

A Systematic Review of Aquagenic Urticaria—Subgroups and Treatment Options



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What is already known about this topic? Aquagenic urticaria (AquaU) is a rare variant of chronic inducible urticaria where wheals occur after skin contact with water. The management of AquaU is a challenge. Little is known about clinical manifestations and treatment outcomes.

What does this article add to our knowledge? AquaU is proposed to be classified into 2 subtypes, familial AquaU and the more common acquired AquaU. The recommended first-line treatment for both types of AquaU is a second-generation H₁ antihistamine (2ndAH₁).

How does this study impact current management guidelines? A standard-dosed 2ndAH₁ should be used as first-line treatment in AquaU. Updosing antihistamines to 4-fold is beneficial when needed. Omalizumab and phototherapy may be considered in patients with refractory AquaU.

BACKGROUND: Aquagenic urticaria (AquaU) is a rare variant of chronic inducible urticaria where wheals occur after skin contact with water. Information on clinical manifestations and treatment outcomes is limited, which makes the management of AquaU challenging.

OBJECTIVE: To systematically review disease features and relevant triggers of AquaU and patients' response to treatment.

METHODS: Related articles were searched by use of the terms "aquagenic urticaria" and "aquagenic angioedema" until June 2021 and reviewed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations.

RESULTS: A total of 77 patients with AquaU were investigated in 59 studies including 47 case reports and 12 case series. AquaU predominantly presented in women (47 patients, 61%), and the mean age of onset of the disease was 19.6 ± 10.8 years (range: 0-54 years). Wheals commonly occurred in localized areas and regardless of the water temperature. Based on the reviewed evidence, AquaU can be classified as familial AquaU (FAquaU, 18.2%) and acquired AquaU (AAquaU, 81.8%). Although many

treatments were used in both subtypes of AquaU, the use of second-generation H₁ antihistamines (2ndAH₁) was reported most often to achieve marked improvement in both subtypes. The use of topical therapies in AquaU, which most commonly use hydrophobic vehicles, is poorly documented and of controversial efficiency.

CONCLUSIONS: AquaU is proposed to be classified into 2 subtypes, FAquaU and the more common AAquaU. Treatment with a 2ndAH₁ is recommended as the first-line treatment for both types of AquaU. Further studies are required to fill knowledge gaps. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2154-62)

Key words: Aquagenic urticaria; Chronic inducible urticaria; Wheals; Clinical manifestation; Treatment

Aquagenic urticaria (AquaU), a rare variant of chronic inducible urticaria (CIndU), is characterized by the occurrence of itchy wheals after skin contact with water, for example, when bathing or swimming. The signs and symptoms of AquaU commonly develop within 30 minutes after exposure to water and last for 30 to 60 minutes.¹ AquaU manifests with small wheals, 1 to 2 mm in size, on the exposed area of the skin.¹ Other signs and symptoms including angioedema, headache, wheezing, difficulty in breathing, dizziness, and anaphylaxis were reported in some patients.^{2,3} AquaU, in most patients, markedly affects daily activities such as bathing, leading to a significant reduction in quality of life.

AquaU was first described in 1964 by Shelley and Rawnsley.⁴ The diagnosis of AquaU is based on the patient's history and the results of provocation testing. According to the EAACI/GA²LEN/EDF/WAO consensus recommendations for CIndU, provocation testing is performed by placing a towel soaked with 35°C to 37°C water or physiological saline on the patient's trunk for up to 40 minutes. The result is positive when wheals are present at the test site 10 minutes after removal of the towel.¹ In

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Abbreviations used

1stAH₁- First-generation H₁ antihistamines
2ndAH₁- Second-generation H₁ antihistamines
AAquaU- Acquired aquagenic urticaria
AH₁- H₁ antihistamines
AH₂- H₂ antihistamines
AquaU- Aquagenic urticaria
BSS- Bernard-Soulier syndrome
CIndU- Chronic inducible urticaria
FAquaU- Familial aquagenic urticaria
PUVA- Psoralen and ultraviolet A
TRPV1- Transient receptor potential 1 vanilloid subtype

the literature, various other techniques of water challenge testing are reported. AquaU should be distinguished from aquagenic pruritus, which is characterized by itch without skin changes on contact with water.⁵ In patients with aquagenic pruritus, potentially associated systemic diseases, especially polycythemia vera and other myelodysplastic syndromes, should be investigated.⁶ Additional differential diagnoses of AquaU include other types of CIndU such as cholinergic urticaria, cold urticaria, and heat urticaria, which should be ruled out by standard provocation tests before diagnosing AquaU.

At present, the pathogenesis of AquaU is unclear, and information on clinical manifestations and treatment outcomes is limited. To address these gaps of knowledge, we performed a systematic literature review to describe the clinical features of AquaU and patients' response to treatment.

METHODS

Protocol and registration

Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations was applied as a standard protocol for systematic reviews in this study.⁷ The literature was searched in 3 electronic databases (PubMed, Scopus, and Embase) using the terms "aquagenic urticaria" and "aquagenic angioedema" through June 2021.

