Cold-induced urticaria, or cold urticaria (CU), is a rare but potentially fatal condition caused by cold exposure from local contact with cold objects, immersion of body parts into cold water or ice, or generalized exposure of the body to cold winds or environments such as swimming pools. While the incidence of CU is estimated to be 0.05 percent,\(^1\) prevalence can vary with climate, with a frequency of 5.2 percent seen in tropical regions, and a higher rate of 33.8 percent reported in colder areas.\(^2\) CU is also seen more frequently in girls, with a female to male ratio of two to one.\(^2\)

The mean age of diagnosis is 18 years, but cases of CU have been described in infants as well.\(^1\) A recent study evaluating 30 CU children under the age of 18 found the mean age of onset to be seven years, with no skew towards adolescence. This observation indicates that CU may occur earlier in life than previously thought, and raises the possibility that it is an under-recognized condition among the pediatric population.\(^4\)

Etiology and Presentation
CU can be classified into familial and acquired forms. The familial form is a rare autosomal-dominant trait disorder associated with mutations in chromosome 1q44.\(^3\) Acquired cases of CU have been subdivided into primary, or idiopathic, and secondary causes. Idiopathic CU accounts for greater than 90 percent of cases, while secondary CU is typically due to cryoglobulinemia.\(^4\) Reports of secondary CU associated with bee stings, infectious mononucleosis, measles, HIV, borreliosis, syphilis, vasculitis, hypothyroidism, and certain medications do exist, but no definite causal relationship has been defined.\(^4\)

Currently, the etiology of CU remains unclear. Histamine seems to be the main mediator involved, but other pro-inflammatory factors such as leukotrienes, prostaglandins, proteinases, and kinins that are released during the reaction may play important roles as well.\(^7\) Involvement of these various mediators suggests a multifactorial and pathophysiological complex mechanism for the development of CU.

Clinically, patients with CU typically present with erythema, pruritus, edema, and wheal-formation in the areas of skin exposed to cold.\(^7\) The cutaneous eruptions can appear popular or present as localized cold-dependent dermatographism and are often associated with a burning sensation.\(^7\) Although lesions are usually localized to sites of contact to cold such as the hands or face, more extensive cold exposure from wind or swimming in cold water can result in systemic symptoms such as headaches, fevers, chills, arthralgia, tachycardia, and diarrhea.

In systemic CU, the rash often appears maculopapular, and sometimes involvement of the oral mucous membranes can be seen.\(^7\)

Anaphylaxis. One serious and potentially fatal manifestation of urticaria that clinicians should be aware of is anaphylaxis. Of note, one study found that of 30 children with CU, one-third demonstrated anaphylactic reactions.\(^4\) According to the researchers, the three key risk factors for the development of systemic reactions to cold include the surface area of skin exposed, the temperature of exposure, and the duration of exposure.\(^4\) It is important to note that in severe cases, hypotension, shock, cardiovascular collapse, and death may occur.

Because aquatic activity is reported as the most common trigger for anaphylactic symptoms, children with CU are at increased risk for drowning. Siebenhaar et al. also noted that patients with a history of oropharyngeal edema were at higher risk for developing shock-like reactions from aquatic activity and that suffocation caused by pharyngeal angioedema could even occur after consumption of cold foods and beverages.\(^1\)

In general, symptoms of CU occur immediately within two to five minutes of exposure and then resolve in about one to two hours; however, delayed urticaria is a rare type of CU that can develop three to 24 hours after cold exposure and persist for up to 24 hours.\(^7\) Among the general population, patients can experience chronic, recurrent symptoms upon cold exposure anywhere from a few months to more than 20 years after initial exposure.
presentation, although improvement of symptoms is seen in approximately 50 percent of patients within five years. In children under the age of 18, mean duration of illness has been reported to be 4.1 years.

Diagnosis

Diagnosis can be confirmed by performing a cold-stimulation test: the most common method is named the “ice-cube test.” For this test, an ice cube is placed on the volar aspect of the patient’s forearm (Fig. 1) for an unstandardized period of time, generally about five minutes. After the ice cube is removed and the skin rewarmed, development of erythema and pruritis within two to four minutes (Fig. 2) and the formation of a hive or wheal within 10 minutes (Fig. 3) indicate a positive test. According to a recent study of the ice-cube test performed on 24 children, the optimal time of ice-cube application necessary for an accurate diagnosis of CU without false positive results was found to be three to five minutes. Studies have shown that an inverse correlation exists between the clinical severity of symptoms and the time necessary for a cold stimulus to induce wheal formation, with the development of hypotensive episodes observed more frequently in patients who develop a positive test result in under three minutes.

