) and a disease-specific questionnaire as measurements, the authors concluded that patients with chronic idiopathic urticaria with or without delayed pressure urticaria experience quality of life impairment which could be compared to the impairment of patients with coronary artery disease.[96]

MANAGEMENT AND TREATMENT

One of the general measures in the management of chronic urticaria is avoiding all eliciting or aggravating factors (see next section). Cooling with antipruritic lotions, such as 1% menthol in aqueous cream can be soothing.[97] Mucocutaneous angioedema can be treated by 2 to 3 puffs of an aqueous 2% ephedrine spray.[26] It can be very helpful for patients if they receive information about the benign character of urticaria (explain that the condition is not related to cancer, or a severe underlying disease, or a HIV-infection), and about the natural course of the condition. Furthermore, it should be explained to the patients that in the majority of cases no specific cause will be identified. To patients with severe angioedema it should be revealed that the condition is rarely life threatening, although it can be very frightening.[26]

Aggravating factors

Aspirin, NSAID's, codeine, and ACE-inhibitors can cause urticaria, but can as well be aggravating factors.[10,62,66,93,98,99,100] Sometimes patients forget to mention that they use 'over the counter' drugs or oral contraceptives, and it is recommended to ask repeatedly about their use. Oral contraceptives or autoimmune progesterone dermatitis can be the cause of chronic urticaria; but both causes are very rare.[101,102] Other aggravating factors are: stress, pressure on the skin/dermographism, overheating, exercise, and consumption of alcohol. Alcohol can be a direct cause of chronic urticaria as well.[103]

Removal or avoidance of the stimulus

Avoidance of the eliciting stimulus is the most obvious and effective treatment option. Unfortunately, this option is only available if exact identification of the cause of urticaria is possible, which in turn can be very difficult.[104] If a specific allergen or stimulus is identified (e.g., certain foods, food additives, contact urticaria, certain drugs) as the cause of

urticaria, this stimulus should be avoided by following a diet, by avoidance of the contactagent, or by discontinuation of the drug use. Treatment of diseases or infections are the logical interventions if these are considered to be the cause. In some patients with physical urticaria, who respond poorly to antihistamines, a change in their way of living (e.g., a change of work or leisure activities, including sports in particular) could diminish their complaints.

Antihistamines

Antihistamines of the H1 type are the mainstay in the management of chronic urticaria. They tend to be more effective in suppressing itching than whealing.[26,104-106] A combination of a non-sedating antihistamine in the morning and a sedating antihistamine in the late evening provides symptomatic relief in many patients.[26]

Although there is no reliable evidence up to now that antihistamines are teratogenic,[2] it is advisable to avoid all antihistamines during pregnancy, especially during the first trimester.[97] Chlorpheniramine is often used during pregnancy because of its long safety record.[2,26,97] Cetirizine, loratadine and mizolastine should be avoided during pregnancy and breast feeding.[97] Terfenadine and astemizole are up to now not considered to be teratogenic.[2] None of the available antihistamines are contraindicated in children older than 12 years.[97] Hydroxyzine (syrup; dosage 5 to 15 mg daily) is recommended for infants of 1 year or less.[107] Cetirizine (oral solution) is shown to be safe in children older than 12 months,[108] and loratadine (syrup) is recommended in children older than 2 years.[107]

Poor response to antihistamines, especially in combination with joint pain, not itchy, but painful and persisting hives, is more common in patients with pressure urticaria, and in patients developing or already suffering from a connective tissue disease or cutaneous vasculitis.[84]

Doxepin, a tricyclic antidepressant drug with marked H1 antihistaminic activity, is useful as a single night time 25 mg dose in patients who experience nocturnal disease activity, especially when associated with anxiety or depression. It is a powerful sedative and patients should be warned that their cognitive functions and reflex activity may be impaired for up to 24 hours after a nocturnal dose of doxepin (or other sedating antihistamines).[109]

The role of H2 receptor antagonists remains controversial[110] and we believe that there is up to now no convincing evidence for the additional use of an antihistamine of the H2 type, alone or combined with an antihistamine of the H1 type.

Corticosteroids

In patients with acute urticaria a short course of a high dosage of oral corticosteroids (50 mg daily for 3 days) shortens the duration of the hives. In patients who received oral corticosteroids and a nonsedating antihistamine, cessation of the hives occurred in 94% after 3 days. In the control group which received only the same nonsedating antihistamine cessation of the hives occurred in 66% after 3 days.[91] Short tapering courses (prednisolon in a starting dose of 30 mg/day, slowly reduced to zero over a period of 10 days) are helpful in special circumstances where, for example, rapid control is needed to cover an important social or occupational event.[109] This intervention is as well useful in patient with severe intermittent facial angioedema which occurs only a few times a year. Short courses may be necessary also for patients with urticarial vasculitis (5 to 10 mg daily) or severe delayed pressure urticaria.[97,104] In general, prolonged corticosteroid therapy almost always leads to severe systemic toxicity and the development of tolerance.

Other therapies

For patients with life threatening attacks of laryngeal angioedema or anaphylaxis, an emergency self-administration epinephrine pen (Epipen®) for intramuscular injection is available for adults and adolescents. It should be used with caution in patients with hypertension and ischemic heart disease.[97]

Immunosuppressive therapies such as plasmapheresis,[111] or intravenous immunoglobulins[112,113] may be tried in severe cases. Cyclosporin A (3 to 4.5 mg/kg) is effective in autoantibody positive (FcεRIα) and autoantibody negative chronic urticaria.[114,115] If it is used for 3 months 75% of the patients show excellent response.[109] Of these, one third remain in remission, one third relapse but only mildly, and one third relapse to the extent that they were affected before cyclosporin A treatment.[109] Blood pressure and renal function should be monitored appropriately.

Treatment for urticarial vasculitis includes NSAID's (particularly indomethacin), especially if combined with joint pain; but this treatment is disappointing with regard to the skin manifestations.[25] Treatment with hydroxychloroquine and dapsone (50 to 500 mg daily)[116] is useful in many patients.[25] Also the combination of dapsone and pentoxifylline was shown to be effective.[117]

GUIDELINE DEVELOPMENT

Guideline development has its origins in the problems that most healthcare systems face: rising healthcare costs, increased demand of care, more expensive technologies, variations in service delivery among providers and among different geographical regions and the presumption that at least some of this variation stems from inappropriate care, either over-use or under-use of services; and the desire of healthcare professionals to offer, and of patients to receive, the best care possible.[118] There is a growing interest in the development of practice guidelines for clinical care in dermatology,[119] because empiric, uncontrolled, and non systematically collected data form the basis of much of dermatological practice.[120] The development of practice guidelines may as well be explained by the increasing clinical knowledge and literature, the rising complexity of diagnostic and therapeutic decision making, and the wish to create strategies which may facilitate this process of decision making. According to the principles of evidence-based medicine, the best medical care is provided by integrating the best external evidence (e.g., systematic reviews with homogeneity of the results) obtained from clinically relevant studies, into the clinical management decisions for daily practice. Systematic reviews of the literature or statistical meta-analyses are instruments to summarize the evidence that is available in the medical literature and are important tools to develop practice guidelines. Up to now the majority of these reviews provide information on therapeutic interventions. A search in the online Database of Abstracts of the Reviews of Effectiveness (DARE), maintained by the University of York, revealed about 800 reviews on therapeutic interventions and only about 30 reviews on diagnostic interventions.[121] The advantage of evidence-based clinical guidelines is that they enhance the accuracy and diminish the subjectivity of recommendations. Compliance with clinical guidelines has been shown to be enhanced if the guideline is developed and adopted by those who will eventually use them.[122] But unfortunately, after the introduction of a clinical guideline there is no guarantee that it will be used by clinicians, no matter how well-designed, and more guidelines have been made than have been implemented.[123] Obstacles for actual implementation and maintenance may be related to a lack of resources, relapsing into old routines, or dissatisfaction about the results of the new guideline.[124] Continued motivation of clinicians remains necessary.

Chapter 1

AIMS OF THE STUDIES

The primary aim of this thesis was:

- the development of evidence-based practice guidelines for the diagnostic procedure in patients with chronic urticaria or angioedema.

A preliminary guideline was developed and tested in the prospective study (chapter 3), which was designed to confirm the hypothesis that such a guideline can effectively be used for the management of chronic urticaria. The guideline was further validated and its implementation in clinical practice was analyzed in a retrospective study (chapter 6). The final guideline was based on a systematic review of the literature (chapter 7), and the prospective and retrospective studies. All studies were performed at the outpatient department of dermatology of the Academic Medical Center in Amsterdam.

Secondary aims were:

- the development and validation of a questionnaire for history taking in patients with chronic urticaria (chapter 2 and 3),
- the evaluation of the value of extensive routine laboratory screening in identifying the cause of chronic urticaria in a prospective study (chapter 3),
- the evaluation of the value of history taking in identifying the cause of urticaria in a retrospective study (chapter 6),
- the investigation of the natural course of different subtypes of chronic urticaria in a prospective study (chapter 4).

REFERENCES

1. Juhlin L. The history of the urticaria and angio-oedema. Clin Exp Dermatol 2000;25:331.
2. Kobza Black A, Champion RH. Urticaria. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Rook, Wilkinson, Ebling. Textbook of Dermatology. 6th edition. Oxford. Blackwell Science; 1998:2113-2139.
3. Henz BM. The spectrum of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998:1-17.
4. McKee WD. The incidence and familial occurrence of allergy. J Allergy 1966;38:226-235.
5. Swinny B. The atopic factor in urticaria. South Med J 1941;34:855-8.
6. Hellgren L, Hersle K. Acute and chronic urticaria. Acta Allergol 1964;19: 406-420.
7. Paul E, Greilich KD, Dominate G. Epidemiology of urticaria. Monogr Allergy 1987;21:87-115.
8. Margolis CF, Nisi R. Urticaria in a family practice. J Fam Pract 1985;20:57-64.
9. Douglas HMG. Chronic urticaria. Clinical and pathogenetic studies on 141 patients. Thesis 1975; Dijkstra Niemeyer, Groningen.
10. Mekkes JR, Schaar WW van der, Bos JD. Anamnese en diagnostiek van chronische urticaria. Ned Tijdschr Geneeskd 1986;130:1801-1805.
11. Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter- & episode- & process-oriented standard output from the Transition Project. Part 1 and 2. Amsterdam: Department of General Practice 1991; Amsterdam University press.
12. Hamilton NJT, Bendkowski B. Incidence of allergic diseases in general practice. BMJ 1954;1:1069-1070.
13. Haas N, Klapproth I, Czarnetzki BM. Vergleichende Studie zur Häufigkeit, Diagnostik und Therapie der Urticaria in einer Hautpoliklinik. Allergologie 1995;18:110-113.
14. Metcalfe DD. Acute anaphylaxis and urticaria in children and adults. In: Schocket AL. Clinical management of urticaria and anaphylaxis. New York, Basel, Hong Kong; Marcel Dekker Inc. 1993; 1-20.
15. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Eng J Med 1993;328:1599-1603.
16. Fiebiger E, Maurer D, Holub H, Reiniger B, Hartmann G, Woisetschläger M, Kinét JP, Stingl G. Serum IgG autoantibodies directed against the α chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606-2612.

17. Hide M, Francis DM, Grattan CEH, Barr RM, Winkelmann RK, Greaves MW. The pathogenesis of chronic idiopathic urticaria: new evidence suggests an auto-immune basis and implications for treatment. Clin Exp Allergy 1994;24:624-627.
18. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996;98:89-98.
19. Fiebiger E, Wichlas S, Stingl G, Maurer D. Autoantibodies directed against FcεRIα: IgG subtype composition, prevalence, and disease specificity. J Invest Dermatol 1996;107:492.
20. Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Immunol 1997;99: 461-465.
21. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεRIα-autoantibodies in autoimmune-mediated disorders; identification of a structure-function relationship. J Clin Invest 1998;101:243-251.
22. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1997;133:1003-1008.
23. Czarnetzki BM. Acute and chronic urticaria. In: Czarnetzki BM. Urticaria. Berlin: Springer Verlag; 1986:26-46.
24. Haas N, Toppe E, Henz BM. Microscopic morphology of different types of urticaria. Arch Dermatol 1998; 134: 41-46.
25. Nürnberg W, Henz BM. Urticarial vasculitis syndrome. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998: 115-124.
26. Greaves MW, Sabroe RA. Allergy and the skin. I-Urticaria. BMJ 1998;316: 1147-1150.
27. Paul E, Greilich KD. Zur Epidemiologie der Urtikariaerkrankungen. Hautarzt 1991;42:366-375.
28. Kobza Black A. Urticaria and angioedema. In: Durham SR. Allergy illustrated. London; Current Medical Literature Ltd. 2000:46-62.
29. Jeep S, Henz BM. Physical urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998:55-89.
30. Kontou Fili K, Borici-Mazi R, Kapp A, Matjevic LJ, Michel FB. Physical urticaria: classification and diagnostic guidelines. An EAACI position paper. Allergy 1997;52:504-513.
31. Schocket AL. Physical urticarias. In: Schocket AL. Clinical management of urticaria and anaphylaxis. New York, Basel, Hong Kong; Marcel Dekker Inc. 1993; 69-98.
32. Barlow RJ, Macdonald DM, Kobza Black A, Greaves MW. The effect of topical corticosteroids on delayed pressure urticaria. Arch Dermatol Res 1995;287:285-288.

33. Engler R, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. Ann Allergy 1995;74:155-159.
34. Zuberbier T, Althaus Ch, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. J Am Acad Dermatol 1994;31:978-981.
35. Neittaanmäki H. Cold urticaria. Clinical findings in 220 patients. J Am Acad Dermatol 1984;13:636-644.
36. Wanderer AA. Cold urticaria: Historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis, and management. J Am Acad Dermatol 1990;85:965-981.
37. Caldwell JR, Cluff LE. Adverse reactions to antimicrobial agents. JAMA 1974;230:77-80.
38. Sullivan TJ. Diagnosis and management of drug allergy. In: Schocket AL. Clinical management of urticaria and anaphylaxis. New York, Basel, Hong Kong; Marcel Dekker Inc. 1993; 69-98.
39. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudo-allergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol 1995;75:484-487.
40. Ortolani C, Pastorello E, Ispano E, Ansaloni R. Food allergy diagnosis protocol. Allergy et Immunol 1988;20:48-50.
41. Henz BM, Zuberbier T. Causes of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998:18-38.
42. Turjanmaa J. Incidence of immediate allergy to latex gloves in hospital personel. Contact dermatitis 1987;17:270-275.
43. Kibby T, Akl M. Prevalence of latex sensitization in a hospital employee population. Ann Allergy Asthma Immunol 1997;78:41-44.
44. Liss GM, Sussman GL, Deal K et al. Latex allergy: an epidemiological study of 1351 hospital workers. Occup Environ Med 1997;54:335-342.
45. Mace S, Sussman GL, Stark DF, Thompson R, Kelly K, Beezhold D. Latex allergy in operating room nurses. Ann Allergy Asthma Immunol 1998;80: 252-256.
46. Yassin MS, Lierl MB, Fischer TJ, O'Brien K, Cross J, Steinmetz C. Latex allergy in hospital employees. Ann Allergy 1994;72:245-249.
47. Kelly KJ, Kurup V, Zacharisen M, Resnick A, Fink JN. Skin and serologic testing in the diagnosis of latex allergy. J Allergy Clin Immunol 1993;91: 1140-1145.
48. Ylitalo L, Turjanmaa K, Palosuo T, Reunala T. Natural rubber allergy in children who had not undergone surgery and children who had undergone multiple operations. J Allergy Clin Immunol 1997;100:606-612.
49. Hirsch T, Neumeister V, Weiland SK, von Mutius E. Traffic exposure and allergic sensitization against latex in children. J Allery Clin Immunol 2000; 106:573-578.

50. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427-36.
51. Schnyder B, Helbling A, Pichler WJ. Chronic idiopathic urticaria: Natural course and association with Helicobacter pylori infection. Int Arch Allergy Immunol 1999;119:60-63.
52. Valsecchi RH, Pigatto PD. Chronic Urticaria and Helicobacter pylori. Acta Derm Venereol 1998;78:440-442.
53. Höök-Nikanne J, Varjonen E, Harvima RJ, Kosunen TU. Is Helicobacter pylori infection associated with chronic urticaria. Acta Derm Venereol 2000;80:425-426.
54. Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute Urticaria: Clinical Aspects and Therapeutic Responsiveness. Acta Derm Venereol 1996;76: 295-297.
55. Mathews KP. Chronic urticaria. In: Schocket AL. Clinical management of urticaria and anaphylaxis. New York, Basel, Hong Kong; Marcel Dekker Inc. 1993; 21-68.
56. Brickman CM. Hereditary angioedema. In: Schocket AL. Clinical management of urticaria and anaphylaxis. New York, Basel, Hong Kong; Marcel Dekker Inc. 1993; 99-116.
57. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological an clinical characteristics in 235 patients. Medicine 1992;71:206-215.
58. Greaves MW, Lawlor F. Angioedema: Manifestations and management. J Am Acad Dermatol 1991;25:155-165.
59. Sigurgeirsson B. Skin diseases and malignancies. An epidemiological study. Acta Derm Venereol 1992(suppl);178:1-110.
60. Geha RS, Quinti I, Austen KF, Cicardi M, Sheffer A, Rosen FS. Acquired C1-inhibitor deficiency associated with antiidiotypic antibody to monoclonal immunoglobulins. N Engl J Med 1985;312:534-540.
61. McWhorter WP. Allergy and Risk of Cancer; a Prospective Study Using NHANESI Followup Data. Cancer 1988;62:451-455.
62. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-638.
63. Barlow RJ, Warburton F, Watsen K, Kobza Black A, Greaves MW. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol 1993;29:954-958.
65. Sussman GL, Harvey RP, Schocket AL. Delayed pressure urticaria. J Allergy Clin Immunol 1982:70:337-342.
66. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969;81:588-597.
67. Jacobson MKW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. JAMA 1980;243:1644-1646.
68. Pigatto PD, Valsecchi RH. Chronic urticaria: a mystery. Allergy 2000;55: 306-308.

69. Sillevis Smitt JH, Kozel MMA. Pathofysiologie van urticaria en urticariële vasculitis. In: de Waard-van der Spek FB, Oranje AP. Diagnostiek en therapie in de kinderdermatologie. 8e cursus van de Nederlands Belgische Vereniging voor Kinderdermatologie, Rotterdam 2001, 83-90.
70. Seghal VN, Rege VL, Kharangate VN. An interrogative study of patterns of urticaria in children. J Dermatol 1975;2:1-4.
71. Bonifazi E, Meneghini CL, Ceci A. Pathogenetic factors in urticaria in children. A clinico-experimental study. Dermatologica 1977;154:65-72.
72. Kauppinen K, Juntunen K, Lanki H. Urticaria in children. Allergy 1984;39:469-472.
73. Tuchinda M, Srimaruta N, Habanananda S, Vareenil J, Assatherawatts A. Urticaria in Thai children. Asian Pac J Allergy Immunol 1986;4:41-45.
74. Sörensen HT, Christensen B, Kjaerulff E. A two year follow-up of children with urticaria in general practise. Scand J Prim Health Care 1987;5:24-26.
75. Moreno MV, Cuesta CG de la, Oehling A. Contribution to the etio-pathogenesis of urticaria in children. Allergol Immunopathol 1988;16:225-230.
76. Legrain V, Taïeb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. Ped Dermatol 1990;7:101-107.
77. Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. Ped Dermatol 1993;10: 107-110.
78. Montureux P, Léaute-Labrèze C, Legrain-Lifermann. Acute urticaria in infancy and early childhood. A prospective study. Arch Dermatol 1998; 134:319-323.
79. Harris A, Frank JW, Geha RS. Chronic urticaria in childhood: natural course and etiology. Ann Allergy 1983;51:161-165.
80. Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. Ann Allergy 1992;69:61-65.
81. Soter NA. Acute and chronic urticaria and angioedema. J Am Acad Dermatol 1991;25:146-154.
82. Kobza Black A, Greaves MW, Champion RH, Pye RJ. The urticarias 1990. Br J Dermatol 1991;124:100-108.
83. Friedmann PS. Assessment of urticaria and angio-oedema. Clin Exp Allergy 1999(suppl 3);29:109-112.
84. Champion RH, Highet AS. Investigation and management of chronic urticaria and angio-oedema. Clin Exp Dermatol 1982;7:291-300.
85. Bindslev-Jensen C, Finzi A, Greaves M, Camarasa J, Ortonne JP, Schöpf E, Tennstedt D. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol 2000;14:175-180.
86. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-1772.
87. Cooper KD. Urticaria and angioedema: Diagnosis and evaluation. J Am Acad Dermatol 1991;25:166-176.
88. Zuberbier T, Henz BM. Diagnosis of Urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria. Clinical, Diagnostic and Therapeutic Aspects. Berlin: Springer Verlag; 1998:139-159.

89. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-381.
90. Aoki T, Kojima M, Horiko T. Acute urticaria: history and natural course of 50 cases. J Dermatol 1994;21:73-77.
91. Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Derm Venereol 1996;76: 295-297.
92. Urbach E. In Allergy, 2nd ed., by Urbach E, Gottlieb PM. Grune and Stratton, New York, 1946.
93. Quaranta JH, Rohr AS, Rachelefsky GS, Siegel SC, Katz RM, Spector SL, Mickey MR. The natural history and response to therapy of chronic urticaria and angioedema. Annals of Allergy 1989;62:421-424.
94. Finlay AY, Khan GK. Dermatology life quality index (DLQI) - a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-216.
95. Poon E, Seed PT, Greaves MW, Kobza Black A. The extent and nature of disability in different urticarial conditions. Br J Dermatol 1999;140:667-671.
96. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197-201.
97. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. Br J Dermatol 2001;144:708-714.
98. Stevenson DD. Adverse reactions to nonsteroidal anti-inflammatory drugs. Immunol & Allergy Clin North America 1998;18:773-792.
99. James J, Warin RP. Chronic urticaria: the effect of aspirin. Br J Dermatol 1970;82:204-209.
100. Sabroe RA, Kobza Black A. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol 1997;136:153-158.
101. Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. J Am Acad Dermatol 1995;32:25-31.
102. Herzberg AJ, Strohmeyer CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. J Am Acad Dermatol 1995;32:335-338.
103. Sticherling M, Brasch J, Brüning H, Christophers E. Urticarial and anaphylactoid reactions following ethanol intake. Br J Dermatol 1995;132: 464-467.
104. Henz BM, Zuberbier T, Monroe E. Urticaria therapy. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998:161-181.
105. Urticaria, angioedema and anaphylaxis. In: Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC, eds. Dermatology. 2nd ed. Berlin: Springer Verlag; 2000:431-456.
106. Henderson RL, Fleischer AB, Feldman SR. Allergists and dermatologists have more expertise in caring for patients with urticaria than other specialists. J Am Acad Dermatol 2000;43:1084-1091.
107. Greaves MW. Chronic urticaria in childhood. Allergy 2000;55:309-320.

108. ETAC® Study Group. Allergic factors associated with the development of asthma an the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: First results of ETAC®. Pediatr Allergy Immunol 1998;9:116-124.
109. Greaves MW. Chronic urticaria. J Allergy Clin Immunol 2000;105:664-672.
110. Ormerod AD. Urticaria: recognition, causes ant treatment. Drugs 1994;48: 717-730.
111. Grattan CECBF, Francis DM, Slater NGP, Barlow RJ, Greaves MW. Plasmapheresis for severe unremitting, chronic urticaria. The Lancet 1992;339:1078-1080.
112. O'Donnell BF, Barlow RJ, Kobza Black A, Greaves MW. Response of severe chronic urticaria to intravenous immunoglobulin (IVIG) Br J Dermatol 1994;131:23.
113. O'Donnell BF, Barr RM, Kobza Black A, Francis DM, Kermani F, Niimi N, Barlow RJ, Winkelmann RK, Greaves MW. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998;138:101-106.
114. Barlow RJ, Black AK, Greaves MW. Treatment of severe, chronic urticaria with cyclosporin A. Eur J Dermatol 1993;3:273-275.
115. Grattan CECBF, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, Kobza Black A, Greaves MW. Randomized double-blind study of cyclosporin A in chronic idiopathic urticaria. Br J Dermatol 2000;143:365-372.
116. Thiers BH. Urticaria and angioedema. Dermatol Clin 1996;14:171-198.
117. Nürnberg W, Grabbe J, Czarnetzki BM. Urticarial vasculitis syndrome effectively treated with dapsone and pentoxifylline. Acta Derm Venereol 1995;75:54-56.
118. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: Potential benefits, limitations, and harms of clinical guidelines. BMJ 1999;318:527-530.
119. Ladhani S. The need for evidence-based management of skin diseases. Int J Dermatol 1997;36:17-22.
120. Bigby M. Evidence-based medicine in dermatology. Dermatol Clin 2000; 18:261-276.
121. Database of Abstracts of the Reviews of Effectiveness (DARE). at: http://agatha.york.ac.uk
122. Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines, II: ensuring guidelines change medical practice. Qual Health Care 1994;3:45-52.
123. Delamothe T. Wanted: guidelines that doctors will follow. BMJ 1993;307: 218.
124. Grol R. Beliefs and evidence in changing clinical practice. BMJ 1997;315: 418-421.

Chapter 2

A questionnaire for history-taking in chronic urticaria and explanation of the questionnaire

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SUMMARY

In chronic urticaria, detailed history taking is more effective for detecting underlying disorders than routine laboratory investigations. In this paper we present a questionnaire for chronic urticaria, which can be filled in by the patient at home.

The questionnaire contains questions concerning the frequency and pattern of attacks, duration of wheals, associated symptoms, provoking physical factors, history of atopic disease, occupation and leisure activities, food and drug intolerance and use of drugs. The second part contained questions on associated signs and symptoms, medical history and general health (the questionnaire is available on request).

The background of each question is explained and some information is provided to guide the doctor in the interpretation of the answers of the patient, especially how to translate them into useful actions such as laboratory investigations or medical interventions.

Questionnaire for patients with chronic urticaria (hives, wheals) or angioedema (swelling of the skin)

Name: ..... male ❒ / female ❒

Birth date: ...../...../..... date: ...../...../.....

Please tick the appropriate box(es):

1. How long do you have hives and/or deep swellings?
   - ❒ I have it since .....
   - ❒ I have hives only
   - ❒ I have deep swellings only
   - ❒ I have both, urticaria and deep swellings.

2. How frequently do you have a bout of hives and/or angioedema?
   - ❒ I have hives:
   - ❒ I have deep swellings:

   I have them:
   - ❒ continuously
   - ❒ daily
   - .... times a week
   - .... times a month
   - different, namely ..... .

3. How long does an individual hive persists before it disappears? (You can check this by marking an individual hive with a ballpoint and verify when the hive is gone.) ..... .
   How many hours does the hive or swelling persists? ..... .

4. Did you ever had a hive or swelling which persisted more than 24 hours? Yes ❒ / No ❒

5. What is the size of your hives in general?
   in centimeters: ..... .

6. Are there areas of your body where you frequently have hives or swellings?
   - ❒ I have hives:
     - ❒ all over my body
     - ❒ especially on the arms and/or legs
     - ❒ on pressure sites (for example under the belt or the bra)
     - ❒ or on the following parts of my body .....

- ❒ I have swellings:
  - ❒ of my eyelids
  - ❒ of my lips
  - ❒ of my hands and/or fingers
  - ❒ of my feet
  - ❒ of my tong and/or throat
  - ❒ or of the following parts of my body ..... .

7. Do the hives leave blue, purple, brownish spots or red dots after disappearing? Yes ❒ / No ❒

8. Do you experience itch on the site of your body where you have hives and/or swellings? Yes ❒ / No ❒

9. Did you scratch? Yes ❒ / No ❒
   Is your skin dry and scaling on the sites of your body where you have hives or swellings? Yes ❒ / No ❒

10. Do you feel another sensation different from itch in the affected skin? Yes ❒ / No ❒
    - ❒ pain
    - ❒ burning sensation
    - ❒ tense sensation
    - ❒ an other sensation, namely ..... .