Eligibility criteria for a systematic review

Case reports, case series, and other types of studies that disclosed clinical manifestations and/or treatment responses in patients with AquaU were recognized as eligible and included in this analysis. Two independent reviewers (CR and KK) reviewed all titles and abstracts for eligibility. Consequently, suitable articles were reviewed in full-text to evaluate their final eligibility. The same 2 reviewers performed this process independently. In case of disagreements, a consensus-driving discussion was performed. Of 719 potentially eligible articles, 95 articles from PubMed, 180 articles from Embase, and 444 articles from Scopus were determined. Of these, 226 articles were duplicates and removed. The remaining 493 articles were processed for title and abstract review, and 434 articles were excluded because they did not meet our inclusion criteria. Finally, our systematic review consisted of 59 studies, including 47 case reports and 12 case series (Figure 1).

Data extraction

The following details were extracted from each study: (1) first author's name and the year of publication; (2) number of reported patients; (3) clinical presentations; (4) the type of water challenge test; (5) laboratory investigations; (6) dose and duration of

treatment; and (7) treatment outcomes. To evaluate the treatment outcomes, complete control was defined as free of AquaU signs and symptoms on continuation of treatment. Marked improvement was defined as a considerable but not complete reduction of signs and symptoms. Partial and no improvement was defined as some and no reduction of signs and symptoms in response to treatment, respectively. The same 2 investigators who evaluated the studies for eligibility independently performed the data extraction.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows (version 18.0; SPSS Inc, Chicago, Ill).

RESULTS

Demographic data and clinical features of patients with AquaU (Table I)

A total of 77 patients with AquaU were reported in 59 publications. The mean age at onset of disease was 19.6 ± 10.8 years (range, 0-54 years). AquaU predominantly presented in women (48 patients, 63.2%). On the basis of the evidence reviewed, AquaU patients fall into 2 groups: (1) familial AquaU (FAquaU) and (2) acquired AquaU (AAquaU). Sixty-three patients (81.8%) had AAquaU, and 14 patients (18.2%) had FAquaU.^{4,8-15}

Familial aquagenic urticaria

FAquaU was observed in 9 families, 23 family members affected in total and 14 described in detail.^{4,8-15} Most of these 14 patients with FAquaU (12 of 14) had a first-generation family member who also had the disease, that is, their father (2 patients),^{4,10} mother (2 patients),^{13,14} brother (1 patient),¹⁵ sister (4 patients),^{9,12} monozygotic twin (2 patients),¹¹ and daughter (1 patient).¹³ Two patients (14.3%) had affected second-generation family members, a niece and aunt, respectively.⁸ Two families with FAquaU were affected by an additional hereditary disease, the first with Bernard-Soulier syndrome (BSS), a rare autosomal recessive bleeding disorder,¹² and the second with familial lactose intolerance.¹⁴ Three of 4 family members with BSS also had FAquaU, and 3 of 5 family members with familial lactose intolerance also suffered from FAquaU.^{12,14} The mean age at FAquaU onset was 15.9 ± 1.9 years (range, birth-29 years). FAquaU predominately affected females (11 patients, 78.6%).

Types of water that trigger signs and symptoms and body areas affected.

Across all 14 patients with FAquaU, skin contact with tap water was the most common trigger reported (11 patients)^{4,8,9,11-15} (Figure 2, A). Based on patient history, the mean time of occurrence of wheals after the start of water contact in FAquaU was 8.9 ± 1.8 minutes (range, 2.5-15 minutes), whereas the mean time until resolution was 50.7 ± 4.7 minutes (range, 30-60 minutes). Among the 7 patients for whom wheal distribution was described, 5 and 2 patients had localized and generalized whealing, respectively. The trunk was most often reported to be the predominant location of wheals (5 patients)^{8,9,11,12,14,15} (Figure 2, B). Palms and soles were reported as uninvolved locations in 2 patients (14.3%).^{14,15} No patient had angioedema, and 1 patient reported systemic involvement (ie, dizziness).¹⁴ Wheals occurred regardless of the water temperature in all patients by history, and 10 patients underwent water challenge testing to confirm the diagnosis. The other 4 patients were diagnosed with FAquaU by history.

