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## **Cholinergic urticaria: subtype classification and clinical approach**

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## **Abstract**

Cholinergic urticaria (CholU) is a subtype of chronic inducible urticaria with a chief complaint of itching and/or stinging pain papular wheals that developed simultaneously with sweating. This review specifically focused on several subtypes of CholU and specifically investigated the relationship between CholU and anhidrosis. We reviewed recent publications and updated the evidence around CholU, including the epidemiology, clinical features, diagnostic approaches, physiopathology, subtype classification, and therapeutic approaches. Multiple mechanisms contribute in a complex manner to the development of CholU, including histamine, sweat allergy, cholinergic-related substances, poral occlusion, and hypohidrosis/anhidrosis. A new schematic diagram of the currently known pathological conditions has been created. Specific methods for diagnosing CholU, provocation test, and evaluation methods for disease severity/activity and disease burden of CholU are summarized. The characteristics of the disease that should be differentiated from CholU and examination methods were also summarized. The primary finding of this review is that CholU should be categorized based on the etiology and clinical characteristics of each subtype to properly manage and treat the disease. This categorization leads to improvement of therapeutic resistance status of this disease. In particular, sweating abnormality should be given more attention when examining patients with CholU. Because CholU is not a homogeneous disease, its subtype classification is important for selection of the most suitable therapeutic method. Further elucidation of the pathophysiology of each subtype is expected.

**Key points**

- The etiology of CholU remains unclear, but it is clinically important to focus on the subtypes of CholU, including sweating dysfunction.
- Various tests, including the thermal sweating test, are required to classify the subtypes of CholU.
- Focusing on the subtypes of CholU will significantly contribute to effective therapeutic decision-making.

## 1. Introduction

Cholinergic urticaria (CholU), first described by Duke [1] in 1924, manifests as pinpoint, highly pruritic or often painful wheals with surrounding erythema. These wheals occur after sweating induced by an increase in the body temperature, which occurs in response to hot bathing, physical exercise, and emotional stress [2, 3]. CholU is a common form of chronic inducible urticaria, which is a subgroup of chronic urticaria (a group of diseases characterized by the recurrence of itchy wheals and/or angioedema (AE) for longer than 6 weeks), and affects up to 20% of young adults [4-6]. CholU is defined as inducible urticaria in the Japanese Dermatological Association guidelines for the diagnosis and treatment of urticaria [7]. The symptoms usually subside rapidly, usually within 1 hour. However, most patients with CholU complain of stinging or tingling pain and/or itching at the onset of symptoms, and these sensations impact to disturb their quality of life [8-12]. Severe symptoms such as AE, respiratory symptoms, and/or anaphylaxis often accompany CholU and disturb patients' activities of daily living, including study and work [2, 8, 13-17]. CholU is sometimes associated with cold urticaria [18]. The etiology of each subtype of CholU is being gradually elucidated, but the overall pathophysiology is not yet well understood. The pathophysiology involves acetylcholine (ACh), poral occlusion, cholinergic/Ach receptor M3 (CHRM3), sweat allergy, serum factors, and dyshidrosis, and each subtype of CholU has different causes [19-22]. We have proposed four subtypes of CholU based on the pathogenesis and clinical characteristics of this condition: (i) conventional sweat allergy-type CholU, (ii) follicular-type CholU with a positive autologous serum skin test (ASST) result, (iii) CholU with palpebral AE (CholU-PA), and

(iv) CholU with acquired anhidrosis and/or hypohidrosis (CholU-Anhd) [10, 17, 19, 21, 23-25]. Conventional sweat allergy-type CholU and CholU with palpebral AE are characterized by type I allergy to the patient's own sweat; thus, both can be considered sweat allergy-type CholU. CholU-Anhd is characterized by a reduced amount of sweat without a clear cause and can be classified as acquired idiopathic generalized anhidrosis (AIGA) accompanied by CholU [26]. Because the etiology and therapeutic approach differ greatly for each subtype, it is very important to not only consider CholU as a single disease but also conduct medical examinations with awareness of the subtypes.

In the present review, we focus on the classification of CholU, especially with respect to the relationship between CholU and sweating function, and present an overview of the current knowledge of the pathogenesis and therapeutic methods of CholU.