11. Did you ever experience one of the following symptoms during or shortly after a bout of hives or swellings? Yes ❒ / No ❒

    - ❒ running nose / tearing eyes
    - ❒ asthma or shortness of breath
    - ❒ hoarseness
    - ❒ swollen tongue, palate or throat
    - ❒ headache / fatigue
    - ❒ dizziness / fainting
    - ❒ gastric pain or abdominal spasm
    - ❒ nausea or vomiting
    - ❒ diarrhea
    - ❒ fever.

12. At which time during the day do you have most complaints?
    - ❒ in the morning or after getting up
    - ❒ during the day
    - ❒ in the evening
    - ❒ during the night
    - ❒ do you wake up during the night because of itch
    - ❒ not predictable.

13. When or where do you have more hives and/or swellings?
    - ❒ inside the house
    - ❒ outside the house
    - ❒ on your work
    - ❒ in the weekend
    - ❒ during the week
    - ❒ on vacation less complaints
    - ❒ on vacation more complaints.

14. Did your complaints start after a particular infection or disease? (for example after extraction of one of your teeth, ear-, nose- or throat-infections, worm infections, pneumonia, cystitis or other infections)
    Yes ❒ / No ❒
    If so, following which infection? ..... .

15. Did your complaints start:
    - ❒ after an X-ray with radio contrast media?
    - ❒ after taking a particular tablet or injection? Namely .....
    - ❒ after vaccinations? Namely .....
    - ❒ after other events, namely ..... .

16. Is there a relationship between the season/weather conditions and your complaints? Yes ❒ / No ❒
    When do your complaints aggravate? ..... .

17. Have you ever been in a tropical area? Yes ❒ / No ❒
    Where and when? ..... .

Sometimes bouts of hives and/or swellings may be related to particular circumstances. We describe some of them in the following questions. If you recognize one or more of the circumstances, please mark the involved question.

18. Did the hives started approximately 15 minutes after:
    - ❒ rubbing or scratching of the skin
    - ❒ wearing tight clothing
    - ❒ leaning against something (for example a chair).

19. Did the hives or the swellings occur after intense pressure on the skin mostly after an interval period of 4-12 hours? If this happened in your case, what kind of activities did you perform?
    - ❒ staying or walking for a longer period resulting in swelling of the soles
    - ❒ sitting or riding bicycle resulting in swelling of the buttocks
    - ❒ working with tools (like pincers or a hammer)
    - ❒ carrying heavy things
    - ❒ other circumstances, namely ..... .

20. Did the hives occur after exposure to:
    - ❒ cold weather (snow, cold wind or rain)
    - ❒ cold water (shower or in a swimming pool)
    - ❒ cold objects or food (eating ice-cream or cold drinks with ice cubes)
    - ❒ a changing in the outside temperature.

21. Did you experience hives after:
    - ❒ exposure to hot or warm weather
    - ❒ after physical exercise or during sports
    - ❒ after sexual intercourse
    - ❒ after taking a hot shower or bath
    - ❒ after consuming spicy or hot foods or drinks
    - ❒ after contact of your skin with warm objects
    - ❒ if you are exited, frightened or under stress
    - ❒ if you are perspiring.

22. Did you ever experience hives or swellings after exposure to sunlight?
    Yes ❒ / No ❒

23. Did you ever experience white, blue, painful or insensible fingers after exposure to cold? Yes ❒ / No ❒
    If so, please describe the circumstance ..... .

24. Do you think that your complaints worsen:
    - ❒ under stress or nervousness
    - ❒ if you have problems of any kind.

25. Did you ever notice that contact of your skin with one of the following caused itch, redness, hives or swelling of the skin?
    - ❒ wool or other clothes
    - ❒ animals or plants
    - ❒ cosmetics or perfume
    - ❒ drugs or particular food (e.g. meat, fish, vegetables, fruit)
    - ❒ chemical or other products, namely ..... .

26. Did any member of your family ever had hives or swellings?
    If yes, who? ..... .

27. Did you (or any member of your family) ever suffer from one of the following diseases?
    - ❒ hay fever, attacks of sneezing (allergic rhinitis)?
    - ❒ allergic conjunctivitis?
    - ❒ allergic asthma?
    - ❒ childhood eczema?
    - ❒ eczema in arm pits or the back of the knees (atopic dermatitis)?

    If yes, who? ..... .

28. Are you allergic for house dust mite, pollen, animals, wasp- or bee venom, rubber (in latex gloves or condoms), or to other things?
Yes ❒ / No ❒

If so, for what are you allergic? ..... .

Was this confirmed by a laboratory test? Yes ❒ / No ❒

29. Did you ever observe that your complains are related or worsen after consuming certain foods (like fish, mussels, crustaceans, pulse, celery, strawberries, pears, banana, peanuts, nuts, soy, cheese, alcohol, chocolate, juices with quinine, eggs, milk products, ice-cream, conserved food or deep frozen food products, artificial sweetener, others.
If yes, after which foods? ..... .

30. Did you ever experience one of the following complaints after eating certain foods? Yes ❒ / No ❒

❒ tingling or a burning sensation of the tongue
❒ swelling of the tongue or the lips
❒ cramps of the intestine or diarrhea.

30. Do you have an aversion against certain foods? Yes ❒ / No ❒
If yes, against which ones? ..... .

31. Are you allergic to certain foods? Yes ❒ / No ❒
If yes, against which ones?

32. Did you ever followed a diet to diminished your complaints?
Yes ❒ / No ❒

Was the diet effective? Yes ❒ / No ❒
Did you had professional help from a dietician? Yes ❒ / No ❒
Did you constantly followed the diet? Yes ❒ / No ❒

33. Do you have animals at home? Yes ❒ / No ❒
If so, what kind of animals and since when? ..... .

34. Do you have a lot of contact with one of the following products?
❒ plants, flowers
❒ cosmetics
❒ cleaning or washing products
❒ paint or glues
❒ other specific products, namely ..... .

35. What is your profession? ..... .

36. What kind of hobbies do you have? ..... .

37. Are you exposed to chemicals or industrial products in your profession or is there any chance of inhaling these products (for example fluids, steam, vapours or dust)?

Yes ❒ / No ❒

If so, what kind of product? ..... .

38. Do you have any metallic implants (e.g. pacemaker, artificial joints, metallic screws, dental implants) or other types of implants in your body?

Yes ❒ / No ❒

If so, what kind of metal implant do you have? ..... .

39. **Women only**

Do you take contraceptives or other hormones? Yes ❒ / No ❒
If yes, which type of contraceptive and since when? ..... .

Did you ever experience more complaints during certain times of your menstrual cycle? Yes ❒ / No ❒

40. Will you please specify the drugs you used to suppress your urticaria or angioedema in the past year:

name of the drug	amount	in which period
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

41. If you used antihistamines to prevent urticaria or angioedema will you please indicate when you used them for the last time? ..... .

42. Will you please mention all the drugs you used in the last year in relation to other complaints or for example vaccinations? You can also ask your pharmacy to provide a list with the medications you used over the last year. Please mention antibiotics, pain medication (like aspirin), medication against the flue, anti-rheumatic drugs, sleeping pills, sedatives, psycho-pharmacologic drugs, drugs related to epilepsy, laxatives, cough medications, hormones (like oral contraceptives, estrogen, insulin), vitamins, homeopathic drugs or other drugs? If yes, which ones, when and how frequently?

name of the drug	amount	in which period
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

43. Are you allergic for certain drugs? Yes ❒ / No ❒
If so, which one and what kind of allergic reaction did you have?

..... .

44. Where you ever hospitalized or under treatment of a medical specialist?
If so, for what kind of complaints?

..... .

45. Do you have any other physical complaints at the moment?

..... .

46. Do you have any idea or suggestion about the possible cause of your complaint or did you find any relationship between certain circumstances or certain surroundings and your complaints?

..... .

Questions related to your general health:

Did you experience in the last 8 weeks before the development of your hives or at this moment one or more of the following complaints?

a. Do you feel tired or weak? Yes ❒ / No ❒
b. Did you experienced fever at this moment or recently? Yes ❒ / No ❒
c. Did you lose weight? Yes ❒ / No ❒

d. Are you currently suffering from coughing? Yes ❒ / No ❒
Do you have palpitations or pain in the heart region? Yes ❒ / No ❒
Do you have shortness of breath during exercise? Yes ❒ / No ❒
Do you have swollen ankles in the evening? Yes ❒ / No ❒

e. Do you frequently feel nausea or do you vomit? Yes ❒ / No ❒
Do you have gastric or stomach pain? Yes ❒ / No ❒
Do you have diarrhea or constipation? Yes ❒ / No ❒
Did you ever had blood in your stools? Yes ❒ / No ❒

f. Do you often have headache? Yes ❒ / No ❒
Or throat pain, or pain in your teeth or elsewhere in your mouth? Yes ❒ / No ❒
Or do you often have a cold, a stuffed nose or a sinusitis? Yes ❒ / No ❒
Do you have frequently pain in your ears? Yes ❒ / No ❒

g. Do you have frequently muscle pain? Yes ❒ / No ❒
h. Do you have frequently joint pains? Yes ❒ / No ❒

i. Did you ever had a kidney disease, or recurrent cystitis? Yes ❒ / No ❒
j. Did you ever had a disease of your thyroid gland? Yes ❒ / No ❒
k. Do you have diabetes? Yes ❒ / No ❒

l. Did you ever received a blood transfusion? Yes ❒ / No ❒
m. Did you ever experienced jaundice or a liver disease (hepatitis)? Yes ❒ / No ❒

n. Did you ever had Pfeiffer's disease? Yes ❒ / No ❒
o. Do you have rheumatoid arthritis or lupus erythematodes (SLE)? Yes ❒ / No ❒

p. Did you ever had sexually transmitted diseases? Yes ❒ / No ❒

q. Did you ever had malignant diseases? If yes, which one? Yes ❒ / No ❒

r. Are you smoking? If so, how many cigarettes a day? Yes ❒ / No ❒
s. Are you consuming alcohol? If so, how many glasses a day?
Yes ❒ / No ❒

t. Are you using drugs? If so, which ones? ..... Yes ❒ / No ❒

u. Only for women: Do you have vaginal discharge? Yes ❒ / No ❒
v. Only for men: Do you have complaints with prostate? Yes ❒ / No ❒

w. Did you regularly visit your dentist? How often in a year? Yes ❒ / No ❒

x. Do you have other diseases not questioned yet? Yes ❒ / No ❒
If so, which ones? ..... .

Thank you very much for your cooperation

Chapter 2

EXPLANATION OF THE QUESTIONNAIRE

Age and gender. Physical urticaria is uncommon in patients older than 45 years.[2] Chronic urticaria is infrequent in patients under ten years or older than 60 years.[3-5] Most of the patients with chronic urticaria (60-70%) are woman.[2,3]

Question 1 asks for the duration of the complaints. Urticaria longer than six weeks are by definition chronic.[6] It should be noted that this division is arbitrarily. In most patients there is a spontaneous remission of the urticaria within three months. In 80% of the patients even in one month.[7] If a patient is not suffering intensively, it is permissible to prescribe antihistamines and to wait six weeks or even three months for a spontaneous remission before starting with a diagnostic approach.
Acute and chronic urticaria differ from each other regarding the pattern and the frequency of the underlying causes. In acute urticaria (<6 weeks) the diagnoses adverse drug reaction, adverse food reaction, atopy, and infection (viral or bacterial) were mostly found. In patients with chronic urticaria the following causes could be found, starting with the most frequent cause: physical urticaria (urticaria factitia, cholinergic urticaria, cold urticaria, pressure urticaria), adverse reactions to drugs, adverse reaction to food, inhalation- and contact urticaria, non-immunologic contact urticaria, infections, immune-complex related diseases, psychological factors, sunlight, exercise-induced food related urticaria, heat-contact urticaria, familiar cold urticaria, delayed pressure urticaria, delayed dermographism, hereditary angioedema and acquired C1-inhibitor deficiency.[8] It is important to know when the urticaria appeared for the first time, because this could help to correlate the urticaria with a potential cause.

Question 2 is about the frequency of the urticaria which gives some information on the severity of the complaints. The severity is also depending on the extensiveness of the urticaria and associated symptoms. Although patients may have hives continuously every day, most patients have chronic recurrent urticaria.

Question 3 and 4 ask about the duration of the individual hive. This can be measured by marking a newly developing hive with a pen and observing when the hive disappears. Urticaria are by definition transient, that means that the hives disappear within 24 hours.[4,9] Normally hives persist for 3 to 6 hours. Pressure urticaria hives disappear more slowly, normally between 8-24 hours.[2,5] If hives persist for longer than 24 hours, urticarial vasculitis should be considered, or the very rare form of familiar cold urticaria or delayed dermographism.[2,5] If the lesions persist for more than 48 hours, the diagnosis urticaria must be doubted. The differential diagnosis for these longer lasting lesions is urticarial vasculitis, persistent reaction to insect bites, drug eruptions, macular or papular exanthems, first stage of erythema exsudativum and pemphigoid, Sweet's syndrome, polymorphous light eruption and figurate erythemas. If the hives persist definitely for longer than 24 hours and one of the above mentioned causes is highly unlikely, then taking a biopsy for histopathological evaluation and laboratory investigations are necessary (more information could be found in the explanation of question 7). Angioedema persists mostly longer (hours to days).[4] Factitious urticaria persist normally for 30 minutes up to 3 hours, cholinergic urticaria 30 to 60 minutes, cold urticaria 1 to 2 hours, urticaria solaris 15 minutes to 3 hours, pressure urticaria 8 to 24 hours.[2-4]

Question 5. The size can differentiate between different forms of urticaria. Most hives are 0.5 to 5 cm in size, but incidently hives may be bigger than 10 centimeter (giant hives[10]), and small hives may merge into bigger lesions. Small papules (1-3 mm) surrounded by a large reflex erythema are typical for cholinergic urticaria. Small pigmented papules are characteristic for urticaria pigmentosa. In that disease dermographism of a single lesion can be provoked (Darier's sign). In urticaria solaris small papules occur as well, but also an erythematous swelling of the area which was exposed to sunlight.

Question 6. Registration of the localisation of the angioedema is important. Swelling of the tongue and throat may be dangerous and may be a reason to start earlier with laboratory investigations, to prescribe antihistamines or prednisolon, and if necessary an epinephrine auto-injector. Epinephrine diminishes the edema of the mucosa and spasms of the bronchi. Chronic urticaria is mostly spread over the whole body. If the hives are only in a specific region of the body contact urticaria, dermographism, pressure, or urticaria solaris should be considered.

Question 7. Blue or purple discolourations implicate extravasation of erythrocytes which may be related to vasculitis. Brownish pigmentations may be related to vasculitis in the recent history, hyperpigmentation after inflammation, or urticaria pigmentosa. In the questionnaire some questions are related to vasculitis, like the duration of the hives (question 3), the discolouration (question 7), related complaints or diseases (like Raynaud's disease, question 23), muscle pain, joint pain, rheumatoid arthritis or systemic lupus erythematodes (SLE) (questions related to general health). If urticarial vasculitis is considered more laboratory tests should be performed at one of the firsts visits: biopsy for histopathological evaluation and for immunofluorescence (depositions of IgM, IgG, IgA, C1q, C4, or C3), serum analysis for C4, circulating immune complexes, liver and kidney function tests, rheumatoid factor, serologic tests for SLE (anti-double-stranded DNA), paraproteins, immunoglobulins (IgM, IgG, IgA), ANCA's, and urine analysis for proteins.
Chronic urticaria may be related with internal diseases (auto-immune disorders, chronic infections, or malignancies).[8] The pathological factors for the development of hives in these diseases include circulating immune complexes, auto-immune reactions, or circulating abnormal proteins. For example, hives developed after activation of complement and release of anaphylatoxins (C3a and C5a) which result in mast cell degranulation.

Question 8-10. Itch is one of the major symptoms of urticaria. Angioedema is often more painful or with a burning and tense sensation. Pressure urticaria and urticarial vasculitis may be painful also. Most patients scratch on their hives but mostly without causing bleeding. Scratch marks, dryness and scaling of the skin are more related to eczema. Patients with eczema may have dermographism as well; and itching may cause factitious urticaria like reactions. This combination is relatively common.

Question 11 inquires about other symptoms during a bout of hives or angioedema. Rhinitis, conjunctivitis, and asthma may accomplish any bout independent from the cause of the disease. These complaints may sometimes be related to inhalation allergens. Complaints of the gastro-intestinal tract can be seen in severe bouts, but could also be a sign of an adverse reaction to food. Hoarseness could be the first symptom of angioedema. Swelling of the tongue, the palate, the throat, and dyspnea

may indicate non-hereditary angioedema, an adverse reaction to food, or the very rare hereditary angioedema. Fatigue, fever and chills during a bout of urticaria are non-specific accomplishing symptoms of moderate or severe bouts of hives.

Question 12. This question is related to the specific moment of the day when the patient is having urticaria. In some cases a relation may be found to an activity which is performed shortly before at a specific moment of the day.

Question 13 asks whether there is a relation with the environment. Urticaria may be provoked by inhalation allergens, but this is a rare condition.[4] The environment at work could contain inhalation allergens, contact allergens or irritating agents which provoke immunological or non-immunological contact urticaria (see also question 25).[11] This question also informs whether stress could be a possible factor (see also question 24).

Question 14. The importance of focal infection as the cause of chronic urticaria is highly overestimated and mostly based on case reports. In rare cases a type I- or III- immune reaction to microbial allergens may be the cause of acute or chronic urticaria. Examples are hepatitis A, B and C, mononucleosis infectiosa (urticaria and angioedema may develop in the prodromal stage of the disease), infection with Coxsackie virus, and measles.[12-14] Children may develop hives after an infection with rhinovirus or enterovirus (ECHO, Coxsackie).[6,15] Candida infection may cause hives.[16] It is not useful to perform screening laboratory investigations in patients without any complaint related to an infection.

Question 15. X-Ray contrast media may cause hives.[17] In addition, the question is raised whether the patient used particular drugs only once, and in general whether something special occurred before the first bout of hives.

Question 16. Seasonal influences may help to point to responsible inhalation allergens. Differences in outside temperature like cold, warmth and sun may be responsible for the development of physical urticaria.

Question 17. Parasite infections (Ancylostoma, Anisakis, Ascaris, Ecchinococcus, Enterobius, Fasciola hepatica, Filariasis, Schistosoma, Strongyloides, Trichinella, Trichomonas, Toxocara, Toxoplasma) may cause hives, but this is rather rare.[6,18] If there is no elevation of blood eosinophils and if urticaria did not occur after a prolonged stay in a tropical country, is it not useful to investigate serum or faeces for parasites.

Question 18-22. These are questions related to the group of physical urticaria. The questions are designed to discover dermographism, pressure urticaria, cold urticaria, cholinergic urticaria, and urticaria solaris. The relation between exposure to pressure and the appearance of hives is sometimes difficult to recognize for the patient because the interval between exposure and hives can be long. For all forms of physical urticaria it is possible to perform specific provocation tests, but with the exception of the test for dermographism, these provocation tests are time consuming. Often they are not necessary in daily clinical practice.[6] Some very rare variants of physical urticaria exist such as exercise-induced food-triggered urticaria,[10] heat contact urticaria, vibratory angioedema, and delayed dermo-graphism.[6]

Question 23. Raynaud's phenomenon may be an indication for a systemic auto-immune disorder, such as SLE, and may be a prodromal sign of an internal disease.[19,20]

Question 24. Stress and psychological factors could provoke hives and are often mentioned by patients as an aggravating factor. Older studies showed that patients with urticaria experience more stress and psychological problems than control groups.[3,21] On the other hand suffering from chronic urticaria is a reason to experience stress.[22] In patients with cholinergic urticaria a bout may be provoked by stress. In patients with idiopathic urticaria a bout may be as well provoked by an acute stressful moment like an argument or something anxious. Furthermore, there is a possible relation between stress and the use of alcohol, sleeping drugs or sedatives (barbiturates, benzodiazepines, phenothiazine).

Question 25. If a hive develops after contact of the skin with a specific allergen or agent this is described as contact urticaria. The reaction is mostly limited to the place of contact, but generalized urticaria, asthma, rhinitis, conjunctivitis, edema of the gastro-intestinal tract, and even shock may occur.[11] Many drugs, food, cosmetics, plants, animal products, and industrial products may cause contact urticaria.

Question 26-28. In atopic families urticaria occur more often than in non-atopic persons. In these persons the hives are caused by an IgE-dependent mechanism, like in some allergic reactions to food. Normally the interval between the ingestion of food and the development of the hives is short, hence patients easily recognize that this is the cause of their urticaria and avoid the specific food. Because in these patients a cause is found more easier, they do not tend to visit out-patient departments. This is the reason why atopy is not more common in cohorts of patients with chronic urticaria. Therefore there is no reason to test IgE and perform a radioallergosorbent test (RAST) routinely.
Rare familiar forms of urticaria exist including familiar cold urticaria, familiar vibratory angioedema, and hereditary angioedema.[6,23] Hereditary angioedema is caused by the deficiency or insufficient activity of the C1-esterase inhibitor (C1-INH). The diagnosis is made on the basis of family history, the combination of angioedema, gastro-intestinal complaints and edema of the larynx, and the absence of hives. The serum C4 value is always decreased, 0-37% of the normal value. If a patient has these complaints and laboratory results, only then it is advised to perform more laboratory investigations like C1-INH, C1, C2, C3, C1q, and CH50.

Question 29-32. An adverse reaction to food could be a cause of acute and chronic urticaria. In question 30 a number of suspected foods are mentioned. Sometimes there is a suspicion because the patient is avoiding some food products. Keeping a diary of ingested food and bouts of hives can help to identify a specific food as the cause. Urticaria due to IgE-mediated food allergy develops mostly in a few minutes and the relationship is obvious. Patients often experience itch, tinkling or burning sensation in the oral cavity (question 31), swelling of the tongue or lips, discomfort of the gastro-intestinal tract, diarrhea, or rhinitis and dyspnea. Sometimes food contains antibiotics (eggs, milk, meat), yeast, fungi, Candida albicans (beer, wine, bread, raisins, cheese) which could provoke IgE-mediated urticaria, and then the association is less obvious. Foods more often cause non-immunologic reactions (intolerance

reaction), for example they cause direct histamine release (strawberries, white of egg, crustaceans), contain histamine (wine, cheese, tainted fish or meat), or other amines. Some food products contain salicylates, like apricots, peaches, or plums. Many patients with chronic urticaria develop hives after oral provocation with salicylates, dyes or benzoate.[6] Alcohol (ethanol, colourings in wine) may cause acute urticaria and may aggravate existing urticaria.
If an adverse reaction to food is suspected it is advisable to request RAST for food allergens. But the results may not be truly relevant, and this must be discussed with the patient in advance. This laboratory test provides information that IgE-mediated reaction might be involved, or may reveal a food product not suspected earlier. Oral provocation tests are the only reliable tests, but might be to dangerous to perform. If an adverse reaction to food is highly suspected it is possible to refer the patient to a dietician. A diet without the offending food product may be followed by a period of reintroduction of food if during the diet the patient has less complaints. This diet may be used as a diagnostic and therapeutic instrument.

Question 33. Pets: patients with generalized urticaria could react on epidermal products of animals at home, or parasites of these animals. This occurs very rarily.[24]

Question 34 and 37. This question relates to the possibility that the patient is exposed to specific products which can cause hives during his or her profession (especially inhalation- or contact urticaria). For example, exposure to flour in a bakery, or exposure to flowers, plants, or gloves made of natural rubber.

Question 35 (what is your profession?) **and question 36** (what are your hobbies?) are asked to receive information about the contact of patients with products or materials in their environment.

Question 38. In very rare cases a metal implant was responsible for hives.[25]

Question 39. Oral anti-conception may cause urticaria.[26]

Question 40. Most patients are already treated with antihistamines. It is important to know which ones they already tried and how they responded to them.

Question 41. The time of the last use of an antihistamine or prednisolon is important if the physician wants to perform tests for physical urticaria (dermographism) or intracutaneous allergy tests.

Question 42 and 43. The drug use of the patient is very important, because if a particular drug is responsible for urticaria the treatment is simple, namely stopping or replacing the drug. The time when the patient started to use the particular drug could be helpful in finding a relationship between a particular drug and hives. In question 42 a number of drugs are mentioned which are often responsible for hives or angioedema. It is of particular importance to ask specifically for the use of oral anti-conception, painkillers and 'over the counter' drugs, because patients tend not to mention them.

Question 44 and 45. These questions are about the medical history (question 44) and physical complaints (question 45) of the patient. Furthermore, a questionnaire related to general health is added. This will help to detect imminent causes as well.

Question 46. In this question the patient is asked to describe his or her own ideas or explanation of the cause of the hives.

DISCUSSION

The questionnaire is a helpful instrument which can be used to detect underlying causes in patients with chronic urticaria by means of history-taking. It provides the patient with the possibility and the time to participate actively in the process of finding an explanation for their chronic urticaria. Furthermore, the completeness of the question list, including questions related to general health, and the written information about urticaria that is provided with it, will diminish the patient's concern and fear that an underlying severe disease might be overlooked. In a lot of patients the questionnaire and the results of the laboratory tests will not reveal an underlying cause, but it is easier for the patient to accept this, because of the attention paid to them.

REFERENCES

1. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-1580.
2. Jorizzo JL, Smith EB. The physical urticarias, an update review. Arch Dermatol 1982;163:151-159.
3. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969;81:588-597.
4. Bromberg Schneider S, Atkinson JP. Urticaria and angioedema. Update Dermatology in general medicine. McGraw-Hill 1983;61-79.
5. Champion RH, Warin RP. Urticaria. In: Major problems in Dermatology, volume 1, London; Saunders WB, 1974.
6. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1988.p.183-189 (Appendix A).
7. Erlings M, Jongedijk-Bröndsted H. Etiologie van urticaria' een retrospectief onderzoek bij 200 patiënten. Ned Tijdschr Geneeskd 1976;120:1565-1558.
8. Mekkes JR, Bos JD. Urticaria en erythemen. In: van Vloten (ed). Dermatologie en venereologie. Wetenschappelijke Uitgeverij Bunge, Utrecht, 1992; 2e druk 1996, pp 124-131.
9. Soter NA, Wasserman SI. Urticaria/angioedema. A consideration of pathogenesis and clinical manifestations. Int J Dermatol 1979;18:517-532.
10. Romano A, Di Fonso M, Venuti A, Palmieri V, Zeppilli P. Food-dependent exercise-induced anaphylaxis: report of two cases. International Journal of Sports Medicine 1992;13:585-587.

11. Von Krogh G, Maibach HI. The contact urticaria syndrome - an updated review. J Am Acad Dermatol 1981;5:328-342.
12. Scully LJ, Ryan AE. Urticaria and acute hepatitis A virus infection. Am J Gastroenterol 1993;88:277-278.
13. Geller M. Association of chronic localized angioedema of the tongue with hepatitis B. Ann Allergy Asthma Immunol 1998;81:96.
14. Llanos F, Raison-Peyron N, Meunier L, Ducos J, Meynadier J. Hepatitis C virus infection in patients with urticaria. J Am Acad Dermatol 1998;38:646.
15. Cherry JD. Viral exanthems. Current Problems in Pediatrics 1983;13:1-44.
16. Numata T, Yamamoto S, Yamura T. The role of mite, house dust and Candida allergens in chronic urticaria. J Dermatol 1980;7:197-202.
17. Nemcek A Jr. Contrast material reactions. J Vascular & Interventional Radiology 1996;7:541.
18. Pasricha JS, Pasricha A, Prakash OM. Role of gastro-intestinal parasites in urticaria.Ann Allergy 1972;30:348-351.
19. Bisaccia E, Adamo V, Rozan SW. Urticarial vasculitis progressing to systemic lupus erythematosus. Arch Dermatol 1988;124:1088-1090.
20. D'Cruz DP, Wisnieski JJ, Asherson RA, Khamashta MA, Hughes GR. Autoantibodies in systemic lupus erythematosus and urticarial vasculitis. J Rheumatol 1995;22:1669-1673.
21. Rees L. An aetiological study of chronic urticaria and angioneurotic edema. J Psychosom Res 1957;2:172-189.
22. O'Donnel BFO, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197-201.
23. Gelfand JA, Boss GR, Conley CL, Reinhart R, Frank MM. Acquired C_1-esterases inhibitor deficiency and angioedema. Medicine 1979;58:321-328.
24. Dominguez Lazaro AR, Bootello Gil A, Garcia Cubero A. Bronchial asthma and urticaria caused by sensitization to animal dander (review and report of 4 cases). Revista Clinica Espanola 1968;108:136-143.
25. Hensten-Pettersen A. Skin and mucosal reactions associated with dental materials. Eur J Oral Sciences 1998;106:707-712.
26. Warin RP, Cunliffe WJ, Greaves MW, Wallington TB. Recurrent angio-edema: familial and oestrogen-induced. Br J Dermatol 1986;115:731-734.