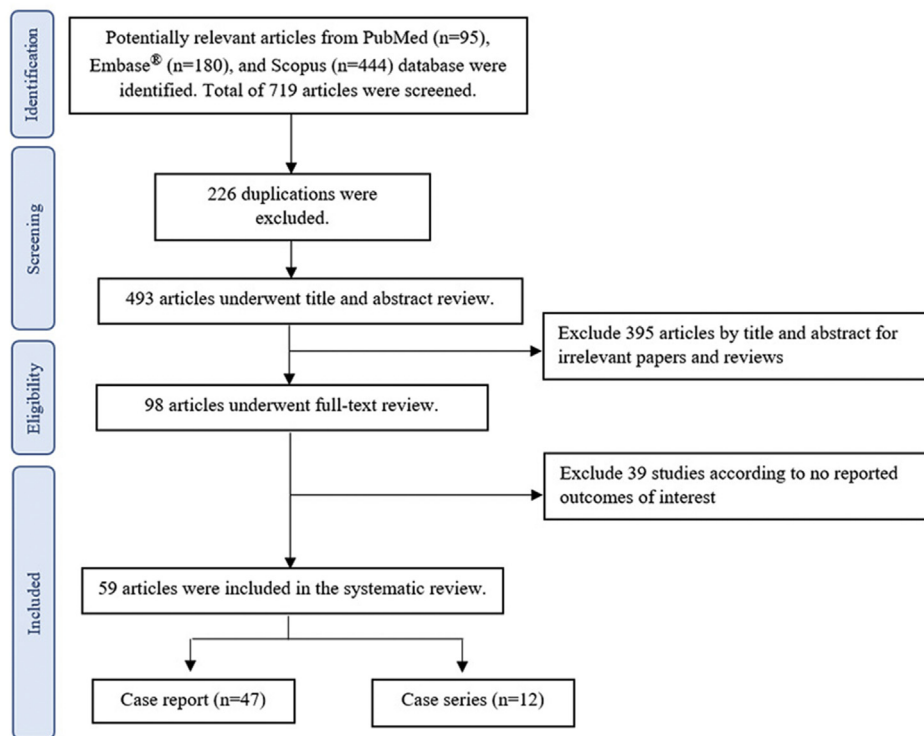


FIGURE 1. Flow diagram of the literature review in this systematic review. Fifty-nine articles met the inclusion criteria and were included in our systemic review. There were 47 case reports and 12 case series.

Symptomatic dermographism and chronic spontaneous urticaria with cholinergic urticaria were reported as coexisting conditions in 1 patient with FAquaU each^{8,9} (Table I).

Water challenge test. Provocation tests with water were performed in 10 patients with FAquaU.^{4,8,9,12,13,15} All 10 patients were tested with tap water and showed a positive response^{4,8,9,12,13,15} (Figure 3, A). The average provocation time, that is, duration of water exposure, was 16.8 ± 12.6 minutes (range, 5-30 minutes). Only 2 studies described the test locations (Figure 3, B).

Investigations. For laboratory investigations, half of the patients evaluated for total serum IgE had elevated levels^{9,14} (Table I). One patient underwent skin biopsy of a wheal, which showed edema of the papillary dermis with normal numbers of mast cells.¹⁴

Treatments and clinical course (Figure 4, A). Of 8 patients with FAquaU treated with H₁-antihistamines (AH₁), 5, 1, and 2 showed complete control, marked improvement, and partial improvement, respectively. Treatment with a second-generation AH₁ (2ndAH₁) in 6 patients led to complete control in 5 patients and partial improvement in 1 patient. Psoralen and ultraviolet A (PUVA) showed marked improvement in 1 patient.¹⁰

Acquired aquagenic urticaria

Across 63 patients with AAquaU, the mean age at onset was 20.0 ± 11.4 years. Nearly two-thirds were female (37 cases, 59.7%).

Types of water that trigger signs and symptoms and body areas affected. In patients with AAquaU, skin contact with tap water was the most common trigger reported (42 of 63 patients). Across all 63 patients with AAquaU, AAquaU symptoms were induced only by nonseawater in 26 patients and only by seawater in 11 patients.¹⁶⁻²² Three patients were reported to have symptoms related to water ingestion, with 2 of them having angioedema after drinking water. Body fluids including sweat (16 patients),^{4,23,24,25-34} saliva (1 patient),³⁰ and tears (1 patient)²⁴ were also reported to induce AAquaU (Figure 2, C).

The mean time of occurrence of wheals after the start of water contact in AAquaU was 13.0 ± 7.3 minutes (range, 2.5-30 minutes), and the mean time to resolution was 37.1 ± 27.3 minutes (range, 10-150 minutes). Of the 56 patients for whom wheal distribution was described, 49 patients (87.5%) had localized wheals despite contact with water on the whole body, for example, by bathing or swimming, whereas 7 patients had generalized urticaria after whole-body contact of water.^{2,3,22,35-38} Most patients reported the trunk to be the predominant location of whealing (26 patients, Figure 2, D).^{4,9,15,17,18,23,25,28,29,33,35,37,39,40,41-46} All 11 patients in whom whealing only occurred in response to seawater had reactions that were localized, that is, to the neck (6 patients),^{17,18-21,47} the face (5 patients),^{17,19-21,47} and the submandibular skin (3 patients).^{17,47} The most reported uninvolved locations were the palms and soles (5 patients).^{3,26,28,33,42} In the majority of patients, wheals occurred regardless of the water temperature (56 patients, 88.9%). No patients reported an association between AAquaU and stress or psychogenic factors.

