URTICARIA is a common, heterogeneous group of diseases characterised by the sudden appearance of wheals, angioedema or both. This skin disorder is commonly encountered in dermatology and general practice. The key feature that defines urticaria is that the individual lesions resolve within 24 hours without leaving any marks. This article presents an overview of urticaria with a focus on the investigation and treatment.

The key pathological phenomenon in urticaria is vasodilation, and increased permeability of the cutaneous and submucosal microvasculature causing transient intracutaneous oedema. For wheals, the area of oedema involves the entire epidermis, and extends into the upper and middle dermis. There is dilatation of the post-capillary venules and lymphatic vessels in the upper dermal area. These urticarial lesions blanch with pressure and account for the central pallor. In angioedema, swelling occurs in the deeper dermis and subcutaneous region as a result of increased vascular permeability with plasma extravasation (oedema) and recruitment and subsequent infiltration of neutrophils and other immune cells. The mast-cell mediators also stimulate cutaneous sensory nerves that causes pruritus and the burning sensation that is commonly encountered in urticaria.

The pathogenesis of urticaria is complex, involving multiple types of inflammatory cells and cytokines. Regardless of the aetiology, it ultimately involves activation of cutaneous mast cells with subsequent degranulation, resulting in histamines and many other inflammatory cytokines being released. This action induces vasodilation (erythema), increased vascular permeability with plasma extravasation (oedema) and recruitment and subsequent infiltration of neutrophils and other immune cells.

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Urticaria may be classified into three broad categories based on clinical presentation — spontaneous urticaria, physical urticaria and other urticarial syndromes. Depending on duration of symptoms, spontaneous urticaria may be further classified as acute — symptoms lasting for less than six weeks, and chronic — symptoms occurring for most of the days of the week for more than six weeks.

Physical urticaria such as dermographism, cholinergic urticaria and many other subtypes as summarised in Table 1, are distinct subtypes of urticaria in which symptoms are triggered by specific physical factors.

It is clinically important to distinguish urticaria from urticarial dermatoses — a morphological group that mimics urticaria. This group includes urticaria drug eruptions, urticarial vasculitis and even bullous pemphigoid in these conditions, which take more than 24 hours to resolve. Figure 1 shows the relationship between the different classes of urticaria. Chronic urticaria has a peak prevalence in the middle-aged population, especially females (male to female ratio of 4:1). 3

Spontaneous urticaria
Pruritic wheals of variable sizes may appear on any part of the body, and resolve within 2-24 hours without residual bruising. Lesions may occur at any time of the day, but more commonly in the evening or just after waking. Systemic symptoms such as sweats, chills, fatigue and arthralgias may be present with severe disease, but the presence of fever or arthritis suggests the possibility of another diagnosis, such as urticarial vasculitis or cryopyrin-associated periodic syndromes. Females may also complain of a premenstrual flare of urticarial lesions.

Acute urticaria
In most cases, spontaneous acute urticaria will resolve within days or weeks. It occurs more commonly in children than adults. 4

Patients may describe their symptoms as episodic and attribute them to a preceding event, but most cases of acute urticaria are idiopathic, followed by a similar proportion caused by upper respiratory tract infections, and a smaller number caused by drug reactions and food allergy.

Drug and food reactions are more common in adults, while streptococcal infections and viral respiratory tract infections are common causes in children. 5 An acute urticarial eruption may be associated with life-threatening angioedema or anaphylaxis.

Chronic urticaria
Chronic urticaria refers to urticarial lesions occurring at least twice a week for more than six weeks. 6 Lesions occurring less frequently than this are known as recurrent or episodic urticaria. Fifty per cent of patients with chronic urticaria (with or without angioedema) become free of lesions within one year, 65% within three years, and 85% within five years.

Chronic urticaria has a peak prevalence in the middle-aged population, especially females (male to female ratio of 4:1). 3

The mean duration of chronic urticaria is four years. 

Most cases of chronic urticaria are characterised by periods of asymptomatic disease lasting days to weeks. Common causes of chronic urticaria are autoimmunity, infection and thyroid disease. Chronic urticaria also has a strong association with autoimmune conditions.

