Urticaria: chronic

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> "I get completely covered in this itchy rash – it's horrible. I come out in these big lumps but by the time I can get an appointment to see you, they have disappeared." And, if you are lucky, they then offer you a picture on their phone to help you to confirm the diagnosis!

Chronic spontaneous urticaria is pretty common, affecting 0.5–1% of adults at any given time. It is more common in women and tends to present between the ages of 20 and 40y. It can be tricky to manage and we often end up using off-licence doses of antihistamines. This was the subject of a DTB review (DTB 2018;56:45).

The seemingly random occurrence of episodes and the intense, sleep-disrupting itch can significantly affect quality of life: a 2022 NEJM review

points out that the quality-of-life reduction in chronic urticaria is similar to that seen in patients waiting for CABG! (NEJM 2022;387:824)

This article is based on the DTB and NEJM reviews mentioned above and was reviewed in November 2022.

1.1. Aetiology

All types of urticaria tend to have a similar clinical presentation – transient, intermittent, red, raised, itchy skin eruptions which occur as a result of mast cell activation and the release of histamines and other inflammatory mediators into the epidermis. These intensely itchy lesions can range from a few millimetres to several centimetres in diameter. Each individual lesion should resolve within 24h without bruising or pain (bruising and/or pain would point to vasculitis).

Usually, urticaria occurs in isolation. However, in some cases, it may be associated with angioedema where a similar process occurs in the deeper dermis and is much more severe, potentially affecting swallowing and breathing. Angioedema may also affect the genitals and GI tract.

Chronic urticaria is defined as symptoms lasting >6w. It is then further defined by whether a trigger can be identified.

1.2. Types of chronic urticaria

Trigger identified	No trigger identified
Physical/inducible urticarias: • Heat. • Cold. • Pressure (either seen immediately as dermatographia or as delayed pressure urticaria, e.g. from a belt or bra). • Vibration. • Sunlight. • Stress. • Menstruation. • Exercise – note that people with exercise-induced urticaria are at risk of exercise-induced anaphylaxis! (NEJM 2022;387:824) Associated with drugs, e.g. NSAIDs, opiates, ACE inhibitors, alcohol.	Chronic spontaneous urticaria – common. Chronic urticaria associated with systemic illness (e.g. rheumatological disease, haematological malignancy, infections such as hep B and C, TB) – rare.

The DTB article focuses on chronic spontaneous urticaria; note that NSAIDs, opiates, ACE inhibitors and alcohol can all make it worse.

1.3. Diagnosis and investigations

Chronic spontaneous urticaria is mainly diagnosed on the history and an absence of the factors mentioned above. The DTB article recommends very

simple blood tests:

- FBC – to look for underlying infection, eosinophilia suggesting parasites or haematological malignancy.
- ESR/CRP – to look for underlying infection or inflammatory disorder.

The NEJM review states that we do **not** need to screen for potential underlying infectious causes in an otherwise healthy person as these are very rare.

There are scoring systems to monitor the severity of the condition and its impact on quality of life – *I suspect these are more useful in trial settings and secondary care if experimental treatments are being considered, but there is a link below if you think they might be useful.*

1.4. Management

Avoiding exacerbating factors, e.g. overheating, tight clothes, NSAIDs and alcohol, may be all that is necessary for those with mild symptoms.

Standard-dose antihistamines

Standard-dose, non-sedating, long-acting, second-generation antihistamines are the first-line choice if medication is needed. The NEJM review advises that these should be taken regularly in chronic urticaria to prevent flares, rather than on an as-needed basis in response to them. There are no head-to-head trials comparing different drugs so we can't say which is most effective.

- **Choose the cheapest over-the-counter preparation first, e.g.**

cetirizine or loratadine.

- If one drug is ineffective at standard dose, it is worth trying an alternative as response varies. Options include:

Drug at standard licensed dose
Loratadine 10mg Cetirizine 10mg Desloratadine 5mg Fexofenadine 180mg Levocetirizine 5mg Mizolastine 10mg Bilastine 20mg Rupatadine 10mg

First-generation antihistamines (e.g. chlorphenamine and promethazine) are not recommended first line as they only have an antipruritic effect for 4–6h, while their sedative effect lasts at least 12h.

