# Chronic Urticaria in Children

Irene Lara-Corrales, Alexandra Balma-Mena and Elena Pope

*Clin Pediatr (Phila)* 2009; 48; 351 originally published online Dec 17, 2008;
DOI: 10.1177/0009922808328543

Clinical Pediatrics
Volume 48 Number 4
May 2009 351-355

10.1177/0009922808328543
http://clp.sagepub.com
hosted at
http://online.sagepub.com

# Chronic Urticaria in Children

Irene Lara-Corrales, MD,
Alexandra Balma-Mena, MD, and Elena Pope, MD

Chronic urticaria (CU) is a common problem encountered by pediatricians in their practice. Although rarely life threatening, it is anxiety provoking for the affected patients and family because of its persistence, poor response to treatment, and lack of identifiable causes.

## Definition

Urticaria consists of transient swelling and redness of the skin caused by plasma leakage. This clinically translates to the appearance of wheals (Figure 1). Depending on the duration, it can be divided into acute urticaria or CU. Acute urticaria is defined as the presence of hives for less than 6 weeks, whereas CU lasts longer. CU can present with or without angioedema, which is characterized by subcutaneous involvement, resulting in deeper swelling. "Urticaria-like" rashes (Figure 2) have been described in the literature, and clinically present as CU but are less itchy.

## Epidemiology

Urticaria is a common entity. Up to 25% of the population will experience at least one episode of urticaria in their lifetime,[1] and a fourth of these cases will present as CU.[2] CU in pediatrics is less common than in the adult population, affecting 0.1% to 3% of children.[3]

From the Department of Pediatric Dermatology, Hospital for Sick Children, Toronto, Ontario, Canada.

Address correspondence to: Irene Lara-Corrales, Department of Pediatric Dermatology, Hospital for Sick Children, 555 University Avenue, Toronto M5G1H4, Ontario, Canada; e-mail: irelaraco@gmail.com.

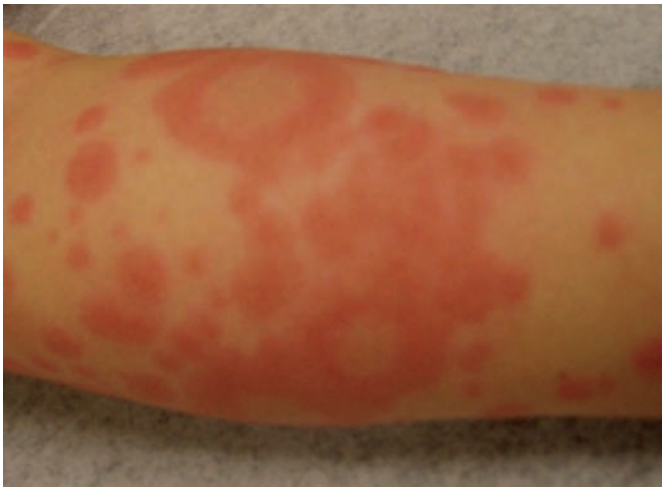

**Figure 1.** Wheals in chronic urticaria.

## Pathogenesis

For a wheal to develop, a given antigen has to bind to an antigen-specific IgE present on the surface of a mast cell. As a result, the mast cell degranulates, releasing histamine and vasoactive mediators. These mediators produce vasodilatation, increased blood flow, and vascular permeability. The final result is fluid extravasation and swelling of the superficial dermis that clinically translates as a wheal. Subsequently, an axonal reflex produces the surrounding flare. This reaction is known as the triple response of Lewis.[4] (see Figure 3).