## **2. Definition, subtype classification, pathophysiology of CholU**

### **2.1 Definition and clinical characteristics**

CholU is characterized by itching and/or stinging pain, redness, and papular whealing, AE, or both induced by exercise and passive warming. Some patients develop symptoms of CholU when they are emotionally stressed or eat hot or spicy foods. A typical cutaneous symptom is the development of punctate, short-duration (15–60 min) wheals of 1 to 3 mm, but these punctate wheals occasionally become larger in size and coalesce form a large wheal (Fig. 1a). The eruptions may occur anywhere on the body except the palms, soles, and axillae, and the most commonly affected part of the body is the trunk [2, 3, 5]. CholU is often associated with serious symptoms such as anaphylaxis, AE (Fig. 1b), dyspnea, and

severe pain [12, 16, 17, 27]. Further investigation and discussion is needed regarding the difference between food-independent exercise-induced anaphylaxis (EIA) [28] and CholU with anaphylaxis. In many patients, symptoms of CholU become exacerbated in hot weather; some patients, however, including those who have subtypes of CholU with anhidrosis, often experience worsening in colder living environments with temperature differences.

## 2.2 Subtype classification

As mentioned above, we have proposed four subtypes of CholU based on the pathogenesis and/or clinical features: (i) conventional sweat allergy-type CholU, (ii) follicular-type CholU with a positive ASST result, (iii) CholU-PA, and (iv) CholU-Anhd [10, 17, 19, 21, 23-25, 29]. It is particularly important to differentiate subtypes (i), (ii), and (iii) from subtype (iv). The reason is that the presence or absence of abnormal sweating function makes a big difference in the treatment strategy. A thermoregulatory sweat test (most standard), drug-induced sweat test, quantitative sudomotor axon reflex test, and thermography should be used to evaluate the presence or absence of abnormal sweating function [30]. In rare cases, however, the subtypes may overlap, and it may be difficult to clearly distinguish these subtypes. Therefore, this classification has some limitations, and the classification of CholU needs further investigation, however we herein describe the clinical and pathological characteristics of each subtype in the present situation.

### 2.2.1 Conventional sweat allergy-type CholU

Investigation of the immediate response to sweat in CholU began in 1989 with a report by Adachi et al. [31]. They proposed that patients with CholU had a type I allergy to their own sweat based on the results of Prausnitz–Küstner tests of the patients’ serum and the sweat-induced release of histamine after passive transfer of the patients’ serum to healthy leukocytes. We reported that 11 of 17 patients with CholU showed immediate-type skin reactions and confirmed that the level of histamine release from basophils in the response with autologous sweat was well correlated with response shown by the autologous sweat skin test (ASwST) in 2005 [24]. This report proposed to classify CholU into two subtypes: (i) the sweat-hypersensitivity type (non-follicular type) characterized by non-follicular wheals, development of satellite wheals following local ACh injection, a positive ASwST result, and lack of a positive ASST result, and (ii) the follicular type characterized by follicular wheals, lack of development of satellite wheals following local ACh injection, and a positive ASST result. Takahagi et al. [32] found that 23 of 35 patients with CholU exhibited histamine release from basophils in response to semipurified sweat antigen, which induced histamine release from mast cells and basophils via antigen-specific IgE in patients with atopic dermatitis, in 2009. In their report, the group that tested positive for the semipurified sweat antigen tended to have more complications involving atopic diseases such as atopic dermatitis and asthma. The group that tested positive for the semipurified sweat antigen in their report and the first subtype in our report (sweat-hypersensitivity type; i.e., non-follicular type) may have a common element. Hiragun et al. [33] identified a putative protein, MGL\_1304 of *Malassezia globosa* (a commensal yeast), as a major allergen in the sweat of humans with atopic dermatitis. Moreover, the concentration of

purified MGL\_1304-specific IgE in the sera of patients with CholU was significantly higher than that in the sera of normal controls, and 14 of 24 patients with CholU were positive for purified MGL\_1304-specific IgE [34]. These findings suggest that MGL\_1304 in sweat is an important antigen in most patients with CholU with sweat allergy. We recently demonstrated that *Malassezia*-specific IgE is detected more frequently in patients with CholU who have a positive than negative ASwST result [35]. From these data, it may be possible to easily infer the complication of sweat allergy in patients with CholU by measuring *Malassezia*-specific IgE in patients with CholU.