Chapter 3

The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema

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SUMMARY

Objective: To assess the value of extensive laboratory screening for the identification of causes in patients with chronic urticaria and/or angio-edema.

Design: In a prospective study in 220 patients, 2 diagnostic strategies were compared: the combination of detailed history taking and limited laboratory screening, vs detailed history taking and extensive laboratory screening. The results of the extensive screening program were initially kept secret for the patients and the physicians. Later, all results were disclosed, and an investigation was undertaken to find out whether this information changed the initial diagnosis. The patients were followed up for 1 year to evaluate the results of interventions and to detect latent causes.

Setting: The study was performed in the outpatient department of a secondary and tertiary care centre with institutional practice.

Patients: A total of 238 consecutive new patients with chronic urticaria and/or angio-edema were referred, 18 of them refused participation. One patient was unavailable for follow-up.

Main Outcome Measure: The difference in the number of identified causes between both approaches and the nature of the causes that would have been missed by omitting extensive laboratory screening.

Results: With a questionnaire and the limited laboratory tests, a cause was found in 45.9% of the patients, compared to 52.7% with the questionnaire and the extended screening program. Except for one parasite infection, missed diagnoses were mainly adverse reactions to drugs or food detected by standard elimination procedures, and not by laboratory investigations.

Conclusion: Routine laboratory screening did not contribute substantially to the diagnosis of chronic urticaria nor to the detection of underlying disorders.

INTRODUCTION

Approximately 12-24% of the population will have urticaria or angio-edema at least once in their lifetime.[1-3] In patients visiting general practitioners, an incidence of acute and chronic urticaria of 4.3 per 1000 patients and a prevalence of 5.0 per 1000 patients were reported; 5.1% had urticaria longer than 4 weeks, and 4.1% were referred to a dermatologist.[4] In patients visiting dermatology outpatient departments, 1.4% to 2.4% had urticaria or angioedema.[5,6] Urticaria can be intensely pruritic and may interfere with daily activities or sleep. Symptomatic treatment with antihistamines cannot completely suppress all symptoms in all patients.

Despite extensive (laboratory) investigations, 70% to 90% of chronic urticaria and/or angioedema remains idiopathic.[1,6-8] In a subset (approximately 30%) of patients with chronic idiopathic urticaria, circulating IgG antibodies against the high-affinity IgE receptor (FcεRIα) were detected on mast cells.[9,10] This recent finding, although rather a mechanism than a cause, is relevant for the pathogenesis of chronic urticaria and may have implications for future treatment.[11-15] Still, in the majority of chronic urticaria, neither a cause nor a mechanism can be discovered.

The sometimes poor response to symptomatic treatment and the inability of the physician to provide information on cause and prognosis are disappointing for the patients. Both patients and physicians may fear that the symptoms could be a manifestation of an underlying illness. Because of this fear, extensive and costly investigations are performed (eg, physical examination, provocation tests, blood chemistry profiles, allergy tests, complement profiles, and screening for infections, autoimmune diseases, and malignancies).[16-21] Large clinical studies have shown that the frequency of severe underlying diseases in urticaria patients is low.[1,5,7,8,22-24] In the literature, it has been suggested that too much time and money is spent on routine investigations and that more time should be spent on history taking.[25-28] Despite these recommendations, extensive routine screening procedures are still widely used. In this time of evidence based medicine, the only way to change this attitude would be to provide the evidence that extensive screening is unnecessary. To achieve this, we prospectively investigated the additional diagnostic value of laboratory screening. The aim of this study was to investigate the hypothesis that when the patient's history is recorded thoroughly, extensive laboratory screening does not substantially disclose more causative factors than does the limited set of laboratory tests.

Chapter 3

METHODS

The study was designed as a per-patient comparison of 2 diagnostic strategies: a *history-based diagnostic approach*, consisting of detailed history taking and a very limited set of laboratory tests, followed by additional tests only if necessary because of abnormal findings in the history, vs a *routine approach*, consisting of detailed history taking and an extensive laboratory screening program. In the course of a prospective, protocolized study design, during which results from laboratory investigations became progressively available, dermatologists were asked to make a differential diagnosis at 2 successive occasions.

Study population

From January 1992 to July 1994, 238 consecutive new patients who were older than 15 years, who had urticaria or angioedema for at least 6 weeks, and who consulted the outpatient Department of Dermatology were asked to participate. They received written and oral information about the purpose and special design of the study and gave their informed consent. Patients were excluded if diagnostic tests had been performed (apart from the limited set listed below) or if their reference letter contained any information regarding possible causes. The Department of Dermatology of the Academic Medical Center in Amsterdam is a secondary and tertiary care center. The protocol was approved by the Medical Ethical Committee.

Study design and follow-up

A schematic representation of the study design is shown in figure 1. Based on a questionnaire, which was filled in by all patients, and the results of a limited set of laboratory tests (determination of haemoglobin level, haematocrit, erythrocyte sedimentation rate, white blood cell count, and differential blood cell count), the dermatologist made a first differential diagnosis regarding the cause of the urticaria. Simultaneously, an extended diagnostic work-up was performed by the investigators, but the results were kept secret. Additional laboratory tests could be requested by the dermatologist; all requests were recorded on the evaluation form. After 4-6 months, the remaining results were revealed to the dermatologist and a second, sometimes revised, differential diagnosis was made. After a follow-up period of at least 1 year, each patient was interviewed again and asked about any remaining or new complaints and, if indicated, laboratory investigations were repeated. The follow-up was necessary to detect causes initially not traced, and to evaluate the results of interventions.

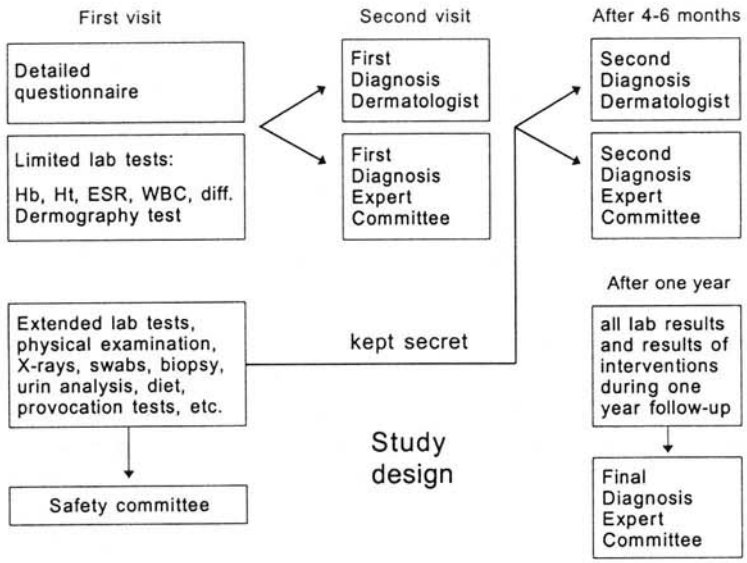

Figure 1. Summary of study design. In all patients, extensive screening took place at the first visit, but the results were kept secret for the treating dermatologists. Only a safety committee saw the results to check for abnormal values that would require immediate intervention. Both the dermatologists and an expert committee made a first diagnosis on the basis of a detailed questionnaire and a very limited set of lab results. Four to 6 months later, all results were revealed and an analysis of how this additional information influenced the diagnosis was performed. The final, most likely diagnosis was made by the expert committee on the basis of all available information after 1 year of follow-up. Hb indicates haemoglobin; Ht, haematocrit; ESR, erythrocyte sedimentation rate; WBC, white blood cells; and diff, differential cell count.

Patient questionnaire

A standard patient questionnaire containing 66 items was developed, based on earlier published questionnaires.[29-31] The first part consisted of questions concerning frequency and pattern of attacks, duration of wheals, associated symptoms, provoking physical factors, history of atopic disease, occupation and leisure activities, food and drug intolerance and use of drugs. The second part contained questions on associated signs and symptoms, medical history and general health (the questionnaire is available on request).

Extended diagnostic work-up

The extensive laboratory investigations included haemoglobin level, haematocrit; erythrocyte sedimentation rate; white blood cell count; differential blood cell count; total eosinophil count; liver and kidney function tests; determination of levels of glucose, protein, complements, circulating immune complexes, cryoglobulin; serologic tests for rheumatoid factor, IgE and antinuclear antibodies, hepatitis B, syphilis, anti-streptolysin titre, *Strongyloides*, and anti-double-stranded DNA; radioallergosorbent tests (RASTs) for inhalation allergens (mixtures of rodents, birds, fungi, grass pollen, birch pollen, mugwort pollen, cat dander, dog dander, house dust mite), food allergens (mixtures of crustaceans, fish, meat, wheat, fruits, vegetables, soy, peanuts, peas), and other allergens if suspected. Urinanalysis and examination of stools for parasites and occult blood were performed. Smears from throat were cultures for streptococci, and smears from the vagina were investigated for *Candida* organisms. Radiographs of the chest, paranasal sinuses and teeth were obtained to search for possible infections or malignancies. Skin biopsy specimens were obtained from urticarial lesions. Each patient was given a routine physical examination and provocation tests for physical urticarias as described by Henz[31] (dermatographism and cold urticaria). Other physical provocation tests were performed when deemed necessary. If the patient used drugs, a determination was made as to whether there was a possible time relationship with the urticaria, and treatment with all drugs was discontinued or replaced with chemically unrelated equivalents. Suspected underlying diseases were treated whenever possible, to examine the association with chronic urticaria. An elimination diet (ie, a diet without salicylates, dyes, benzoates, sorbic acid, sodium glutamate, sulfites, antioxidants, sodium nitrate, parabens, vasoactive amines, histamine liberators, sugar, yeast, spices, coffee, crustaceans, fish, meat, eggs, milk products, and potatoes) was prescribed for at least three weeks to screen for adverse reactions to food. Drug provocation tests and oral food rechallenge tests were performed when necessary.

Safety committee and expert committee

A safety committee examined the results from the extended diagnostic work-up when they became available to check for abnormal values that would require immediate intervention. An expert committee also tried to discern the most likely cause(s) of the urticaria in each patient, initially based only on the history and findings of the limited laboratory tests, later based on all the available information. The (differential) diagnosis

of the expert committee was not disclosed to the dermatologist to avoid bias due to a "learning effect".

Analysis

The effectiveness of the history-based diagnostic approach (table 1) was assessed by comparing the number of causes identified correctly by the dermatologists in their first differential diagnosis (based on limited laboratory tests) with the number of causes in their second differential diagnosis (based on the extended diagnostic work-up). The first and the second differential diagnoses of the dermatologists were compared with the final expert diagnosis, defined as the most likely cause of the urticaria. A diagnosis was considered correctly identified if the final expert diagnosis was mentioned on the evaluation form as possible cause of the urticaria.

Also, for each individual patient, an analysis was performed to determine whether a cause that was identified by the expert committee was missed by the dermatologists and whether this oversight could have been avoided by the use of routine laboratory tests, provocation tests, or any other diagnostic procedure.

RESULTS

Patient population characteristics

In total 238 urticaria patients were referred to the outpatient department. Eighteen patients refused participation. Seventy-four percent of the patients were referred by a general practitioners (13% of these 74% represented requests for a second opinion); 19% of the patients were referred by a dermatologist, and 7% were referred by other specialists. There were 132 woman and 88 men; the mean age was 37.5 (range 15-79) years. The median duration of their urticaria and/or angioedema at inclusion was 15 month. The distribution of the duration in our patient population is shown in Figure 2.

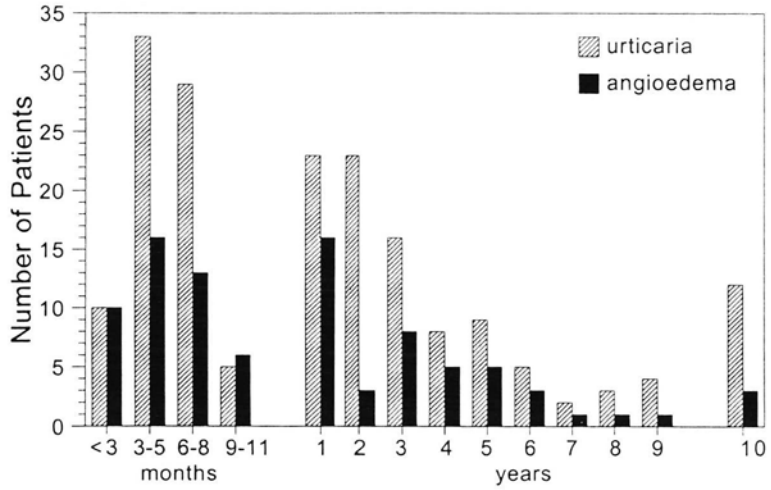

Figure 2. Distribution of the duration urticaria and/of angioedema at inclusion.

Associated symptoms and patient history

Associated symptoms during attacks of urticaria or angioedema were dyspnea (13%), hoarseness (9%), and a swollen tongue or throat (7%). Five patients reported severe anaphylactic reactions. The following complaints related to the atopic syndrome were reported by 40% of the patients; atopic dermatitis (5%), asthma (15%), allergic rhinitis (17%) and conjunctivitis (18%). Forty patients (21%) reported a history of adverse drug reactions and 60 patients (31%) suspected a particular food as the cause of the urticaria.

First diagnosis of the dermatologists

Up to five suspected diagnoses could be recorded on the first evaluation form by the dermatologists; the mean number of recorded diagnoses was 2.3 per patient. The most frequent diagnoses were physical urticarias (182), unknown etiology (111), infection (50), adverse reaction to food (44) or to drugs (43), inhalation allergens (40), and internal diseases (22).

In 33 patients (15%) no additional investigations were requested and in 150 patients (68%) fewer than 5 investigations were requested by the dermatologists on the first evaluation form. The most frequently requested additional investigations were determinations of IgE antibody levels and RASTs for inhalation allergens (81), RASTs for food allergens (34), and an elimination diet (30).

Table 1. Diagnostic categories in chronic urticaria

	Dermatologists		Expert committee		
	First Diagnosis	Second Diagnosis	First Diagnosis	Final Diagnosis	Effectiveness
Diagnoses	**45.9**	**52.7**	**50.8**	**53.1**	**87**
Physical urticaria	33.2	33.2	33.2	33.2	100
Adverse drug reactions	5.0	8.6	9.0	9.0	58
Adverse food reactions	4.0	6.8	4.5	6.8	59
Inhalation allergens	0	0	0	0	---
Contact urticaria	0.9	0.9	0.9	0.9	100
Infection	1.4	1.8	1.8	1.8	78
Internal diseases	1.4	1.4	1.4	1.4	100
Malignancies	0	0	0	0	---
Etiology unknown	**54.1**	**47.3**	**49.2**	**46.9**	---
Idiopathic urticaria	44.6	36.3	37.8	35.5	---
Physical & idiopathic	9.5	11.0	11.4	11.4	86

Table 1: The effectiveness of this diagnostic approach was estimated by comparing the percentages of identified causes of the first diagnoses made by the dermatologists (based on the questionnaire and limited laboratory tests) with those of their second diagnosis (based on the questionnaire and extended diagnostic work-up). The final expert diagnoses were based on the questionnaire, the extended diagnostic work-up and the follow-up. Number of patients, 220. All values are expressed as percentages.

Extended diagnostic work-up and follow-up

The safety committee did not observe any serious abnormal test result which would have required an immediate intervention. Clinically relevant abnormalities of the erythrocyte sedimentation rate were found in 20 patients. In 4 patients, this abnormality could be related to an internal disease (Sjögren's syndrome, systemic lupus erythematosus [SLE], paraproteinemia, or mesothelioma). Twenty-three patients had a decreased level of C4 (<0.2 g/l), including the patients with Sjögren's syndrome and SLE. Circulating immune complexes (C1q-binding test >14%) were found in 17 patients, including the patients with Sjögren's syndrome, SLE and paraproteinemia.

The level of serum IgE were elevated in 20 patients: 500 to 1000 kiU/l in 8 patients and 1000 to 2000 kiU/l in 12 patients. Antibodies (RASTs) to inhalation allergens were present in 69 patients and to food allergens in 19 patients. This antibodies could be related to urticaria in 6 patients. Infections such as vaginitis (26 patients) and cystitis (18 patients), and elevated antistreptolysin titres (42 patients) were found, but treatment did not resolve the urticaria. Occasionally, the results of the other laboratory tests were abnormal, but the abnormalities were not clinically relevant to urticaria. The mean follow-up period was 21 months (range 12-48 months). One patient died of mesothelioma 25 months after the first visit. He had urticaria due to an adverse drug reaction.[32] Only the four patients mentioned above developed an internal disease or malignancy. During the follow-up period, 6 patients became unemployed because of severe daily complaints. One patient was lost to follow-up.

Final expert diagnosis

The final expert diagnosis was based on the questionnaire, results of the extended diagnostic work-up, and all the information obtained during the follow-up period. Sixty patients (33.2%) had urticaria or angioedema due to physical stimuli like pressure, cold, heat or light. Twenty patients (11.4%) had a combination of physical- and idiopathic urticaria (Table). In 10 patients (9.1%) adverse drug reactions were identified as the cause of urticaria. The symptoms recurred in all patients after rechallenge with the suspected drugs, and in every case, the urticaria was cured by permanent elimination of the drug use.

Fifteen patients (6.8%) had adverse food reactions; nine of them had already suspected food as possible cause. Two patients with adverse food reactions had exercise-induced food-dependent reactions. Ten patients had a parasite infection without diarrhea. Eight of the 10 patients had been born in tropical country, and 2 had worked in one for more than one year. Six of the 10 had eosinophilia. In 4 patients, treatment of the parasite infection resulted in disappearance of the urticaria. In these 4 patients, the infection was considered to be related to the urticaria. In 3 patients, an internal disease was found that could be related to urticaria (i.e., Sjögren's syndrome, SLE and para-proteinemia).

In 46.9% of the patients, the cause of the urticaria remained unclear. The patients with physical and idiopathic urticaria were classified as having idiopathic urticaria because most of them considered it their most important complaint. The physical urticarias could be relieved by avoiding eliciting stimuli such as pressure or heat.

Effectiveness of the history-based diagnostic approach

To measure effectiveness, the first and the second differential diagnoses of the dermatologists were compared. This comparison represents the actual circumstances in daily clinical practice, with the potential differences in knowledge of the different dermatologists and the time pressures in an outpatient department. The overall effectiveness was 87% (Table). Nine adverse drug reactions and six adverse food reactions were missed. In 5 of the 6 cases, the patient's history revealed no information regarding adverse food reactions. In 4 patients with physical and idiopathic urticaria, pressure urticaria was not mentioned as a possible cause. One parasite infection was missed.

Chapter 3

DISCUSSION

This study demonstrated that an extended diagnostic work-up (extensive laboratory screening, routine physical examination, and routine provocation tests) is not necessary in patients with chronic urticaria or angioedema if thorough history taking is performed. Nineteen of the 20 missed diagnoses could not have been found with routine laboratory tests. In only one patient with a parasitic infection, which was not suspected by the dermatologist, could routine screening have contributed to the diagnosis. No severe underlying diseases were missed.

A limitation inherent to the study design is that the study was performed in a secondary and tertiary care institution and that the results may not be applicable to other types of clinical settings. In our study, 61% of the patients were directly referred by their general practitioner. It is conceivable that during the investigation, the dermatologists were more precise in history taking because they knew that their diagnoses were going to be recorded. On the other hand, it is possible that some of them were less precise because they knew that all patients were going to be thoroughly evaluated by the expert committee.

The expert committee was able to identify the cause of the urticaria in 53% of the patients. The percentage of identified causes is high compared with those of other patient series,[1,8,22,23] probably because a considerable percentage (33%) of physical urticaria cases were detected through standard provocation procedures. The diagnosis of physical urticaria was only made if the physical factor was the patient's main problem. Similar percentages of physical urticaria cases and the combination physical and idiopathic urticaria were found in other studies.[5,33] Of course, we cannot guarantee that the final cause identified by the expert committee is correct in all cases. It is the most likely cause to the best of our knowledge. The expert committee consisted of the primary investigator and 2 staff members with more than 10 years of experience with chronic urticaria. After detailed examination of all laboratory tests results and all other information in each patient's file, the committee members made their diagnoses without time constraints after 1 year of follow-up.

The dermatologists missed 9 adverse drug reactions, which could have been detected if treatment with all suspected drugs had routinely been discontinued. The pressure urticaria that was missed in 4 patients could have been found if the questionnaire had been read more carefully. The parasitic infection would not have been missed if a search for parasitic infections had been done in all patients who lived or worked in tropical countries. Adverse food reactions were highly overestimated as a cause for urticaria by the patients (31%) and the dermatologists (20%). Therefore, determination of IgE levels and RAST results were requested. The results of the RAST for food allergens was relevant in finding the cause of the urticaria in only 15 patients (6.8%).
On the other hand, six adverse food reactions were missed by the dermatologists and 5 were missed by the expert committee as well because thorough history taking did not reveal them. The adverse food reactions were found with an elimination diet. As a last effort, such a diet could be advised for some motivated patients, even with no indication of an adverse food reaction in the history.

In 3 patients, the most probably cause of the urticaria was an internal disease (ie, Sjögren's syndrome, SLE and paraproteinemia). After treatment the urticaria diminished, but this improvement could also be related to the treatment itself. Because of associated symptoms mentioned in the questionnaire (eg, joint pain or malaise) or because of an elevated erythrocyte sedimentation rate, the dermatologists requested further laboratory tests and therefore the diseases were not missed. One patient with idiopathic urticaria developed Raynaud's phenomenon after 1 year of follow-up. No other complaints or laboratory results indicating an autoimmune disorder were present during three years of follow-up.

In our study, no malignancy related to urticaria was found, but the number of enrolled patients is too small in relation to the low incidence of malignancies in chronic urticaria to provide reasonable security that no underlying malignancy would be missed by using this approach. In patients with lymphoproliferative disorders, a prevalence of 0.5% of symptomatic, acquired, C1-inhibitor deficiency presenting as angioedema was observed.[34] The relationship between urticaria and malignancies was analyzed in a prospective 10 year follow-up study of 6913 allergic adults. The relative risk of leukemia, lymphoma, or myeloma developing in patients with a history of hives was 7.89

(confidence interval, 3.13-19.89).[35] Although the relative risk of malignancies is high in patients presenting with urticaria or angioedema, the absolute risk is very low.[24] Therefore, we believe there is no reason for routine screening without any indication of an underlying malignancy. Although there is an evident trend to reduce laboratory investigations in patients with chronic urticaria, extensive investigations are still recommended in textbooks [19,36] and reviews, [20,21] performed in clinical trials, [16-17] and carried out by many physicians. One of the reasons for requesting extensive investigations is that some patients request them because they fear that their hives are caused by underlying diseases and they want to be reassured. Also, the fear of legal claims force physicians to perform extensive investigations to make sure that no known underlying cause is overlooked. Performing endless screening series owing to the fear of "failure to diagnose" leads to increasing costs and frustration on the part of both the patient and the physician. According to the principles of evidence-based medicine, diagnostic tests that do not contribute to the diagnostic process should not be performed.[37,38] Whether a diagnostic test is useful or not depends on how the outcome of the test can change the pretest probability of a certain underlying disease or causative factor.[37,39] In chronic urticaria, only a few specific laboratory tests, such as the dermographism test for urticaria factitia, appeared to be valuable in this respect.

The history itself can be regarded as the most valuable diagnostic tool. Each item of the history can be considered as a diagnostic test that either increases or decreases the probability of a target disorder.[39] By combining several questions, the probability that certain underlying diseases or factors are present can be reduced to nearly zero or nearly 100%. In both situations, additional laboratory tests are not necessary.

With the history-based approach, the dermatologists requested fewer laboratory investigations and felt more secure that they did not miss underlying diseases. As a consequence of this study, we do not any longer perform routine screening investigations in patients with chronic urticaria.

REFERENCES

1. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969;81:588-597.
2. McKee WD. The incidence and familial occurrence of allergy. J Allergy 1966;38:226-235.
3. Swinny B. The atopic factor in urticaria. South Med J 1941;34:855-858.
4. Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter- & episode- & process-oriented standard output from the Transition Project. Part 1 and 2. Amsterdam: Department of General Practice 1991; Amsterdam University press.
5. Douglas HMG. Chronic urticaria. Clinical and pathogenetic studies on 141 patients. Thesis 1975; Dijkstra Niemeyer, Groningen.
6. Mekkes JR, Schaar WW van der, Bos JD. Anamnese en diagnostiek van chronische urticaria. Ned Tijdschr Geneeskd 1986;130:1801-1805.
7. Jacobson MKW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. JAMA 1980;243:1644-1646.
8. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427-436.
9. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Eng J Med 1993;328:1599-1603.
10. Fiebiger E, Maurer D, Holub H, Reiniger B, Hartmann G, Woisetschläger M, Kinét JP, Stingl G. Serum IgG autoantibodies directed against the α chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606-2612.
11. Hide M, Francis DM, Grattan CEH, Barr RM, Winkelmann RK, Greaves MW. The pathogenesis of chronic idiopathic urticaria: new evidence suggests an auto-immune basis and implications for treatment. Clin Exp Allergy 1994;24:624-627.
12. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996;98:89-98.
13. Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Immunol 1997; 99: 461-465.
14. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεRIα auto-antibodies in autoimmune-mediated disorders; identification of a structure-function relationship. J Clin Invest 1998;101:243-251.
15. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1997;133:1003-1008.
16. Bressler RB, Sowell K, Huston DP. Therapy of chronic idiopathic urticaria with nifedipine: Demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. J Allergy Clin Immunol 1989;83:756-763.

17. Claveau J, Lavoie A, Brunet C, Bédard PM, Hébert J. Chronic idiopathic urticaria: Possible contribution of histamine-releasing factor to pathogenesis. J Allergy Clin Immunol 1993;92:132-137.
18. Kaeser P, Revelly ML, Frei PC. Prevalence of IgE antibodies specific for food allergens in patients with chronic urticaria of unexplained etiology. Allergy 1994;49:626-629.
19. Kaplan AP. Urticaria and angioedema. In Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors: Allergy Principles and Practice 1988, 3rd Ed., Mosby, St. Louis, MO, pp. 1377-1401.
20. Armenaka M, Lehach J, Rosenstreich DL. Successful management of chronic urticaria. Clin Rev Allergy 1992;10:371-389.
21. Kaplan A, Buckley RH, Mathews KP. Allergic skin disorders. JAMA 1987; 20:2905-2909.
22. Nizami RM, Baboo MT. Office management of patients with urticaria: an analysis of 215 patients. Ann Allergy 1974;33:78-85.
23. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-381.
24. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol 1990;123: 453-456.
25. Kobza Black A, Greaves MW, Champion RH, Pye RJ. The Urticarias 1990. Br J Dermatol 1991;124:100-108.
26. Soter NA. Acute and chronic urticaria and angioedema. J Am Acad Dermatol 1991;25:146-154.
27. Cooper KD. Urticaria and angioedema: Diagnosis and evaluation. J Am Acad Dermatol 1991;25:166-176.
28. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-1672.
29. Gross AS, LaTour DL, King LE. Chronic urticaria: a model questionnaire for patient screening. Cutis 1990;46:421-424.
30. Guin JD. The evaluation of patients with urticaria. Symposium on urticaria and the reactive inflammatory vascular dermatoses. Dermatol Clinics 1985;3:31-36.
31. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnosis and therapeutic aspects. Berlin: Springer Verlag, 1998: 183-195 (Appendix A).
32. Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. Clin Exp Dermatol 1995;20:60-61.
33. Barlow RJ, Warburton F, Watsen K, Kobza Black A, Greaves MW. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol 1993;29:954-958.
34. Geha RS, Quinti I, Austen KF, Cicardi M, Sheffer A, Rosen FS. Acquired C1-inhibitor deficiency associated with antiidiotypic antibody to monoclonal immunoglobulins. N Engl J Med 1985;312:534-540.