## Clinical Findings

Wheals are the primary finding that characterizes CU. Individual wheals are raised, pruritic, erythematous, or pale and vary in size from a few millimeters to several centimeters. When large, they may present

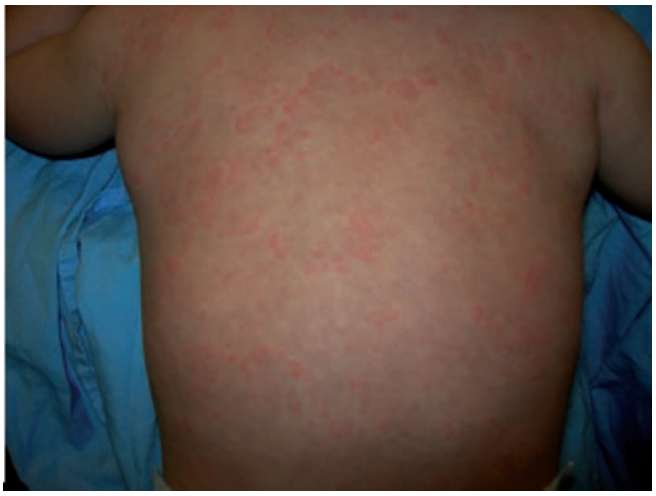

**Figure 2.** Urticaria-like rash.

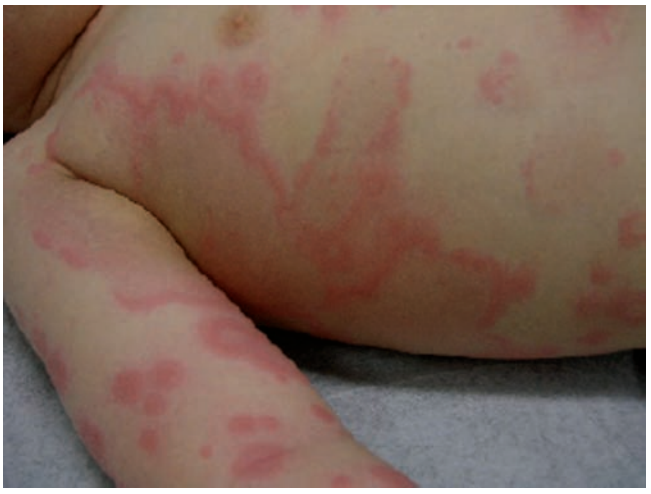

**Figure 4.** Patient with chronic urticaria.

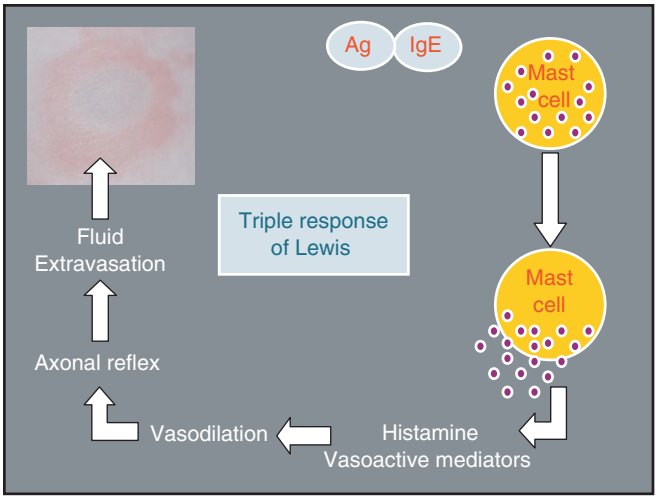


**Figure 3.** Triple response of Lewis.

with a relative central clearing; this can be easily confused with other annular erythemas, such as erythema multiforme. What differentiates urticaria from other erythemas is the fact that lesions are migratory and transient, usually lasting less than 24 hours, and resolve with no residuals. Any area of the body can be involved; the extension and location of the wheals are not related to the outcome (Figure 4).

## Classification

The most common way of classifying CU is by its etiology, breaking it down into idiopathic, immunological, nonimmunological, and cryopyrin-associated syndromes. The IgE-dependent reaction defines immunological CU, whereas nonimmunological CU is the result of direct mast cell degranulation precipitated by various factors. Less common cryopyrin-associated syndromes, such as some of the periodic fever syndromes, constitute a separate group.[5]

The most common type of CU in children is idiopathic. In a study of 226 patients with CU, a cause was determined in only 20%.[6] Less common types of CU in children are the physical urticarias (cold-induced, aquagenic, vibratory, solar, cholinergic, and delayed pressure) and urticarial vasculitis among others.