### 2.2.2 Follicular-type CholU

In our 2005 paper, we proposed classification of CholU into two subtypes, and follicular-type CholU is the second of these two subtypes [24]. Patients with follicular-type CholU tend to have a positive ASST result and negative ASwST result, indicating that this subtype is not associated with sweat allergy. We found that patients with ASST-positive CholU who have no sweat allergy were more likely to have erythematous wheals consistent with hair follicles. Therefore, this subtype of CholU was termed follicular-type CholU (Fig. 1c). The etiological involvement of autologous serum factor and ACh is unknown in this subtype. It has been suggested that serum factor and ACh may act on mast cells around the hair follicles to produce wheals that are coincident with the hair follicles [19]. Furthermore, the presence or absence of anhidrosis in patients with CholU in our 2005 paper has not been considered and requires further study. How to distinguish this subtype of CholU from

aquagenic urticaria, which is characterized by the formation of punctate wheals coincident with follicles, is also an important issue [36, 37].

### 2.2.3 CholU-PA

Exercise-induced AE without trigger foods has been reported as a rare symptom of CholU [38, 39], although the causative allergen and clinical features are not well understood. We reported the clinical features of 15 cases of CholU with AE around the eyelids and proposed this as a new subtype of CholU: CholU-PA in 2017 [17]. This characteristic subtype of CholU was closely associated by AE around the eyelids and often anaphylaxis (7/15), and it was closely related to atopic predisposition (14/15) and female gender (15/15) (Fig. 1b). All patients with CholU-PA had a positive ASwST result, whereas only four patients had a positive ASST result, indicating that all patients with CholU-PA had allergy to autologous sweat and low predisposition to autoimmune urticaria. Interestingly, wheals in these patients with CholU-PA often appeared in lesions with an eczematous response consistent with eyelid-related atopic dermatitis. This means that these lesions are prone to sweat leakage due to impaired sweat duct barriers within the dermis; this easily induces sensitization to sweat, and the subsequent sweat allergy induces an eczematous reaction and urticarial reaction in the lesions. In addition, Mellerowicz et al. [16] subsequently reported that CholU was frequently associated with AE (46% of patients had at least one AE episode). Among patients with CholU, higher rates of concomitant allergies (53% vs. 35%) and atopic dermatitis (16% vs. 5%) were seen in those with than without AE, but these differences were not statistically significant ( $P = 0.053$  and  $P = 0.058$ , respectively). These

findings are similar to the results of our previous study. Interestingly, they found that among patients with CholU, those with AE are significantly more likely to experience extracutaneous signs and symptoms than are those without AE (68% vs. 27%,  $P = 0.001$ ); this finding is also similar to our previous study. Although they do not describe the site of AE and all patients with CholU in our study were Japanese, it is presumed that the racial difference is not large.

#### 2.2.4 CholU-Anhd

CholU-Anhd is a subtype of CholU that is associated with depressed perspiration, ranging from anhidrosis to hypohidrosis [40, 41]. This subtype of CholU has been reported using the term “CholU with anhidrosis and/or hypohidrosis (CholU-Anhd)” [21, 40].

Neurologists have defined AIGA as an acquired impairment in total body sweating despite exposure to heat or exercise without a clear cause. AIGA is associated with neither dysautonomia nor any neurological abnormalities except sudomotor dysfunction. AIGA is assumed to be associated with three pathological conditions: sudomotor neuropathy, idiopathic pure sudomotor failure, and sweat gland failure [30]; among these conditions, idiopathic pure sudomotor failure accounts for a large proportion of cases of AIGA. Many cases of AIGA are associated with CholU [10]. These pathological conditions are predominant in men and are likely to be complicated by pain and paresthesia; however, psychogenic sweating function is preserved [30]. Our recent comparative study of the subjective symptoms of sweat allergy-type CholU (i.e., conventional sweat allergy-type CholU and CholU-PA) and CholU-Anhd demonstrated that CholU-Anhd was predominant

in patients with pain with a negative autologous sweat test or negative basophil activation test and that sweat allergy-type CholU was predominant in patients with itching [12].

