

## CONTINUING MEDICAL EDUCATION

# Urticaria: Its History-Based Diagnosis and Etiologically Oriented Treatment

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## SUMMARY

**Introduction:** The term „urticaria“ refers to any of a group of distinct skin conditions that are characterized by itchy, wheal-and-flare skin reactions (hives). In spontaneous urticaria, the most common type, the hives seem to arise without provocation.

**Methods:** Selective review of the literature, including current guidelines.

**Results:** Spontaneous urticaria is divided into acute (lasting less than six weeks) and chronic types. The pathognomonic itching, hives, and angioedema arise by the same mechanism – cutaneous mast cell activation and release of histamin and other mediators of inflammation – in both acute and chronic urticaria, but these two disorders have different etiological profiles. The underlying cause of acute urticaria cannot be identified in about half of all cases. Chronic urticaria, which is much rarer, is usually caused by autoreactivity, chronic infection, or intolerance to food additives. If the condition persists after the underlying cause has been treated or eliminated, non-sedating antihistamines are the agents of first choice for symptomatic treatment.

**Discussion:** Unlike acute urticaria, which is self-limited and should be treated symptomatically, chronic urticaria should be treated by the identification and elimination of underlying causes, which is usually curative.

Dtsch Arztebl Int 2008; 105(25): 458–66  
DOI: 10.3238/arztebl.2008.0458

**Key words:** acute urticaria, chronic urticaria, hives, mast cells, antihistamines

The most practical and most commonly used classification of urticaria ("hives") is based on the duration of its manifestations: acute urticaria (AU) resolves within six weeks, while chronic urticaria (CU) lasts longer than six weeks, and often for many years; CU may recur or persist steadily for decades (1, 2).

Acute urticaria is between ten and one hundred times more common than chronic urticaria. In both types of "spontaneous" urticaria, the same typical manifestations (itching wheals and/or angioedema), appear at unpredictable times, often in sudden episodes.

As a rule, neither the patient nor the treating physician can determine at first glance how and when an episode of urticaria has been induced ("spontaneous" urticaria). Most patients with certain other types of urticaria, however, know what factors induce their symptoms: physically induced urticaria, for example, might be brought about by cold, rubbing, or sunlight (*box 1*). Patients who know what factors induce their symptoms can prevent attacks by avoiding these factors. Inducible urticaria is said to be only one-third to one-half as common as spontaneous urticaria.

This article is intended to cover the following aspects of urticaria:

- the importance of directed history-taking for the differentiation of physically induced and other forms of urticaria from "spontaneous" urticaria,
- the systematic etiological work-up of urticaria of initially unknown origin,
- the principles of etiologically oriented and symptomatic treatment.

The authors have based their discussion of these topics on a selective review of the literature, on their own research, and on sources known to them from their clinical and scientific activity in the field, as well as on guidelines in whose formulation they participated (11, 20).

## Urticaria

Acute urticaria heals within six weeks; chronic urticaria lasts longer, often persisting or recurring over the course of decades.

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**Acute and chronic urticaria: clinical manifestations and pathogenesis**

Strongly itching cutaneous wheals that can arise on any area of the body are the typical manifestation of both acute and chronic urticaria (figures 1 and 2); some patients also have angioedema (figure 3). The wheals and the itch arise through the activation of subepidermal mast cells, resulting in degranulation with the release of histamine and other inflammatory mediators. This initially produces vasodilatation and thereby increased perfusion of the skin, causing erythema; there follows an increase in vascular permeability that causes intracutaneous edema, i.e., wheal formation. The activation of cutaneous nerves produces itch. These nerves, in turn, release further inflammatory mediators, such as neuropeptides, at the site of wheal formation. This causes skin erythema in the area surrounding the wheal, so-called reflex erythema (figure 1). In both acute and chronic urticaria, these cutaneous manifestations generally resolve within a few hours, and within 24 hours at most. If individual wheals should persist for more than 24 hours (a simple test: draw the perimeter of a wheal with a pen), then urticarial vasculitis should be considered in the differential diagnosis and ruled in or out with a tissue biopsy. Some patients with urticaria complain not only of the cutaneous manifestations but also of systemic problems such as headache, joint pain, or gastrointestinal symptoms. These extracutaneous manifestations can be explained as systemic effects of the inflammatory mediators (primarily histamine) released by the cutaneous mast cells, or else as the local effects of the activation and degranulation of extracutaneous mast cell populations (3).