Autoimmunity. Autoimmunity is the presence of circulating mast-cell activating factors in the serum. This form of chronic urticaria is also known as chronic autoimmune urticaria, in which IgE autoimmune bodies present in the serum bind onto the alpha-subunit of the high-affinity IgE receptor, and activate mast cell degranulation and release of histamine. 7

Infection. Infections that are known to be associated with chronic spontaneous urticaria are viral, parasitic and fungal infections including hepatitis, bacterial infections of the nasopharynx, dental infections and gastrointestinal infections including Helicobacter pylori. 8

The role of H. pylori as an aetiological factor in chronic urticaria remains controversial; it may be associated with exacerbation of urticarial symptoms. However, a systematic review concluded there is weak evidence of symptom improvement upon eradication of H. pylori. 9 Chronic urticaria may be caused or worsened by hypersensitivity reactions to food components such as preservatives, colourants, taste intensifiers and other naturally occurring compounds (aromatic components, etc) through non-immunologically mediated mechanisms, known as pseudo-allergic hypersensitivity. 1

Thyroid. There is a reasonably significant association between chronic urticaria and thyroid disease. Twelve to 30% of patients with urticaria have elevated levels of thyroid peroxidase antibodies or anti-microsomal antibodies compared with the general population. 10 There is a positive association between chronic urticaria and thyroid autoantibodies, but not with histological thyroiditis or altered thyroid function. 11 Only a small number of patients who are positive for antithyroid antibodies have actual thyroid disease. 12 Patients positive for thyroid autoantibodies have more persistent urticaria that is poorly responsive to standard therapies. 13 As patients with chronic urticaria are also at risk for developing autoimmune thyroid disease, they should undergo screening for autoimmune thyroiditis and thyroid dysfunction, to enable early identification of these conditions. 14

The prognostic significance of thyroid autoantibodies has been evaluated in a retrospective study that examined patients who are positive for thyroid autoantibodies and have thyroid dysfunction, to enable early identification of these conditions. 15

Table 1: Types of physical urticarial and other urticarial types

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Triggering factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to mechanical stress</td>
<td>Mechanical (scratching/hubbing, etc)</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>Constant pressure on skin</td>
</tr>
<tr>
<td>Delayed pressure urticaria</td>
<td>Any vibrating force</td>
</tr>
<tr>
<td>Vibriatory urticaria</td>
<td>Urticarogenic substance</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td></td>
</tr>
<tr>
<td>Due to temperature changes</td>
<td>Increased core body temperature</td>
</tr>
<tr>
<td>Cold contact urticaria</td>
<td>Stress</td>
</tr>
<tr>
<td>Heat contact urticaria</td>
<td>Physical exercise</td>
</tr>
<tr>
<td>Due to sweating or stress</td>
<td></td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td></td>
</tr>
<tr>
<td>Adrenergic urticaria</td>
<td></td>
</tr>
<tr>
<td>Exercise-induced urticaria</td>
<td></td>
</tr>
<tr>
<td>Due to other causes</td>
<td></td>
</tr>
<tr>
<td>Solar urticaria</td>
<td></td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td></td>
</tr>
<tr>
<td>Other urticarial types</td>
<td></td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td></td>
</tr>
<tr>
<td>Angioedema without wheels</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Zuberbier T, et al. 1 and Biologics 2

As patients with chronic urticaria are also at risk for developing autoimmune thyroid disease, they should undergo screening for autoimmune thyroiditis and thyroid dysfunction.

Chronic urticaria has a peak prevalence in the middle-aged population, especially females (male to female ratio of 4:1). 3