The diagnosis of idiopathic chronic urticaria (ICU) is made when no apparent trigger or other cause is identified. In the last decade, 40% to 60% of the cases of ICU have been reclassified as autoimmune idiopathic urticaria (AIU).[7] The prevalence of AIU in childhood is 30%.[8] In ICU, about 30% to 50% of patients appear to have circulating autoantibodies—IgG against the α-chain of the IgE receptor.[9]

In physical urticarias, a physical stimulus is identified as the trigger to the urticarial episodes. The diagnosis can be easily made by a challenge or provocation test. Once identified, no further investigations are indicated. The most common of these urticarias is dermographism, affecting about 5% of the general population.[10] Other less common types include delayed pressure urticaria, cholinergic, solar, cold, aquagenic, and vibratory urticaria. Several of these triggers may coexist in a given patient.

Urticarial vasculitis can also be distinguished as a subset of CU. Clinically, individual lesions last longer than 24 hours, may be painful, and leave a purpuric staining behind. Apart from the skin changes, arthralgias and other systemic associations can be present. These patients usually respond poorly to antihistamines. Pathological confirmation is needed to make the diagnosis, and further investigations are required as this may be the presenting finding of conditions such as systemic lupus erythematosus, Henoch-Schönlein purpura, serum sickness syndrome, and so on.

## Associations

Other documented associations have been made with CU in children. Urinary tract infection caused by *Escherichia coli*, upper respiratory tract infections caused by group A *Streptococcus*, and other infections caused by *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and Epstein-Barr virus have all been reported as causes of CU.[11] Parasites have also been associated with this condition and should be ruled out in endemic regions or with a positive travel history.

In addition, autoimmune diseases can explain some cases of CU. Thyroid autoimmunity and celiac disease[12] are the most common autoimmune conditions associated, but type 1 diabetes,[13] inflammatory bowel disease, systemic juvenile arthritis, and systemic lupus erythematosus have also been reported. A Canadian study of 624 patients with CU demonstrated that 14% had antithyroid autoantibodies in comparison to only 3% to 6% of the controls.[14] In AIU, thyroid autoimmunity has been identified in 4% to 16% of the cases.

Although there have been a few case reports of other conditions presenting as CU, for example, occult infections and malignancy, the frequency is very low.[15,16] There is no statistical association between malignancy and CU.[17] Routine investigations to rule out such associations are not mandatory unless the history and physical examination indicate it.

## Management

Investigations to clarify the cause of CU should be based on the clinical history and physical examination. Extensive routine work-up typically fails to clarify the underlying etiology and is not recommended in mild cases responding to conventional treatment. Different screening panels have been suggested, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, lactic acid dehydrogenase, liver function tests, renal function tests, urine, stool, antinuclear antibodies, thyroid function, celiac screening, and others.[18] Skin allergy tests have also been suggested if an allergen has been identified. However, the value of routine, unguided investigations is not widely endorsed. In a study of 130 patients with CU, 68% had normal screening laboratory tests.[15]

A confirmatory test to diagnose AIU is the autologous serum skin test, which demonstrates that intradermal injection of autologous serum causes an immediate wheal and a flare in patients with CU.[9] This method provides a sensitivity of 70% to detect histamine releasing factor. If the autoimmune nature of CU is revealed, the frustrating search for other causes can be avoided.[19] The gold standard for the diagnosis of AIU is the in vitro basophil histamine release assay; however, this test is not widely available yet.[20]

Skin biopsy is not routinely recommended in cases of CU. The settings in which one should consider a skin biopsy are the following: infantile onset CU, persistent lesions, and urticaria that leaves residual changes. It is helpful mainly to confirm the diagnosis of vasculitis because the diagnosis of CU is a clinical one.[2]