**Acute urticaria: causes, diagnostic evaluation, and treatment**

The lifetime prevalence of acute urticaria lies between 10% and 25% (4). This is thus one of the more common medical conditions known to man. In most cases, the symptoms are quite pronounced at first but then usually resolve within a few days or weeks. Most patients, therefore, speak of their ailment as occurring in "attacks" which they often attribute to an immediately preceding event, e.g., a stressful situation or the consumption of an unusual food or beverage. In fact, however, such precipitating factors play no role in the majority of cases of acute urticaria (5); rather, the most common causes of acute urticaria in adulthood are acute infections (ca. 40%) and medication intolerance (ca. 10%). In childhood,

**BOX 1**

**Classification of urticaria**

- **"Spontaneous" urticaria**
  - Acute urticaria
  - Chronic urticaria
- **Urticaria of physical origin**
  - Factitious urticaria
  - Cold urticaria
  - Solar urticaria
  - Delayed pressure urticaria
  - Vibration-induced urticaria
  - Heat urticaria
- **Other types of urticaria**
  - Exercise-induced urticaria/anaphylaxis
  - Cholinergic urticaria
  - Contact urticaria
  - Aquagenic urticaria

infections account for up to 80% of cases of acute urticaria, but food allergies (e.g., against cow milk) are a more common cause than they are in adulthood (6, 7).

Because of the brief duration and self-limited course of a single attack of acute urticaria (remission within six weeks), an extensive search for its etiology is not indicated (8). In particular, there is no indication for laboratory biochemical studies or for allergy testing. The exception to this rule is in severe cases of acute urticaria in which the history suggests a type I allergy as the cause; a prick test and, when appropriate, a measurement of specific IgE to identify the responsible allergen are indicated here so that further attacks can be avoided. In general, however, the main goal of the treatment of patients with acute urticaria is the complete suppression of the clinical manifestations (2). The treatment is therefore based on the extent, intensity, and duration of the symptoms and should be adapted to their further course (figure 4). The most commonly used medications are modern, non-sedating antihistamines or glucocorticoids (both are given systemically), alone or in combination when necessary. Acute urticaria usually arises only once and does not progress to chronic urticaria (9, 10), though the rate of progression has been reported variously in the literature (from below 1% to 30%).

**Clinical manifestations**

Both acute and chronic urticaria typically consist of strongly itching skin wheals that may appear anywhere on the body. In some patients, they are associated with angioedema.

**Lifetime prevalence**

With a lifetime prevalence of 10% to 25%, acute urticaria is one of the more common diseases.

**Figure 1:** Wheals with reflex erythema in chronic urticaria



**Figure 2:** Extensive wheal formation in chronic urticaria



**Chronic urticaria: its causes and possible precipitating factors**

In the context of urticaria, the term "chronic" in its broad sense means nothing more than "lasting more than six weeks." In the current guidelines, however, the term "chronic urticaria" is restricted to apparently spontaneous cases and is thus used to distinguish these cases from physical and other types of urticaria (*box 1*) (11).

Published estimates on the prevalence of CU vary considerably; typical figures from the German-speaking countries are in the range of 1% to 2% (12). If this is so, then there are just over one million patients with CU in Germany. Women are affected about twice as often as men. Both typically develop the condition in the fourth to sixth decades of life.

The manifestations of CU may be present continuously or nearly every day (chronic continuous urticaria) or in the form of attacks separated by symptom-free episodes that may be as long as several weeks (chronic recurrent or intermittent urticaria). The condition persists for four years on average, but its duration in individual cases can range from 0 to 40 years (13). Other authors, however, state that more than 50% of patients still suffer from CU ten years after their initial diagnosis (14).

