

Acute Urticaria

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KEYWORDS

• Acute urticaria • Anaphylaxis • Antihistamines

KEY POINTS

- Acute urticaria is common in adults and children.
- Acute urticaria is most often idiopathic, but it may follow infection, exposure to drugs, or less commonly food ingestion.
- Acute urticaria may be a presenting symptom of anaphylaxis.
- Acute urticaria by definition resolves within 6 weeks, but it often settles within 2 to 3 weeks. It may recur in a small proportion of patients.
- Acute urticaria may be treated with antihistamines or oral steroids if needed.

INTRODUCTION

Urticaria consists of transient red itchy swellings, or weals. Swellings are variable in size and usually last for less than 24 hours. Acute urticaria is defined as the occurrence of weals for less than 6 weeks, after which the disease instead becomes chronic urticaria.¹

Acute urticaria is common, and presents in all age groups.^{2–4} Its transient and usually benign nature means that it may not come to the attention of doctors. Thus, the incidence may be underestimated, typical disease severity may be overestimated, the proportion with causative factors is difficult to ascertain, and the response to treatment is difficult to quantify. Such problems are compounded because patients also present to various different specialties, including generalists, emergency departments, pediatricians, immunologists or allergists, and dermatologists. This situation may explain why there are few publications including large cohorts of patients specifically with acute urticaria. However, the following article summarizes current knowledge on the condition.

EPIDEMIOLOGY

Acute urticaria is common in both adults and children. Indeed, it is one of the most common dermatologic conditions presenting to many emergency departments.^{3,5,6}

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Overall, 12% to 22% of the general population will suffer from at least one subtype of urticaria at some time in their lives,⁷⁻⁹ with a prevalence of 0.11% to 0.6%.^{10,11} Of all patients with urticaria, only a low proportion of 7.6% to 16% have acute urticaria,¹²⁻¹⁴ although in one study the percentage was much higher at 56%.¹⁵ The variation may be related to the population studied and the interests of the department or doctor to whom patients are referred.

The age group studied may be particularly important, because acute urticaria seems to be more common than chronic disease in very young children. Indeed, in one report, all children presenting at less than age 6 months had acute urticaria, and 85% of children less than age 2 years had this subtype.¹⁶ In older children, the ratio of chronic to acute urticaria seems to be similar to that in adults.¹⁷⁻¹⁹

The overall age range for presentation with acute urticaria is wide, in one study 3 months to 88 years,² with an average in the early twenties.²⁻⁴

Most,²⁻⁴ but not all,¹⁵ reports find a female preponderance of about 60%. However, in young children the male to female ratio may be roughly equal.²⁰⁻²²

ETIOLOGY

Attacks of acute urticaria are thought to be idiopathic in 30% to 50% of cases.^{2,15,23,24} Otherwise attacks may be triggered by infections, drugs, or foodstuffs (**Table 1**). The relative proportion of patients with each precipitant varies from study to study.

In children, many studies find respiratory tract and other infections to be the most common trigger for urticaria.^{22,24,25} The association with respiratory tract infections may be related to a seasonal variation in incidence.²⁵ Infections, of many types

Table 1 Some of the reported causes of acute urticaria		
Cause		Reference
Idiopathic		2,15,23,24
Infection		
Viral	Adenovirus	26,56
	"Common cold"	4
	Cytomegalovirus	57
	Enterovirus	26,56,57
	Epstein-Barr	26,57
	Hepatitis A, B, C	56,58
	Herpes simplex	57,59
	Influenza A	57
	Parvovirus B19	57
	Respiratory syncytial virus	26
	Rotavirus	26
	Varicella/Zoster	26
Bacterial	Group A beta-hemolytic streptococcus	60,61
	<i>Haemophilus influenzae</i>	62
	<i>Staphylococcus aureus</i>	62
Other	<i>Anisakis simplex</i>	33
	<i>Blastocystis hominis</i>	63,64
	Malaria	65
	Mycoplasma	57,66
	Scabies	15

(continued on next page)

Table 1
(continued)