Do standard dose antihistamines work?

A Cochrane review showed only modest benefits of standard-dose antihistamines for some patients. Some did not respond at all (Cochrane 2014 CD 6137).

High-dose antihistamines

Several national guidelines, including those from British Association of Dermatologists (British Journal of Dermatology, 2022;186:398) and British

Society for Allergy and Clinical Immunology (Clinical & Experimental Allergy, 2015;45:54), recommend that higher-than-licensed doses of second-generation antihistamines (e.g. loratadine, cetirizine) may be used as a second-line option if symptoms have not responded adequately to a trial of a standard dose of at least 2 of the drugs listed above.

- They recommend doses up to four times the standard dose in both adults and children (with less preference for cetirizine in children as it will sometimes cause drowsiness, especially at above the licensed dose).
- A number of small, imperfect RCTs have shown that these higher doses can be effective where lower doses have failed, and appear to be safe and well tolerated. They are not effective for everyone.
- A systematic review of 15 studies, 5 of which were high quality, compared standard and very-high-dose regimens. It found no difference in the number of weals but a greater improvement in itch in the higher-dose group. Of patients not responding to standard-dose antihistamines, 60% responded to higher-dose antihistamines.
- Prescribing second-generation antihistamines at these doses is off licence and should be discussed with patients as per GMC guidance.

Leukotriene receptor antagonists (e.g. montelukast)

- Off licence but indicated if antihistamines are not effective. None of the publications we looked at for this article specify whether montelukast should be started in primary or secondary care for urticaria, but we suggest it would be sensible to seek secondary care advice if using it for this indication.

Secondary care options

- **Oral steroids** are sometimes used to achieve control of chronic urticaria while arranging other treatments, but the NEJM article points out the risks of adverse effects and the risk of relapse of urticaria on stopping them (NEJM 2022;387:824). The British Association of Dermatology guideline reminds us to use the lowest possible dose for the shortest possible period.
- **Monoclonal antibodies for chronic urticaria**: anti-IgE monoclonal antibodies can be considered for use by specialists only in the context of severe persistent allergic urticaria. They are given by subcutaneous injection. A 2015 NICE technology appraisal (NICE TA339, 2015) supports the use of omalizumab in secondary care for severe chronic urticaria that hasn't responded to antihistamines and leukotriene receptor antagonists. The evidence base for its safety and efficacy is growing. A 2021 systematic review looked at ten RCTs involving 1620 patients; it found that higher-dose omalizumab improved disease activity, itch and quality of life, with a suggestion that omalizumab might reduce overall drug-related adverse events by reducing rescue medication use (Allergy 2021;76:59).
- In severe disease, cyclosporine or other immunosuppressant drugs may be used.

1.5. Natural history

Spontaneous remission is the most common outcome but 10% will still be affected after 5y. Prolonged symptoms are more common in the physical/inducible urticaria group – i.e. those **with** an identifiable trigger such as heat or pressure.

This is somewhat positive: we can either tell patients that symptoms may improve with avoiding their identified trigger, or, if there are no triggers, we can tell them they're in the group most likely to spontaneously remit within a year!

Relapses also occur so urticaria can be quite unpredictable!

1.6. Referral

NICE recommends referral to dermatology/immunology if symptoms are not adequately managed with antihistamines, or if there is diagnostic doubt (NICE TA339, 2015).

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- Avoid exacerbating factors and triggers.
- Try standard-dose, over-the-counter cetirizine or loratadine first.
- Try at least two standard-dose, second-generation antihistamines if the first is ineffective.
- Up to 4 times standard-dose, second-generation antihistamines are recommended second line in guidelines, and there is some evidence to support this. It is unlicensed, and usual GMC guidance for discussion and documentation applies.
- In chronic urticaria, if antihistamines are not working, refer to secondary care where a range of treatments are available.

Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

BAD – urticaria and angio-oedema

- DermNet NZ – chronic spontaneous urticaria