The management of this condition involves the avoidance of detected triggers. If triggers are not identified or impossible to avoid, antihistamines are the first-line treatment. The efficacy and safety of these drugs have been well demonstrated; however, the response and tolerance can vary from patient to patient. It is generally recommended to start with a nonsedating second-generation antihistamine that has fewer side effects and interferes less with daily activities.[21] If there is a lack of response, increasing the dose or adding a first-generation antihistamine in the evening should be considered. Second-line treatment includes adding a H2 receptor antagonist, which has shown benefit as adjuvant therapy, but not as monotherapy. Third-line approaches include doxepin and antileukotrienes. In refractory cases or in cases of AIU, immunomodulating therapies can be considered. Oral steroids may decrease the duration of episodes but may have rebound effects when

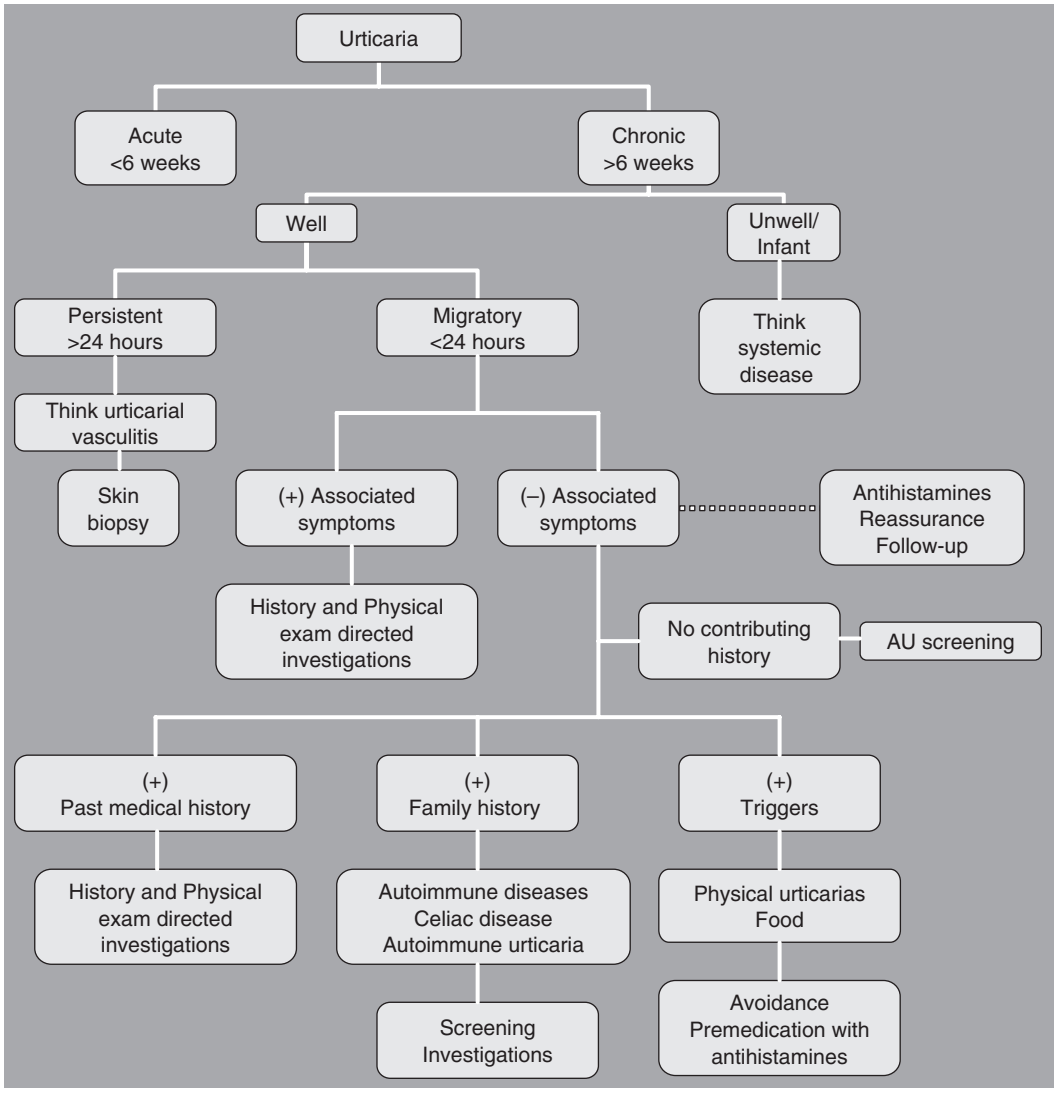


**Figure 5.** Flowchart: approach to chronic urticaria in pediatrics.

discontinued, so they are generally avoided. Steroids can also mask underlying etiologies (except for cases of urticarial vasculitis).

## Prognosis

In about 50% of patients with CU alone, clearing occurs within 6 months.[16] In contrast, in cases of CU with angioedema, 50% are still active 5 years after onset. In Figure 5, we suggest a practical approach to pediatric CU.[16]

## References

1. Monge C, Demarco P, Burman KD, et al. Autoimmune thyroid disease and chronic urticaria. *Clin Endocrinol*. 2007;67:473-475.
2. Greaves MW. Chronic urticaria. *N Engl J Med*. 1995;332:1767-1772.
3. Kaplan AP. Clinical practice: chronic urticaria and angioedema. *N Engl J Med*. 2002;346:175-179.
4. Grattan Clive EH, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol*. 2002;46:645-657.
5. Bailey E, Shaker M. An update on childhood urticaria and angioedema. *Curr Opin Pediatr*. 2008;20:425-430.

6. Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy*. 1992;69: 61-65.
7. Kozel MM, Sabroe RA. Chronic urticaria aetiology, management and current and future treatment options. *Drugs*. 2004;64:2515-2536.
8. Brunetti L, Francavilla R, Miniello VL, et al. High prevalence of autoimmune urticaria in children with chronic urticaria. *J Allergy Clin Immunol*. 2004;114:922-927.
9. Sheikh J. Autoantibodies to the high-affinity IgE receptor in chronic urticaria: how important are they? *Curr Opin Allergy Clin Immunol*. 2005;5:403-407.
10. BolognaJL, Jorizzo JL, Rapini RP. *Dermatology*. St. Louis, MO: Mosby; 2003.
11. Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol*. 2002;46:645-657.
12. Camminiti L, Passalacqua G, Magazzu G, et al. Chronic urticaria and associated celiac disease in children: a case control study. *Pediatr Allergy Immunol*. 2005;16: 428-432.
13. Dalal I, Levine A, Somekh E, et al. Chronic urticaria: expanding the "autoimmune kaleidoscope." *Pediatrics*. 2000;106:1139-1141.
14. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol*. 1989;84:853-858.
15. Kozel MM, Bossuyt PM, Mekkes JR, et al. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. *J Am Acad Dermatol*. 2003;48:409-416.
16. Grattan CEH, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol*. 2007;157:1116-1123.
17. Lindelof B, Sigurgeirsson B, Wahlgren CF, et al. Chronic urticaria and cancer: an epidemiological study: study of 1155 patients. *Br J Dermatol*. 1990;123: 453-456.
18. Thomas P, Perkin MR, Cox H, et al. The investigations of chronic urticaria in childhood: which investigations are being performed and which are recommended? *Clin Exp Allergy*. 2008;38:1061-1062.
19. Asero R, Lorini M, Tedeschi A. Chronic autoreactive urticaria at 6 years of age. *J Investig Allergol Clin Immunol*. 2004;14:343-344.
20. Sabroe RA, Greaves MW. Chronic idiopathic urticaria with functional autoantibodies: 12 years on. *Br J Dermatol*. 2006;154:813-819.
21. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2007;37:631-650.