TABLE I. Clinical features of reported aquagenic urticaria patients

Clinical features	Total (N = 77)	Familial AquaU (N = 14)	Acquired AquaU (N = 63)
Sex			
Female	48/77 (63.2)	11/14 (78.6)	37/63 (59.7)
Mean age at onset $\pm$ SD* (y)	19.6 $\pm$ 10.8	15.9 $\pm$ 1.9	20.0 $\pm$ 11.4
Symptoms			
Wheal alone	73/77 (94.8)	14/14 (100)	59/63 (93.7)
Angioedema alone	1/77 (1.3)	0/14 (0)	1/63 (1.6)
Wheal with angioedema	4/77 (5.2)	0/14 (0)	4/63 (6.3)
Median onset time of AquaU $\pm$ SD* (min)	12.3 $\pm$ 7.1	8.9 $\pm$ 1.8	13.0 $\pm$ 7.3
Median resolved time of AquaU $\pm$ SD* (min)	38.9 $\pm$ 26.1	50.7 $\pm$ 4.7	37.1 $\pm$ 27.3
Systemic involvement†	10/77 (13)	1/14 (7.1)	9/63 (14.3)
Respiratory system (respiratory distress, wheezing, cough, hoarseness)	10/77 (13)	0/14 (0)	10/63 (14.3)
Neurologic systems (headache, syncope, dizziness)	6/77 (7.8)	1/14 (7.1)	5/63 (7.9)
Cardiovascular system (palpitation, substernal chest pain)	2/77 (2.6)	0/14 (0)	2/63 (3.2)
Gastrointestinal system (difficult swallowing, nausea, abdominal pain)	3/77 (3.9)	0/14 (0)	3/63 (4.8)
Anaphylaxis	1/77 (1.3)	0/14 (0)	1/63 (1.6)
Comorbidities			
Thyroid diseases‡	2/77 (2.6)	0/14 (0)	2/63 (3.2)
Gastrointestinal diseases§	6/77 (7.8)	3/14 (21.4)	3/63 (4.8)
Infections	2/77 (2.6)	1/14 (7.1)	1/63 (1.6)
Others¶	10/77 (13)	7/14 (50)	3/63 (4.8)
Personal history of atopy	13/77 (16.9)	2/14 (14.3)#	11/63 (17.5)
Asthma	3/13 (23.1)	1/2 (50)	2/11 (18.2)
Allergic rhinitis	7/13 (53.8)	1/2 (50)	6/11 (54.5)
Atopic dermatitis	3/13 (23.1)	0/2 (0)	3/11 (27.3)
Allergic conjunctivitis	1/13 (7.7)	1/2 (50)	0/11 (0)
Unspecific food allergy	1/13 (7.7)	0/2 (0)	1/11 (9.1)
Family history of atopy	4/77 (5.2)	2/14 (14.3)	2/63 (3.2)
Asthma	2/4 (50)	2/2 (100)	0/2 (0)
Atopic dermatitis	1/4 (25)	1/2 (50)	0/2 (0)
Unspecific atopy	2/4 (50)	0/2 (0)	2/2 (100)
Coexistence of other urticarias**	16/77 (20.8)	2/14 (14.3)	14/63 (22.2)
SD	9/16 (56.3)	1/2 (50)	8/14 (57.1)
Cold urticaria	3/16 (18.8)	0/2 (0)	3/14 (21.4)
CholU	3/16 (18.8)	1/2 (50)	2/14 (14.3)
Heat urticaria	1/16 (6.3)	0/2 (0)	1/14 (7.1)
CSU	2/16 (12.5)	1/2 (50)	1/14 (7.1)
DPU	1/16 (6.3)	0/2 (0)	1/14 (7.1)
Investigation			
Elevated serum histamine	1/3 (33.3)	—	1/3 (33.3)
Elevated serum tryptase	1/4 (25)	—	1/4 (25)
Elevated serum IgE	6/13 (46.2)	1/2 (50)	5/11 (45.5)
Elevated serum IgA	1/3 (33.3)	—	1/3 (33.3)
Peripheral eosinophilia	1/9 (11.1)	—	1/9 (11.1)
Normal ESR	13/13 (100)	—	13/13 (100)
Normal C-reactive protein	2/2 (100)	—	2/2 (100)
Normal C3	13/13 (100)	1/1 (100)	12/12 (100)
Normal C4	13/13 (100)	1/1 (100)	12/12 (100)
Normal C1 inhibitor	5/5 (100)	—	5/5 (100)
Normal CH50	5/5 (100)	2/2 (100)	3/3 (100)
Negative ANA	2/2 (100)	—	2/2 (100)
Normal antithyroid antibodies	5/5 (100)	—	5/5 (100)
Normal cryoglobulinemia	1/1 (100)	—	1/1 (100)
Normal cold agglutinin	1/1 (100)	—	1/1 (100)

(continued)

TABLE I. (Continued)

Clinical features	Total (N = 77)	Familial AquaU (N = 14)	Acquired AquaU (N = 63)
Treatment options††			
1 st AH ₁	20/64 (31.3)	1/8 (12.5)	19/58 (32.8)
2 nd AH ₁	44/64 (68.8)	7/8 (87.5)	37/58 (62.8)
AH ₂	2/64 (3.1)	0/8 (0)	2/58 (3.4)
Other systemic treatment	10/64 (15.6)	0/8 (0)	10/58 (17.2)
Topical treatment	6/64 (9.4)	0/8 (0)	6/58 (10.3)
Phototherapy	4/64 (6.3)	1/8 (12.5)	3/58 (5.2)

Data are presented as n (%) unless otherwise indicated.

1stAH₁, First-generation H₁ antihistamines; 2ndAH₁, second-generation H₁ antihistamines; AH₂, H₂ antihistamines; ANA, antinuclear antibodies; AquaU, aquagenic urticaria; C, complement factor; CholU, cholinergic urticaria; CH50, 50% hemolytic complement activity; CSU, chronic spontaneous urticaria; DPU, delayed pressure urticaria; ESR, erythrocyte sedimentation rates; FAquaU, familial aquagenic urticaria; N, number; SD, symptomatic dermatographism.

*SD, standard deviation.

†One patient may have more than 1 symptom of systemic involvement.