35. McWhorter WP. Allergy and risk of cancer; a prospective study using NHANESI follow-up data. Cancer 1988;62:451-455.
36. Mathews KP. Chronic urticaria. In Schocket AL. Clinical management of urticaria and anaphylaxis. Marcel Dekker Inc. New York 1993.
37. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: a basic science for clinical medicine. 2nd ed. Boston, Mass: Little, Brown and Company; 1991.
38. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? JAMA 1994;271:389-391.
39. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? JAMA 1994;271: 703-707.

Chapter 4

Natural course of physical and chronic urticaria and angioedema in 220 patients

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SUMMARY

Background: Information about spontaneous remission of chronic urticaria is limited.

Objective: To investigate the natural course of chronic urticaria we followed up 220 adults in a prospective study.

Methods: Patients were followed up for one to three years to evaluate interventions, to detect latent causes, and to study the natural course of urticaria. The diagnosis was made by detailed history taking as well as laboratory and provocation tests.

Results: Thirty-five percent of all patients were free of symptoms after one year. In 28.9% of patients, symptoms had decreased. Spontaneous remission occurred in 47.4% of the patients in whom no cause of their urticaria and/or angioedema could be identified, and in only 16.4% of the patients with physical urticaria. A cause could be identified in 53.1% of the patients. Thirty-six percent of the patients had idiopathic urticaria. Chronic idiopathic urticaria combined with physical urticaria occured in 10.9%.

Conclusion: In general, the prognosis for spontaneous remission is reasonable, with the exception of the subgroup (33.2%) with physical urticaria.

INTRODUCTION

Urticaria is characterized by a well-demarcated eruption of transitory, usually itchy and sometimes even painful erythematous skin swellings that can recur for month or years. Previous investigators have defined chronic urticaria as episodes recurring for more than six weeks.[1] Urticaria and angioedema are common disorders.[2] Approximately 5% of patients with a bout of urticaria will be symptomatic for longer than four weeks.[3] Thirty percent of patients with urticaria seen in a family practice have chronic urticaria.[3] In clinical studies percentages of causes found for urticaria vary between 20 and 90%.[2,4-7] The percentages of found causes differ because different inclusion and exclusion criteria (eg inclusion of physical urticarias) were used.

Chronic urticaria may be caused by internal diseases or malignancies, but these underlying diseases are rarely found.[2,4,8-10] In the past, extensive laboratory screening has been performed to exclude an underlying disease. Recent diagnostic guidelines recommend thorough history taking and only a very limited amount of laboratory tests.[11,12] In a prospective study we evaluated the benefit of extensive laboratory testing and concluded that tests not based on the history do not contribute to the detection of underlying causes of chronic urticaria.[13] This study was performed in the same patient cohort.

Very little is known about the natural course of chronic idiopathic or physical urticaria. A literature search including articles from 1966 to 2000 revealed more than 5500 medical articles on urticaria or angioedema (or both), but only 13 articles referred to the natural course of the disease.

The aim of this prospective cohort study in consecutive patients was to investigate the natural course and the prognosis of chronic urticaria and/or angioedema, including subtypes such as physical urticaria.

SUBJECTS AND METHODS

Patient recruitment, patient population and study design

The study was performed at the outpatient Department of Dermatology of the Academic Medical Center in Amsterdam, The Netherlands, which is a secondary and tertiary care center. From January 1992 to July 1994, all consecutive patients older than 15 years with urticaria and/or angioedema of unknown origin and with at least a 6-week duration of the symptoms were included.

Two hundred twenty patients were investigated. One hundred thirty-two women and 88 men were enrolled in the study; their mean age was 38 (range 15-79) years. Forty-one patients (19%) had urticaria only, 64 patients (29%) had urticaria and angioedema, and 18 patients (8%) had angioedema without urticaria.

After informed consent had been obtained, the patients were subjected to a diagnostic protocol, which included a detailed questionnaire, physical examination, laboratory tests, provocation tests for physical urticaria, and adverse reactions to food and drugs. The protocol was approved by the Medical Ethical Committee.

Patient questionnaire

A detailed history was obtained from all patients, using a standardized questionnaire with particular attention for possible causes of urticaria, based on earlier published questionnaires[14-16] and personal experiences.

Laboratory investigations and provocation tests

The study was part of a research project for the development of evidence-based clinical guidelines for laboratory investigations in patients with chronic urticaria and/or angioedema.[13] Therefore many haematologic, immunologic, biochemical, allergy tests; cultures; and x-rays were performed, as described earlier in detail elsewhere.[13] Provocation test for physical urticaria were performed.[17,18] To evaluate dermographism, firm stroking of the skin was performed, which induces itchy, linear hives within minutes. The test for pressure urticaria was performed with a special device that applied 3 different weights on back of the patient for 20 minutes; the appearance of whealing was checked during the day. Cold urticaria was tested with a steel container with ice cubes applied to the forearm for 20 minutes. Cholinergic urticaria was provoked by a hot shower or exercise until sweating. Screening for food allergy or intolerance was investigated by an elimination diet for at least 3 weeks. All drugs used were discontinued or replaced with chemically

unrelated equivalents. Drug provocation tests and oral food rechallenge tests were performed if necessary.

Follow-up

After a follow-up period of at least one year, patients were asked whether they had remaining or new complaints and whether they still used antihistamines, oral corticosteroids, or other drugs. Laboratory tests were repeated, if indicated. The follow-up was directed at detecting causes of urticaria not traced initially by the questionnaire, to evaluate the effect of interventions, and to obtain information about the natural course of the different subtypes of urticaria.

Chapter 4

RESULTS

Patient questionnaire

Twenty-five percent of the patients had urticaria continuously, 30% of them had daily bouts, 22% had more than 2 bouts every week, and the remaining group less frequently had hives or only angioedema. In 94% of the patients the itch was the most important complaint. Sleeping disorders occurred in 25% of the patients with urticaria and in 4% of the patients with angioedema. Twenty-eight percent of the patients reported intense pruritic whealing from insect bites or stings. This was mainly seen in patients with chronic urticaria and urticaria factitia. Occurrence of urticaria in the family (parents, siblings, grandparents, aunts, uncles, cousins, or nieces) was reported by 10% of the patients, angioedema by 6%, and allergies (not further specified) by 45%. A history of atopy was reported in 40% of the study population.

A large percentage of the patients mentioned that factors such as stress (36%), warm environment (23%), dermographism (13%), and consumption of alcohol (9%) or analgesic drugs (8%) aggravated their urticaria.

Laboratory investigations and provocation tests

In 89% of the patients no abnormalities were found during the physical examination. Dermatological problems (eg, tinea pedis, vaginal discharge, lipoma, different forms of eczema, acne, or folliculitis) were found and treated in 19 patients. Three patients had emphysema and 2 had arterial insufficiency of the lower legs.

In patients with more than one type of physical urticaria, the type which interfered most with normal life was used for the classification. Of all patients, 10.9% had a combination of physical urticaria and urticarial lesions of unknown origin. In Table 1 we described this group of patients as having a combination of (one type of) physical urticaria and idiopathic urticaria.

After discontinuation of suspected drugs, provocation tests were performed by reintroducing the drug in a symptom-free period, which resulted in a relapse of symptoms in all patients. The responsible drugs are listed in Table 1.

In two patients exercise-induced, food-dependent urticaria was found. In both patients consumption of cereals in combination with exercise resulted in urticaria and angioedema; radioallergosorbent tests (RASTs) to cereals were positive, and provocation tests confirmed the diagnosis.

Table 1. Causes of physical urticaria (PU), chronic urticaria (CU) and/or angioedema (A), and type of reaction in 220 patients

	number of patients	% of study population	type of reaction
physical urticaria	**73**	**33.2%**	
dermographism	37	16.8%	PU
pressure	7	3.2%	PU
cold	11	5.0%	PU, PU+CU+A
cholinergic	11	5.0%	PU
heat contact	1	0.5%	PU
solar	4	1.8%	PU
exercise-induced	2	0.9%	CU+A
combination of physical urticaria and chronic idiopathic urticaria	**24**	**10.9%**	
dermographism	10	4.5%	PU+CU
pressure	13	5.9%	PU+CU
cold	1	0.5%	PU+CU
drugs	**20**	**9.0%**	
aspirin	5	2.3%	PU+CU, CU, A
NSAID's	3	1.4%	CU+A, A
codeine	1	0.4%	CU+A
propyphenazon	2	0.9%	PU+CU, A
antibiotics	3	1.4%	PU+CU, CU, A
antidepressives	1	0.4%	PU
ACE inhibitors	2	0.9%	A
oral contraceptives	2	0.9%	CU+A
methotrexate	1	0.4%	CU
food	**15**	**6.8%**	
normal hives and/or angioedema	10	4.5%	CU+A, CU, A
dermographism	3	1.4%	PU
exercise-induced, food dependent	2	0.9%	CU+A
infections	**4**	**1.8%**	PU, CU
internal diseases	**3**	**1.4%**	CU, CU+A
contact urticaria	**2**	**0.9%**	CU
malignancies	**0**	**0%**	
hereditary angioedema	**0**	**0%**	
chronic idiopathic urticaria	**78**	**36.0%**	CU+A, CU, A

ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drugs.

In two patients urticaria factitia developed after consumption of food containing vasoactive amines (eg, wine and cheese). RASTs were negative. One patient with severe hay fever had complaints of urticaria factitia after consuming apples and tomatoes. These three causes were found by means of the elimination diet followed by reintroduction of the particular food. Three patients developed severe reactions (eg, syncope and shock) after consuming crustaceans (in one patient), flour (in one), and sesame oil (in one). Scratch tests were highly positive and the oral allergy syndrome was present. Provocation tests would have been dangerous, and the patients were not willing to participate. In seven patients, after following the elimination diet and a period of food reintroduction, the following foods were found to be the most likely cause of the urticaria and/or angioedema: dairy products (three times), eggs (one time), alcohol (one time), beef (one time), and apples/pears (one time). In one patient the specific RAST was positive (apple/pear). Continuing the diet resulted in disappearance of the complaints and by reintroduction of the particular food, hives occurred.
In 4 of 10 patients with a parasitic infection, the complaints disappeared after treatment. Their complaints were urticaria factitia and pruritus, not classic hives or angioedema. In two patients an infection with *Trichuris trichiura* and in two other patients an infection with *Strongyloides stercoralis* was found. These patients were born or had lived for a long period in a tropical country.
The following internal diseases, probably related to the urticaria, were found: Sjögren's syndrome, systemic lupus erythematosus, and paraproteinemia. Hives are still present in them after three years' follow-up. Histopathological evaluation of the skin biopsies specimens did not reveal urticarial vasculitis in this cohort, even in patients who had mentioned that they had wheals for longer than 48 hours. No other severe internal disease or malignancy associated with urticaria or angioedema was found. Contact urticaria to latex and preservatives was found in two patients.

Follow-up
Follow-up data were obtained by interviewing the patient at the outpatient department, by telephone inquiry, or, in three cases, by contacting the general practitioner. The mean follow-up period was 2 year and 4 months (range 12-71 months). One patient was followed-up for only three months because he moved. In this patient no cause of urticaria could be identified.

Ninety percent of the patients used nonsedating antihistamines during follow-up, 46% used sedating antihistamines as well, 16% occasionally used systemic prednisolone during severe bouts, and in 4% of the patients epinephrine for intramuscular use was prescribed.
After 3 months 14% of the 220 patients were free of complaints. After 6, 9, and 12 month, 26%, 30%, and 35%, respectively, were free of symptoms. At the end of the follow-up period, in 28.9% of the patients the symptoms had decreased, in 35% the symptoms remained the same, and in 1.4% the symptoms had worsened. In 25% of the 220 patients, a spontaneous remission occurred after 1 year.
For the entire patient group with idiopathic urticaria and/or angioedema, as well as for the different subtypes (idiopathic urticaria only, idiopathic angioedema only, idiopathic urticaria and angioedema, physical urticaria, and combination of physical and idiopathic urticaria), we investigated the number of patients who were free of symptoms after 1 year (Table 2). In some patients with physical urticaria, a parasite infection or an adverse event to food or drugs was provoking dermographism. These patients were not included in Table 2.

Table 2. Percentages of patients free of symptoms after 1 year.*

Idiopathic, all patients	47.4%	(37 of 78 patients)
urticaria only	38.5%	(10 of 26 patients)
angioedema only	20.0%	(2 of 10 patients)
both urticaria and angioedema	59.5%	(25 of 42 patients)
Physical and idiopathic urticaria	20.8%	(5 of 24 patients)
Physical urticarias	16.4%	(12 of 73 patients)

* *Patients in whom a cause was found which could be treated (like infections, adverse reactions to food or drugs) were not included in the percentages.*

DISCUSSION

This study provides information about the natural course of different types of urticaria. In a disease in which it is often not possible for the clinician to determine the cause of patients' complaints, it is helpful to be able to inform them about their prognosis. In this study, 47.4% of the patients with idiopathic urticaria and/or angioedema were free of symptoms after 1 year, and only 16.4% of the patients with physical urticaria were free of symptoms.
A limitation of this study is that it was performed in a secondary and tertiary care center, and the results may not be applicable to other patient populations. Furthermore, by analyzing the number of patients with different forms of urticaria separately, the percentages are based on smaller number of patients.
An advantage of the study design is that we followed a well-defined cohort of 220 patients. A cohort study is considered to be the best study design to identify prognostic factors and to determine the relationship between a prognostic factor and disease duration.[19]
We performed extended laboratory investigations not because we believed that they are necessary to detect the cause of chronic urticaria, but to provide evidence that routine investigations are not useful if performed without an indication from history-taking or a questionnaire. This hypothesis could be confirmed and is presented in another article.[13]

Only a few studies deal with the natural course of chronic urticaria. Urbach[20] found in 500 patients with urticaria and/or angioedema the following percentages of durations: 3 to 12 months (19%), 1 to 5 years (20%), 6 to 10 years (4%), and after 11 to 20 years (1.5%). Humphreys and Hunter[7] found that symptoms were present for more than 5 years in 5% of the patients when they first attended a general dermatology clinic and in 13% of patients who visited a specialized urticaria clinic. Quaranta et al[21] investigated 86 patients with chronic idiopathic urticaria in whom 27 (31%) resolved, 48 (56%) continued to have symptoms, and in 11 (13%) patients the natural cause was unknown. It made no difference whether the patients had urticaria, angioedema, or urticaria and angioedema. In 32% of their patients, complaints resolved after a 3-years period. In our patients cohort, 47.4% of this subgroup of patients (having idiopathic urticaria and/or angioedema) were free of symptoms after 1 year. Information on the natural course of chronic urticaria in a large group of patient was described by Champion et al[2] in 1969. In their study approximately 45% of patients with idiopathic urticaria only still

had complaints after 1 year. In our study group 61.5% of the patients with idiopathic urticaria only still had complaints. Champion et al found that for patients with idiopathic angioedema only and for patients with idiopathic urticaria and angioedema, about 55% and 70%, respectively, still had symptoms after 1 year. We found this in 80% and 40.5%, of our patients with idiopathic angioedema only and patients with idiopathic urticaria and angioedema, respectively. We could not confirm that patients with idiopathic urticaria and angioedema had the worst prognosis. In our study physical urticaria was the worst prognostic factor; 84% of the patients still had complaints after one year.

In many of the previously published studies the percentages of identified causes are smaller than in our study.[2,4] In particular, the number of physical urticaria cases is high, probably because efforts were made to detect them with detailed questions and provocation tests. Physical urticaria was found in 12% to 57% in different studies in the literature from 1937 to 1985, including 120 to 500 patients, depending on the care center.[22]
In 3.6% of the patients the urticaria was caused by medication and not by the internal disease or infection for which the drugs were prescribed. One patient had a mesothelioma, but his angioedema was not related to his malignancy and cleared after discontinuing medication.[23] In another patient with severe rheumatoid arthritis, methotrexate induced the urticaria. In some patients exacerbation occurred during viral infections. This was often related to the use of analgesic drugs.
An elimination diet followed by reintroduction of the food was helpful in a few patients motivated to find a cause, but the frequency of food reaction was very low. During the follow-up period all found infections (parasite infections, vaginitis, or cystitis) were treated, and only in four patients with a parasite infection was there a probable relation with urticaria factitia.

In conclusion, spontaneous remission occurs in approximately 47% of the patients with chronic idiopathic urticaria and/or angioedema within one year after referral. Only 16% of the patients with physical urticaria were free of symptoms after 1 year. In patients referred to a tertiary care center for chronic urticaria, the prognosis is reasonable. This is an other argument for adopting an attitude of waiting regarding extensive laboratory screening.

REFERENCES

1. Henz BM. The spectrum of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998.p.3.
2. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969;81:588-597.
3. Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter- and episode- and process-oriented standard output from the Transition Project. Part 1 and 2. Amsterdam: Amsterdam University press;1991.
4. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427-436.
5. Zuberbier T, Chantraine-Hess S, Hartmann K, Henz BM. Pseudoallergen-free Diet in the Treatment of Chronic Urticaria. A Prospective Study. Acta Derm Venereol 1995;75:484-487.
6. Henz BM, Zuberbier T. Causes of Urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria. Clinical, Diagnostic and Therapeutic Aspects. Berlin: Springer Verlag; 1998:29.
7. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-638.
8. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-381.
9. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol 1990;123: 453-456.
10. McWhorter WP. Allergy and Risk of Cancer; a Prospective Study Using NHANESI Followup Data. Cancer 1988;62:451-455.
11. Friedman PS. Assessment of urticaria and angio-oedema. Clin Exp Allergy 1999;29:109-112.
12. Bindlev-Jensen C, Finzi A, Greaves MW, Camarasa J, Ortonne JP, Schöpf E, et al. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol Venereol 2000;14: 175-180.
13. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-1580.
14. Gross AS, LaTour DL, King LE. Chronic urticaria: a model questionnaire for patient screening. Cutis 1990;46:421-424.
15. Guin JD. The evaluation of patients with urticaria. Symposium on urticaria and the reactive inflammatory vascular dermatoses. Dermatol Clinics 1985;3:31-36.
16. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1988.p.183-189 (Appendix A).

17. Kontou Fili K, Borici-Mazi R, Kapp A, Matjevic LJ, Michel FB. Physical urticaria: classification and diagnostic guidelines. An EAACI position paper. Allergy 1997;52:504-513.
18. Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998.p.193-195 (Appendix C).
19. Laupacis A, Wells G, Ricardson S, Tugwell P. Users' Guides to the Medical Literature. V. How to Use an Article About Prognosis. JAMA 1994;272:234-237.
20. Urbach E. In: Urbach E, Gottlieb PM. Allergy, 2nd ed. New York: Grune and Stratton, 1946.
21. 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 of Allergy 1989;62:421-424.
22. Paul E, Greilich KD. Zur Epidemiologie der Urtikariaerkrankungen. Hautarzt 1991;42:366-375.
23. Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. Clin Exp Dermatol 1995;20:60-61.

Chapter 5

Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients

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SUMMARY

Adverse reactions to drugs are well recognized as a cause of acute or chronic urticaria, and angio-oedema.[1] Angiotensin-converting enzyme (ACE) inhibitors, used to treat hypertension and congestive heart failure, were introduced in Europe in the middle of the eighties, and the use of these drugs has increased progressively. Soon after the introduction of the ACE inhibitors, acute bouts of angio-oedema were reported in association with the use of these drugs.[2,3] We wish to draw attention to the possibility of adverse reactions to ACE inhibitors after long-term use in patients with pre-existing angio-oedema.

Case report 1

An 42-year-old atopic patient had recurrent angio-oedema for 5 years. This occurred initially annually for 3 years, but after therapy with 50 mg captopril for hypertension, angio-oedema gradually increased in frequency to once every two weeks. She visited our department because the duration of the angio-oedema increased from 2 days to 6 days after treatment with captopril. In addition, before treatment only the lips were involved, whereas after treatment she had swollen lips and facial oedema. Treatment with cetirizine for 2 months was ineffective, and oral corticosteroids were necessary during severe bouts. She had been treated with captopril daily for the past eighteen months; there was no other drug history. She discontinued captopril for five months and remained free of symptoms of angio-oedema and hypertension, but reintroduction of captopril for two days only led to a severe bout of facial oedema. Four months after the reintroduction she developed slight swelling of the lips on two occasions.

Case report 2

An 49-year-old man had intermittent facial oedema, and swelling of the lips and sometimes the tongue for the past 4 years, without associated urticaria, difficulties in breathing or swallowing, or anaphylactic reactions. The symptom-free interval between two bouts decreased gradually from one bout in 6 months to once every month. The duration

of the angio-oedema increased from 2 days to 4 days and in the last year swelling of the tong and coughing occurred as well. He had a history of allergic rhinitis, and developed wheals, but not angio-oedema, after consuming strawberries or tomatoes which he avoided eating. He was treated with cetirizine for four months unsuccessfully and during severe bouts he used clemastine orally. Because of hypertension due to inherited polycystic renal disease, he was treated with triamterene 50 mg, epitizide 4 mg, and metoprolol 10 mg daily for 15 years, and enalapril 10 mg daily for 5 years. No other drugs were used. Three and half years after the first bout of angio-oedema he presented with right-sided pleural mesothelioma. Abnormal laboratory investigations included an ESR of 91 mm/h, haemoglobin 7.6 mmol/L, eosinophilia of $500x10^6$/L, and elevated serum creatinine of 275 µmol/L and elevated urea of 15.5 mmol/L. The IgE level was 213 IU/ml. Enalapril was stopped, and during the following two years he developed no bouts of angio-oedema, except for one bout three days after rechallenge with enalapril. The patient received no specific treatment for the mesothelioma for the first 6 months; later on pain was treated with diclofenac.

DISCUSSION

From January 1992 to September 1993 150 patients with chronic urticaria or angio-oedema were seen in our department. Thirteen patients had chronic angio-oedema without urticaria. Two patients with chronic angio-oedema (case report 1 and 2) and one patient with chronic urticaria used ACE inhibitors. The routine approach of discontinuing all drugs and rechallenge with the suspected drug, did not lead to disappearance of the symptoms in the patient with urticaria, but revealed the relationship with ACE inhibitors in the two patients with angio-oedema. Patient 1 had a history of idiopathic angio-oedema and developed the first bout 3.5 years before using an ACE inhibitor. Patient 2 developed the first bout of angio-oedema 1 year after treatment with ACE inhibitors. Both patients reported that the frequency, intensity and duration of the bouts increased during long-term use of ACE inhibitors (1.5 and 5 years), but no life threatening reactions occurred.

Community screening has revealed that in up to 20% of the population aged 50 years mild hypertension (diastolic blood pressure between 90 and 104 mm Hg) is present.[4] In addition, the risk of stroke is increased in

patients with mild hypertension, and drug treatment has been shown to reduce this risk.[4] Categories of drugs available for treatment of mild hypertension are diuretics, β-adrenoreceptor blocking drugs, calcium antagonists and ACE inhibitors.[1] Monotherapy with ACE inhibitors is now one of the possible first choice drugs for mild hypertension and is frequently used by general practitioners. Consequently, more adverse events like angio-oedema are likely to occur.[5]

Reports of ACE-inhibitor-induced angio-oedema are well documented.[2,3,5,6] The cumulative incidence of angio-oedema within the first week of treatment has been reported to be 1 case per 1000 patients treated.[6] With the WHO's international drug information system 1309 individual case reports of angio-oedema were related to treatment with ACE inhibitor between 1981 and 1991, but analysis of data from central registers and not from prospective clinical trials will result in under-reporting of cases.[5] There has only been one reported death related to angio-oedema from world-wide marketing data on more than 1.2 million patients.[6] The reported number of cases of ACE inhibitor induced angio-oedema after long term-use is much lower than that occurring soon after starting such a drug.[3,5,6] In 20% of the cases in a Swedish study the onset of angio-oedema occurred more than 6 weeks after the start of the treatment.[5] When the ACE inhibitor is not discontinued after the first bout of angio-oedema a life-threatening second bout, one year later, is described by Chin.[7]

Studies of ACE-inhibitor-induced angio-oedema which used central registers did not found predisposing factors.[5,6] Patients with a history of idiopathic angio-oedema (patient 1) or urticaria (patient 2) could have an increased risk of developing ACE-inhibitor-induced angio-oedema. Orfan et al.[8] reported four cases of severe angio-oedema related to ACE inhibitors in patients with a history of mild idiopathic angio-oedema. These patients developed severe bouts during the first week of treatment. The patients we report here had a history of angio-oedema or urticaria, and continued treatment for more than one year, with resultant progressive worsening of their symptoms and signs. To our knowledge this has not been reported previously.

In conclusion, the increased word-wide use of ACE inhibitors could lead to an increased number of adverse events, and angio-oedema as one of these adverse events can occur early in treatment or after long-term use. We wish to highlight the possible role of ACE inhibitors in chronic

angio-oedema. In patients with a history of recurrent angio-oedema or urticaria being treated with an ACE inhibitor, careful follow-up for late adverse events is important. Discontinuing all drugs is an important step in the management of chronic angio-oedema.

REFERENCES

1. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-381
2. Wood SM, Mann RD, Rawlins MD. Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. BMJ 1987;294:91-92.
3. Inman WHW, Rawson NSB, Wilton LV et al. Postmarketing surveillance of enalapril. I: Results of prescription-event monitoring. BMJ 1988;297: 826-829.
4. Zanchetti A, Chalmers J, Corvol P et al. 1989 Guidelines for the management of mild hypertension: memorandum from a WHO/ISH Meeting. J Hypertens 1989;7:689-693.
5. Hedner T, Samuelsson O, Lindholm L et al. Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. BMJ 1992; 304:941-946.
6. Slater EE, Merill DD, Guess HA et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. JAMA 1988; 260:967-970.
7. Chin HL. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. Ann Intern Med 1990;112:312.
8. Orfan N, Patterson R, Dykewicz MS. Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. JAMA 1990; 264:1287-1289.

Chapter 6

Implementation and validation of a clinical guideline for the diagnoses of chronic urticaria and/or angioedema

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Submitted

SUMMARY

Objective: In this retrospective study, the feasibility and implementation of a clinical guideline in 130 consecutive patients with chronic urticaria was evaluated.

Design: It was analysed how often a questionnaire was used, how often routine laboratory tests were performed, and on which information (history taking, questionnaire, laboratory or provocation tests) the diagnosis was made. In this validation sample the number of identified diagnoses was compared with the number of identified diagnoses of a prospective study performed in the same hospital.

Results: In 58 patients (45%) a cause was found. In 50 of the 58 patients (86%) the cause was identified by history taking, in 8 patients by the additional use of the questionnaire. In 38 patients the questionnaire was not in the patient's file. In 89 of 130 patients (68%) laboratory tests were performed without a reason suggested by the patients' history. This did not reveal a cause in any patient.

Conclusion: In general, the diagnostic guideline was followed reasonably well. For identifying a cause of urticaria careful history taking was important; routine laboratory tests were not helpful.