Table 2: Differential diagnoses of urticaria

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria pigmentosa (mastoctosis)</td>
<td>Brown patches; urticaria on pressure</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td>Lasts &gt;24 hours, leaves bruising/purpura</td>
</tr>
<tr>
<td>Non-histaminergic angioedema</td>
<td>Facial and/or oral edema</td>
</tr>
<tr>
<td>• Hereditary angioedema</td>
<td></td>
</tr>
<tr>
<td>• Acquired angioedema with C1 inhibitor</td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Usually worse in extremities; purpura</td>
</tr>
<tr>
<td>Polymorphic eruption of pregnancy</td>
<td>Pregnant females</td>
</tr>
<tr>
<td>Associated syndromes</td>
<td>Associated features</td>
</tr>
<tr>
<td>Cryopyrin-associated periodic syndrome</td>
<td>Development of wheels early in life that are resistant to antihistamine treatment; unprovoked attacks of facial, oral, genital or neurologic manifestations</td>
</tr>
<tr>
<td>• Muckle–Wells syndrome</td>
<td></td>
</tr>
<tr>
<td>• Familial cold urticaria</td>
<td></td>
</tr>
<tr>
<td>Hypereosinophilic syndromes</td>
<td></td>
</tr>
<tr>
<td>• Well’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Schnitzler syndrome</td>
<td></td>
</tr>
<tr>
<td>Nonpuritic urticarial rash with recurrent fever, bone pain, joint pain, organomegaly, and monoclonal IgM gammopathy</td>
<td></td>
</tr>
</tbody>
</table>
from page 26

**Differential diagnoses**

Other non-related systemic diseases may present with wheals and urticarial skin lesions. These include urticaria pigmentosa, urticaria vasculitis, familial cold urticaria and non-histaminergic angioedema.

These conditions are not classified as subtypes of urticaria as they possess a distinctly different pathophysiological basis that is not largely mediated by histamine.

Other associated dermatological syndromes that may present with wheals and angioedema are shown in table 2 (page 26).

Those non-related conditions presenting with urticarial lesions have to be excluded in the routine workup of all patients presenting with urticarial skin reactions.

Angioedema without wheals that involve the throat, tongue or lips suggests drug-induced angioedema.

Angioedema of the larynx without wheals suggests hereditary angioedema or acquired C1 inhibitor deficiency.

Both conditions are characterised by recurrent episodes of angioedema caused by the relative lack of C1 inhibitor, leading to excessive activation of the classical complement pathway. This results in the production of anaphylactic, chemotactic and vasoactive peptides, leading to massive localised oedema.

**Clinical manifestations**

**Wheat**

Clinically, a wheal is defined as a transient, well-circumscribed, raised, erythematous plaque often with central pallor (figure 2). It consists of a central area of intracutaneous oedema affecting the epidermis and upper dermis, with a peripheral area of reflex erythema that is fleeting in nature. Urticarial lesions are usually associated with an itching or burning sensation. Lesions may be round, annular, or serpiginous (wavy or serpent-like) in shape.

A ‘wheat and flare’ reaction usually resolves within 1-24 hours. Lesions lasting longer than 24 hours accompanied with painful or burning sensation or that result in scarring are suggestive of urticarial vasculitis.

**Angioedema**

In contrast, angioedema is defined as an abrupt and episodic swelling of the submucosal or subcutaneous tissues, usually affecting the lower dermis and subcutis. It is a non-pitting swelling that develops in minutes or hours, and takes a longer time to resolve, up to 72 hours. The affected areas feel numb, tingling or painful rather than pruritic. Swelling develops in an asymmetrical fashion and frequently involves the facial mucous membranes (figure 3) and those of the genitalia. The oropharynx and membranes (figure 3) and those of the genitalia. The oropharynx and

Angioedema of the face.

Lesions lasting longer than 24 hours accompanied with painful or burning sensation or that result in scarring are suggestive of urticarial vasculitis.

**History and examination**

The diagnosis of urticaria is primarily clinical. A detailed history and thorough examination is essential in establishing the diagnosis.

Given the heterogeneity of urticaria, it is important to identify any causative factors, exclude possible differential diagnoses and assess the impact of disease.

Important details that should be elicited in the history include those shown in the box, right.

In addition, patients should also be asked about any recent travel, infections, associated atopic conditions, sexual history and systems review. It is estimated that in 80-90% of all chronic urticaria cases, the exact cause is unknown.

To exclude other systemic causes of urticaria, it is important to note any relevant signs and symptoms, including fever, weight loss, arthralgia, arthritis, cold or heat sensitivity, abdominal pain and bone pain.

As there is a significant association between chronic urticaria and autoimmune thyroid disease, any history of thyroid disease is important.

On physical examination, test for dermatographism by stroking the affected skin in the areas indicated by the history. Ideally, patients should stop taking antihistamines and related medications 2-3 days before the examination. Subsequent investigations are guided by clinical impression and findings from the history and physical examination. Acute urticaria is typically self-limiting and requires minimal investigation.