‡Unspecified thyroid diseases and papillary carcinoma of thyroid.

§Gastroesophageal reflux disease, duodenal ulcer/*Helicobacter pylori* infection, lactose intolerance, and congenital biliary atresia.

||Hepatitis C infection, human immunodeficiency virus infection.

¶Bernard-Soulier syndrome, gout, bipolar affective disorders, hypertension, adenoid vegetation, secondary adrenal failure, polymorphous light eruption, and palmar hyperhidrosis.

#One patient had allergic rhinitis with allergic conjunctivitis.

**Four patients had 2 comorbid urticarias including SD and CholU (2 FAquaU patients), CSU and CholU (1 AAquaU patient), and SD and DPU (1 FAquaU patient).

††The treatment outcomes and detail of other systemic treatment, topical treatment and phototherapy were shown in Figure 4. One patient may require more than 1 type of treatment.

Associated symptoms. Angioedema in response to water exposure was observed in 4 patients (6.3%).^{2,39,48,49} Systemic symptoms were reported in 9 patients (14.3%)^{2,3,30,35,48-52} most commonly respiratory distress (5 patients, 55.6%, Table I). Systemic symptoms were induced by drinking water in 3 cases.^{2,30,39}

History of atopy and comorbid other types of chronic urticaria. A positive personal and family history of atopy is reported in Table I, and 14 patients (22.2%), in addition to their AAquaU, had another type of chronic urticaria, most often symptomatic dermatographism (8 patients, Table I).^{3,4,25,28,30,41,48,51}

Water challenge test. Fifty-one patients with AAquaU (81%) underwent a water challenge test. Tap water was most commonly used, with 28 of 38 patients showing a positive test result (Figure 3, C). The average time of water exposure sufficient to induce wheals was 19.8 ± 7.8 minutes (range, 4-30 minutes, n = 46). The trunk was the most common location for testing in 15 of 42 patients (35.7%, Figure 3, D).^{4,9,25,27-32,35,39-41,43,45,48,50,51,53,54} In the 11 patients who had AAquaU induced by seawater only, water challenge testing was performed with 3.5% sodium chloride (ie, seawater osmolarity) in 7 patients,^{16,17,20,21} followed by seawater (2 patients).^{16,19} Ten patients tested with tap water showed negative water challenge tests. The mandibular area including the neck was the most common testing location (5 patients).^{17,20}

Organic solvents were used for testing in 12 patients with AAquaU. Among these, 1 patient each tested positive with 70% alcohol,⁵⁰ acetone,³⁰ acetone with water,⁴⁴ acetone with 5% saline,³¹ and ethanol.³⁰ The number of wheals increased when acetone was added to 5% saline in 1 patient.³¹ In another patient, wheals developed earlier when water was added to acetone and to ethanol.³⁰

Investigations. Nearly 30% of the patients tested showed elevated serum histamine levels after the development of AquaU reactions,⁴⁴ and histamine release in basophil activation testing

was also positive in 1 of 3 patients.⁹ Elevated levels of serum tryptase linked to AquaU reactions, all without anaphylaxis, were seen in 1 of 4 patients³⁶ (Table I).

Of 6 patients who underwent skin biopsies of provocation-induced wheals, 2 showed mast cell degranulation.^{30,44} One and 2 studies reported increased and normal skin mast cell numbers, respectively.^{27,39,44}

Treatments and clinical course (Figure 4, B). Treatment responses were reported for 58 patients, and 25 different treatments were used across them. A standard dose of any AH₁ was used in 39 patients and led to complete control, marked, partial, and no improvement in 18, 10, 4, and 7 patients, respectively. Updosing of 2ndAH₁ (desloratadine 5 mg) up to 4-fold was used in 2 patients resulting in complete control.^{17,32} The water challenge tests were repeated in 3 patients reporting to be controlled by desloratadine (2 patients) and loratadine 10 mg (1 patient) and confirmed negative results.^{20,52} The combination of first-generation AH₁ (1stAH₁) and 2ndAH₁ (standard dose) used in 3 patients showed partial improvement in 1 patient and no improvement in 2 patients.^{3,12,26} The combination of systemic corticosteroid with a 1stAH₁ was used in 1 patient, but the treatment outcome was not reported.³⁰ The combination of 1stAH₁ (cyproheptadine) with sertraline and methscopolamine bromide patch was used in 1 patient and led to complete control.⁵¹ In 2 cases who did not respond to the combination of 1stAH₁ and 2ndAH₁, omalizumab (300 mg every 4 weeks) was used in 1 patient and led to complete control after 2 injections.⁵⁵ Stanazolol was applied in another patient with human immunodeficiency virus infection and reported complete control; however, his symptoms relapsed after discontinuation of stanozolol.² In 1 case of AAquaU with anaphylaxis, the patient responded well to epinephrine.⁴⁹

Among 3 patients with AAquaU treated with phototherapy, PUVA showed partial improvement in 1 patient.²⁴ Narrowband UVB combined with antihistamines showed marked improvement in 1 patient and partial improvement in another.^{35,56}