INTRODUCTION

In many patients with chronic urticaria, the etiology remains unclear.[1] Symptomatic treatment with antihistamines is unfortunately not successful in all patients[2], a cause for frustration for both patient and physician. In the past many efforts have been made to discover underlying diseases by performing an extensive diagnostic work-up. Studies including large numbers of patients showed that these diagnostic work-ups are of little value in patients with chronic urticaria.[2-5] Large clinical studies have shown that is it safe to omit routine laboratory screening if thorough history taking is performed.[3-5] Current recommendations limit the number of routine laboratory tests in patients with chronic urticaria, suggesting to perform additional laboratory tests only if history taking provides an indication.[6-11]

There is a growing interest in the development of practice guidelines for clinical care in dermatology.[12] Guidelines are developed to improve medical care, to control variations in medical practise, and to make use of health care resources more effectively.[13] After the introduction of a clinical guideline there is no guarantee that it will be used by clinicians, no matter how well-designed, and more guidelines have been made than have been implemented.[14] Obstacles for actual implementation and maintenance may be related to a lack of resources, relapsing into old routines, or dissatisfaction about the results of the new guideline.[15] Obviously, guidelines are not self-implementing.[16] Continued motivation of clinicians and a continued evaluation of the progress of implementation is necessary.

The purpose of this study was to investigate the use of the clinical guideline for patients with chronic urticaria and we investigated how often and why clinicians deviate from the guideline. Furthermore, we wanted to confirm the earlier performed prospective study and analyse whether a comparable number of causes could be identified in this retrospective study, which represents the diagnostic process in daily clinical practice.

MATERIALS AND METHODS

Study population

All patients with urticaria and/or angioedema for at least 6 weeks who consulted our outpatient department of Dermatology between January 1998 and February 2000 were included in this study. The study was performed in the Academic Medical Center of the University of Amsterdam. The study was approved by the Medical Ethics Committee.

Description of the guideline

During the first visit the following actions were recommended: history taking (in general, information was obtained about when the symptoms started, in which circumstances hives occur, about physical causes, about drug intake, and about additional complaints) and handing out of a questionnaire (questions concerning duration, frequency and pattern of attacks, associated symptoms, duration and size of the wheals, provoking physical factors, history of atopic disease, reaction to drugs, food- or inhalation-allergens, the possibility of contact allergy, the use of any drugs, including "over-the-counter-drugs", medical history, and general health; the questionnaire is available on request), inspection of hives (if present), and a dermography test. Only five laboratory tests should be requested (haemoglobin level, haematocrit, erythrocyte sedimentation rate, white blood cell count, and differential blood cell count). No routine laboratory screening should be performed. If necessary, a (non)-sedating antihistamine should be prescribed. During the next visits the guideline recommended: reevaluate the patients history, discuss the questionnaire, confirm suspected causes with laboratory tests or provocation tests (if necessary), stop or replace suspected drugs, ask again for "over-the-counter" drugs, and prescribe an antihistamine (same or different).

Study design

All clinical records were investigated for the following items: history taking performed, questionnaire in patients' file, dermography test performed, limited set of laboratory tests requested, and whether any other laboratory tests were requested.

All clinical records were analysed by an expert committee who had to select the most probable cause of the urticaria. For all performed laboratory tests we analysed wether the test only confirmed a diagnosis already suspected by history or wether the laboratory test revealed a diagnosis by itself, not suspected by history. The number of deviations from the study protocol was counted and analysed.

RESULTS

Patient population and diagnoses

In our department the diagnosis of every patient is recorded and available for research purposes. We searched in the computerized diagnosis-registration-system for (subtypes of) urticaria and (subtypes of) angioedema. 159 patients were identified, all their records were available and could be analysed. Nineteen of them had acute urticaria and were excluded. Ten hospital workers with a contact urticaria to natural rubber were referred by the company doctor for epicutanous patch tests with latex. They were excluded as well.
49 patients were male (38%). Patients mean age was 37.2 (age range 1-71). In 61 patients (47%) a cause for the urticaria could be identified. The distribution of causes is shown in table 1.

Table 1. Diagnoses found in this retrospective study compared with the diagnoses found in the prospective study[3] (in %)

	retrospective study (n=130)	prospective study (n=220)
Diagnoses	**45**	**46**
physical urticaria	33	33
adverse drug reactions	3.1	5.0
adverse food reactions	5.4	4.0
contact urticaria	0.8	0.9
infection	0	1.4
internal diseases	2.3	1.4
malignancies	0	0
Etiology unknown	**55**	**54**

Implementation and guideline deviations
Before the introduction of the clinical guideline the diagnostic actions performed by each physicians were different and less complete. Although one or more guideline deviations occurred in 100 of the 130 patients (77%), the guideline was reasonably followed by the physicians; the number of unnecessarily requested laboratory tests was much lower than in the period before the introduction of the guideline. During this retrospective study no effort was made to interfere with the clinical decisions of each physician and the use of the flow-chart was voluntarily. In all 130 patients thorough history taking and examination of the hives (if visible) were performed. Protocol deviations were measured per patient, and more than one deviation occurred in many patients. The different guideline deviations are presented.

Extended laboratory tests
In 89 patients routine laboratory tests were performed at the first visit. In most patients liver- and/or kidney function tests (55 patients), radioallergosorbent tests (RASTs) for inhalation and/or food allergens (59 patients), and/or epi- or intracutaneous allergy test (20 patients) were requested. In 23 out of these 59 patients a positive result was found. In 22 patients the RAST-test showed a positive result, but this could not be related to the patient's complaints. In only one patient this additional laboratory test (RAST) was relevant in finding a cause (adverse reaction to shrimps). This patient mentioned complaints of the oral allergy syndrome in the history. In 12 patients epicutanous patch tests were performed. This revealed the diagnosis in one patient with a contact allergy to fluticason. An elimination diet was performed in 30 patients, based on the history or the questionnaire. In 3 patients the decrease or absence of hives during the elimination diet and the increase of the symptoms during the reintroduction period made the diagnosis of an adverse food reaction likely. In the 130 patients 88 additional laboratory test (except the above mentioned ones) were requested: mainly level of glucose and proteins, bacterial or parasite cultures, and serum tests for autoimmune diseases.

Questionnaire
Most of the patients already knew from their general practitioners that very often no cause for their complaints will be found and appreciate the thorough search with the questionnaire. In 38 of 130 patients the questionnaire, which was the same as in the previous prospective study[3], was not in the patients' file. In the patient with a contact allergy to

fluticason the questionnaire seemed superfluous and allergy tests were performed immediately. In 13 patients with physical urticaria, and in 4 patients with an adverse reaction to food or drugs the cause seemed to be clear during history-taking. In 12 patients the questionnaire was handed out but the patient did not return for a following visit. In the remaining 8 patients no explanation for the missing questionnaire could be identified.

Dermography test

This test was not performed in 45 patients: in the patient with a contact allergy, in 11 patients with pressure or cholinergic urticaria, and in 10 patients who were using antihistamines or oral corticosteroids. Other explanations for not performing this test were that one patient had only angioedema, and in another 5 patients an adverse reaction to drugs or food was suspected. In 17 patients with idiopathic urticaria no explanation was found for not performing this test.

Limited laboratory tests

In 32 patients (25%) no limited laboratory tests were performed, including the patient with a contact allergy and 20 patients with physical urticarias. In one patient with a suspected and confirmed adverse reaction to a drug, and in one young child limited laboratory tests were not performed. The remaining 9 patients had chronic idiopathic urticaria, and no explanation could be found why these tests were not performed.

Validation and diagnostic procedure

To validate our prospective study[3] we compared the identified causes of both studies. Almost equal percentages were found (table 1). The number of identified causes is high (45%) because a large number of patients with physical urticaria (33%) were referred to our hospital.

Relevance of history-taking and the questionnaire

All identified causes of this study were suspected during history taking or during the discussion of the questionnaire. In most patients the suspected causes were later confirmed with laboratory or provocation tests. 43 patients had physical urticaria (26 times urticaria factitia, 10 times pressure urticaria, 7 times cholinergic urticaria). In 35 of them, the cause could be identified after history taking, and in 8 of them after using the questionnaire. In 4 patients an adverse reaction to a specific drug was confirmed by elimination and oral provocation. In 7 patients an adverse reaction to food was suspected after the history. This was

confirmed in 3 patients by intracutaneous allergy tests, and in 3 other patients by an elimination diet (and reintroduction of the particular food). In one patient the diagnosis was based on history only. One patient had a contact allergy to nasal spray containing fluticason. This contact allergy was suspected during history taking and confirmed by epicutanous patch testing. Three patients had an internal disease. A-34-year old woman was developing a not yet identified autoimmune disorder (joint pain, fever without any infection and antinuclear antibodies), one patient had hypocomplementemic urticarial vasculitis, and one patient had an IgM-paraproteinaemia.

Relevance of the dermography test

Performing the dermography test routinely resulted in a fast and easy detection of dermographism, the cause of urticaria which was found most. In 94 patients the dermography test was performed. In 26 patients dermographic urticaria was suspected based on information from history or the questionnaire. In 23 of them the cause was confirmed with the dermography test. In 1 patient dermographic urticaria was detected because intracutaneous allergy tests were performed and all injections caused whealing. In 2 patients the diagnosis was based on the questionnaire only.

Relevance of the limited laboratory tests

In none of the patients the cause of the urticaria was found with the results of the limited set of laboratory tests.

Expert committee

Whenever the suspected cause of the physician was not confirmed with laboratory- or provocation tests or no convincing information was mentioned in the patient's file, the expert committee decided that the cause of the urticaria was unknown. This occurred in 23 patients. In most of them the physician suspected certain drugs, food, or contact allergens. Sometimes a member of the expert committee asked the patient a few months later wether a specific intervention had been helpful in decreasing the urticaria.

DISCUSSION

The purpose of this study was to evaluate the implementation of a clinical guideline for the diagnosis of chronic urticaria, based on the available literature[5-11, 17] and a study[3] performed in the same care center. Although the number of guideline deviations was high (77%), in most cases a reasonable explanation for the deviation could be found. Deviations were that 20% of the patients did not receive the questionnaire; and in 68% unnecessary laboratory tests were performed.
This retrospective study showed that with careful history taking most of the causes of chronic urticaria could be identified. In this validation study and the prospective study[3] almost identical percentages of causes of the subtypes of urticaria were found (table 1). In both studies, the information received by laboratory tests which were not linked to the history was not helpful in the identification of any cause. This study contributed to the reduction of the number of laboratory tests.

To improve the quality of clinical care our department is developing clinical guidelines. A prospective study was previously published.[3] The number of identified causes in a history based approach was compared with an approach that included a large number of routine laboratory tests. Almost no differences between the two strategies in the number of identified causes of urticaria were observed. With this prospective study[3] we had shown that routine investigations are not useful if performed without an indication from history taking or a questionnaire. During this study all possible efforts were made to find an underlying cause. For the validation study, a retrospective design was chosen, to prevent the dermatologists from being more precise than they would have been in normal daily clinical practice, if they had known that the patients files were analysed for guideline deviations.
By analysing the data from this validation sample, which was performed 4 to 5 years after completing the prospective study and in which the same staff but different residents were involved, we did not found a change in the amount of identified diagnoses. With this study we enhanced the generalizability of our hypothesis, that with thorough history taking routine laboratory screening does not substantially disclose more causes of chronic urticaria, and we proved that history taking is the most important diagnostic instrument in identifying causes of chronic urticaria. The results of both studies show that the recommendation given fulfil the criteria of reproducibility and partly of

transportability (historical and methodologic transportability).[18] This study tested the accuracy of the guideline in data collected after the development of the guideline (prospective validation), evaluated reproducibility, and tested susceptibility of the guideline to mild differences in historical time frame.[18] Because this study was performed in the same care center we cannot provide information of the geographic transportability.

50 out of 58 diagnoses (86%) were found by history taking only. This shows that careful history taking is the most important instrument to discover causes of chronic urticaria. In the remaining 8 patients, the cause was found thanks to the questionnaire. The causes were all physical urticarias: 2 times urticaria factitia, 2 times pressure urticaria, and 4 times cholinergic urticaria. The high percentages of causes identified by history taking only in this patient cohort can partly be related to a learning or training effect of the clinicians during the preceding years. The introduction of this guideline has proven to be a valuable educational instrument in our department. The questionnaire for patients with chronic urticaria was introduced in 1992. Every resident and dermatologist analysed the questions frequently before the data for this study were collected, and approximately every year a lecture about the evaluation of patients with chronic urticaria was given by one of the authors.

If thorough history taking is performed, handing out the questionnaire to the patient may not yield that many additional data. The importance of the questionnaire is that it gives the patient the opportunity to provide all possible relevant information, and to participate actively in the diagnostic process by suggesting possible causes. Without the participation of the patient it is very difficult to find underlying causes because of the diversity of causes of urticaria. The questionnaire should not be regarded as a replacement for careful history taking, but as another useful instrument to search together with the patient for causes. A very important item is that the patient is requested to provide the physician with a list of drugs used, including information about the exact period the drugs were prescribed during the previous year. This reduces the time-consuming search for the patients' drug-intake during visits. The large number of questions related to very different causes and diseases allows for more possible causes to be evaluated by the physician. This may decrease the patient's concerns.

The benefit of the limited set of laboratory tests was nihil in this patient cohort. In the prospective study[3] the results of the limited laboratory tests had been helpful in finding internal diseases (elevated erythrocyte sedimentation) and parasite infections (differential blood cell count). In both studies (including a total of 350 patients), the results of the haemoglobin level and haematocrit were not helpful in finding a cause of urticaria. Therefore, we recommend to reduce the laboratory tests to the erythrocyte sedimentation rate, white blood cell count, and differential blood cell count. We experienced that patients may be disappointed and look for further consultation in other care centers if no laboratory tests are performed. Furthermore, we believe the number of enrolled patients in the retrospective study is too small in relation to the low incidence of internal diseases as a cause in chronic idiopathic urticaria. The possibility to miss an important diagnosis motivated us to keep these laboratory tests included in the guideline, but these may be superfluous in a large number of patients.

Even if the test for dermographism did not reveal that pressure on the skin is the cause for all complaints of the patient, it is often an aggravating factor, and this information is helpful for patients in handling their urticaria. In some patients history-taking could easily reveal dermographism, and than this test might be superfluous and it could be unnecessary to motivate patients to stop antihistamines. The test for dermographism remained in the diagnostic procedure because if the relationship is clear the test could be omitted, but if the test is not mentioned in the guideline it could be easily forgotten.

Although additional laboratory tests not based on the history were requested in 64% of the patients at the first visit, the amount of tests is much lower compared to the period before introduction of the flow-chart. Reasons for requesting additional laboratory tests were: special request of the patient, some dermatologists were afraid to miss an allergy or wanted to have a global impression of the patients condition (tests for liver- and kidney function), and a blood sample was already taken for the limited laboratory tests and than it is easy to request more laboratory tests. It was very disturbing that in 59 of the 130 patients investigations were performed to disclose an allergy. This implies still an expensive misunderstanding by physicians, since allergen-specific IgE is unrelated to chronic urticaria in almost all patients.[3-11] The routine use of allergy tests should be strongly discouraged.

In several papers, mostly opinion-based diagnostic recommendations,[8,10,11] sometimes in flow-charts,[5,7,9,11] or algorithms[6,17,19] have been presented for patients with chronic urticaria and/or angioedema. All emphasize the importance of the history and stress that extensive work-ups are not necessary. A flow-chart is very useful to remind physicians to follow the guideline. In our outpatient department the flow-chart is attached to the questionnaire, and this questionnaire is to be handed out to patients with chronic urticaria. Putting the flow-chart as a reminder in the patients file is the simplest strategy to remind physicians.[20]

The implementation of the guideline was only partly successful, despite that the physicians knew the guideline. This was accomplished by attaching the flow-chart to the questionnaire, and by the fact that the staff supervised every consultation with new patients seen at the outpatient department. The deviations from this clinical guideline confirmed that guidelines should not be regarded as rigid but as flexible criteria that are allowed to be adjusted to specific circumstances, settings, and patients' preferences. Patients often request or sometimes even demand laboratory investigations because of the fear of having a severe underlying disease. In these patients it is important to assure them that the chances of finding an underlying disease by careful history are much higher than by routine laboratory screening only.

REFERENCES

1. Greaves MW. Chronic urticaria. J Allergy Clin Immunol 2000;105:664-72.
2. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-638.
3. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-1580.
4. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981;104:369-381.
5. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427-436.
6. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-1772.
7. Champion RH, Highet AS. Investigation and management of chronic urticaria and angio-oedema. Clin Exp Dermatol 1982;7:291-300.
8. Soter NA. Acute and chronic urticaria and angioedema. J Am Acad Dermatol 1991;25:146-154.
9. Bindslev-Jensen C, Finzi A, Greaves M, Camarasa J, Ortonne JP, Schöpf E, Tennstedt D. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol 2000;14:175-180.
10. Kobza Black A, Greaves MW, Champion RH, Pye RJ. The urticarias 1990. Br J Dermatol 1991;124:100-108.
11. Friedmann PS. Assessment of urticaria and angio-oedema. Clin Exp Allergy 1999;29(suppl 3):109-112.
12. Ladhani S. The need for evidence-based management of skin diseases. Int J Dermatol 1997;36:17-22.
13. Woolf SH. Practice Guidelines: A New Reality in Medicine. III. Impact on patient Care. Ach Intern Med 1993, 1993;153:2646-2655.
14. Delamothe T. Wanted: guidelines that doctors will follow. BMJ 1993,307: 218.
15. Grol R. Beliefs and evidence in changing clinical practice. BMJ 1997,315: 418-421.
16. Grol R. Implementing guidelines in general practice care. Qual Health Care 1992;1:184-191.
17. Cooper KD. Urticaria and angioedema: Diagnosis and evaluation. J Am Acad Dermatol 1991;25:166-176.
18. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Int Med 1999;515-524.
19. Zuberbier T, Henz BM. Diagnosis of Urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E. Urticaria. Clinical, Diagnostic and Therapeutic Aspects. Berlin: Springer Verlag; 1998:141.
20. Grimshaw JM, Russell IT. Achieving health gain through clinical guidelines. II: Ensuring guidelines changes medical practice. Qual Health Care 1994;3:45-52.

Chapter 7

Laboratory tests and identified diagnoses in patients with chronic urticaria and angioedema: a systematic review

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Submitted

SUMMARY

Objective: To assess the value of laboratory tests in clinical studies concerning the diagnosis in adult patients with chronic urticaria, and to identify factors explaining the variation in the number of identified causes.

Data Sources: Four electronic databases, covering 1966 to May 2001 were searched, and a manual literature search was performed. 53 studies were identified.

Study Selection: Only unselected patient series with more than 50 patients, and performed after 1930 were included. Studies involving patients with acute urticaria, or children only were excluded. 24 studies were excluded because they contained insufficient or inappropriate data. In total 29 studies were included, involving 6462 patients.

Data Extraction: From each included study predefined items were recorded to assess their quality (consecutive patients, use of standardized diagnostic criteria) and validity (follow-up, assessment of treatment effects, level of evidence).

Data Syntheses: The verification of the validity of the results and the level of evidence of the included studies were limited. No relationship between the number of identified diagnoses and the number of performed laboratory tests, the different settings, the study design, or the publication period was found.

Conclusions: Although the studies varied in the percentage of identified diagnoses, the number of performed laboratory tests, the study settings, the study design, and the publication year, their conclusions were comparable. In patients with chronic urticaria routine laboratory tests are of little value (13 studies), and the history is very important (10 studies). Based on this systematic review and the relevant literature, a clinical guideline in the form of a flow-chart is presented.

INTRODUCTION

In the literature, several different suggestions for the management of patients with chronic urticaria can be found. Especially the way history taking is performed and the amount of laboratory tests that are requested vary considerably. If a large number of laboratory tests are performed, the chance of detecting an abnormal value will increase. Abnormal values, however, may be false-positive, or otherwise irrelevant in a particular patient. The detection of abnormal values may elicit more, possibly invasive diagnostic procedures which may be harmful for the patient. On the other hand, even a low prevalence of severe underlying diseases as a cause for chronic urticaria would justify an extensive diagnostic search. But in case of a very low or near-total absence of such diseases, screening leads to over-investigation and a waste of health care resources. An explanation for extensive laboratory screening is the fear to miss underlying disorders, and the fear of the clinician that the patient may not be satisfied if thorough laboratory screening is not performed. Hence, the clinician confronted with a patient with chronic urticaria faces a dilemma: extensive investigation offers a very small chance of a benefit. Is this enough to subject every patient to an extensive battery of investigations?

For this question evidence-based medicine (EBM) can be of value. EBM is the integration of best research evidence with clinical expertise and patient values.[1] Identifying and assessing the evidence is best done by performing a systematic review.[2] Conducting a systematic review is one step in the development of a clinical practice guideline. If possible this should be followed by an evaluation of the implementation of the guideline to analyze its generalizability. Guideline development in general has its origin in the current problems that most healthcare systems face: rising healthcare costs, increased demand of care, more expensive technologies, variations in service delivery among providers and among different geographical regions and the presumption that at least some of this variation stems from inappropriate care, either over-use or under-use of services; and the desire of healthcare professionals to offer, and of patients to receive, the best care possible.[3]

The aim of this systematic review was to identify factors explaining the variation in the reported percentages of identified causes of chronic urticaria. Furthermore, we try to obtain epidemiological data from these studies in order to make a more accurate estimate of the prevalence of causative factors of chronic urticaria. We investigated if there was a relationship between the number of identified diagnoses and the amount of laboratory tests requested, and we counted the number of severe internal diseases probably related to chronic urticaria. Based on the results and main conclusions of this systematic review, and the relevant literature, a flow-chart is presented.

METHODS

Data sources

The following bibliographic databases: MEDLINE (National Library of Medicine, Bethesda, Md; 1966-2000), EMBASE (Elsevier Science BV, Amsterdam, The Netherlands; 1988-2000), PubMed (National Library of Medicine), and Current Contents were searched for clinical studies or reviews published between 1966 to May 2001. Selected keywords were: (chronic) urticaria, angioedema, etiology, diagnosis, laboratory test(s), clinical trial, (practice) guideline(s). Other sources were textbooks, existing guideline articles, monographs, theses, and the reference lists of all articles identified.

Inclusion- and exclusion criteria

Diagnostic clinical studies with (mainly) adult patients with chronic urticaria and/or angioedema were included (table 1, explanation of the notes, inclusion criteria). Studies performed before 1930, or including less than 50 patients were excluded. Studies focusing predominantly on patients with acute urticaria (less than six weeks duration) or children only were excluded. Therapeutic studies were excluded as well.

Data extraction

The initial relevance of the retrieved articles was evaluated by one of the authors (MMAK) on the basis of title and abstract. The selected articles were then independently read by two of the authors (MMAK, JRM). Disagreements were solved by consensus. If necessary, the opinion of a third author was solicited (PMB).

The following items were extracted from included articles: publication year; prospective or retrospective design; setting; number, age and gender of patients; patient cohort with chronic urticaria only, or acute and chronic urticaria; inclusion and exclusion criteria of each study; percentages of identified diagnoses; use of standardized diagnostic criteria; performed laboratory tests; diagnostic consensus panel; duration of follow-up, methods to assess the outcome of intervention; and conclusions made by the authors.

RESULTS

Study characteristics

The search retrieved 53 clinical studies on the diagnosis of chronic urticaria or reviews including data of a clinical study.

Twenty-four studies had to be excluded. Two studies had included less than 50 patients. In seven studies it was impossible to analyze the number of identified diagnoses. Three studies, published between 1933 and 1953, did not separate acute and chronic urticaria. In one study an unusual test method was used, and in another study only multifactorial causes were identified. In ten studies the value of particular laboratory tests or a diagnostic procedure was investigated in an already selected group of patients with chronic idiopathic urticaria. The tests of interest were intradermal injection of autologous serum (3), double-blind placebo-controlled food challenge (2), or a search for infections (5).

Twenty-nine studies with unselected patients were included (table 1). In each of them patients with urticaria pigmentosa and papular urticaria were excluded from the total number of patients. In total, these studies included 6462 patients. Twenty studies were published in English, nine studies in German, Dutch or French. Sixteen studies were performed in university hospitals (secondary and tertiary care centers), and 13 studies in community hospitals (secondary care centers).

The inclusion criteria of the different studies varied considerably (table 1, notes). In 19 studies the included patients had urticaria for more than six weeks, and in four studies for more than four weeks. Only nineteen studies included consecutive patients. The level of evidence of the different studies was determined according to the criteria described by Sackett et al.[33] Almost all studies (26 of 29) were case series without controls. Their level of evidence was 4 (scale 1-5, and 1a is the best evidence) and their grade of recommendation is C (scale A-D, and A is the best grade of recommendation). The level of evidence of one study was 3b (individual case-control study),[28] the grade of recommendation is B. One study reached a level of evidence of 1b and the grade of recommendation is A.[10]

The description of routine laboratory- and provocation tests was clearly reported in 23 of 29 included studies. Assessment of physical causes was performed by standardized diagnostic criteria in all studies. In contrast, assessment of psychological causes was performed by standardized diagnostic criteria in one study only.[28] To assess the value of food or drugs as an identified cause the following tests were performed: (double blind) placebo controlled oral challenge, standardized elimination diets, reintroduction of suspected drug or food, cutaneous allergy tests, serum allergy tests, and history taking.

In many studies the procedure used for the verification of the identified diagnoses (eg. performing follow-up, or evaluation of interventions to confirm that the diagnosis was correct) was not properly performed or described. In these studies the likelihood that the identified diagnoses were the most probable cause of the urticaria is smaller (table 1). In one study independent blind comparison of patients and controls undergoing both a new diagnostic strategy (including a few laboratory tests) and the reference standard (with extensive laboratory tests) was made.[10] Data of almost complete follow-up were available in two studies.[10,22] In these 99-100% of the patients were followed-up for 9-12 months. In seven studies 70-90% of the patients were followed-up for at least 6 months, in these studies 23-84% of diagnoses were identified.[4,6,7,14,16,18,31] Assessment of treatment effects was performed in 19 studies. In all of them identified infections were treated; if the hives continued the particular infection was not considered to be the cause of the urticaria.

Table 1. Systematic review of clinical trials concerning the etiology in unselected patients with chronic urticaria and/or angioedema (references 4-32)

Author(s)	n*	found causes	number of routine laboratory tests			study design**	setting■	notes
		(%)	< 10	10-20	> 20			
Zuberbier (1995)	64	84			x	pros.	D-inp.	a,c,f,l,s,z
Miller (1968)	50	84		x		pros.	M	b,c,f,j,m,o,q,x
Trachsel (1999)	168	65			x	retros.	A-outp.	b,c,f,j,l,m,s,v
Doeglas (1975)	141	60			x	pros.	D-outp.	b,c,f,i,j,s,u,v
Schnyder (1999)	115	57		x		pros.	A-outp.	a,c,f,m,p,q,y
Wedi (1998)	100	46			x	pros.	D-outp.	a,c,g,h,m,q,u,x,z
Kozel (1998)	220	46	x			pros.	D-outp.	a,c,f,j,t,u,v,w
Wallenstein (1984)	200	44			x	retros.	A-outp.	a,c,g,j,q
Meynadier (1979)	150	43			x	pros.	D	a,c,m,n,q,x
Erlings (1976)	109	43			x	retros.	D-in+outp	c,f,j,q,u,v
Kleine (1973)	127	43			x	retros.	D-inp.	c,f,m,s,u,v,w
Schultz (1987)	90	39			x	pros.	D-inp.	a,c,m,r,y
Nizami (1974)	194	38	x			pros.	M	d,f,l,o,s,u,v
Small (1982)	231	36			x	retros.	M	b,c,p,q,y
Quaranta (1989)	128	33		x		retros.	A-outp.	b,c,f,j,s,v,w
Sibbald (1991)	254	32			x	pros.	D-outp.	c,j,q,z
Mekkes (1986)	109	29		x		retros.	D-outp.	b,c,f,q,u,v,w
Wüthrich (1980)	279	25			x	retros.	D	b,d,f,q,x,y
Giam (1983)	100	23			x	pros.	D	b,c,g,t,u,x
Jacobson (1980)	125	20			x	pros.	M	b,c,f,h,m,q,u,v,w
Pigatto (2000)	348	19			x	pros.	D	a,c,f,h,l,r,v
Zweiman (1996)	85	18			x	pros.	M	c,f,q,z
Tas (1967)	100	1			x	retros.	D-inp.	c,f,h,q,v
Illig (1985)	?	62	not described			retros.	D	b,c,k,q,z
Rees (1957)	100	52	not described			pros.	P-outp.	b,c,f,n,q
Green (1965)	236	30	not described			retros.	M	c,f,n,q
Champion (1988)	2310#	29	not described			retros.	D-in+outp.	b,e,f,q,u,v,w
Champion (1969)	554	23	not described			retros.	D-in+outp	e,f,i,n,s,v
Humphreys (1998)	329	22	not described			retros.	D-outp.	b,d,g,q,w

Explanation of symbols and notes: see legend on opposite page

Legend table 1 : Explanation of the symbols and notes of table 1

* number of patients with chronic urticaria (symptoms longer than at least 4 weeks)
** study design: prospective (pros.) or retrospective (retros.)
■ setting: department of dermatology (D), allergy (A), internal medicine (M), or psychiatry (P); out-patients (outp.), in-patients (inp.) or both (in+outp) included
including the 554 patients described by Champion in 1969.

inclusion criteria
a adults included only
b patient cohort with children (<20%) and adults included
c patient with chronic urticaria only
d patient cohort with more than 80% of patients with chronic urticaria
e patient cohort with acute and chronic urticaria without specification
f consecutive patients
g no or a limited number of consecutive patients included.

exclusion criteria
h physical urticaria excluded
i adverse reactions to drugs excluded, except aspirin.

high percentages of particular causes identified
j high percentage of physical causes identified (>30%)
k high percentage of adverse reaction to drugs as causes identified (>10%)
l high percentage of adverse reaction to food as causes identified (>10%)
m high percentage of infections as causes identified (>10%)
n high percentage of psychological factors as causes identified (>10%)
o high percentage of inhalation/contact factors as causes identified (>5%)
p high percentage of internal diseases as causes identified (>5%).

follow-up
q no or limited follow-up data available
r partial follow-up data available (eg. during elimination diet or treatment of infection)
s follow-up data of ≥ 6 month available in 70-90% of the patients
t (almost) complete follow-up data available.

conclusions
u history is very important
v routine laboratory tests are of little value
w laboratory tests only useful if based on history
x routine laboratory screening could be useful
y laboratory tests of interest for that study could not identify more causes
z laboratory tests of interest for that study could identify more causes.