Most cases are idiopathic or caused by URTI. Allergic reactions to food or drugs may be confirmed by anaphylaxis, chemotactic and vasoactive peptides. The diagnostic workup of chronic urticaria manifesting as recurrent wheals with or without angioedema is best approached by ascertaining how long it takes for lesions to resolve. Individual wheals lasting less than two hours may suggest physical urticaria, and the appropriate physical challenge tests may be indicated.

For lesions lasting from 2-24 hours, a trial of antihistamines may first be considered. Non-responders would require extensive investigations. If lesions persist for more than 24 hours, a skin biopsy should be taken to rule out the possibility of other urticarial syndromes such as urticarial vasculitis.

**Investigations**

Chronic or systemic causes of urticaria should first be evaluated with a basic blood workup, including an EBC with differential white cell count, ESR or CRP, LFTs and urinalysis. Any medications suspected to be triggering symptoms should be stopped or replaced.

If indicated by the history, additional tests to rule out systemic causes include:

- Hepatitis A, B, C serology.
- Infectious mononucleosis serology.
- Thyroid function tests and autoantibodies (antithyroglobulin and antimicrosomal antibodies).
- Anti-nuclear antibodies (ANA).
- Helicobacter pylori serology.
- Autologous serum skin tests.
- Leucocyte biopsy.

Intensive and expensive general screening to investigate underlying causes is only recommended for individuals with longstanding, persistent urticarial symptoms. A review of laboratory testing for chronic urticaria has revealed that only 1.6% of patients were identified as having an underlying systemic condition, and there was no significant association between the

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**Image 180x671 to 612x872**

**Figure 2:** Wheals present on anterior aspect of the upper thighs.

**Figure 3:** Angioedema of the face.

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**Key components of the history in urticaria evaluation**

1. Time of onset and duration of individual lesions
2. Frequency and duration of symptoms
3. Size, shape and distribution of wheals
4. Associated symptoms, eg, pruritus, pain
5. Associated angioedema
6. Previous treatment and response to treatment
7. Previous and/or current allergies, infections, systemic diseases and other comorbidities
8. Past history or symptoms of thyroid disease
9. Correlation of symptoms with food, weekends, holidays, foreign travel
10. Medication history — especially NSAIDS, ACEIs
11. Past and family history of atopy or urticaria
12. Smoking and alcohol history
13. Correlation of symptoms with weather, exercise or any physical agents
14. Work, hobbies, external stressors
15. Gastrointestinal or psychiatric diseases
16. Surgical implantations and events during surgery

Adapted from Zuberbier T, et al. 2

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## References

1. Zuberbier T, et al. 2

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**Table 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>URTI, food, drugs</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>Autoimmunity, infection</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>Chronic conditions, infection</td>
</tr>
<tr>
<td>Systemic causes</td>
<td>Systemic diseases</td>
</tr>
</tbody>
</table>

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**Figure 2:** Wheals present on anterior aspect of the upper thighs.

**Figure 3:** Angioedema of the face.
How to treat carpal vasculitis.3 With testing for immunoglobulins, immunofluorescence microscopy or freshly snap-frozen for direct skin, placed in Michel’s media obtaining a skin biopsy, patients Skin biopsies A skin biopsy should be obtained when urticarial lesions persist for more than 24 hours. When obtaining a skin biopsy, patients should ideally stop taking anti-histamines, glucocorticoids and leukotriene-modifiers (eg, montelukast) for several days. Biopsy samples should be obtained from fresh lesional skin and placed in formalin or haematoxylin and eosin staining. In chronic urticaria with episodic features of systemic mast cell mediator release, such as flushing, abdominal cramping and diarrhoea, wheezing, light-headedness and syncope, a biopsy should be obtained to rule out mastocytosis.3 If patients present with: • Painful rather than pruritic urticarial lesions, associated petechial or purpuric character-istics and residual pigmen-tation; • Elevated ESR or CRP with sys-temic symptoms; and/or • Unresponsiveness to antihista-mines therapy, a 3mm punch biopsy of lesional skin, placed in Michel’s media or freshly snap-frozen for direct immunofluorescence microscopy with testing for immunoglobulins, may be indicated to rule out urti-carial vasculitis.3

Table 3: Skin provocation tests for different physical urticarias.1,2,13 The triggering threshold, maximal reaction and reaction time should be noted.