For these reasons, the treatment of chronic urticaria – unlike that of acute urticaria – is causally oriented with the intention of curing the condition, particularly when it has persisted for a long time or is very severe (2). Causally oriented treatment can only be provided, of course, when the underlying cause has been successfully identified. The possible causes are numerous and varied. They are grouped into four categories (*table 1*):

- autoreactive chronic urticaria,
- chronic urticaria due to infection,
- chronic urticaria due to intolerance, and
- chronic urticaria of other causes.

A thorough search for a cause results in a diagnosis of chronic urticaria of one of the first three types listed above in up to 80% of patients. The three causes are of roughly equal prevalence (2).

**Autoreactive urticaria**

This type of urticaria is produced by mast cell activating substances that circulate in the blood (15). In at least some patients, the responsible substances appear to be autoantibodies directed against the IgE receptor Fc<sub>ε</sub>RI or against immunoglobulin E itself.

**Definition of chronic urticaria**

"Chronic," as applied to urticaria, means only that the condition has lasted for more than six weeks. The term "chronic urticaria" is used only when the condition has apparently arisen spontaneously.

**The treatment of chronic urticaria**

Patients with chronic urticaria should be treated with an etiologically oriented approach, and with the intention of curing the condition, when chronic urticaria has taken a severe course or has been present for a long time.



**Figure 3:** Angioedema of the left hand in chronic urticaria

A suspected diagnosis of autoreactive chronic urticaria can be easily confirmed with an autologous serum skin test (ASST). Serum is extracted from a freshly obtained specimen of whole blood and 50 µL of it is injected into the volar skin of the forearm. Normal saline and a histamine solution are injected simultaneously as negative and positive controls. The results of the test are then read off at 15 and 30 minutes.

The test reaction is said to be positive when the serum-induced wheal is greater than 2 mm in diameter, or more than 2 mm in diameter larger than the saline-induced wheal, if there is one. Some patients in whom positive tests are found do not have either of the two types of autoantibodies mentioned above, so that there must also be other serum factors for urticaria that have not yet been identified.

Patients with autoreactive CU often have a high degree of urticarial activity in comparison with patients who have other types of CU. Nonetheless, their manifestations can usually be well controlled with symptomatic treatment in a sufficiently high dose.

**Chronic urticaria due to infection**

It has long been known that chronic urticaria can arise as a response to chronic inflammatory, and particularly infectious, processes (16). *Helicobacter pylori* infections of the gastrointestinal tract and bacterial infections of the nasopharynx (recurrent sinusitis and tonsillitis)

**Autoreactive chronic urticaria**

Patients with autoreactive chronic urticaria, unlike those with other types of chronic urticaria, often have a high degree of urticaria activity.

**BOX 2**

**Basic algorithm for the diagnostic assessment of chronic urticaria**

**History**

- Onset (change in living conditions?)
- Frequency, duration, severity, and localization of wheals and itching
- Dependence of symptoms on the time of day, day of the week (weekend?), season (vacation?), menstrual cycle
- Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.)
- Family history of urticaria and atopy
- Known allergies, intolerances, infections, systemic illnesses or other possible causes
- Known precipitating factors of urticaria (physical stimuli, exertion, stress, food, medications)
- Use of medications
- Occupation and leisure activities
- Impairment of the quality of life
- Response to treatment

**Physical examination and laboratory tests**

- Physical examination (with special attention to dermatographism)
- Objectification of symptoms of urticaria (possibly with a photograph)
- To rule out autoreactive chronic urticaria: autologous serum testing (if positive, test serum for anti-IgE and anti-Fc<sub>ε</sub>R1α where indicated), antinuclear autoantibodies, antithyroid autoantibodies
- To rule out chronic urticaria of infectious origin: differential blood count with erythrocyte sedimentation rate or C-reactive protein, *Helicobacter* test (breath test or demonstration of antigen), anti-streptolysin test, hepatitis serology, stool for fungi and parasites, ENT and dental examination
- To rule out chronic urticaria due to intolerance: pseudoallergen- and histamine-poor diet for 3–4 weeks
- To exclude chronic urticaria of other causes: total IgE

**The diagnosis of autoreactive urticaria**

If suspected, the diagnosis of autoreactive urticaria can be simply confirmed with an autologous serum test.