Identified causes

The number of identified diagnoses varied from 1% to 84% (table 1). If the highest (84%, 2 studies) and lowest (1%) percentages of identified diagnoses were omitted, the number of identified diagnoses would vary between 18 to 65%. The median of the number of identified diagnoses is 37%.

A description of percentages of identified diagnoses was available in 28 studies. In the one study only the total number of identified diagnoses was mentioned.[25] Four studies excluded physical causes; three of them reported the lowest percentages of identified diagnoses (1, 19, and 20%).[23,24,26] In one study without physical urticaria a very high percentage of infections was found (31%); the percentage of all identified diagnoses was 46%.[9]

In 21 studies certain etiological subgroups seemed to be overemphasized (table 1, notes). Eight studies reported a more than average amount of infections (11 to 31%).[5,6,8,9,12,14,15,23] In 11 studies detailed data of identified diagnoses were available, and infections were designated as the cause in 0-6% of the patients. Seven studies reported a large number of physical causes, and in 4 studies high percentages of psychological factors and adverse reactions to food were identified.

Associations

Three studies reported an unusual high or low percentage of identified causes. The two studies with the lowest number of included patients (64 and 50 patients)[4,5] identified a diagnosis in 84% of their study population. Tas excluded physical causes, and identified only one diagnosis in 100 patients.[26] The following given percentages are calculated after exclusion of these three outliers.

No relationship between the number of identified diagnoses and the number of performed laboratory tests was found. In 17 of the 23 studies, in which data on the number of performed laboratory tests were available, more than 20 routine laboratory tests were requested. In these studies the percentages of identified diagnoses varied between 18% to 65% (n=15), omitting the three outliers. In studies that had performed less than 20 laboratory tests the percentages of identified diagnoses varied between 29% and 57% (n=5). There were no associations

between the number of identified diagnoses and setting, study design, or publication period (table 1, notes).

Internal diseases

In 105 out of 6462 patients (1.6%), an internal diseases was considered to be the cause of the chronic urticaria. The following diseases were mentioned: cutaneous vasculitis (60 times), thyroid diseases (17 times), systemic lupus erythematosus (SLE, 7 times), other connective tissue diseases (16 times), paraproteinemia (3 times), and hereditary angioedema (2 times).

In one study a relationship with malignancies in two patients was mentioned, without further explanation.[24] In another study acute myeloid leukaemia (once) and breast cancer (once) were mentioned.[9] Polycythemia vera and a renal-cell carcinoma were found prior to the onset of urticaria in respectively four and one patients in one study.[17] In one patient cohort one patient had a mesothelioma, but his chronic angioedema was caused by enalapril.[34]

Conclusions

Most authors concluded that the history is very important (10 studies), that routine laboratory tests are of little value (13 studies), and that laboratory tests are only useful if based on the history (7 studies). In five studies, it was stated that routine laboratory screening could be useful.

COMMENT

In this systematic review of 29 studies describing 6462 patients with chronic urticaria, we found considerable differences in the number of reported causes. Excluding three outliers, the number of identified diagnoses varied from 18% to 65%. In most studies (21, table 1) the number of identified diagnosis was between 18 and 46%. We consider this a more accurate estimation of the prevalence of detectable causes. The proportion of reported causes was not associated with the number of routine laboratory screening tests performed. In 1.6% of the patients, internal diseases were detected. Factors such as patient selection, evaluation of intervention effects, and whether the natural course of the disease was followed were possibly responsible for the difference in the percentages of identified causes, but sufficient data were not available in the included studies. Setting (different medical specialities, and in- or outpatients), publication periods, and study design were not responsible for the differences in the percentages of identified diagnoses.

Limitations

Despite the substantial number of included studies the overall impact of the evidence is limited. There was little homogeneity in the number of identified causes reported in the studies in this systematic review. Almost all studies had methodological shortcomings. Most were case series without controls, not using consecutive patients, with no or a short follow-up period, studies without blinding, no independent interpretation of results, and improvement after treatment was not documented in all patients. Variations in patient characteristics and testing procedures are common sources of heterogeneity of systematic reviews which reflect daily clinical practise. Without thoroughly performed follow-up, including assessment of the outcome of interventions the number of identified diagnoses can easily be overestimated. Therefore, the given percentages of identified diagnoses should only be regarded as approximations.

We can only speculate on the reasons for the large differences in the number of identified causes. It is possible that these differences represent in part the variation in geographical region, and the kind of setting (secondary or tertiary care center). Different diagnostic assessment made by the referring physicians may also have contributed to the variability. Unfortunately, the data on referral patterns were very limited. The differences may reflect as well the personal prejudices and

preconceived opinions of the investigators, especially in studies were high percentages of certain causes were identified, and in studies were the data verification was limited.

Implications of Results

Despite the variability, the majority of the authors of the papers concluded that there is no need for routine laboratory tests. Laboratory tests should only be requested if there is a clue in the history, and the history is the most important instrument in identifying causes of chronic urticaria.

A flow-chart for the diagnosis of chronic urticaria

Despite the limitations of this systematic review, the conclusions and other extracted data were very helpful in developing a flow-chart, depicted in figure 1. One of the main conclusions of this systematic review is that *history-taking* is the most important instrument for identifying a cause of chronic urticaria. Leading authorities emphasize this as well.[35,36] For example, history taking only revealed 72% of detectable causes in one study.[20] In a retrospective study including 130 consecutive patients, we evaluated the value of history taking. In them 86% of identified diagnoses were found by history taking alone. A *questionnaire* is a time saving and often the most effective way to insure that a complete history is obtained.[36,37] If possible, *examination of hives* should be performed as a verification of the diagnosis.[35-37] A *test for dermographism* is a fast and easy procedure to rule out factitious urticaria.[36] In the studies included in this systematic review factitious urticaria was diagnosed in 4-9% of the patients in 11 studies,[5,11,13-16,19-21,30,32] and in 17-23% in 5 studies.[6,7,10,17,18]

Avoid routine laboratory screening is one recommendation which is highly supported by this systematic review. A literature search revealed that there is a tendency to perform very few laboratory tests. Sometimes, these test were only performed to reassure the patient and doctor that no causes have been missed.[38] The following laboratory tests were recommended by different experts: erythrocyte sedimentation rate (ESR), white blood count (WBC) and differential count, full blood count, eosinophil count, and urinalysis.[6,35,38-40] Other investigators advise no laboratory tests at all for chronic ordinary urticaria.[41,42] We investigated the value of the hemoglobin level, ESR, WBC and differential count in 350 patients, including the 130 patients of the

retrospective study mentioned above.[10] The results of the hemoglobin level were not helpful in finding any cause of urticaria. The *ESR, WBC and differential count* were helpful but not necessary in finding internal diseases in two patients; in one patient with idiopathic urticaria only the elevated ESR lead to the detection of paraproteinemia .[10]

Antihistamines of the H1 type are still the mainstay in the management of chronic urticaria, although they tend to be more effective in suppressing itching than whealing.[37,43-45] A combination of a non-sedating antihistamine in the morning and a sedating antihistamine in the late evening affords symptomatic relief.[43] Poor response to antihistamines, especially in combination with joint pain, not itchy, but painful and persisting hives, is more common in patients with pressure urticaria, and in patients developing or already suffering from a connective tissue disease or cutaneous vasculitis.[10,35] Seven studies, involving 3591 patients, mentioned improvement with antihistamines in 44 to 91% of the patients.[6,11,18,29,30,32,46]

Avoid aspirin, NSAID's, and codeine: In 18 studies of the systematic review data were available of the number of adverse drug reaction considered to be responsible for chronic urticaria. In these studies 148 reactions were identified in 3374 patients (4.4%).[5,6,9-18,20-22,29,31,32] In at least 55% (87 of 148 patients) analgesics (aspirin, non steroidal anti-inflammatory drugs [NSAIDs], and codeine) were considered to be the cause. Of the patients prescribed angiotensin-converting enzyme (ACE) inhibitors 0.1-0.7% may develop angioedema.[47] Therefore, we, like many others, recommend to *stop or replace all (suspected) drugs*, and repeatedly *ask for 'over the counter' drugs*. Even if aspirin or other analgetic drugs are not the main cause for chronic urticaria, they can be an aggravating factor in 7 to 50%.[11,19,22,29,35,46,48]

The following aggravating factors were mentioned by patients in questionnaires: stress (16 to 40%), pressure on the skin/dermographism (13 to 52%), heat (23 to 31%), exercise (15 to 22%), (analgetic) drugs (8 to 15%), coldness (13%), and consumption of alcohol (4 to 9%).[11,19,29,35,46] Alcohol can be a direct cause of chronic urticaria as well.[49] Based on these data, we included in the flow-chart: *avoid overheating, stress, pressure on the skin, and alcohol.*

At the first visit the patient should be informed that the diagnosis is clear, even if the cause is not, that the condition is not contagious, serious, or a sign of cancer or a major disease, and that the outlook is good.[41] *Information on benign character* is strongly supported by the large epidemiological study of Sigurgeirsson; he found no association between chronic urticaria and malignancies.[50] Of 1155 patients with chronic urticaria, a malignancy was diagnosed in 36, while the expected number was 41. Of the 6462 patients included in this systematic review, 23 patients developed a connective tissue disease and three patients paraproteinemia. Three studies provide *information on the natural course*. Champion analyzed that 45-70% of patients will be free of symptoms after one year. The worst prognosis was found in patients with both idiopathic urticaria and angioedema.[31] In another study idiopathic urticaria resolved after 3 years follow-up in 32% of 86 patients.[18] In our patient cohort 47% of 220 patients with chronic urticaria were free of symptoms after one year, and only 16% of patients with physical urticaria.[46] We recommend to explain to patients *that in most patients no specific cause of the urticaria will be found*, as shown by this review and recommended by others.[42,51]

As a further outpatient measure, patients can be asked to keep a *diary* around attacks, which often yields additional information about possible causes.[36] The value of an *elimination diet or oral food challenges* is controversial. If food additives are suspected by history[52] to be a cause, and according to some, even if the likelihood of success seems low on the bases of the history,[10,36] a diet low of food dyes and preservatives can be tried. If there is substantial improvement, a double-blind placebo-controlled challenge should be considered[37] or is mandatory.[43] The role of adverse food reactions is controversial; reported frequencies range from 5 to 73%.[4,53]

Figure 1: Flowchart for the diagnosis of chronic urticaria or angio-edema (references 35-54)

Visit 1

- History-taking
- Hand out questionnaire
- Examination of hives (if visible)
- Dermography test, if possible (no use of antihistamines)
- Avoid routine laboratory screening
- Perform ESR, WBC and differential count in idiopathic urticaria
- Prescribe non-sedating antihistamine
- Avoid aspirin, NSAID's, and codeine
- Avoid overheating, stress, pressure on the skin, and alcohol intake
- Information on benign character and natural course
- Information that in most patients no cause will be found

Visit 2

- History-taking
- Discuss questionnaire
- Confirm suspected causes with provocation or laboratory tests
- Stop or replace suspected drugs, if possible
- Ask (again) for over the counter drugs
- Prescribe antihistamine (same or different)

Visit 3 and further visits

- History-taking
- Urticaria diary, relationship with special events, drug intake
- Elimination diet or oral food challenge, if indicated
- Prescribe antihistamine (same or different)

ESR, erythrocyte sedimentation rate; WBC, white blood cell count; NSAID, nonsteroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme.
To keep the flowchart brief, we used short phrases rather than complete sentences. All phrases are meant to be recommendations.

Final remarks

An infection with *Helicobacter pylori* is a new subject of interest as a cause for chronic urticaria. Most controlled prospective studies showed no relationship.[8,54,55] In studies where a relationship was detected, often using very accurate diagnostic procedures for *Helicobacter pylori*, no controls were evaluated or the number of included patients was small.[9,56] This is a recent example of how dangerous it can be to associate detected diseases with chronic urticaria without performing properly controlled studies. It will again lead to long lists of routine laboratory tests and eventually, considering the risk of gastroscopies and treatment with several antibiotics, could cause more harm than good.

The practice of evidence-based medicine is integrating individual clinical expertise with the best available external clinical evidence from systematic research. We feel that this systematic review showed that paying more attention to history taking, introducing a questionnaire for the diagnostic process, and providing information about the benign character of urticaria, the prognosis, and possible aggravating factors will help to improve the quality of care.

REFERENCES

1. Sackett DL. Introduction. In: Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB, eds. Evidence-based Medicine. How to practice and teach EBM. 2nd ed. Edinburgh London New York Philadelphia St Louis Sydney Toronto; Churchill Livingstone; 2000:1-12.
2. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing guidelines. BMJ 1999;318:593-596.
3. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: Potential benefits, limitations, and harms of clinical guidelines. BMJ 1999;318:527-530.
4. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudo-allergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol 1995;75:484-487.
5. Miller DA, Freeman GL, Akers WA. Chronic Urticaria. A Clinical Study of Fifty Patients. Am J Med 1968;44:68-86.
6. Trachsel Ch, Pichler WJ, Helbling A. Importance of laboratory investigations and trigger factors in chronic urticaria. Schweiz Med Wochenschr 1999;129:1271-1279.
7. Douglas HMG. Chronic urticaria. Clinical and pathogenetic studies on 141 patients. Thesis 1975; Dijkstra Niemeyer, Groningen.
8. Schnyder B, Helbling A, Pichler WJ. Chronic idiopathic urticaria: Natural course and association with Helicobacter pylori infection. Int Arch Allergy Immunol 1999;119:60-63.
9. Wedi B, Wagner S, Werfel Th, Manns MP, Kapp A. Prevalence of Helicobacter pylori-associated gastritis in chronic urticaria. Int Arch Allergy Immunol 1998;116:288-294.
10. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol 1998;134:1575-1580.
11. Wallenstein B, Kersten W. Findings on a patient group with urticaria. Allergologie 1984;7:115-119.
12. Meynadier J, Guilhou JJ, Meynadier J, Lavanture N. Chronic urticaria. Etiology and therapeutic evaluation of 150 cases. Ann Dermatol Venereol 1979;106:153-158.
13. Erlings M, Jongedijk-Brøndsted. The etiology of urticaria; a retrospective study of 200 patients. Ned Tijdschr Geneeskd 1976;120:1565-1569.
14. Kleine-Natrop HE, Sebastian G. Analyse und Kritik der Urticaria-Diagnostik. Dermatol Monatsschr 1973;159:769-778.
15. Schultz-Ehrenberg U, Gilde O. Results of examination in chronic urticaria with special consideration of nutrition factors. Z Hautkr 1987;62(suppl.1): 88-95.
16. Nizami RM, Baboo MT. Office management of patients with urticaria: an analysis of 215 patients. Ann Allergy 1974;33:78-85.

17. Small P, Barrett D, Boskin N, Caplin E. Chronic urticaria and angio-edema. Clin Allergy 1982;12:131-136.
18. Quaranta J, Roar AS, Rachelefsky GS, et al. The natural history and response to therapy of chronic urticaria and angioedema. Ann of Allergy 1989;62:421-424.
19. Sibbald RG, Cheema AS, Lozinski A, Tarlo S. Chronic Urticaria. Evaluation of the role of physical, immunologic, and other contributory factors. Int J Dermatol 1991;30:381-386.
20. Mekkes JR, Schaar WW van der, Bos JD. Anamnese en diagnostiek van chronische urticaria. Ned Tijdschr Geneeskd 1986;130:1801-1805.
21. Wüthrich B, Häcki-Herrmann D. Zur Ätiologie der Urticaria. Eine retrospektive Studie anhand von 316 konsekutiven Fällen. Z Hautkr 1980; 55:102-111.
22. Giam YC, Rajan VS. An approach to urticaria. Ann Acad Med Singapore 1983;12:74-80.
23. Jacobson MKW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. JAMA 1980;243:1644-1646.
24. Pigatto PD, Valsecchi RH. Chronic urticaria: a mystery. Allergy 2000;55: 306-308.
25. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996;98:89-98.
26. Tas J. Chronic Urticaria. A survey of 100 hospitalized cases. Dermatologica 1967;135:90-96.
27. Illig L, Paul E. Aetiopathogenetical diagnosis in non physical urticaria (and angioneurotic edema): Strategy and results. Allergologie 1985;8:431-436.
28. Rees L. An aetiological study of chronic urticaria and angioneurotic oedema. J Psychosomatic Res 1957;2:172-189.
29. Green GR, Koelsche GA, Kierland RR. Etiology and pathogenesis of chronic urticaria. Ann Allergy 1965;23:30-36.
30. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427-436.
31. Champion RH, Roberts SOB, Carpenter RH, Roger JG. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969;81:588-597.
32. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients. Br J Dermatol 1998;138:635-638.
33. Guidelines. In: Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB, eds. Evidence-based Medicine. How to Practice and Teach EBM. 2nd ed. Edinburgh London New York Philadelphia St Louis Sydney Toronto; Churchill Livingstone; 2000:169-182.
34. Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. Clin Exp Derm 1995;20:60-61.
35. Champion RH, Highet AS. Investigation and management of chronic urticaria and angio-oedema. Cain Exp Dermatol 1982;7:291-300.

36. Zuberbier T, Henz BM. Diagnosis of Urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998:139-159.
37. Urticaria, angioedema and anaphylaxis. In: Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC, eds. Dermatology. 2nd ed. Berlin: Springer Verlag; 2000:431-456.
38. Ormerod AD. Urticaria and angio-oedema. BMJ 1984;289:903-906.
39. L Juhlin. Additives in chronic urticaria. Ann Allergy 1987;59:119-123.
40. Soter NA. Acute and chronic urticaria and angioedema. J Am Acad Dermatol 1991;25:146-154.
41. Levine MI. Chronic urticaria. J Allergy Clin Immunol 1975;55:276-283.
42. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. Br J Dermatol 2001;144:708-714.
43. Greaves MW, Sabroe RA. Allergy and the skin. I-Urticaria. BMJ 1998;316: 1147-1150.
44. Henz BM, Zuberbier T, Monroe E. Urticaria therapy. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria. Clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998: 161-181.
45. Henderson RL, Fleischer AB, Feldman SR. Allergists and dermatologists have more expertise in caring for patients with urticaria than other specialists. J Am Acad Dermatol 2000;43:1084-1091.
46. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol 2001;45: 387-391.
47. Sabroe RA, Kobza Black A. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol 1997;136:153-158.
48. James J, Warin RP. Chronic urticaria: the effect of aspirin. Br J Dermatol 1970;82:204-209.
49. Sticherling M, Brasch J, Brüning H, Christophers E. Urticarial and anaphylactoid reactions following ethanol intake. Br J Dermatol 1995;132: 464-467.
50. Sigurgeirsson B. Skin diseases and malignancies. An epidemiological study. Acta Derm Venereol Suppl 1992;178:1-110.
51. Mathews KP. Urticaria and angioedema. J Allergy Clin Immunol 1983;72:1-14.
52. Kobza Black A, Champion RH. Urticaria. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. Rook, Wilkinson, Ebling. Textbook of Dermatology. 6th edition. Oxford. Blackwell Science; 1998:2113-2139.
53. Bindslev-Jensen C, Finzi A, Greaves MW, et al. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol 2000;14:175-180.
54. Ortolani C, Pastorello E, Ispano E, Ansaloni R. Food allergy diagnosis protocol. Allergy et Immunol 1988;20:48-50.
55. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Int Med 1999;130:515-524.

56. Valsecchi RH, Pigatto PD. Chronic Urticaria and Helicobacter pylori. Acta Derm Venereol 1998;78:440-442.
57. Höök-Nikanne J, Varjonen E, Harvima RJ, Kosunen TU. Is Helicobacter pylori infection associated with chronic urticaria. Acta Derm Venereol 2000;80:425-426.
58. Wedi B, Kapp A. Helicobacter pylori infection and skin diseases. J Physiol Pharmacol 1999;50:753-776.

Chapter 8

Summary and conclusions

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Chapter 8

SUMMARY AND CONCLUSIONS

Changes in the society, such as the increased involvement of patients with decisions concerning their disease, and the governments' intention to reduce health care costs, have forced the medical profession to develop practice guidelines. Clinical guidelines are helpful to both the physician and the patient, because they can be applied when complex decisions have to be made. Medical decisions become more and more complex because of the increasing amount of knowledge, medical literature and the amount of possible medical interventions. The purpose of practice guidelines is to improve the efficacy and quality of medical interventions and to reduce unnecessary medical interventions. Practice guidelines can facilitate decision making for both the patient and the doctor. Practice guidelines can also be used to check retrospectively whether the applied diagnostic and therapeutic interventions were appropriate. With the use of precise practice guidelines questions or complaints of patients can be answered easier. At this moment there is no practice guideline for the diagnostic process in chronic urticaria and angioedema available in the Netherlands.

The purpose of this thesis was the development of an evidence-based guideline for the diagnostic process in chronic urticaria and/or angioedema. To develop this guideline, different steps were necessary, which are explained in the chapters 2,3,4,6 and 7.

Chapter 1: Introduction and aims of the study.

In this chapter, the goals of the study are described. In addition, some general background about urticaria and angioedema is provided. Urticaria (hives, wheals) is a common disorder. About 15% of the population will have a period of urticaria or angioedema at least once in their lifetime. Most patients will experience acute urticaria, which is by definition lasting for up to six weeks. In 38 practices of general practitioners in Amsterdam, data of the incidence and prevalence of several variable complaints of patients were collected during one year. In this study an incidence of acute or chronic urticaria of 4.3 per 1000 patients and a prevalence of 5.0 per 1000 patients was reported. 5.1% of the patients with urticaria had complaints for longer than 4 weeks, and 4.1% of them were referred to a dermatologist. Accordingly, only a small number of patients is referred to a hospital, most likely this will be the patients who have severe complaints or complaints for a long time. In Dermatology outpatient departments of the Netherlands 1.4-2.4% of the patients had urticaria or angioedema.

Having chronic urticaria can be very disturbing, because it can be intensely pruritic. The appearance of hives is unpredictable and it may interfere with daily activities or sleep. For these reasons patients with urticaria desire an explanation for their complaints. In the past this desire was one of the reasons to perform extensive laboratory investigations. Despite these extensive laboratory investigations, in 70-90% of patients with chronic urticaria and/or angioedema no cause could be identified. This was very frustrating for both patients and doctors, and sometimes resulting in even more laboratory investigations. Another reason for extensive laboratory investigations is that both patients and doctors may fear that the symptoms could be a manifestation of an underlying illness. Large clinical studies have shown that the frequency of severe underlying diseases in urticaria patients is low. In the literature, it has been suggested not to perform routine investigations in patients with urticaria, but this recommendation is not yet followed in all outpatient clinics. In the time of evidence-based medicine it is only possible to change the behavior of physicians by performing a controlled study applicable to clinical practice, or to perform a systematic review. The purpose of such studies is to provide the necessary evidence to stimulate a change in the behavior of physicians taking care for patients with chronic urticaria.

Chapter 2: A questionnaire for patients with chronic urticaria and an explanation of the questionnaire.

The necessity of routine laboratory investigations is more and more doubtful. Since approximately 1990 the value of history taking is more and more stressed in the literature.
These alterations were the reason why in the outpatient department of Dermatology of the Academic Medical Center of Amsterdam a questionnaire for patients with chronic urticaria was developed and introduced. In this questionnaire, which was based on earlier published questionnaires and our own experience, patients were asked about the type of urticaria, the severity and the frequency of the bouts, and about a large number of eliciting causes and provoking circumstances. Furthermore, the questionnaire contains questions about general health, predominantly to search for underlying internal diseases, and patients were encouraged to reflect on their own thoughts about possible causes. The questionnaire was used in the studies described in the following chapters and its value was investigated.

For the interpretation of the answers given on the questionnaire it is helpful to have some background information about the causes and mechanisms responsible for chronic urticaria and angioedema. This was the reason to present brief information about every question in the questionnaire. The use of the questionnaire is a helpful instrument that does not replace history taking, but it is an instrument which involves the patient in the search for a cause. The involvement of the patient is very important in patients with chronic urticaria, and with the questionnaire the patient has the opportunity and the time to entertain possible causes.

Most questions asking for underlying conditions can be answered by the patients with 'no'. But because attention is given to all these issues and possible underlying causes, the patients will be reassured that no underlying diseases are missed. Additionally, patients are asked about their drug intake, including over the counter drugs. Patients are asked to write down the drugs they used during the last year, or to present a recent printout of their pharmacy. This strategy diminishes the time-consuming search for the patients' drug intake, and makes it easier to discover a possible time-relationship between a particular drug used by the patient and the start of the urticaria.

Chapter 3: The effectiveness of a history-based diagnostic approach for patients with chronic urticaria and the introduction of the preliminary guideline.

In this prospective study involving 220 consecutive adults with chronic urticaria the value of extensive laboratory screening for the identification of causes was investigated in the out-patient department of a secondary and tertiary care center. The study design was a per-patient comparison of two diagnostic strategies: the combination of history taking (using a detailed questionnaire) and a limited set of laboratory tests (hemoglobin level, hematocrit, erythrocyte sedimentation rate, white blood cell count and differential blood cell count), versus history taking (using the same detailed questionnaire) and an extensive laboratory screening (blood chemistry, allergy tests, complement profile, screening for infections, autoimmune diseases and malignancies; in total approximately 35 laboratory tests for each patient). A special study design was developed to investigate the two diagnostic strategies in each patient.

Every new patient with complaints of urticaria and/or angioedema for at least six weeks was asked to participate in the study. At the first visit at the outpatient department the questionnaire mentioned above was handed out to the patient by the physician dealing with the patient (the dermatologists). A limited number of laboratory tests was requested and the test for dermographism was performed. After receiving the questionnaire which was filled in by the patient at home, the dermatologists were asked to mention on an evaluation form the most probable cause of the chronic urticaria (based on the questionnaire and the results of the limited number of laboratory tests). Simultaneously, the patients were seen by another physician, the research physician, who checked the answers of the questionnaire and performed the extensive laboratory tests. The results of this extensive screening were kept secret for the patients and the dermatologists. A safety committee checked the results of the extensive screenings for deviant data. Additional laboratory tests could be requested by the dermatologist if motivated. After 4 to 6 months, all results were disclosed to the dermatologists and to the patients. Again, the dermatologists were asked to fill in on an evaluation form the most probable cause of the chronic urticaria for each particular patient. Patients were followed-up for at least one year to evaluate the results of interventions (e.g. treatment of infections or discontinuation of used drugs) and to detect latent causes. An expert committee defined the most probable cause of the chronic urticaria on two points in time, based on the same amount of data which were available for the dermatologists (first, including the limited set of laboratory tests; and later, including the extensive set of laboratory tests). The different percentages of identified causes of the first and second diagnoses of the dermatologists and the expert committee were compared.