<table>
<thead>
<tr>
<th>Types</th>
<th>Routine investigations</th>
<th>Additional investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold contact urticaria</td>
<td>Cold provocation and threshold tests (contact with cold objects)</td>
<td>Exclude other light-induced dermatoes</td>
</tr>
<tr>
<td>Delayed pressure urticaria</td>
<td>Application of localised percutaneous pressure</td>
<td></td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Exposure to UV and visible light of different wavelengths</td>
<td></td>
</tr>
<tr>
<td>Localised heat contact urticaria</td>
<td>Application of localised heat source</td>
<td></td>
</tr>
</tbody>
</table>

Skin provocation tests In suspected cases of physical urticaria, skin provocation tests should be performed to identify physical triggers. For diagnosis, it is important to identify the trigger and determine its threshold, which is helpful for assessment of disease severity and treatment response.

Corticosteroids A short course of corticosteroids may be considered for patients with chronic or severe urticaria refractory to aggressive treatment with antihistamines and leukotriene antagonists. They should only be used for urticaria and in the treatment of acute flares of chronic spontaneous urticaria. Dosing should not exceed 25mg every other day or 10mg daily, and should be tapered over 2-3 weeks. Chronic urticaria improves with time and can eventually be managed without corticosteroids.18

Immunotherapy If patients fail to respond to any of the above-mentioned approaches, various immunomodulatory effects and demonstrates clinical response, is rapid in small doses, but in some
patients it can take several weeks to take effect. This drug is generally well tolerated and can maintain disease remission even after stopping treatment. It is necessary to monitor for a predictable drop in haemoglobin levels in all patients it can take several weeks to achieve within 1-2 weeks. However, there may be significant adverse effects that warrant frequent monitoring.

A retrospective case review of 16 patients concluded that methotrexate may be useful for refractory chronic urticaria as a alternative or substitute for third-line treatments (such as cyclosporine) when such treatments are ineffective or contraindicated. IV immunoglobulin can achieve rapid responses ranging from transient partial relief to long-lasting complete remission. However, treatment with IV immunoglobulin has only been reported in limited case reports and short series on patients, therefore the optimum dose and number of infusions is unclear.

Adrenaline
Adrenaline may be indicated for severe or life-threatening urticarial eruptions and angioedema leading to anaphylaxis. Injectable adrenaline solution has rapid onset but limited duration of action. They are usually administered as 10 μg/kg (0.01mL) to a maximum of 500μg (0.5mL) doses in 1:1000 solution IM or IV every five minutes if necessary. Adrenaline and intramuscular adrenaline may be necessary for patients who demonstrate little response to antihistamines and corticosteroids. This is particularly so in patients with angioedema presenting with oedema of the larynx, pharynx or tongue.

Adrenaline can only be used in severe urticaria.

**Adrenaline**
- **Initial dose**: 0.1mg/kg IM or IV
- **Side effects**: Palpitations, headache, tremors, nausea, flushing

**Corticosteroids**
- **Prednisone**
  - Adult: 10mg once daily
  - Children: 0.5mg/kg once daily
- **Side effects**: Hyperglycaemia, hypertension