Cause		Reference
Drugs	ACE inhibitors	67
	Antibiotics/anti-infective drugs, especially cephalosporins and penicillins	3,4,15,23,24,26,29,30,32
	Antihistamines	68
	Anti-TNF alpha drugs	69
	Aspirin and other nonsteroidal antiinflammatory drugs	3,4,15,24,26,30,53
	Blood products	70,71
	Candesartan	23
	Epidural hyaluronidase	72
	Gadolinium-containing radiocontrast media	73
	Intravenous immunoglobulins	74
	Iodine-based contrast agents, eg, iopromide	3,75
	Isotretinoin	76
	Methylprednisolone (oral)	77
	Opiates and tramadol	53,78
	Paracetamol	29,49,53
	Proton pump inhibitors	79
	Vaccination	2,80,81
Food	Cow's milk	16,17,24,26,82
	Egg	24,26
	Fish and seafood	3,17
	Fruit, eg, peach and kiwi	12,24,26
	Nuts	12,24,26
	Tomato and other vegetables	12,17
	Wheat	19
Other	Yeast	23
	"Gomutra" (cow's urine) gargle	83
	Hedgehog spines	84
	Insect bites or stings	2-4,15,23,24
	Latex	12,26
	Systemic lupus erythematosus	34
	Thyroid papillary carcinoma or other thyroid disease	23,85

(see **Table 1**), may also be associated with urticaria in adults.^{2,4} However, it may be difficult to know if the urticaria was due to the infection itself or the drug used to treat it.^{2,4,16,24,26}

Urticaria/angioedema is one of the most common types of drug-induced rash, and has been reported to account for 11.3% and 16.6% of drug eruptions in hospitalized patients aged 13 to 88 years and children, respectively.^{27,28} It may be more common for a drug eruption to be of an urticarial nature in younger patients.²⁹ Urticaria may be more commonly drug induced in the elderly, especially due to nonsteroidal antiinflammatory drugs (NSAIDs).³ Overall, drugs are reported as being the cause of acute urticaria in 9.2% to 27% of cases.^{3,4} Multiple drugs have been implicated in acute urticarial reactions (see **Table 1**). In a recent study, 147 drugs were presumed to have caused attacks.³⁰ However, the most common are antibiotics and NSAIDs.^{29,30} Reactions to one cephalosporin or one NSAID may or may not indicate cross-reactivity with other drugs in the same group.^{31,32}

Various foodstuffs have been reported as causing urticaria (see **Table 1**). In children younger than 6 months, cow's milk allergy may be important.¹⁶ However, generally

food is implicated less often in more recent reports, with estimates of causality ranging from 0% to 18% of cases.^{2-4,24}

Some other causes of acute urticaria are listed in **Table 1**, and include contact with latex,¹² insect bites or stings,^{2,3,15,23} ingestion of the fish nematode *Anisakis simplex*,³³ and rarely acute urticaria may occur as part of a systemic disease such as systemic lupus erythematosus.³⁴ Acute contact urticaria is not covered in this article.

DISEASE MECHANISMS

The mechanism for mast cell degranulation in acute urticaria is not always understood.

In some cases, acute urticaria is due to a type I hypersensitivity reaction, in which case the urticaria may occur alone or as part of an anaphylactic reaction. A broad range of allergens may trigger urticaria in this way, including some antibiotics, latex, foodstuffs such as peanuts or tomatoes, and insect stings.¹² However, type I hypersensitivity reactions are now thought to be less common than before as an etiologic factor in acute urticaria.^{4,24}

Other mechanisms are thought to be involved in mast cell degranulation in urticaria induced by opiates, angiotensin-converting enzyme (ACE) inhibitor, and NSAIDs. Opiates trigger mast cell degranulation independent of IgE receptor activation.³⁵ ACE inhibitor-induced urticaria may be due to elevated levels of bradykinin.³⁶

In NSAID-induced urticaria, the arachidonic acid pathway is implicated, possibly with an inhibition of prostaglandin synthesis and an increase in leukotrienes.³⁷ There may be a genetic tendency for patients to develop aspirin sensitivity. Indeed, several promoter polymorphisms have been identified, such as in *TBXA2R* (the thromboxane A2 receptor) gene,³⁸ in the genes of aspirin-metabolizing enzymes,³⁹ and in other genes encoding enzymes and receptors of the arachidonic acid pathway.⁴⁰ In aspirin sensitivity, promoter polymorphisms have also been identified in some cytokine genes, including *IL-18*,⁴¹ *IL-10*,⁴² and *TNF α* .⁴³