The final diagnosis of the expert committee was based on all available information (answers of the questionnaire, results of the extensive laboratory screening, and the data of the follow-up period). This was considered to be the gold standard for the diagnosis of chronic urticaria. In 53.1% of the patients a diagnosis could be identified. With a questionnaire and the limited laboratory tests, a cause was found in 45.9% of the patients by the dermatologists. The missed diagnoses were: 9 adverse drug reactions, 6 adverse food reactions, 1 parasite infection, and 4 patients with chronic idiopathic urticaria had as well pressure urticaria. Except for the parasite infection, all other missed causes could not have been found by extensive laboratory screening. With this study it is shown that routine laboratory screening did not

contribute substantially to the diagnosis of chronic urticaria nor to the detection of underlying disorders, and therefore, is not recommended.

Chapter 4: The natural course of chronic urticaria and the identified causes in 220 patients with chronic urticaria.

The most important reasons for performing the prospective study including 220 patients with chronic urticaria is described in chapter 3. Due to the study design which made it necessary to follow-up patients for at least one year, it was possible to investigate the natural course of chronic urticaria as well. Information regarding the natural course of chronic urticaria was found to be very limited in the medical literature. In this study 35% of the patients were free of symptoms after one year, including the patients in whom a cause was identified (e.g. a cause which could be treated). In 29% of the patients the complaints had diminished. In patients in whom no cause for the chronic urticaria could be identified spontaneous remission occurred in 47% after one year. The worst prognosis was found in patients with physical urticarias, such as pressure on the skin, cold, warmth, or exercise. In this group of patients only 16% were free of symptoms after one year follow-up.

In this patient cohort a large number of physical courses was identified (33.3%), possibly due to routinely performed provocation tests (tests for dermographism), and due to specific questions and the explanation about the different physical causes in the questionnaire. In all patients the physical causes were confirmed by specific provocation tests. Other frequently identified causes were adverse reactions to drugs and food. In all patients suspected drugs were routinely discontinued or replaced, and in 20 patients an adverse reaction to a specific drug was identified as the cause of the chronic urticaria; in 11 patients this specific drug was an analgetic drug. In 15 patients food was considered to be the cause of the chronic urticaria. In ten patients ordinary hives occurred, three patients had urticaria factitia after consuming particular food, and two patients experienced exercise-induced food-dependent urticaria. In ten patients a parasite infection was diagnosed. All of these patients were born in a (sub)tropical country or were working there for a longer period. In four of these ten patients the hives disappeared after treatment of the parasite infection. In three patients the chronic urticaria was found to be related to an internal disease (Sjögren's disease, systemic lupus erythematodes, paraproteinaemia). In 24 patients a combination of physical urticaria and idiopathic urticaria was found.

Chapter 5: An example of an adverse reaction to drugs: Two patients with chronic angioedema due to angiotensin-converting enzyme inhibitors.

In the patient cohort, including 220 consecutive patients, in two patients an adverse drug reaction to one of the angiotensin-converting enzyme (ACE) inhibitors was identified as the cause of the angioedema. Shortly after the introduction of ACE inhibitors in the eighties it was known that these drugs, like almost all drugs, could provoke urticaria and angioedema. At first, only case reports were described that mentioned a bout of angioedema briefly after the administration of the new drug. Later on, it became known that in 20% of the patients the symptoms start after 6 weeks after the first administration of a daily taken drug. In one of the patients described in this chapter an aggravation of already existing angioedema occurred after the use of ACE inhibitors. In the other described patient the complaints started one year after the regular use of an ACE inhibitor. In this patient a malignancy was detected during the follow-up period, but there was no relationship between the angioedema and the malignancy because after the discontinuation of the new drug the angioedema disappeared.

Chapter 6: Implementation, validation, and improvement of the preliminary guideline for the diagnosis in patients with chronic urticaria.

In this retrospective study, the use of a clinical guideline was investigated in 130 consecutive patients with chronic urticaria. The clinical guideline recommended the following items at the first visit: history taking, handing out a detailed questionnaire, examination of hives, performing the dermography test, requesting five routine hematological tests, (no extensive routine laboratory tests), and prescribing a non-sedating antihistamine. At the second visit the guideline recommended once again history taking, discuss the questionnaire with the patient, confirm suspected causes with laboratory or provocation tests, stop or replace all suspected drugs, ask (once again) for over the counter drugs (especially for analgesics), and prescribe an antihistamine, if necessary an alternative one.

It was evaluated how often the questionnaire was used, how often routine or other laboratory tests were performed at the first visit, and which information (history taking, questionnaire, laboratory tests or

provocation tests) was crucial for detecting the cause of the urticaria. With this retrospective study we validate our earlier prospective study (see chapter 3) by comparing the number of found diagnoses of both studies. These numbers of identified diagnoses in the different subgroups were almost identical. In the retrospective study, in 58 of the 130 patients (45%) a cause was identified. In 50 of the 58 patients (86%) the cause was identified by history taking, and in 8 patients the diagnosis was identified by the additional use of a questionnaire. In 38 of the 130 patients the questionnaire was not in the patient's file; in 12 of the 38 patients the questionnaire was handed out but not returned by the patient. In 89 of 130 patients (68%) more laboratory tests were requested without a reason suggested by the patients' history or the questionnaire, but the number of unnecessary requested laboratory tests was much lower than in the period before the introduction of the guideline. The unnecessarily requested laboratory tests did not reveal a cause in any patient. This study contributed to the reduction of the number of laboratory tests which we recommend in patients with chronic idiopathic urticaria (erythrocyte sedimentation rate, white blood cell count and differential blood cell count). This study shows that the guideline for the diagnosis of chronic urticaria can be successfully introduced in clinical practice and that with this guideline most of the diagnoses could be identified by history taking.

Chapter 7: A systematic review of the literature about the value of laboratory tests in patients with chronic urticaria and the description of the final practice guideline.

This chapter describes the results of a systematically performed literature search. The purpose of this literature search was: first, to analyze the value of laboratory tests in patients with chronic urticaria in the selected studies; second, to investigate and explain the variations in the number and sort of the identified causes in the selected studies; and third, the further development and confirmation of the final clinical guideline with data obtained by the literature search. For this systematic review of the literature four electronic databases were searched, a large number of articles and books were searched as well, and all the references of the selected articles were analyzed for their suitability to be included in this systematic review. An article was included in the systematic review if it contains a study including more than 50 patients with chronic urticaria, and if the study was published after 1930. 29 studies fulfilled these criteria, and in them in total 6462 patients were

included. The following data of each study were collected: publication year; study design; number, age, and gender of the included patients; inclusion and exclusion criteria of the studies; percentage of the identified causes; number of requested laboratory tests; duration of the follow-up period; and the conclusion of each selected study. No relationship was found between the number of identified diagnoses and the number of requested laboratory tests, the publication year, and the study design (retrospective or prospective study design). Unfortunately, in many studies the procedure used for the verification of the identified causes (to confirm that the suspected cause was the most probably cause of the chronic urticaria) was not properly performed or not described. Therefore, the value of the presented data is limited and the number of identified diagnoses should be regarded as approximations. Despite the heterogeneity of the results of the selected studies, most of the studies came to the same conclusions, namely, routinely performed laboratory tests are not useful, only laboratory tests based on the history are useful, and history taking is the most important instrument in identifying causes in patients with chronic urticaria.

Based on the results of this systematic review, several relevant articles, and our own experience, we developed a brief flow-chart for the diagnosis for patients with chronic urticaria which is depicted in chapter 7 (figure 1).

Conclusions

* According to the principles of evidence-based medicine, it is only useful to perform diagnostic tests if they contribute to the diagnostic process.

* Routinely performing extensive laboratory tests hardly supports the identification of a cause in patients with chronic urticaria.

* The best instrument to identify a cause of chronic urticaria is detailed history taking, for example with the use of a questionnaire.

Chapter 9

Samenvatting en Nederlandse vragenlijst

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SAMENVATTING EN CONCLUSIES

Maatschappelijke veranderingen, zoals de toegenomen mondigheid van de patiënt, en de wens van de overheid om de kosten van de gezondheidszorg te beheersen, hebben de medische professie ertoe gebracht om op korte termijn praktijkrichtlijnen op te stellen. Richtlijnen helpen de behandelaar en de patiënt bij het nemen van klinische beslissingen die steeds ingewikkelder worden door de toename van behandelmogelijkheden, kennis en literatuur. Het doel van richtlijnen is het bevorderen van de doelmatigheid en de kwaliteit van het medisch handelen en tevens het terugdringen van overbodig medisch handelen. Richtlijnen kunnen hulpmiddelen zijn om samen met de patiënt een behandelplan op te stellen, maar kunnen ook gebruikt worden om achteraf te toetsen of een zinvolle diagnostische of therapeutische strategie gevolgd is. Met duidelijke richtlijnen kunnen eventuele vragen of klachten van patiënten beter beantwoord worden. Momenteel bestaat er in Nederland nog geen richtlijn voor de diagnostiek van chronische (langer dan 6 weken bestaande) urticaria en chronisch angio-oedeem.

De doelstelling van dit proefschrift was het ontwikkelen van een zogenaamde *'evidence-based'* richtlijn voor de diagnostiek bij patiënten met chronische urticaria en/of angio-oedeem. Om deze richtlijn te ontwikkelen zijn verschillende stappen nodig geweest, die worden beschreven in de hoofdstukken 2,3,4,6 en 7.

Hoofdstuk 1: Inleiding en doelstellingen.

Dit hoofdstuk bevat naast de boven reeds genoemde doelstelling ook een beknopte beschrijving van het ziektebeeld urticaria. Urticaria (galbulten, netelroos) is een frequent voorkomende ziekte. Ongeveer 15% van de bevolking zal ooit in het leven een periode doormaken met urticaria of angio-oedeem. Meestal gaat het dan om acute urticaria (per definitie korter bestaand dan 6 weken). In 38 huisartsen-praktijken in Amsterdam werd gedurende een jaar de incidentie en prevalentie van diverse klachten van patiënten onderzocht. Hierbij werd voor urticaria (acuut en chronisch samen) een incidentie van 4.3 en een prevalentie van 5.0 per 1000 patiënten gevonden. 5,1% van de patiënten met urticaria had langer dan 4 weken klachten, en 4,1% werd verwezen naar

een dermatoloog. Dus slechts een klein percentage wordt doorverwezen, en dit zullen doorgaans de patiënten zijn die gedurende een langere periode klachten hebben of die ernstige klachten hebben. In dermatologische poliklinieken heeft 1,4-2,4% van de patiënten urticaria en/of angio-oedeem.

Door de hinderlijkheid van de aandoening, die gepaard gaat met jeuk en het verschijnen van galbulten, soms continu en soms op totaal onvoorspelbare momenten, bestaat onder de patiënten een grote behoefte om een verklaring te vinden voor hun klachten. Dit heeft in het verleden geleid tot het uitgebreid aanvragen van laboratorium bepalingen. In 70-90% van de gevallen werd ondanks uitgebreid laboratoriumonderzoek geen oorzaak gevonden die de urticaria kon verklaren. Dit leidde tot frustratie bij zowel arts als patiënt, soms resulterend in het aanvragen van nog meer lab bepalingen. Ook de angst van de behandelaar en de patiënt om een mogelijke onderliggende ernstige ziekte te missen, kan leiden tot uitgebreid laboratoriumonderzoek. In grote klinische studies is echter aangetoond, dat de kans op onderliggende ernstige aandoeningen zeer klein is. In de literatuur wordt al langer geadviseerd om geen uitgebreid screenend laboratoriumonderzoek meer te verrichten, maar toch wordt dit advies in de praktijk nog vaak niet gevolgd. In deze tijd van 'evidence-based medicine' is het alleen mogelijk een gedragsverandering teweeg te brengen door ofwel een praktijkgerichte gecontroleerde studie uit te voeren, ofwel een op systematische wijze samengesteld literatuuroverzicht te geven, en hiermee het nodige bewijsmateriaal (evidence) te leveren.

Hoofdstuk 2: Een vragenlijst voor patiënten met chronische urticaria, en een toelichting op de vragenlijst.

Het nut van routinematig uitgevoerd laboratoriumonderzoek wordt sinds de jaren negentig steeds meer betwijfeld, terwijl het belang van een goede anamnese steeds meer benadrukt wordt. Tegen deze achtergrond werd in 1992 op de polikliniek Dermatologie van het Academisch Medisch Centrum in Amsterdam een gestructureerde vragenlijst voor patiënten met chronische urticaria geïntroduceerd. In deze vragenlijst wordt geïnformeerd naar het type urticaria, de lokalisatie, de ernst en de

frequentie, en naar een groot aantal mogelijke oorzaken en uitlokkende omstandigheden. Verder bevat de vragenlijst een aanvullende algemene gezondheidslijst waarmee eventuele onderliggende ziekten kunnen worden opgespoord, en de patiënt wordt gevraagd de eigen gedachten en theorieën over mogelijke oorzaken op te schrijven. Deze vragenlijst werd gebruikt voor de studies, die in de volgende hoofdstukken zijn beschreven en de waarde ervan werd geanalyseerd. De vragenlijst in het Nederlands is aan het eind van dit hoofdstuk te vinden.

Voor de interpretatie van de m.b.v. de vragenlijst verkregen anamnese gegevens is het nodig om over enige beknopte achtergrond-informatie te beschikken over de oorzaken en mechanismen die bij chronische urticaria een rol kunnen spelen. Dit was de reden om bij elke vraag een korte toelichting te geven. Het gebruik van de vragenlijst is een handig hulpmiddel dat een anamnese niet vervangt, maar wel de patiënt intensief betrekt bij het zoeken naar een mogelijke oorzaak. Het geeft de patiënt de gelegenheid en de tijd om maximaal mee te denken, hetgeen bij chronische urticaria erg belangrijk is. Veel vragen naar onderliggende ziekten zullen door de patiënt negatief kunnen worden beantwoord. Dit zal de angst voor ernstige onderliggende ziekten verminderen. Verder wordt aan de patiënt gevraagd om alle gebruikte geneesmiddelen van het laatste jaar op te schrijven of een uitdraai van de apotheek mee te nemen. Dit vermindert het tijdrovende speurwerk naar wat de patiënt precies gebruikt heeft, en wanneer.

Hoofdstuk 3: De effectiviteit van het anamnese-gestuurd aanvragen van laboratoriumdiagnostiek bij patiënten met chronische urticaria en de introductie van de voorlopige richtlijn.

In deze prospectieve studie werden 220 opeenvolgende volwassen patiënten met chronische urticaria en/of angio-oedeem geïncludeerd. Om de waarde van uitgebreid screenend onderzoek te analyseren werden twee diagnostische strategieën met elkaar vergeleken. In beide strategieën stond het zorgvuldig afnemen van de anamnese met behulp van de gedetailleerde vragenlijst centraal, maar in de ene strategie werd alleen beperkt laboratoriumonderzoek verricht (haemoglobine, haematocriet, bezinking, leukocyten en differentiatie), terwijl de andere

strategie een uitgebreid laboratoriumonderzoek omvatte (klinische chemie, eiwit-spectrum, immunologisch en allergologisch onderzoek, microbiologisch onderzoek, urine en faeces onderzoek, röntgenfoto's; totaal ongeveer 35 verschillende bepalingen per patiënt). Het onderzoek vond plaats in de polikliniek Dermatologie van het Academisch Medisch Centrum te Amsterdam, een tweede en derde lijns ziekenhuis. Een bijzondere opzet werd gekozen om beide strategieën binnen één patiënt te kunnen vergelijken.

Iedere nieuwe patiënt met klachten van urticaria of angio-oedeem langer dan 6 weken, werd gevraagd om aan de studie deel te nemen. Bij het eerste consult werd door de behandelend arts de vragenlijst meegegeven, beperkt laboratoriumonderzoek aangevraagd en een dermografietest verricht. Na ontvangst van de ingevulde vragenlijst werd de behandelaar gevraagd om, op basis van de anamnesegegevens en de uitslagen van het beperkt lab, de meest waarschijnlijke oorzaak in te vullen op een evaluatieformulier. Parallel hieraan werden de patiënten ook gezien door een andere arts (de onderzoeker), die ook de vragenlijst doornam en regelde dat er uitgebreid laboratoriumonderzoek werd verricht. De uitslagen van het uitgebreid lab-onderzoek werden echter gedurende 4-6 maanden *niet* aan de behandelaar en de patiënt bekend gemaakt (wel was er een panel dat screende op sterk afwijkende uitslagen die een interventie zouden vereisen). In deze periode kon de behandelaar eventueel wel om andere uitslagen vragen, maar alleen als dit gemotiveerd kon worden. Na 4-6 maanden werden alle uitslagen aan de behandelaar ter beoordeling gegeven en moest opnieuw op een evaluatieformulier worden ingevuld wat nu de meest waarschijnlijke oorzaak van de klachten van de patiënt was. De patiënten werden tenminste 1 jaar gevolgd om onderliggende oorzaken te kunnen opsporen en om het effect van interventies (het behandelen van infecties of het stoppen van geneesmiddelen) te kunnen beoordelen. Een expert commissie definieerde op twee tijdstippen en op basis van dezelfde sets aan gegevens (eerst beperkt, dan uitgebreid lab) ook de meest waarschijnlijke oorzaak. De verschillende percentages van de gevonden oorzaken van de eerste en tweede diagnoses van de behandelaars en de expert commissie werden met elkaar vergeleken.

De uiteindelijke diagnose van de expert commissie was gebaseerd op alle beschikbare informatie (antwoorden vragenlijst, resultaten uitgebreid laboratorium onderzoek en de gegevens van de follow-up) en werd beschouwd als de gouden standaard voor het vaststellen van de diagnose van chronische urticaria. Er werd in 53,1% van de patiënten een diagnose gevonden. In de eerste diagnose van de behandelaars werd in 45,9% van de patiënten een oorzaak gevonden. De gemiste oorzaken waren: 9 geneesmiddel-bijwerkingen, 6 reacties op een voedingsmiddel, 1 parasitaire infectie en 4 patiënten met chronische urticaria hadden ook drukurticaria. Behalve de gemiste parasitaire infectie hadden alle andere gemiste oorzaken niet kunnen worden gevonden d.m.v. uitgebreid laboratorium-onderzoek. Met deze studie is aangetoond dat routine-matig uitgevoerd uitgebreid laboratorium onderzoek niet zinvol is.

Hoofdstuk 4: Het natuurlijk beloop en de gevonden oorzaken bij 220 patiënten met chronische urticaria.

De belangrijkste redenen om een prospectieve studie uit te voeren bij 220 volwassen patiënten met chronische urticaria zijn al beschreven in hoofdstuk 3. Vanwege het feit dat het voor de studieopzet nodig was om patiënten tenminste een jaar lang te volgen, werd het mogelijk om tevens nader onderzoek te doen naar het natuurlijk beloop van chronische urticaria. Informatie omtrent dit natuurlijk beloop blijkt zeer beperkt beschikbaar in de medische literatuur. In dit onderzoek was 35% van alle patiënten klachtenvrij na 1 jaar, inclusief de patiënten bij wie een (behandelbare) oorzaak was gevonden. Bij 29% van de patiënten waren de klachten verminderd. Bij de patiënten waarbij geen oorzaak voor de chronische urticaria kon worden gevonden, trad bij 47% na 1 jaar spontane remissie op. De slechtste prognose werd gevonden voor patiënten met fysische oorzaken, zoals druk op de huid, koude, warmte of inspanning. In deze groep waren slechts 16% zonder klachten na verloop van een jaar.
In dit patiënten cohort werden veel fysische oorzaken gevonden (33,2%) waarschijnlijk door het routinematig uitvoeren van de dermografietest en door er in de vragenlijst heel specifiek naar te vragen, na eerst duidelijk uitgelegd te hebben wat fysische oorzaken zijn. Bij alle patiënten zijn de fysische oorzaken bevestigd met een specifieke provocatietest. Andere

frequente oorzaken waren geneesmiddelen en voedingsmiddelen. Door het routinematig stoppen of vervangen van verdachte geneesmiddelen werd bij 20 patiënten een geneesmiddel gevonden dat verantwoordelijk was voor de chronische urticaria; bij 11 patiënten was dit een pijnstiller. Bij 15 patiënten veroorzaakte een voedingsmiddel urticaria, meestal klassieke galbulten (10 patiënten), bij 3 patiënten ontstond urticaria factitia na het eten van bepaalde voedingsmiddelen en bij 2 patiënten ontstond urticaria door een combinatie van inspanning en voedingsmiddelen. Bij 10 patiënten werd een parasitaire infectie gevonden. Allen waren geboren of hadden langdurig gewerkt in een tropisch land. Bij 4 van deze 10 patiënten verdween de urticaria na behandeling. Bij 3 patiënten kon de urticaria gerelateerd worden aan een interne ziekte (M. Sjögren, systemische lupus erythematodes, paraproteinaemie). Bij 24 patiënten werd een combinatie gevonden van fysische oorzaken en idiopathische urticaria.

Hoofdstuk 5: Een voorbeeld van een geneesmiddel-bijwerking: Twee patiënten met chronisch angio-oedeem ten gevolge van angiotensin-converting enzyme-remmers.

In het patiënten cohort, bestaande uit 220 opeenvolgende patiënten met chronische urticaria of angio-oedeem, waren twee patiënten bij wie een bijwerking van een geneesmiddel uit de groep 'angiotensin-converting enzyme (ACE) inhibitors' werd gevonden. Dat geneesmiddelen uit deze groep, zoals bijna alle geneesmiddelen, urticaria en angio-oedeem kunnen veroorzaken is bekend sinds kort na de introductie van deze geneesmiddelen, in het begin van de jaren tachtig. Aanvankelijk werden alleen aanvallen van angio-oedeem beschreven, die vlak na het starten van het nieuwe geneesmiddel waren begonnen. Later werd duidelijk dat, waarschijnlijk in ongeveer 20% van de gevallen, de klachten ook pas 6 weken na het starten van de nieuwe therapie konden beginnen. Bij één van de in dit hoofdstuk beschreven patiënten ontstond een verergering van reeds bestaande klachten door het gebruik van een angiotensin-converting enzyme inhibitor. Bij de andere beschreven patiënt ontstonden de klachten pas een jaar na het starten van het nieuwe geneesmiddel. Bij deze patiënt werd later tevens een maligniteit gevonden. Er bestond echter geen oorzakelijk verband tussen het angio-oedeem en de maligniteit, omdat na het staken van het 'nieuwe' geneesmiddel de klachten verdwenen.

Hoofdstuk 6: Implementatie, validatie en verbetering van de (voorlopige) richtlijn voor diagnostiek bij patiënten met chronische urticaria

In deze retrospectieve studie werd het nut en het gebruik van een klinische richtlijn voor diagnostiek bij patiënten met chronische urticaria onderzocht bij 130 opeenvolgende patiënten die de polikliniek Dermatologie van het Academisch Medisch Centrum te Amsterdam bezochten. De richtlijn adviseerde om bij het eerste bezoek van een patiënt aan de polikliniek de volgende handelingen te verrichten: anamnese-gesprek voeren, vragenlijst meegeven, huidafwijkingen onderzoeken, dermografie-test verrichten, beperkt lab-onderzoek doen (geen uitgebreid routine laboratorium onderzoek), en een niet-sederend antihistaminicum voorschrijven. Voor het tweede bezoek werd geadviseerd om opnieuw een anamnese-gesprek te voeren, de vragen lijst met de patiënt door te nemen, verdachte oorzaken d.m.v. laboratorium-onderzoek of provocatieproeven te bevestigen, alle verdachte geneesmiddelen te stoppen of te vervangen, (nogmaals) te informeren naar het gebruik van vrij verkrijgbare geneesmiddelen (vooral pijnstillers) en opnieuw een antihistaminicum voor te schrijven, zonodig een ander type.

In dit onderzoek werd geëvalueerd hoe vaak de vragenlijst was gebruikt, hoe vaak routinematig uitgebreid laboratorium-onderzoek tijdens het eerste bezoek was aangevraagd, en op grond van welke informatie (anamnese, vragenlijst, laboratorium-onderzoek, of provocatie proeven) de uiteindelijke oorzaak van de chronische urticaria werd gevonden. Met deze retrospectieve studie valideerden wij onze eerdere prospectieve studie (zie hoofdstuk 3) door de aantallen gevonden diagnoses in beide studies met elkaar te vergelijken. De aantallen gevonden oorzaken waren vrijwel identiek, ook in de verschillende subgroepen. In de retrospectieve studie werd een oorzaak gevonden bij 58 van de 130 patiënten (45%). Bij 50 van de 58 patiënten (86%) werd de oorzaak gevonden op basis van de eerste anamnese en in de resterende 8 patiënten werd de oorzaak gevonden met behulp van de vragenlijst. Bij 38 van de 130 patiënten was de vragenlijst niet in de status van de patiënt aanwezig (bij 12 van de 38 was de vragenlijst wel uitgereikt, maar niet terug gestuurd door de patiënt). Bij 89 patiënten (68%) werd toch uitgebreider laboratorium onderzoek aangevraagd, zonder dat daarvoor duidelijke redenen aanwezig waren in de anamnese of in de

vragenlijst. Wel werd er beduidend minder laboratoriumonderzoek aangevraagd dan in de periode voor de introductie van de richtlijn. In geen van de gevallen werd door dit uitgebreider laboratorium-onderzoek een extra oorzaak van chronische urticaria gevonden. Deze studie heeft een bijdrage geleverd aan het nog verder verminderen van het al zeer beperkte laboratorium-onderzoek dat wij bij patiënten met chronische idiopathische urticaria adviseren, tot alleen nog de bezinking, het aantal leukocyten en de leukocytendifferentiatie. Deze studie liet ook zien dat de richtlijn voor diagnostiek bij chronische urticaria redelijk succesvol kon worden geïntroduceerd in de klinische praktijk en dat m.b.v deze richtlijn de meeste geïdentificeerde oorzaken werden gevonden m.b.v de anamnese.

Hoofdstuk 7: Richtlijnen voor laboratoriumdiagnostiek bij chronische urticaria: een systematisch literatuuronderzoek.

Dit hoofdstuk beschrijft de resultaten van een systematische literatuur studie. Het doel van deze studie was drieledig: 1) analyseren hoe er in de beschikbare studies wordt geoordeeld over de waarde van uitgebreid laboratoriumonderzoek, 2) het zoeken naar verklaringen voor de grote variaties in het aantal en de aard van de gevonden onderliggende oorzaken voor chronische urticaria in de verschillende studies, en 3) het verder ontwikkelen en beter onderbouwen van de uiteindelijke richtlijn met gegevens uit het systematische literatuur onderzoek en de relevante overige literatuur. Hiervoor werden vier elektronische data-bestanden en een groot aantal artikelen en boeken over bestaande richtlijnen bestudeerd, en van alle referenties uit de al geselecteerde artikelen werd nagegaan of zij ook in het literatuur onderzoek konden worden opgenomen. Een artikel werd geïncludeerd in het literatuuronderzoek als er een studie in werd beschreven met tenminste 50 patiënten en als deze studie gepubliceerd was na 1930. Er werden 29 studies in het literatuuronderzoek opgenomen. Deze 29 studies beschreven in totaal 6462 patiënten. Van deze studies werden de volgende gegevens verzameld: jaar van de publicatie; studie opzet; aantal, leeftijd en geslacht van de geïncludeerde patiënten; inclusie- en exclusie-criteria van de studies; percentage en type gevonden oorzaken; aantal uitgevoerde laboratoriumtesten; duur van de follow-up periode en de conclusie van elk artikel. Er werd geen samenhang gevonden tussen

het aantal uitgevoerde laboratoriumtesten, het publicatiejaar en de studie opzet (prospectieve of retrospectieve opzet). Bij veel studies was echter de verificatie-validatie procedure (het op een of andere manier bevestigen dat de vermoede onderliggende oorzaak ook werkelijk de oorzaak was) van de gevonden oorzaken slecht uitgevoerd of niet beschreven. Hierdoor is de waarde van de gegeven 'evidence' beperkt. Ondanks dit feit komen veel studies tot overeenkomstige conclusies, namelijk dat het routinematig uitvoeren van laboratoriumtesten niet zinvol is, dat alleen laboratoriumtesten gebaseerd op de anamnese zinvol zijn en dat de anamnese het belangrijkste instrument is om een oorzaak voor chronische urticaria te vinden.