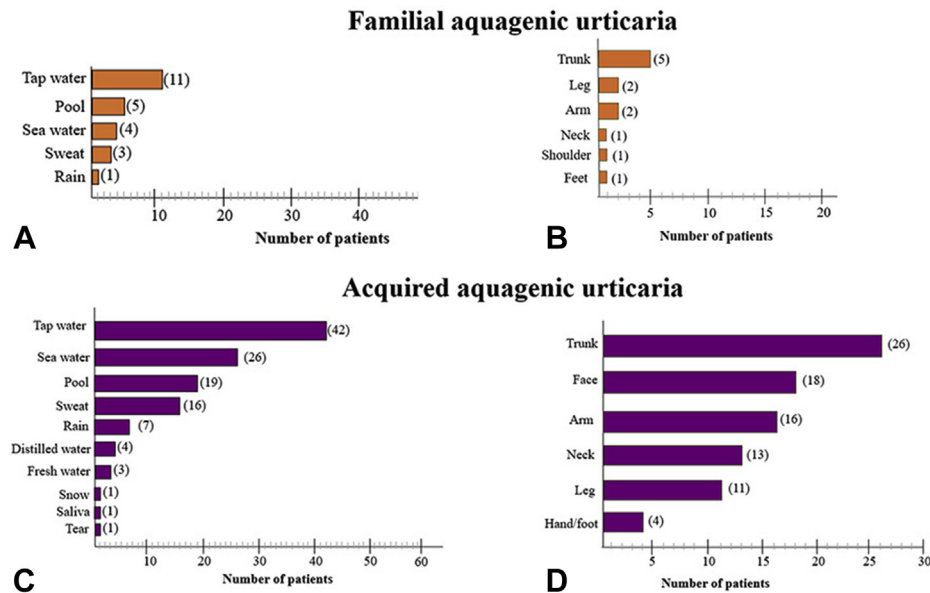


FIGURE 2. (A, C) Types of trigger water and (B, D) locations reported in familial aquagenic urticaria and acquired aquagenic urticaria. One aquagenic urticaria patient may be triggered by more than 1 type of water and develop lesions at more than 1 location.

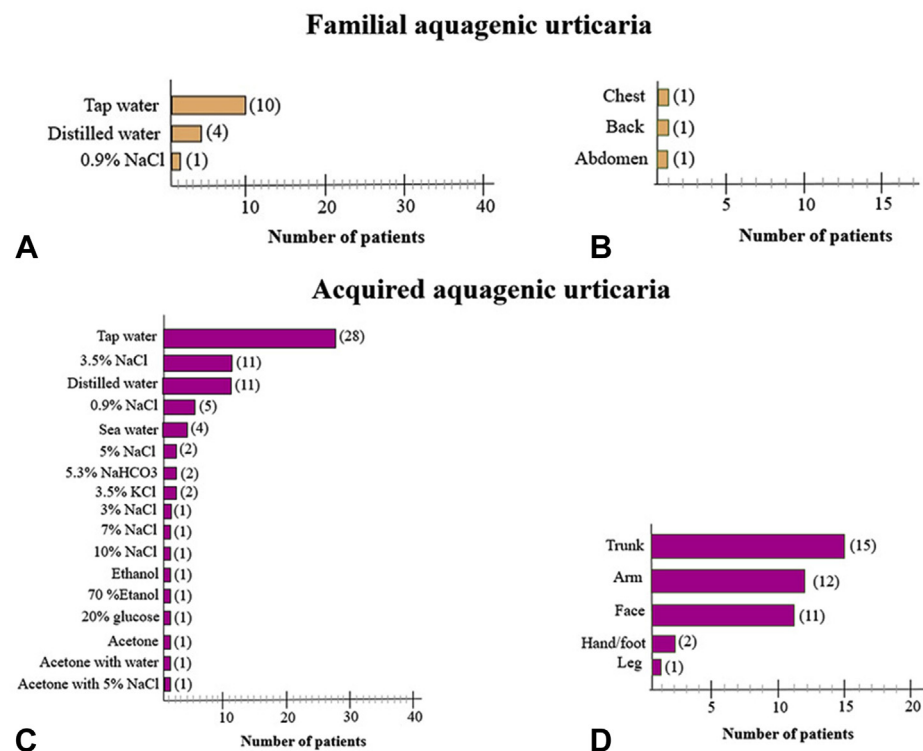


FIGURE 3. (A, C) Types of water and (B, D) locations reported in water challenge tests in familial aquagenic urticaria and acquired aquagenic urticaria. One patient may have used more than 1 type of water and/or location for water challenge tests.

Topical therapies including topical 1% diphenhydramine combined with oral AH₁ petrolatum-containing cream, alpha keri solution, coconut oil, and topical capsaicin led to complete and partial control in 3 and 2 patients each,

respectively^{4,17,31,33,57} (Table II). Alkalization of bath water (pH 8-9) by the addition of NaHCO₃ showed partial improvement in 1 patient.³⁵ In 1 patient with AAquaU diagnosed with papillary thyroid carcinoma, AAquaA disappeared after thyroidectomy.³⁵