TABLE

The classification of chronic urticaria: causes, precipitating factors, mast cell activating factors

	Autoreactive CU	CU due to infection	CU due to intolerance	CU of other causes	CU of unknown cause
Cause	Autoreactivity	Chronic infection	Intolerance	Various	Unknown
Precipitating factor (specific)	Unknown	Unknown	Food, medications	Various (generally unknown)	Unknown
Mast cell activating factor	Circulating mast cell activator	Unknown* <sup>1</sup>	Unknown* <sup>2</sup>	Various (generally unknown)	Unknown

\*<sup>1</sup>Potentially relevant mechanisms: (a) host-mediated (e.g., complement factors), (b) antigen/host interaction (e.g., immune complexes, IgE antibodies against antigen), (c) antigen-mediated (e.g., toxins)

\*<sup>2</sup>Potentially relevant mechanisms: neuropeptides or complement factors in pseudoallergic increases of mast cell reactivity. CU = chronic urticaria. The table is based on the authors' own data.

appear to be the two major types of causative infection. Infections of the roots of the teeth can also cause urticaria. Pathological gastrointestinal microbes and parasites are a relatively rare cause of CU in Germany.

The importance of intestinal candidiasis is a controversial matter. The eradication of *Candida albicans* is recommended in patients with intense colonization or who manifest type I sensitization to this organism (grade D recommendation). The diagnosis of chronic urticaria due to infection should only be given when CU resolves completely, or at least improves markedly and lastingly, a short time after the eradication of the putatively causative infection.

**Chronic urticaria due to intolerance**

CU patients often themselves suspect that their urticaria is due to the previous intake of certain kinds of food. They might, indeed, suffer from CU because of food intolerance. The mechanism is not an IgE-mediated type I reaction to food, but rather a dose-dependent, usually delayed (4 to 12 hours) pseudoallergic reaction to food coloring, artificial flavoring, or preservatives (17).

Chronic urticaria due to intolerance is diagnosed when

- after at least three weeks of strict adherence to a low-pseudoallergen diet, the manifestations of urticaria have improved by at least 50% (as documented in an "urticaria diary"), and
- provocative testing with food additives (through the intake of food high in pseudoallergens for 2 to 4 days) is seen to worsen the symptoms.

If the symptoms fail to respond to a low-pseudoallergen diet, the reason may be that the patient was not adhering to the diet strictly enough. Skin tests and laboratory studies are of no diagnostic value.

**Chronic urticaria of other causes**

About 10% of patients have urticaria due to other, much rarer causes, e.g., allergic urticaria (an entity that is much less common than generally thought) (17), CU as a hormone-dependent event, or CU as a paraneoplastic phenomenon. No cause at all can be found in only a small minority of patients (less than 10% in specialized urticaria centers). Such patients are said to have CU of unknown cause.

Urticaria of whatever cause can be exacerbated or intensified by a large number of non-specific factors, e.g., stress, physical exertion, spicy or hot foods or beverages, flu-like infections, alcohol, acetylsalicylic acid and other non-steroidal anti-inflammatory agents, and angiotensin converting enzyme inhibitors.