Op grond van de gegevens uit het literatuuronderzoek, enkele andere relevante artikelen, alsmede onze eigen onderzoekservaringen, is een beknopte 'flow-chart' ontwikkeld voor het beleid bij chronische urticaria (zie volgende pagina). Om de 'flow-chart' beknopt te houden zijn voor alle aanbevelingen korte omschrijvingen gebruikt i.p.v volledige zinnen.

CONCLUSIES

- Volgens de principes van 'evidence-based' medicine is het alleen zinvol om testen uit te voeren die een bijdrage leveren aan het diagnostisch proces.

- Routinematig uitvoeren van screenend laboratoriumonderzoek of ongericht aanvragen van laboratorium onderzoek bij patiënten met chronische urticaria bevordert het vinden van onderliggende oorzaken nauwelijks.

- Het beste instrument om onderliggende oorzaken te vinden bij patiënten met chronische urticaria is het afnemen van een gedetailleerde anamnese, bijvoorbeeld met behulp van een vragenlijst.

Klinische richtlijn voor de diagnostiek bij chronische urticaria en/of angio-oedeem

1e bezoek:

- anamnese
- vragenlijst meegeven
- onderzoek van de huidafwijkingen, als deze aanwezig zijn
- dermografie-test, liefst zonder antihistaminicum
- geen routinematig uitvoeren van uitgebreid laboratorium-onderzoek
- beperkt lab bij idiopathische urticaria: BSE, leukocyten en differentiatie
- voorschrijven van een niet-sederend antihistaminicum
- vermijden van aspirine, NSAID's en codeïne
- vermijden van een te warme omgeving, stress, druk op de huid en alcohol
- informatie over het goedaardig karakter en natuurlijk beloop geven
- informatie geven dat waarschijnlijk geen oorzaak zal worden gevonden.

2e bezoek:

- anamnese
- vragenlijst met de patiënt bespreken
- verdachte oorzaken d.m.v. lab-onderzoek of provocatie proeven bevestigen of uitsluiten
- verdachte geneesmiddelen stoppen of vervangen
- (nogmaals) informeren naar het gebruik van 'over the counter drugs'
- voorschrijven van een niet-sederend of zonodig ander type antihistaminicum.

3e bezoek en vervolgbezoeken:

- anamnese
- urticaria-dagboek (relatie met bepaalde gebeurtenissen of medicijnen)
- eliminatie-dieet of 'oral food challenge'
- voorschrijven van een niet-sederend of zonodig ander type antihistaminicum.

Vragenlijst voor patiënten met chronische urticaria of angio-oedeem

Uw naam: ..... man ❒ / vrouw ❒

Geboortedatum: ...../...../..... Datum: ...../...../.....

Kruis de hokjes aan die van toepassing zijn en beantwoord de vragen:

1. Sinds hoelang heeft u last van galbulten (urticaria, netelroos) en/of dieper in de huid liggende zwellingen (angio-oedeem)? (a.u.b. de datum, of de maand, en het jaar invullen wanneer het begonnen is)

   ❒ Ik heb galbulten (of zwellingen) sinds: .....
   ❒ Ik heb alleen galbulten
   ❒ Ik heb alleen diepere zwellingen
   ❒ Ik heb beide

2. Hoe vaak heeft u gemiddeld een aanval van galbulten of angio-oedeem ?

   ❒ Ik heb galbulten: ❒ continu ❒ elke dag
   ❒ een paar keer per week
   ❒ een paar keer per maand
   ❒ anders, namelijk: .....

   ❒ Ik heb angio-oedeem: ❒ continu ❒ elke dag
   ❒ een paar keer per week
   ❒ een paar keer per maand
   ❒ anders, namelijk: .....

3. Hoelang duurt het voordat één afzonderlijk bultje weer wegtrekt ?

   ..... uur

   (U kunt dit nagaan door een nieuw ontstane galbult met viltstift om te trekken en op te letten wanneer deze niet meer verheven is).

   Hoelang duurt het voordat een dieper liggende zwelling (b.v. rond de ogen of de mond) weer wegtrekt ?

   ..... uur

4. Heeft u ooit een galbult of zwelling gehad die **langer dan 24 uur** op dezelfde plek aanwezig bleef? Ja ❒ / Nee ❒

   Zo ja, waar ? .....

5. Hoe groot worden de galbulten gemiddeld bij u ?

   ..... millimeter ..... centimeter

6. Op welk lichaamsdeel heeft u meestal last van galbulten of angio-oedeem ?

   ❒ Ik heb galbulten:
   - ❒ verspreid over het gehele lichaam
   - ❒ vooral op armen en/of benen
   - ❒ op aan zon blootgestelde delen
   - ❒ op drukplaatsen (b.v. onder riem of BH-bandje)
   - ❒ elders op het lichaam, namelijk:

     .....

   ❒ Ik heb zwellingen
   - ❒ van de oogleden
   - ❒ van de lippen
   - ❒ aan handen en/of vingers van de tong en/of de keel
   - ❒ elders op het lichaam, namelijk:

     .....

7. Zijn er ooit blauw, paars, of bruinachtig verkleurde plekken of rode puntjes achtergebleven op de plaats waar de galbulten zaten ? Ja ❒ / Nee ❒

8. Jeuken de gebieden met galbulten of het angio-oedeem ? Ja ❒ / Nee ❒

9. Heeft u de huid kapot gekrabd op de jeukende plekken ? Ja ❒ / Nee ❒
   Is de huid op die plekken ook droog of schilferend ? Ja ❒ / Nee ❒

10. Voelt u nog een andere sensatie in de aangedane huid ? Ja ❒ / Nee ❒

    Zo ja, hoe zou u deze sensatie beschrijven?

    ❒ pijnlijk ❒ brandend ❒ gespannen aanvoelend
    ❒ nog anders, namelijk:

    .....

11. Er zijn een aantal klachten (hieronder genoemd) die **tijdens of direct na een aanval** van galbulten of angio-oedeem kunnen optreden.
Als u dit soort klachten heeft gehad, kruis dit dan aan:

❒ loopneus ❒ tranende ogen
❒ heesheid ❒ dikke tong ❒ gezwollen verhemelte of keelholte
❒ astma (piepende ademhaling, kortademigheid)
❒ benauwdheid door zwelling van de keelholte of luchtpijp
❒ hoofdpijn ❒ duizeligheid ❒ flauwvallen
❒ buikpijn ❒ buikkrampen ❒ misselijkheid
❒ overgeven ❒ diarree
❒ koorts ❒ koude rillingen ❒ vermoeidheid

12. Op welk moment van de dag heeft u meestal last ?

❒ 's nachts ❒ ik wordt 's nachts wakker van de jeuk
❒ 's ochtends ❒ direkt bij het opstaan
❒ 's middags ❒ op willekeurige momenten
❒ 's avonds ❒ direkt na thuiskomen

13. Wanneer heeft u meer last van urticaria of angio-oedeem:

❒ binnenshuis meer last ❒ buitenshuis meer last ❒ geen verschil
❒ op het werk meer last ❒ op het werk minder last ❒ geen verschil
❒ in weekend meer last ❒ doordeweeks meer last ❒ geen verschil
❒ op vakantie meer last ❒ op vakantie minder last ❒ geen verschil

14. Zijn uw klachten begonnen na een bepaalde ziekte of ontsteking ?
Ja ❒ / Nee ❒
(B.v. tand- of kiesontstekingen, keel-, neus- of oor-infecties, huidinfecties, worminfecties, longontsteking, blaasontsteking, of andere ontstekingen of ziekten). Zo ja, welke ?

.....

Heeft u toen geneesmiddelen voorgeschreven gekregen of zelf gebruikt ?
(zo ja vul in bij vraag 33)

15. Zijn uw klachten begonnen na onderstaande gebeurtenissen ?

❒ na het maken van röntgenfoto's met behulp van contrastvloeistof of andere contrastmiddelen ?
❒ na het gebruik van bepaalde medicijnen, of na injecties of infusies ?
Zo ja, welke:

.....

❒ Andere bijzondere gebeurtenissen? Zo ja, welke:

.....

16. Is er een verband tussen uw klachten en het seizoen/weersomstandigheden ? Ja ❒ / Nee ❒
    Zo ja, wanneer verergeren uw klachten ?

    .....

17. Bent u **ooit** in een tropisch gebied geweest ? Ja ❒ / Nee ❒
    Zo ja, wanneer en waar :

    .....

Soms treden aanvallen van galbulten en/of angio-oedeem op in bepaalde omstandigheden. Wij hebben hieronder een aantal voorbeelden genoemd. Als bij u een aanval optrad in **één of meerdere** van de genoemde omstandigheden wilt u deze dan aankruisen:

18. Treden de galbulten op ongeveer **binnen 15 minuten** na:

    ❒ wrijven of krabben over de huid ?
    ❒ na het dragen van strakke kleding ?
    ❒ ergens tegenaan leunen (b.v. tegen de harde rugleuning van een stoel)?

19. Treden de galbulten / angio-oedeem op als er iets geweest is dat grote druk heeft uitgeoefend op de huid (meestal ontstaan de galbulten / zwellingen dan niet meteen maar **6 tot 12 uur later**) ?
    Als dit bij u het geval is, bij wat voor werkzaamheden of omstandigheden treedt dit dan op ?

    ❒ langdurig staan of lang lopen ? ❒ langdurig zitten of fietsen ?
    ❒ werken op knieën ?
    ❒ werken met gereedschap ? ❒ zware lasten dragen ?
    ❒ andere omstandigheden, zo ja welke:

    .....

20. Treden de galbulten / angio-oedeem meestal op:

    ❒ in koude omgeving (bv. sneeuw, regen, wind) ?
    ❒ bij contact met koude voorwerpen (bv. ijs eten, aanraken koud fietsstuur)
    ❒ in koud water (bv. douche of zwembad) of ijsblokjes ?
    ❒ bij de overgang van koude naar warmte of omgekeerd ?

21. Treden de galbulten / angio-oedeem meestal op:

    ❒ in warme omgeving ? ❒ bij inspanning of tijdens sport ?
    ❒ bij opwinding, schrik of stress ? ❒ tijdens een warme douche of bad ?
    ❒ bij transpireren ? ❒ tijdens of na sex ?
    ❒ bij contact met warme voorwerpen ?
    ❒ bij sterk gekruid eten of warme koffie drinken ?

22. Zijn de galbulten of het angio-oedeem ontstaan na blootstelling aan (zon)licht ? Ja ❒ / Nee ❒

23. Krijgt u wel eens witte, blauwe, pijnlijke of gevoelloze vingers door koude ? Ja ❒ / Nee ❒

24. Denkt u dat uw klachten verergeren onder invloed van:

❒ werkstress of andere stress ? ❒ zenuwachtigheid ?
❒ problemen ?

.....

25. Kreeg u ooit galbulten, jeuk of een rode huid na direct huidcontact met:

❒ wol of andere kleding ? ❒ dieren of planten ?
❒ cosmetica of parfum ? ❒ genees- of voedingsmiddelen ?
❒ chemische produkten ?
❒ andere produkten ? Zo ja, welke ?

.....

26. Is er in uw naaste familie iemand die ook galbulten of angio-oedeem heeft ? Zo ja, wie ? Ja ❒ / Nee ❒

.....

27. Van welke van de onderstaande klachten heeft u last of ooit last gehad:

❒ hooikoorts, niesbuien in huis, loopneus (allergische rhinitis) ?
❒ tranende ogen (conjunctivitis) ?
❒ benauwdheid, piepende ademhaling (astmatische klachten) ?
❒ eczeem (dauwworm als baby of atopisch eczeem op jonge leeftijd) ?

28. Komen in uw naaste familie deze allergische klachten voor ?Ja ❒ / Nee ❒ (dauwworm, atopisch oftewel constitutioneel eczeem, andere vormen van eczeem, hooikoorts, of astma) ? Zo ja, welke van deze klachten en bij wie ?

.....

.....

29. Is bij u ooit een allergie voor bepaalde voedings-middelen vastgesteld ? Ja ❒ / Nee ❒
Zo ja, voor welke producten, en hoe is dit vastgesteld ?

.....

.....

30. Denkt u zelf dat uw klachten verergeren door bepaalde voedingsmiddelen ? Ja ❒ / Nee ❒

(b.v. vis / mosselen / garnalen / kreeft / peulvruchten / selderij / aardbeien / appels / peren / banaan / pinda's / noten / soja(bonen) / kaas / alcohol / chocolade / (kinine-houdende) frisdrank / eieren- of melkprodukten / ijs / voeding uit blik / diepvriesmaaltijd / kunstmatige zoetstoffen / overige)
Zo ja, bij welke voedingsmiddelen ?

.....

31. Heeft u ooit na het eten van één van bovengenoemd(e) voedingsmiddel(en) één van onderstaande verschijnselen waargenomen ? Ja ❒ / Nee ❒

❒ tintelend of brandend gevoel in de tong of op de lippen ?
❒ zwelling van de tong of lippen ?
❒ buikkrampen en/of diarree ?

32. Heeft u ooit een dieet gevolgd om van uw klachten af te komen ? Ja ❒ / Nee ❒

Zo ja, heeft dit dieet de klachten verminderd ? Ja ❒ / Nee ❒
Is het dieet door een diëtist voorgeschreven ? Ja ❒ / Nee ❒
Heeft u het dieet strikt gehouden ? Ja ❒ / Nee ❒
Wat was dit voor dieet en hoelang heeft u dit dieet gevolgd ?

.....

33. Heeft u huisdieren ? Ja ❒ / Nee ❒
Zo ja, welke en sinds wanneer ?

.....

34. Komt u veel in contact met één van onderstaande stoffen ? Ja ❒ / Nee ❒

❒ planten / bloemen ?
❒ cosmetica ?
❒ schoonmaak- en wasmiddelen ?
❒ verf / lijm / rubber ?
❒ andere bijzondere stoffen, zo ja welke ?

.....

35. Wat is uw beroep of wat voor werkzaamheden verricht u op het ogenblik ?

.....

36. Wat zijn uw hobby's ?

.....

37. Komt u (b.v. door uw beroep) veel in contact met chemische of industriële produkten en/of bestaat er kans op het inademen van deze produkten ? (b.v. vloeistoffen / dampen / nevels / stofwolken ?) Ja ❒ / Nee ❒
Zo ja, om welke produkten gaat het ?

.....

38. Heeft u metalen voorwerpen in uw lichaam ? Ja ❒ / Nee ❒
(bv. pacemakers, gewrichtsprothesen, metalen platen of schroeven, metaal in uw mondholte) ? Zo ja, welke ?

.....

39. Alleen voor vrouwen: gebruikt u de anticonceptie pil? Ja ❒ / Nee ❒
Zo ja, welke, en sinds hoelang ?

.....

Heeft u meer klachten vlak voor de menstruatie ? Ja ❒ / Nee ❒

40. Wilt u hieronder zo nauwkeurig mogelijk noteren welke geneesmiddelen u in het afgelopen jaar gebruikt heeft **voor uw galbulten of angio-oedeem** ?

naam geneesmiddel:	hoeveelheid per dag:	in welke periode:
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

41. Indien u antihistaminica voor uw galbulten of angio-oedeem heeft gebruikt, hoeveel dagen geleden heeft u de laatste ingenomen, en welke was dat ?

.....

42. Wilt u hieronder zo nauwkeurig mogelijk **alle andere geneesmiddelen opschrijven die u het afgelopen jaar heeft gekregen** voor andere aandoeningen (inclusief injecties of inentingen) ?
(Met name antibiotica, pijnstillers en ontstekingsremmende middelen, slaapmiddelen, kalmerings-middelen, psychofarmaca, anti-epileptica, laxeermiddelen, geneesmiddelen tegen gewrichtspijn of griep, anti-hoest tabletten, hormoonpreparaten (anticonceptiepil, oestrogenen, insuline), vitamine-tabletten, homeopathische middelen, drugs, overige)?

NB: vraag uw apotheek om een uitdraai van het afgelopen jaar.

naam geneesmiddel:	hoeveelheid per dag:	in welke periode:
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

43. Bent u allergisch voor bepaalde geneesmiddelen ? Ja ❒ / Nee ❒
Zo ja, voor welke, en waaruit is dat gebleken ?

.....

44. Bent u ooit in een ziekenhuis opgenomen of onder specialistische behandeling geweest ? Zo ja, voor welke klachten ? Ja ❒ / Nee ❒

.....

.....

45. Heeft u op het ogenblik nog andere lichamelijke klachten ? Ja ❒ / Nee ❒

.....

.....

46. Heeft u zelf nog ideeën of opmerkingen over een mogelijke oorzaak of heeft u een relatie kunnen ontdekken met bepaalde omstandigheden of een bepaalde omgeving ? Ja ❒ / Nee ❒

.....

.....

.....

.....

.....

Vragenlijst over uw algemene gezondheid. Heeft u in de periode 8 weken voorafgaande aan het ontstaan van de galbulten en/of angio-oedeem tot op heden één van de onderstaande klachten gehad ?

a.	Voelt u zich moe of slap ?	Ja ❒ / Nee ❒
b.	Hebt u nu koorts of hebt u dit onlangs gehad ?	Ja ❒ / Nee ❒
	Zoja, hoeveel: ..... °C ?	
c.	Bent u de laatste tijd afgevallen ?	Ja ❒ / Nee ❒
	Zoja, hoeveel: ..... Kg ?	
d.	Heeft u last van veel hoesten ?	Ja ❒ / Nee ❒
	veel slijm of bloed opgeven ?	Ja ❒ / Nee ❒
	kortademig bij inspanning ?	Ja ❒ / Nee ❒
	hartkloppingen ?	Ja ❒ / Nee ❒
	regelmatig 's avonds dikke enkels ?	Ja ❒ / Nee ❒
	pijn in de hartstreek ?	Ja ❒ / Nee ❒
e.	Heeft u last van buikpijn ?	Ja ❒ / Nee ❒
	misselijkheid of overgeven ?	Ja ❒ / Nee ❒
	vaak diarree of verstopping ?	Ja ❒ / Nee ❒
	bloed bij de ontlasting ?	Ja ❒ / Nee ❒
	zwarte kleur van de ontlasting ?	Ja ❒ / Nee ❒
	hoe vaak heeft u ontlasting ?	
	..... x per week ?	
f.	Heeft u vaak last van hoofdpijn ?	Ja ❒ / Nee ❒
	kiespijn of pijn in de mond ?	Ja ❒ / Nee ❒
	keelpijn ?	Ja ❒ / Nee ❒
	oorpijn ?	Ja ❒ / Nee ❒
	neusverstoptheid ?	Ja ❒ / Nee ❒
	verkoudheid ?	Ja ❒ / Nee ❒
	neus-amandelontsteking?	Ja ❒ / Nee ❒
	neusbijholte ontsteking ?	Ja ❒ / Nee ❒
g.	Heeft u regelmatig last van spierpijn ?	Ja ❒ / Nee ❒
h.	Heeft u regelmatig last van gewrichtspijn ?	Ja ❒ / Nee ❒
i.	Heeft u ooit een nierziekte gehad ?	Ja ❒ / Nee ❒
j.	Heeft u ooit schildklierziekten gehad ?	Ja ❒ / Nee ❒
k.	Heeft u suikerziekte ?	Ja ❒ / Nee ❒
l.	Heeft u ooit een bloedtransfusie gehad ?	Ja ❒ / Nee ❒
m.	Heeft u ooit geelzucht gehad ?	Ja ❒ / Nee ❒
n.	Heeft u ooit leverziekten gehad ?	Ja ❒ / Nee ❒

o. Heeft u ooit de ziekte van Pfeiffer gehad ? Ja ❒ / Nee ❒

p. Heeft u ooit reuma, of SLE gehad ? Ja ❒ / Nee ❒

q. Heeft u ooit geslachtsziekten gehad ? Ja ❒ / Nee ❒

r. Heeft u ooit kwaadaardige ziekten gehad ? Ja ❒ / Nee ❒

s. Rookt u (Zo ja, hoeveel) ? Ja ❒ / Nee ❒
..... Per .....

t. Gebruikt u alcohol (Zo ja, hoeveel) ? Ja ❒ / Nee ❒
..... Per .....

u. Gebruikt u drugs (Zo ja, welke) ? Ja ❒ / Nee ❒
.....

v. Heeft u onlangs een blaasontsteking gehad ? Ja ❒ / Nee ❒

w. **Alleen voor vrouwen:** heeft u last van een verhoogde of abnormale vaginale afscheiding ? Ja ❒ / Nee ❒

x. **Alleen voor mannen:** heeft u last van prostaatklachten ? Ja ❒ / Nee ❒

y. Heeft u nog andere ziekten, nog niet genoemd ? Ja ❒ / Nee ❒
Zo ja, welke ?

.....

.....

.....

.....

z. Wanneer bent u voor het laatst bij uw tandarts geweest ?

.....

Wat is de naam en het telefoonnummer van uw tandarts ?

.....

Chapter 10

Bibliografie en dankwoord

BIBLIOGRAFIE

Dutrée-Meulenberg ROGM, Kozel MMA, van Joost Th. Burning mouth syndrome: A possible etiologic role for local contact hypersensitivity. J Am Acad Dermatol 1992;26:935-940.

van Joost Th, Kozel MMA, Tank B, Troost RJJ, Prens EP. Cyclosporine in atopic dermatitis. Modulation in the expression of immunologic markers in lesional skin. J Am Acad Dermatol 1992;27:922-928.

Troost RJJ, Kozel MMA, van Helden-Meeuwsen CG, van Joost Th, Mulder PGH, Benner R, Prens EP. Hyposensization in nickel allergic contact dermatitis: Clinical and immunologic monitoring. J Am Acad Dermatol 1995;32:576-583.

Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related long-term therapy with angiotensin-converting enzyme inhibitors in two patients. Clin Exp Dermatol 1995;20:60-61.

Mekkes JR, Kozel MMA. New diagnostic and therapeutic possibilities in chronic idiopathic urticaria. Neth J Medicine 1998; 53:139-140.

Kozel MMA, Mekkes JR, Bos JD. Ernstige geneesmiddelbijwerking op basis van minocycline. Ned Tijdschr Dermatol & Venereol 1998;8:261-263.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The Effectiveness of a History-Based Diagnostic Approach in Chronic Urticaria and Angioedema. Arch Dermatol 1998;134:1575-1580.

Mekkes JR, Kozel MMA, Bossuyt PMM, Bos JD. Een vragenlijst voor patiënten met chronische urticaria: gestructureerde anamnese als basis voor diagnostisch beleid. Ned Tijdschr Geneeskd 1999;143:1748-1749.

Spuls PhI, Kozel MMA, Mekkes JR, Hoekzema R, Baan J, van Lieshout JJ, Brinkhuis M, van der Wal AC. Panniculitis geassocieerd met een kleincellig bronchuscarcinoom. Ned Tijdschr Dermatol & Venereol 2000;10:135-137.

Kozel MMA, Chin-A-Lien RAM, Faber WR. Gedissemineerde infectie met Mycobacterium asiaticum. Ned Tijdschr Geneeskd 2000;144:2432-2433.

Kozel MMA, Krijnen RMA, Blom DJM, Sillevis Smitt JH. AHOI-syndroom (Acute Haemorrhagic Oedema of Infancy-syndroom). Ned Tijdschr Dermatol & Venereol; 2000;10:200-201.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Diagnostisch beleid bij chronische urticaria patiënten. Ned Tijdschr Dermatol & Venereol; 2000;10: 200-205.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Urticaria: een zinvolle benadering. Ned Tijdschr Dermatol & Venereol; 2000;10:344-346.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural course of physical and chronic urticaria and/or angioedema in 220 patients. J Am Acad Dermatol 2001; 45:387-391.

Vermeer MH, Stoof TJ, Kozel MMA, Blom DJM, Nieboer C, Sillevis Smitt JH. Acuut hemorrhagisch oedeem van de kinderleeftijd en het onderscheid met Henoch-Schönlein purpura. Ned Tijdschr Geneeskd 2001;145:834-839.

Sillevis Smitt JH, Kozel MMA. Pathofysiologie van urticaria en urticariële vasculitis. In: de Waard-van der Spek FB, Oranje AP (eds). Diagnostiek en therapie in de kinderdermatologie. 8e cursus van de Nederlands Belgische Vereniging voor Kinderdermatologie. De Wezenlanden, Zwolle, 2001, 83-90.

Abstracts:

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a structured diagnostic approach in a prospective aethiological study of 218 patients with chronic urticaria or angioedema. Clin Exp Dermatol 1995;20:270.

Mekkes JR, Kozel MMA, Bossuyt PMM, Bos JD. Reduction of laboratory investigations by introducing a standard questionnaire. Clin Exp Dermatol 1995; 20:269.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Anamnese bepalend in diagnostiek bij patiënten met chronische urticaria en angio-oedeem. Ned Tijdschr Geneeskd 1996;140:1154.

Kozel MMA, Sillevis Smitt JH, Caron HN, Muntendam J. Syndroom van Rothmund-Thomson en bottumoren. Ned Tijdschr Geneeskd 1996;140:1156.

Köycü B, Kozel MMA, Meinardi MMHM, Bos JD. No association between Helicobacter pylori and chronic urticaria. Eur J Acad Derma Venereol 1998; 11:S179.

Sillevis Smitt JH, Kozel MMA. Etiologic factors of urticaria in the paediatric population. Sixth Congress of the European Society for Pediatric Dermatology & Third International Days on Pediatric Dermatology 1999. Rome, Italië. September 13-18, 1999.

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural course of chronic urticaria and angioedema in 220 patients. Eur J Acad Derm Venereol; 1999:S122.

Stellingen behorende bij het proefschrift:

"Guidelines for the diagnosis of chronic urticaria and angio-edema"

1. Volgens de principes van "evidence-based" medicine is het alleen zinvol om testen uit te voeren die een bijdrage leveren aan het diagnostisch proces (dit proefschrift).

2. Routinematig uitvoeren van screenend laboratoriumonderzoek of ongericht aanvragen van laboratoriumonderzoek bij patiënten met chronische urticaria bevordert het vinden van onderliggende oorzaken nauwelijks (dit proefschrift).

3. Het beste instrument om onderliggende oorzaken bij patiënten met chronische urticaria te vinden is het afnemen van een gedetailleerde anamnese, bijvoorbeeld met behulp van een vragenlijst (dit proefschrift).

4. Performing studies on the value of laboratory tests in chronic urticaria is like the reinvention of the wheal (one of the reviewers).

5. Guidelines are not self-implementing (R. Grol, Quality in Health Care 1992; 1: 184-191).

6. Wie schrijft die blijft, wie kopieert die promoveert.

7. Passief sporten bestaat niet.

8. Follow-up onderzoek wordt ernstig belemmerd door geheime telefoonnummers.

9. Gott erhalte uns die Freundschaft. Man möchte beinah glauben, man sei nicht allein (Kurt Tucholsky, Pause auf dem Töpfchen, 1930).

10. Die Basis jeder gesunden Ordnung ist ein großer Papierkorb (Kurt Tucholsky, Das kann man noch gebrauchen - !, 1930).

11. Denn es ist ausgezeichneter Menschen unwürdig, gleich Sklaven Stunden zu verlieren mit Berechnungen (G.W. Leibniz, 1646 - 1716).

Martina Kozel, 30 november 2001.