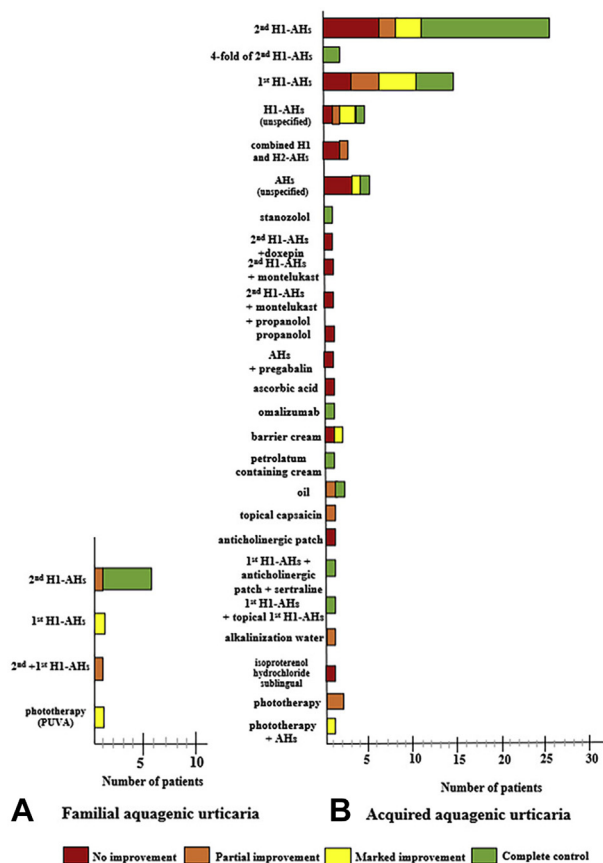


FIGURE 4. Treatment options and treatment responses reported in (A) familial aquagenic urticaria and (B) acquired aquagenic urticaria patients. One patient may have used more than 1 type of treatment. 1stAH₁, First-generation of antihistamines; 2ndAH₁, second-generation antihistamines; AH₁, H₁-antihistamines; AH₂, H₂-antihistamines; AHs, antihistamines; PUVA, psoralen and ultraviolet A.

Sixteen of 18 patients (88.9%) were free of AAquaU signs and symptoms while on treatment (range, 1-12 months).^{33,35,38-41,43,51-53,57,58} There were no reports on long-term outcomes or spontaneous remission in patients with AAquaU.

DISCUSSION

This review is justified as AquaU is a very uncommon form of inducible urticaria and because controlled trials of effective therapies are unlikely due to the rarity of this disorder. From the results of our systematic review, we propose to classify AquaU into the 2 subtypes of FAquaU and AAquaU. In FAquaU, patients have a positive family history of AquaU and are usually younger than patients with AAquaU at the time of onset. Both AAquaU and FAquaU affect predominantly females, and the symptoms usually develop after bathing, swimming, or after contact with various types of water. Wheals commonly occur localized, especially on the trunk, despite whole body exposure to the water. This is different to the other CIndUs, for example, cold urticaria or symptomatic dermographism, where usually all of the trigger-exposed skin is affected.

Our systematic review identified several other important clinical features of AquaU: systemic symptoms and angioedema can occur, and they are quite frequent, affect 1 in 7 patients, and can occur in response to drinking water. Physicians who treat patients with AquaA should be aware of this and inform their patients accordingly. One in 5 patients has another CIndU, most often symptomatic dermographism. Many patients do not react to all types of water. Physical examination is unremarkable in all patients, and most basic laboratory investigations are within normal limits in patients with AAquaU and FAquaU except for elevated total serum IgE levels, which are elevated in 46% of cases.^{9,21,30,39,50,53}

A water challenge test should be conducted in all patients who have a clinical history compatible with AquaU according to the EAACI/GA2 LEN/EDF/WAO consensus recommendations for CIndU.¹ Our systematic review revealed that tap water was most commonly used for testing in both FAquaU and AAquaU. The trunk is the most often reported location where wheals occurred. However, some patients developed localized symptoms despite being exposed to water by bathing or swimming at all body sites. Thus, water challenge tests should be performed at sites previously reported to be affected by the patient or the trunk. For patients who report whealing in response to seawater, challenge tests should be performed with seawater, 3.5% NaCl or 10% NaCl. They showed a negative water challenge test by tap water.^{16,17,21}

Our systematic review shows that many different treatments are used for AquaU, with different outcomes. In FAquaU and AAquaU, standard-dosed 2ndAH₁ treatment benefits about one-third of patients. As of now, there are no randomized controlled trials on the efficacy of up dosing of 2ndAH₁ in AquaU. In fact, up dosing of 2ndAH₁ up to 4-fold was reported in only 2 patients, both complete responders.^{17,32} We suggest that the use of a higher than standard-dosed 2ndAH₁ may be considered in patients with AquaU who are refractory to standard-dosed treatment, mostly based on the extrapolation of evidence from chronic spontaneous urticaria. In contrast, 1stAH₁, H₂ antihistamines (AH₂), and the combination of 1stAH₁, 2ndAH₁, and AH₂ often fail to show a significant response. In antihistamine refractory cases with high disease activity, phototherapy (PUVA or narrowband ultraviolet B) alone or combined with antihistamines can provide a good response and may be tried. How phototherapy helps in AquaU is unknown, but relevant mechanisms may include the induction of epidermal thickening, immunosuppression, and decreasing mast cell responses.^{3,59} Treatment with omalizumab has been reported in only 1 patient, where 2 injections led to complete control.⁵⁵ Besides systemic treatments, topical treatments by petrolatum-containing cream or coconut oil were reported to be of benefit for patients with AquaU, and patients should be made aware of this well-tolerated and safe treatment option.^{33,57} (Table II). All in all, there is a need for therapeutic studies in AquaU as well as the development of new and better treatments including topical ones.^{4,17,31,33,57}