Although the ice-cube test is the most common diagnostic test performed in most clinics, up to 20 percent of patients with CU can have a negative test result. Patients with a negative ice-cube test may develop a positive reaction if tested for longer periods of time (15-20 minutes), or if they experience cold exposure via other methods. Two alternate cold-stimulation tests include the immersion test, in which the patient’s hand is placed in ice water for four minutes, and the cold-room test, where the patient is placed in a cold room for 10-30 minutes. Like the ice-cube test, neither of these two alternative tests is standardized.

More recently, a standardized instrument for performing cold provocation testing has been developed in Germany. This electronic device called the TempTest exposes skin to defined temperatures, thus allowing accurate temperature threshold and time to reactivity to be assessed. Although this tool has the added benefit of allowing patients to recognize their temperature threshold and thus hopefully better control cold exposures in their daily life, it may not be as economical or convenient to perform. It is important for health care providers to recognize that not all forms of CU will respond to these cold-provocation methods. Additionally, clinicians should be very cautious when performing any type of cold-stimulation test because systemic reactions can be elicited in sensitive patients.

Although rarely diagnostic, laboratory evaluations help to rule out any etiology for secondary CU. Most dermatologists recommend that a complete blood count with differential, an erythrocyte sedimentation rate, and a chemistry profile including liver and renal function tests should be ordered in all patients with suspected CU, in addition to performing a thorough history and physical exam with a cold stimulation test. Some additional tests listed in Table 1 can also be performed if the history, exam, initial lab assessment or clinical suspicion suggests a secondary cause.

![Fig. 1. An ice cube placed on the volar aspect of the forearm.](image1)

![Fig. 2. Development of erythema immediately after removal of the ice.](image2)

![Fig. 3. Appearance of an enlarging wheal after 5 minutes of rewarming.](image3)
Management
Treatment involves prevention, the use of prophylactic antihistamines, and the carriage of epinephrine to prevent anaphylaxis. Avoiding triggers and preventing episodes is a critical aspect of therapy. Patients should avoid cold environments, consumption of cold foods and beverages, and swimming in cold water if possible. If such exposures are unavoidable, patients must limit the duration of cold exposure. In addition, all patients, but especially children, should always have present with them during aquatic activities an adult who knows how to use the emergent epinephrine. Because children with CU are at greater risk for drowning, all patients should be provided with and educated on the use of an epinephrine autoinjector. Wearing a MedicAlert bracelet can also be useful in more cold-sensitive patients.

Traditionally, cyproheptadine hydrochloride has been the mainstay of antihistamine therapy, but doxepin, hydroxyzine, cetirizine, and cinnarizine have also been shown to be effective. A starting dose of 10mg/d of doxepin at bedtime is effective, and this dose can be titrated up gradually as tolerated. Non-sedating antihistamines can be alternative; they have been reported to have fewer side effects, but clinical responses are variable. In patients with suspected secondary CU, the underlying disease must be treated in order to resolve symptoms.

For refractory patients who do not respond to more conservative therapies, induction of cold tolerance may be helpful. This involves very close supervision and typically hospitalization of the patient and prophylaxis with antihistamines while the patient undergoes serial application of cold water several times daily to increasing areas of body surface and with decreasing temperatures. However, cold desensitization is difficult to continue in daily life over an extended period, since it involves high patient compliance with daily cold showers. Otherwise, discontinuation results in complete recurrence of symptoms.

Cold Hard Fact
Children with CU often present with a history of pruritic urticaria, wheals, erythema, edema, or more severe systemic symptoms occurring after cold exposure, usually from swimming. Remember that all children with suspected CU should undergo a cold stimulation test (ice-cube test) to verify the diagnosis, and basic labs should be performed, with more extensive investigations reserved for patients with suspected secondary CU. Because patients with CU are at increased risk for drowning, it is imperative to counsel children and their families regarding avoidance of cold exposure and use of the epinephrine autoinjector, while stressing the importance of close adult supervision of affected patients while swimming.

Treatment with prophylactic antihistamines can also be helpful to suppress milder symptoms and should be implemented when cold exposure is unavoidable.

In general, symptoms of CU occur immediately within two to five minutes of exposure and then resolve in about one to two hours.

The authors have no relevant disclosures.


Table 1. Additional Laboratory Investigations for Suspected Secondary CU

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<tr>
<td>Serum Immunoglobulin Levels</td>
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<tr>
<td>Complement C3, C4, and Total Hemolytic Complement (CH50) Levels</td>
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<tr>
<td>Antinuclear antibody level</td>
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<td>Serum protein electrophoresis</td>
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