**Chronic urticaria: diagnosis and treatment**

A thorough and detailed history is very important for the correct diagnosis and treatment of chronic urticaria. The aspects that should be kept in mind are listed in *box 2*. Patient questionnaires like the ones that can be downloaded at [www.urtikaria.net](http://www.urtikaria.net) can be useful. Furthermore, patients should keep an "urticaria diary" (blank forms for this can also be downloaded at [www.urtikaria.net](http://www.urtikaria.net)) for several weeks; in it, they should document the intensity of the disease manifestations (wheals, itch, angioedema,

**Possible causes of urticaria due to infection:**

- Gastrointestinal tract infections with *Helicobacter pylori*
- Bacterial infections of the nasopharynx
- Infections of the roots of the teeth

**Chronic urticaria of other causes**

- Not as common as often thought: allergic urticaria
- Chronic urticaria as a hormone-dependent event
- Chronic urticaria as a paraneoplastic phenomenon

extracutaneous symptoms), their association with food intake and other activities (e.g., sports, emotional stress), and all of the medications that they are taking.

The physical examination of patients with CU should include the objectification of the disease manifestations as well as testing for urticarial dermatographism, which is a cutaneous reaction to being stroked with a hard object that presents as bank-like wheal formation in patients with factitious urticaria. Because the disease manifestations are so transient, they often can be objectified only with a detailed description or with a photograph that the patient has taken at home and brought along to the consultation. Routine blood tests and a directed search for evidence of autoreactive CU, CU due to infection, or CU due to intolerance round out the basic diagnostic evaluation (box 2). If any evidence for one of these types of CU is found, further evaluation may require consultation with a specialized dermatologist/allergologist or referral to a specialized urticaria center.

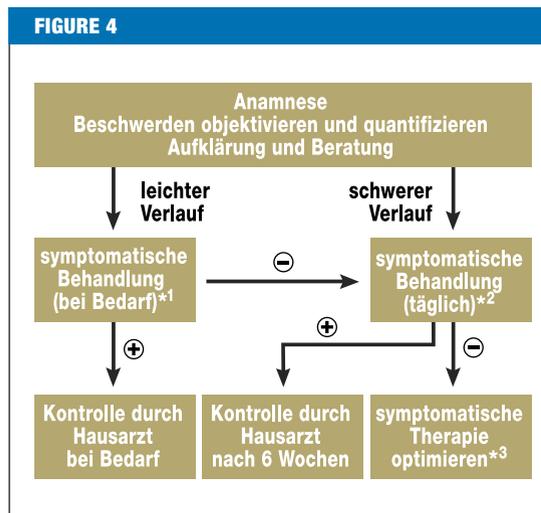
### Acute and chronic urticaria: treatment

#### Eradication of causes, precipitating factors, and aggravating factors

The eradication of causes, precipitating factors, and aggravating factors is the treatment of choice for patients with chronic urticaria. Patients should be told about the non-specific factors that can worsen chronic urticaria, both so that they can avoid them as far as possible and so that any attacks that do occur will be easier to explain.

The most important goal of the diagnostic measures discussed above is to identify the actual etiology of the condition, yet it is only the actual response of urticaria (disappearance or not) to the elimination of each putative cause that enables a final etiological judgment. This is especially true of chronic infections. Because the literature contains highly variable estimates of the rate of response of urticaria to the eradication of infection, the relevance of infections of various types to urticaria remains a contentious issue today. A positive effect appears to be well established at least for the eradication of *Helicobacter pylori* (grade C recommendation) (18). When this infectious organism or others (streptococci, staphylococci, *Yersinia*) are eradicated with antibiotics, the urticaria generally disappears only after a latency period of several weeks (16).

The etiological treatment of patients with autoreactive CU is considerably more difficult. If antibodies to the IgE receptor can be demonstrated that cannot be dismissed as an epiphenomenon, and if conventional



Flowchart for the treatment of acute urticaria

+, successful; -, unsuccessful; \*1 non-sedating antihistamine, possibly high-dosed; \*2 if indicated, initially IV under brief in-hospital supervision; on an ambulatory basis, e.g., non-sedating antihistamine (up to three times daily for 4 weeks), if necessary combined with a glucocorticoid (e.g., prednisolone 0.5–1 mg/kg body weight qd for 3 weeks, with gradual lowering of the dose by 50% every 3 days; \*3 if the course of the condition is severe, consider searching for the etiology after the transition to chronic urticaria (diagram based on the authors' experience).

treatment is ineffective, immune suppression sometimes results in therapeutic success: positive reports are available for cyclosporine A (grade C recommendation), plasmapheresis, and high-dose immunoglobulin therapy (grade D recommendation).