CLINICAL FEATURES

During an attack of acute urticaria, weals are variable in number and size. More than 50% of the body surface area may be involved, and in one study the rash was described as generalized in 48% patients.^{3,4}

Urticarial weals may occur alone or with angioedema. Coexistent angioedema has been reported in 16% to 31% of patients^{3,23} but may be more common in children younger than 3 years (60%) who may also get hemorrhagic weals.^{16,26}

Systemic symptoms occur in up to a quarter of patients.²³ Wheezing, breathlessness, cough, rhinorrhea, dizziness, flushing, gastrointestinal upset (nausea, vomiting, diarrhea, or abdominal pain), headache, fever, tachycardia, joint pain, or conjunctivitis can occur with an attack of acute urticaria.^{3,4} Such symptoms may indicate anaphylaxis if of rapid onset.

DIFFERENTIAL DIAGNOSIS

The key feature distinguishing urticaria from other rashes is the transient nature of the weals, and this usually makes it easy to diagnose within 24 to 36 hours. In addition, weals usually do not blister or form scales and disappear without residual changes. A detailed review of the differential diagnoses was published in 2010.⁴⁴

The differential diagnosis includes the following:

- Erythema multiforme. Urticarial weals can sometimes clear centrally and spread out, giving an annular appearance. However, true target lesions do not occur in

urticaria, and the lesions of erythema multiforme persist for several days in the same place, sometimes with central blisters and sometimes with associated mucous membrane erosions.

- Toxic erythema. The lesions of a toxic erythema may be urticated and so initially confused with urticaria, but the lesions are usually symmetric, and remain fixed in the same place for several days.
- Acute eczema or acute contact dermatitis. Eczema may be red and swollen, but unlike urticaria it is associated with epidermal changes (weeping or vesicle formation followed by scaling) and takes a few days to settle.
- Autoimmune bullous diseases. Prodromal lesions may be urticarial or urticated.
- Polymorphic eruption of pregnancy. This condition may present with urticated lesions, but the distribution on stretch marks on the abdomen and duration of the lesions, which again are more prolonged than in urticaria, should distinguish the two.
- Cellulitis or erysipelas. These can be confused with large urticarial weals, but involved areas are unilateral, persistent and painful and the patient may be pyrexial and unwell. Similarly, in Well's syndrome or eosinophilic cellulitis, the areas of redness persist, and here a skin biopsy may aid diagnosis.
- Progesterone-induced dermatosis. Here, weals recur premenstrually.
- Urticarial vasculitis. Prolonged urticarial weals followed by bruising may suggest urticarial vasculitis, especially if associated with systemic symptoms. A skin biopsy should then be taken to look for features suggestive of urticarial vasculitis, such as red cell extravasation, endothelial cell swelling, leukocytoclasia, and rarely fibrinoid necrosis.⁴⁵
- Systemic lupus erythematosus. Urticaria or urticarial vasculitis may occur as a presenting feature of systemic lupus erythematosus, and so if other suspicious features are present, an autoimmune screen should be performed.
- Scrombroid fish poisoning. Acute urticaria may be a presenting symptom.⁴⁶

INVESTIGATIONS

In many cases no investigations, other than a thorough history, are required (**Box 1**).⁴⁷ Overinvestigation should be avoided.

Sometimes a full blood count may be helpful, as alterations in the differential white cell count may indicate infection.

An elevated C-reactive protein (CRP) level and/or erythrocyte sedimentation rate may point toward an infective or inflammatory cause, and the CRP level may also be elevated in NSAID-induced urticaria.⁴⁸

Box 1

Investigations to consider

Thorough history
 ? Nothing else
 Full blood count, with differential white cell count
 CRP level and/or erythrocyte sedimentation rate
 Culture relevant specimens
 Serum allergen-specific IgE tests
 Prick tests
 Oral drug challenge tests

Relevant samples should be sent for culture if infection is suspected.

If indicated, serum allergen-specific immunoglobulin E tests and/or prick tests may be used to investigate suspected type 1 hypersensitivity reactions.⁴⁷ To minimize risks of misinterpretation of false-positive and false-negative test results, careful correlation of exposure history and relevant ancillary allergic history is required.