**Immunotherapy**
- **Cyclosporine**
  - Initial dose: 100mg bd PO
  - Top-up: 250-500mg q2-3weeks

**Phototherapy**
- **Narrowband UV-B phototherapy**

**Topical measures**
- **Tea tree oil**
- **Cooling lotions**

**Table 4: Pharmacological treatments for urticaria**

<table>
<thead>
<tr>
<th>Severity of disease</th>
<th>Treatment option</th>
<th>Initial dose</th>
<th>Side effects</th>
<th>Drug use in pregnancy (Category)</th>
<th>Monitoring/preventive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Cetirizine</td>
<td>Adults: 10mg once daily, Children (6-12): 5mg bd.</td>
<td>Headache, sedation, fatigue, dry mouth.</td>
<td>B1</td>
<td>If persistent symptoms, may titrate dose up to four times normal dosage. Not to be co-administered with CYP3A4/CYP2D6 drugs</td>
</tr>
<tr>
<td></td>
<td>Loratadine</td>
<td>10mg once daily</td>
<td>Headache, sedation, fatigue, dry mouth.</td>
<td>B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desloratadine</td>
<td>Adults: 5mg daily, 6-11 years old: 2.5mg daily, 1-5 years old: 1.25mg daily</td>
<td>Headache, fatigue, dizziness or drowsiness and nausea</td>
<td>B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fexofenadine</td>
<td>180mg daily</td>
<td>Headache, fatigue, dizziness or drowsiness and nausea</td>
<td>B2</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Hydroxyzine</td>
<td>25-50 mg PO or IM tds-qid.</td>
<td>REM sleep interference, learning difficulties, sedation</td>
<td>A</td>
<td>Interacts with alcohol and many drugs including sedatives, hypnhetics and monoamine oxidase inhibitors. Patients must be advised against driving.</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>Adults, children 12 years: 10mL or 50mg tab daily 25-75mg noce or 10-20mg bd/tid</td>
<td>Drowsiness and somnolence</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promethazine</td>
<td>4mg tds, not exceeding 32mg tds</td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyproheptadine</td>
<td>20mg-50mg daily</td>
<td>Itching, swelling, lightheadness, drowsiness, dizziness, feeling flushed, throat tightness, nausea, palpitations, metallic taste, headache, tongue swelling, blurry vision, rash, urticaria, exfoliative dermatitis, pruritis</td>
<td>B1</td>
<td>Inhibits P-450 CYP enzymes and potentiates effects of drugs metabolised by this pathway.</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>20mg bd PO</td>
<td>Fatigue, fever, abdominal pain</td>
<td>B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td></td>
<td>Throat irritation, cough and transient bronchospasm</td>
<td>B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
<td></td>
<td></td>
<td>B3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nizatidine</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>Adults: 10mg daily</td>
<td></td>
<td>B1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium Cromoglicate</td>
<td>20mg bd PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mast cell stabiliser)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>30mg daily PO</td>
<td>Sedation, xerostomia and constellation</td>
<td>C</td>
<td>May be considered for refractory chronic urticaria can also interacts with other drugs metabolised via the cytochrome P-450 pathway (eg, erythromycin, ketoconazole)</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>10mg daily PO</td>
<td>Hyperglycaemia, hypertension</td>
<td>A</td>
<td>Not recommended for long-term use</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>100mg bd PO</td>
<td>Anaemia, toxic hepatitis, jaundice, pancreatitis, vertigo</td>
<td>-</td>
<td>Monitor blood pressure, serum creatinine, blood urea nitrogen level, FBC, LFTs and urinalysis should be performed every 6-8 weeks</td>
</tr>
<tr>
<td></td>
<td>Dapson</td>
<td>100mg daily PO</td>
<td></td>
<td>B2</td>
<td>FBC, LFTs, G6PD levels</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>10-15mg weekly</td>
<td></td>
<td>D</td>
<td>FBC, LFTs, EUC</td>
</tr>
<tr>
<td>Adjunctive</td>
<td>Topical antipruritic lotion (pramoxine lotion)</td>
<td>As needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cooling lotions (Sarna lotion)</td>
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<td>Tepid showering or tepid oatmeal baths</td>
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**Table 4:** Pharmacological treatments for urticaria

- **H1 antihistamines**
- **Sedating H1 antihistamines**
- **Non-sedating H1 antihistamines**
- **H2 antihistamines**
- **Leukotriene antagonists**
- **Tricyclic antidepressants**
- **Corticosteroids**
- **Immunotherapy**
- **Topical measures**
**Children**

The diagnostic workup and management of urticaria in children should be the same as that in adults, as the differential diagnosis underlying the causes of chronic urticaria is similar. As children and adults have been associated with teratogenic effects, it is important to assess the risk of teratogenicity and benefits of using antihistamine therapy during pregnancy.25

First-generation sedating H1 antihistamines such as chlorpheniramine and diphenhydramine, and second-generation non-sedating H1 antihistamines loratadine, levocetirizine and cetirizine, are all US Food and Drug Administration category B drugs that do not have a major teratogenic effect.25 Paraoxonase, deinosoratadine, terfenadine and astemizole are classified as category C drugs that may be teratogenic, therefore their use is contraindicated in pregnancy.25 The Australian classification of these drugs for use during pregnancy is shown in Table 4 (page 31).