The pathophysiology of AquaU is very interesting and still mysterious. Although our review did not aim to provide insights on the pathogenesis of AquaU, our findings do point to possible strategies to do so. Investigations of families with FAquaU and especially in monozygotic twins could point to genetic and molecular drivers that may also be relevant in AAquaU.¹¹ The relation of FAquaU with other genetic diseases including familial lactose intolerance and BSS is interesting; however, the genetic

TABLE II. The properties of topical therapies in acquired aquagenic urticaria treatment

Topical therapy	Composition	Property of pH	Water solubility
1. Topical 1% diphenhydramine ointment	Diphenhydramine hydrochloride	Acidic	N/A
2. Petrolatum-containing cream ³³	Dimethicone Silicone	Neutral	Hydrophobicity
3. Alpha keri solution ⁴	Lanolin oil Mineral oil Nonionic emulsion*	Lanolin oil (acidic, pH 5.5) Mineral oil (neutral, pH 7)	Hydrophobicity
4. Coconut oil	Coconut oil	Alkaline (pH 8.5-8.8)	Hydrophobicity
5. Topical capsaicin	Capsaicin	Acidity (pH < 5.2)	N/A

N/A, Not available.

*The nonionic emulsion was not identified in the study. Therefore, the exact properties of alpha keri solution were not identified.

mutations are different, and there is, as of yet, no knowledge of common pathogenic drivers.^{12,14} BSS, a rare autosomal recessive bleeding disorder, is caused by mutations in 1 of 3 genes: GPIb α , GPIb β , or GPIX. The genes GPIb α , GPIb β , and GPIX map to chromosomes 17 (17q12), 22 (22q11.2), and 3 (3q21), respectively.⁶⁰ Familial lactose intolerance is caused by the decrease in the expression of the LCT gene on chromosome 2q21.⁶¹ At present, possible shared pathways between FAquaU and other genetic diseases are still unclear and need further studies.

Regarding the pathogenesis of AAquaU, the generation of a toxic substance by water-soluble components in sebum, the sebaceous gland, or the epidermis has been proposed to be a possible underlying mechanism.⁹ Mostly, the reactions appear on trunk, where the skin is normally more exposed to “water” (sweat). The mast cells in this area could be more highly populated with the specific IgE, and thus, these mast cells respond more easily after exposure anywhere in the body. The mechanisms that result in local symptoms and the explanation of generalized symptoms and anaphylaxis both require further studies. Histamine is believed to be an important mediator in the pathogenesis of AAquaU due to the evidence of mast cell degranulation during an acute attack and oral antihistamines being effective to suppress the symptoms of AAquaU in some patients. Acetylcholine, serotonin, bradykinin, and plasminogen have been suspected to be involved in the pathogenesis of AAquaU.^{3,44,51,62,63} Brini et al⁶⁴ speculated, as water is polar due to its structure and the hydrogen ends of water molecules are positive while the oxygen ends are negatively charged, that water molecules can attract other polar molecules. Water may thus act as a vehicle for polar substances in sebum or sebaceous glands. Unknown polar substances around hair follicles have been suggested to be urticariogenic and involved in the pathogenesis of AAquaU.^{4,31}

In cases of AquaU induced by seawater only, a change of osmolality by salt concentration may enhance the solubilization of an unknown substance in the epidermis, which has been proposed to be another possible mechanism.³¹ The transient receptor potential 1 vanilloid subtype (TRPV1) has been discussed as another pathogenetic factor in 1 patient who responded to topical capsaicin.¹⁷ The TRPV1 channel is a nonselective sodium permeable channel that modulates osmolality in mast cells.⁶⁵ Although it may be involved in the pathogenesis, the evidence is currently not enough to draw a final conclusion.

Our systematic review points to several additional unmet needs in AquaU. There is little data on the prevalence and on the impact of AquaU on the quality of life of affected patients. With less than a hundred cases of AquaU reported, meaningful

analyses of subgroups of patients, for example, of patients who only respond to seawater or only respond to fresh water, are not possible.¹⁶⁻²² The duration of AquaU is also unclear. These gaps in knowledge call for further studies. At present, less than a hundred patients with AquaU are reported in the literature, and the available data of AquaU are limited. The information on treatments and their outcomes comes from anecdotal reports; no controlled studies are published. To gain more information, multicenter efforts are required. The global chronic urticaria registry (CURE) of the GA²LEN network of Urticaria Centers of Reference and Excellence (UCAREs) should be used to gather more cases and improve our understanding of AquaU.

CONCLUSIONS

On the basis of the results of our systematic review, we propose to classify AquaU into 2 subtypes, FAquaU and AAquaU. Second-generation AH₁ treatment is the recommended first-line therapy for both. Extrapolating from what we learnt from other types of urticaria, up dosing of 2nd AH₁ and omalizumab may be considered if symptoms are uncontrolled with a standard-dosed antihistamine. Phototherapy may be used in patients with refractory AquaU. Further studies are required for filling gaps of knowledge.

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