It may be difficult to work out which drug if any was causative, particularly if several were given, or if drugs were given after an infection that might itself have caused the urticaria. On occasion, progression to skin prick or intradermal tests or structured oral drug challenge tests in a qualified immunology unit or expert center may be needed to correctly identify any culprit drugs and make relevant plans for possible future exposures.³¹ Oral drug challenge tests may also be helpful in defining cross-reactivity between similar drugs.^{31,32,49}

MANAGEMENT

In mild cases, treatment may not be required (Box 2). However, if an infection is present, this should be treated appropriately. Causative drugs should be withdrawn and known allergens avoided.

Topically, 1% to 2% menthol in aqueous cream may be helpful to reduce itching.⁵⁰

If further treatment is needed, H1 receptor antagonists are usually introduced first.^{47,51} Low sedating drugs are preferable, but if the patient is still unable to sleep, then sedating drugs, particularly hydroxyzine, may be beneficial for a short period.^{2,4,52} The patient should be warned that such drugs may slow reactions when driving, even if they are not feeling sedated. Some patients known to develop urticaria after taking NSAIDs may be able to tolerate them if an antihistamine, or an antihistamine and a leukotriene receptor antagonist such as montelukast, is given beforehand.^{53,54}

For severe urticaria, particularly if associated with angioedema or marked systemic symptoms, and provided infection is ruled out or treated, oral corticosteroids may be given for a few (3–5) days. Fairly high doses, up to 20 to 50 mg daily of prednisolone, are sometimes needed. Oral corticosteroids may shorten the duration of an attack and reduce symptom severity.^{4,52}

If the urticaria is part of an anaphylactic reaction, then national guidelines and local protocols for anaphylaxis should be followed.⁵⁵ Intramuscular adrenaline, intravenous antihistamines, intravenous corticosteroids, oxygen, salbutamol, fluid replacement, and other supportive treatment may be needed.

Box 2
Management options to consider
? No treatment
Stop causative drugs
Avoid relevant allergens
Treat infection
Menthol, 1% to 2%, in aqueous cream
H1 antihistamines
Oral corticosteroids
Treatment of anaphylaxis according to guidelines
Medic alert bracelet
Self-injectable adrenaline

Medic Alert bracelets may be recommended if there is a confirmed type 1 hypersensitivity reaction, particularly if the urticaria has occurred as part of an anaphylactic reaction. In the latter case, self-injectable adrenaline may be carried provided the patient has been shown how to use it and is capable and willing to do so.⁵⁵

PROGNOSIS

Most attacks of acute urticaria settle within 2 to 3 weeks.^{2,4,22} In a study of 1075 children with urticaria, disease duration was shortest for infants and adolescents, but more prolonged attacks were associated with having an atopic background, an infective cause, or the presence of systemic symptoms.²² This study also reported an association between short attack duration and the presence of angioedema. However, this finding was probably explained by the fact that children with angioedema were treated more aggressively, because the authors also found that aggressive management decreased episode length.²²

Attacks may recur, particularly if the patient is inadvertently exposed to the same allergen or culprit drug. The percentage of children developing a second episode or chronic disease has been variously reported as 20% to 30% in 2 years²⁶ or 3.5% to 5% in 8 years.²¹ In one study, 12% of 109 patients aged 5 to 86 years reported an attack of acute urticaria in the 10 years preceding the presenting episode, again indicating the possibility of recurrent episodes.⁴ None of the patients in this study went on to develop chronic disease, but the follow-up period was only 8 weeks. In another study of 50 patients aged 3 months to 88 years, 5 patients went into remission at 3 months and 2 patients had disease for more than 1 year.² Overall, there are few reports documenting the proportion of patients progressing from acute to chronic disease.

SUMMARY

Acute urticaria is common in adults and children. It is a self-limiting condition, defined by its resolution within 6 weeks, although it usually disappears within 2 to 3 weeks. However, it may be recurrent and can progress to chronic disease. It is most often idiopathic but can be triggered by infection, drugs, and less frequently by foodstuffs. Although acute urticaria can occur as part of a type I hypersensitivity reaction, and sometimes as part of anaphylaxis, the mechanism leading to mast cell release is often unknown. The diagnosis is usually straightforward because of the transient nature of the urticarial weals, but it can be confused with several other conditions, especially in the first 24 hours. Investigations may be unnecessary. Management is aimed at removing or treating any cause, and symptom control, usually with H1 antihistamines. Anaphylaxis should be treated according to current guidelines.

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