In patients with CU due to intolerance, a low-pseudoallergen diet generally leads to the complete disappearance, or at least marked improvement, of disease activity (grade B recommendation). Unlike IgE-dependent urticaria, CU due to intolerance generally improves only after a delay of 10 to 14 days from the start of the low-pseudoallergen diet. Therefore, in order to improve compliance, overlapping symptomatic treatment is usually recommended for about 10 days, followed by observation of disease activity for a further 10 days under dietary treatment alone after the cessation of symptomatic treatment. After this is done, oral provocation testing is used to determine whether any particular food additive is the causative factor. If this turns out to be the case, then the condition can probably be cured by specific

### Physical examination in CU

The physical examination of patients with chronic urticaria includes the objectification of symptoms and testing for urticarial dermatographism.

### The treatment of choice

In principle, the treatment of choice for chronic urticaria consists of the removal of causes, precipitating factors, and aggravating factors.

avoidance of this additive. If no such causative factor is found, then a gradual loosening of restrictions on the patient's diet is recommended, over a period of three to six months.

#### Mast cell directed treatment

In clinical practice, the most important medications for the suppression of mast cell function are glucocorticoids. When used in the short term to treat acute urticaria (e.g., 50 mg of prednisolone daily for three to five days in an adult patient), they are at least as effective as antihistamines (grade D recommendation). Yet, because glucocorticoid doses that are high enough to be effective can have serious side effects if continued over the long term, these agents should be avoided as far as possible in the treatment of chronic urticaria. The same is true of another drug that inhibits mast cells directly, cyclosporine A (grade D recommendation). Cromoglycates are not adequately resorbed for systemic use, and in any case they generally have no effect on cutaneous mast cells. It is not yet known whether the effect of some antihistamines against mast cell degranulation that has been observed in vitro has any clinical relevance for the treatment of urticaria. Thus, mast cell inhibition does not play any significant role today in the treatment of chronic urticaria in clinical practice.

#### Treatment at the end organ

This is the domain of the antihistamines. The only clinical studies published to date with an evidence level of 1++ (grade A recommendation) deal with the newer, non-sedating antihistamine drugs (17), including the following (approved for use in Germany): azelastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and mizolastine. In comparison with the older, sedating antihistamines such as clemastine and dimetindene, these drugs have the advantage of being effective for 24 hours or longer. Because they are less lipophilic, they only rarely have side effects on the central nervous system, such as fatigue. Because patients with clinically severe urticaria often do not respond to these medications when they are given in the approved doses, current guidelines recommend giving them in up to four times the approved dose (grade D recommendation) (11). In view of the wide therapeutic range of the newer antihistamines, giving them in higher doses appears to be generally unproblematic. Some of these preparations, however, should be used with caution in patients with hepatic or renal insufficiency and in patients who are also

taking other drugs. Moreover, one should bear in mind that some of these "non-sedating" antihistamines can indeed produce clinically relevant sedation when given in higher doses.

#### Conflict of interest statement

Professor Dr. med. Marcus Maurer serves as an advisor for Biofrontera AG, Essex Pharma GmbH, Schering-Plough, and Uriach Pharma and has received lecture fees from Almirall Hermal GmbH, Biofrontera AG, Essex Pharma GmbH, Novartis Pharma GmbH, and Schering-Plough. Marcus Maurer conducts studies and basic-science research projects with the financial support of Almirall Hermal GmbH, Biofrontera AG, Essex Pharma GmbH, Novartis Pharma GmbH, Schering-Plough, UCB, and Uriach Pharma. Prof. Dr. med. Jürgen Grabbe serves as an advisor for Novartis Pharma GmbH and has received lecture fees from Essex Pharma GmbH. He conducts studies with the financial support of Novartis Pharma GmbH and Schering-Plough.