Use of antihistamines in the first-trimester antihistamines just before parturition may exert an oxytocin-like effect resulting in premature contractions, and the neonate may have withdrawal symptoms, including irritability. Recent studies have ruled loratadine as a possible causative factor of hypopapdas in infants whose mothers have previously taken loratadine during pregnancy, and suggest that loratadine does not represent a major teratogenic risk.25 Urticarial symptoms during the first trimester are preferably managed with bland topical emollients, and use of systemic antihistamine therapy is best avoided to minimise the risk of teratogenicity.25

First-generation H1 antihistamines are recommended for treating urticaria during pregnancy, as they are widely used and have well-established data on their safety and side-effects.25

In the patient who is intolerant or non-responsive to first-generation H1 antihistamines, the use of second-generation H1 antihistamines — loratadine or cetirizine — is recommended for use, preferably after the first trimester. These drugs are also best avoided during early pregnancy when organogenesis is taking place.25

How to Treat Quiz

Urticaria — 15 February 2013

1. Which THREE statements regarding the pathology of urticaria are correct?
   a) The key feature that defines urticaria is that the individual lesions, wheals and/or angioedema are present for at least one week.
   b) The pathological phenomenon in urticaria is vasodilation and increased permeability of the cutaneous and submucosal microvasculature, causing transient intravascular oedema.
   c) The area of oedema of a wheal involves the entire epidermis and extends into the upper subcutaneous dermis.
   d) Wheals bleach with pressure, which causes central pallor in the lesion.

2. Which THREE statements regarding the pathogenesis of urticaria are correct?
   a) Increased vasopermeability of the microvasculature occurs in the lower dermis and subcutaneous region in angioedema.
   b) The pathogenesis of urticaria involves activation of cutaneous mast cells and their subsequent degranulation, resulting in histamines and many other inflammatory cytokines being released.
   c) Neutrophils have no role in the pathogenesis of urticaria.
   d) Mast-cell mediators stimulate cutaneous sensory nerves that produce the pruritus and burning sensation that is commonly encountered in urticaria.

3. Jane, 45, presents after many episodes over summer of sudden-onset, itchy, raised, red skin lesions on her trunk and limbs, lasting several hours after dipping in the ocean. Which TWO statements are correct?
   a) Jane has phylloysis rosea.
   b) Jane is in the group with the highest prevalence of chronic urticaria.
   c) Jane is likely to have the urticarial subtype of cold urticaria.
   d) Jane’s urticaria would be classified as acute urticaria.

4. Which TWO statements are correct regarding acute and chronic urticaria?
   a) Drug or food reactions are common causes of acute spontaneous urticaria in adults.
   b) The mean duration of chronic urticaria is 10 years.
   c) Chronic autoimmune urticaria occurs when IgG autoantibodies present in the serum bind onto the alpha-subunit of the high-affinity IgE receptor, and activate mast cell degranulation and release of histamine.
   d) Helicobacter pylori has been proven to be a cause of chronic urticaria.

5. Which TWO statements regarding chronic urticaria and thyroid disease are correct?
   a) Three per cent of patients with chronic urticaria have elevated levels of thyroid peroxidase antibodies or anti-microsomal antibodies as compared with the general population.
   b) There is a positive association between chronic urticaria and histological thyroiditis.
   c) Patients with thyroid autoantibodies have more persistent urticaria that is poorly responsive to standard therapies.
   d) Patients with chronic urticaria are at risk of developing autoimmune thyroid disease and should undergo screening for autoimmune thyroiditis and thyroid dysfunction.

6. Which THREE statements are correct regarding wheals and angioedema?
   a) A wheal is a well-defined erythematous plaque that is usually associated with intense pruritus or a burning sensation.
   b) Wheals lasting longer than 24 hours accompanied by a painful or burning sensation or that result in swelling are suggestive of urticarial vasculitis.
   c) Angioedema is a gradually developing pitting oedema that resolves within 1–2 hours.
   d) The swelling of angioedema develops in an asymmetrical fashion and frequently involves the facial mucous membranes and those of the genitilia.