Manuscript received on 16 January 2008; revised version accepted on 30 April 2008.

Translated from the original German by Ethan Taub, M.D.

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### The treatment of chronic urticaria due to intolerance

In patients with this problem, a low-pseudoallergen diet generally leads to the complete or nearly complete remission of disease activity.

### Pharmacotherapy

Because patients with clinically severe urticaria often do not respond to antihistamines in the approved doses, current guidelines recommend raising the dose to as much as four times the approved daily amount.

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**Question 1**

**Which of the following is typical of the manifestations of chronic urticaria?**

- a) They arise spontaneously.
- b) They are precipitated by physical stimuli.
- c) They arise at night.
- d) They arise in a particular region of the body.
- e) They are heralded by prodromal manifestations (auras).

**Question 2**

**Which of the following is a common cause of chronic urticaria?**

- a) Vitamin deficiency
- b) Obesity
- c) Smoking
- d) Autoreactivity
- e) Lack of exercise

**Question 3**

A woman comes to your office complaining of a rash with wheals that arose very suddenly.

**Which of the following questions is relevant to the differential diagnosis of chronic urticaria from urticarial vasculitis?**

- a) Where on the body do the wheals appear?
- b) Do the wheals itch?
- c) What color are the wheals?
- d) How long do the wheals last?
- e) How many wheals appear in one day?

**Question 4**

**Which of the following conditions belongs to the class of physical urticaria?**

- a) Factitious urticaria
- b) Gangrenous urticaria
- c) Pigmented urticaria
- d) Urticarial vasculitis
- e) Cholinergic urticaria

**Question 5**

**What is the typical course of acute urticaria in adults?**

- a) It persists for several years.
- b) It comes back in recurrent attacks.
- c) It usually lasts only a few days or weeks.
- d) It is correlated with food allergies.
- e) It generally appears for the first time after age 60.

**Question 6**

Patients with urticaria sometimes have symptoms that are not just on the skin.

**Which of the following is among the more common extracutaneous symptoms?**

- a) Neurological deficits
- b) Gastrointestinal complaints
- c) Dysuria
- d) Hiccups
- e) Myalgia

**Question 7**

**What is the cause of all of the manifestations of urticaria (wheals, itch, angioedema)?**

- a) Recruitment of neutrophils
- b) Vessel spasm
- c) Elevated epidermal permeability
- d) Mast cell activation
- e) Collagen loss

**Question 8**

**The effectiveness of which of the following drugs against acute or chronic urticaria has been demonstrated with grade A evidence?**

- a) Intravenous broad-spectrum antibiotics
- b) Non-sedating antihistamines
- c) Oral anticholinergic agents
- d) Non-steroidal anti-inflammatory drugs
- e) Intravenous amitriptyline

**Question 9**

A 35-year-old man comes to your office with wheals that arose suddenly. Something similar happened six months ago. He thinks the cause may be food intolerance, as he ate a particular ready-made product just before each of the two episodes. This product contains a preservative that he thinks precipitated the symptoms.

**When and how can you establish the diagnosis of chronic urticaria due to intolerance?**

- a) After at least three weeks of strict adherence to a low-pseudoallergen diet, if it can be documented that the symptoms have improved by at least 50%.
- b) By observation of the cutaneous reaction, if any, six hours after a prick test. Various devices are available to measure the size of the wheal.
- c) By performing blood tests: the diagnosis is confirmed by an elevation of the white blood count, the C-reactive protein (CRP), and the alanine aminotransferase (ALAT).
- d) After two sessions of bioresonance therapy, as described by Mora. This is a scientifically validated method of demonstrating intolerance to various kinds of food, particularly preservatives.
- e) After six weeks of bowel cleansing and simultaneous eradication of a demonstrated *Helicobacter pylori* infection.

**Question 10**

**Which of the following often induces an exacerbation of chronic urticaria?**

- a) Acetylsalicylic acid
- b) Caffeine
- c) Citrus fruits
- d) Gluten
- e) Asparagine