7. Which TWO statements are correct regarding investigations in patients with urticaria?
   a) All patients who have an episode of urticaria should have extensive testing to exclude associated systemic diseases including hepatitis and Epstein–Barr virus serology and a leossal biopsy.
   b) Anti-histamines, glucocorticoids and other relevant medications should ideally be discontinued before skin biopsy.
   c) Skin provocation tests should be performed to identify physical triggers when physical urticaria is suspected.
   d) The autologous serum skin test (ASST) is a highly sensitive and specific test to diagnose chronic autoimmune urticaria.

8. Which THREE statements regarding medication are correct?
   a) Drugs that commonly cause non-allergic hypersensitivity reactions are NSAIDs and ACEIs, both of which can elicit and aggravate pre-existing urticaria.
   b) The older, first-generation H1 antihistamines are considered first-line treatment for urticaria.
   c) Montelukast is reported to be an effective treatment for NSAID-exacerbated chronic urticaria.
   d) Corticosteroids can be used for acute urticaria and for the treatment of acute flares of chronic spontaneous urticaria.
   e) A low dose of cyclosporine is effective against urticaria that is refractory to conventional treatment.
   f) Dapsone is an immune modulator that has a small but immediate response in patients with chronic urticaria.
   g) Methotrexate may be useful for refractory chronic urticaria as an alternative or substitute for third-line treatments when such treatments are ineffective or contraindicated.
   h) Acute onset of hereditary angioedema (HAE) requires immediate adrenaline, intubation and transfusion with fresh frozen plasma or Cl inhibitor concentrate to abort acute episodes.

9. Which THREE statements are correct regarding immunotherapy treatment in urticaria?
   a) A low dose of cyclosporine is effective against urticaria that is refractory to conventional treatment.
   b) Dapsone is an immune modulator that has a small but immediate response in patients with chronic urticaria.
   c) Methotrexate may be useful for refractory chronic urticaria as an alternative or substitute for third-line treatments when such treatments are ineffective or contraindicated.
   d) Acute onset of hereditary angioedema (HAE) requires immediate adrenaline, intubation and transfusion with fresh frozen plasma or Cl inhibitor concentrate to abort acute episodes.

   *The mark required to obtain points is 80%.* Please note that some questions have more than one correct answer.

**GO ONLINE TO COMPLETE THE QUIZ**


**Special considerations**

**Pregnancy**

There has been a lack of evidence for treatment of urticaria in pregnancy. As urticaria and angioedema have been associated with teratogenic effects, it is important to assess the risk of teratogenicity and benefits of using antihistamine therapy during pregnancy.25

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**Algorithm for treatment of chronic urticaria**

The most recent international treatment algorithm for urticaria was published by the GAELIN, Global Allergy and Asthma Network in 2006.27 In summary, non-sedating H1 antihistamines should be initiated as the first-line treatment, and the dosage may be titrated up to four times the baseline amount to achieve symptomatic control. If required, leukotriene antagonists, cyclosporine, H2-antihistamines, dapsone, omaluambal may be added as adjunctive therapy to achieve symptom control. Acute exacerbation of symptoms may be controlled with a tapering course of corticosteroids for 3–7 days.25

**References**

Available on request from howstotre@reedbusiness.com.au

**MedicineNet**

Hives and Angioedema
www.medicinenet.com/hives/article

Royal Children’s Hospital Melbourne
Clinical Practice Guidelines — Urticaria
www.rrg.org.au/clinicalguide/ guideline_index/Urticaria

Therapeutic Goods Administration

**How to Treat** Editor: Dr Barbara Tink

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**NEXT WEEK**

Pertussis or ‘whooping cough’ affects all age groups, but is most serious in infants, who are at risk of dying from it. The next How to Treat gives an up-to-date account of managing this concern in the Australian context. The authors are Dr Brinny Hazlett, advanced trainee in paediatric infectious diseases and microbiology, Centre for Infectious Diseases and Microbiology, Westmead Hospital; and Professor Gwendaonil Gilbert, director, Centre for Infectious Diseases and Microbiology — Public Health, Westmead Hospital, and clinical professor, Sydney Emerging Infectious Diseases Network, University of Sydney, NSW.