Although the reason is unknown, most cases of AIGA have been reported in Asia, especially in Japan. Regarding the clinical picture of CholU-Anhd, we often encounter patients with a goosebump-like punctate rash with a surrounding erythematous halo as shown in Figure 1d. A goosebump-like rash without erythema may also appear in patients with CholU-Anhd.

Few epidemiological data on AIGA, including CholU-Anhd, have been published; therefore, the exact prevalence and morbidity of AIGA remain unclear. It is mentioned that patients with AIGA is rare; however, patients with AIGA can be misdiagnosed, and a precise diagnosis may be achieved in only a small proportion of patients because the presence and diagnostic method of AIGA is not well recognized. Over the past 10 years, approximately 50 patients were newly diagnosed with AIGA in our facility (Kobe University) (Fukunaga et al., unpublished data), suggesting that more patients with AIGA might exist. An epidemiological survey in Japan was carried out by a committee comprising members commissioned by the Japanese Dermatological Association, Japan Society of Neurovegetative Research, and Japanese Society for Perspiration Research [30]. In total, 145 cases of AIGA were identified among 94 departments of neurology or dermatology at Japanese university hospitals from 2010 through 2015, although it is a little old data. The incidence was significantly higher in men (126 men and 19 women), as described in a previous report. As a new finding, in Japan under the COVID-19 epidemic, the number of patients is increasing further as a sense of daily medical care level and as an

expert opinion. An elevated serum carcinoembryonic antigen concentration might be a marker of disease activity of AIGA [42].

## 2.3 Pathophysiology

Although a considerable number of studies have been conducted, the pathomechanisms underlying CholU remain to be elucidated. As mentioned above, it is highly possible that the small number of studies that distinguish among the subtypes of CholU is likely to be related to the delay in elucidating the pathophysiology of CholU. Even in such situations, several factors are known to be involved in the pathological condition of CholU, including histamine, cholinergic-related substances, sweat allergy, serum factors, poral occlusion, leakage of sweat in the dermis, and hypohidrosis/anhidrosis. Below, we summarize which of these factors are most closely related to each subtype.

### 2.3.1 *Histamine*

Quite old studies have demonstrated that the serum histamine level increases during the development of symptoms and after exercise in patients with CholU [43, 44]. Classic histamine receptor antagonists have been proposed as useful, but they are often insufficient in severe cases of CholU. One study showed that administration of ketotifen was clinically effective in all four patients with CholU refractory to conventional classic antihistamine therapy and that the release of mast cell mediators (such as histamine) in the blood was blocked after exercise challenge [45]. At present, second-generation non-sedating histamine H1 receptor antagonists (H1RAs) are recommended as the first-line therapy in patients with

CholU; however, compared to patients with other types of urticaria, some patients with CholU do not respond to standard H1RA therapy [6, 8, 46]. Our previous study found that addition of the histamine H2 receptor antagonist (H2RA) famotidine to H1RA therapy in patients with refractory CholU that was unresponsive to up-dosing of H1RA reduced the severity of itching, frequency of whealing, and size of the wheals [8]. H1RA up-dosing at 4-fold in 32 patients with CholU refractory to standard H1RA therapy substantially improves the disease activity of CholU in fewer than half of all patients [46]. These findings suggest that histamine plays a fairly important role in the development of CholU but that additional mediators other than histamine may also be closely associated with the development of CholU. However, the above-mentioned studies did not examine or mention the subtype of CholU. Although H1RA therapy is recommended for CholU-Anhd, which corresponds to AIGA and idiopathic pure sudomotor failure [30, 47], the effectiveness of this therapy has not yet been studied in a randomized trial. In our experience, H1RA therapy is less effective in CholU-Anhd than in sweat allergy-type CholU, suggesting lower involvement of histamine in the pathophysiology of CholU-Anhd. Further study of this topic is required.

### *2.3.2 Sweat allergy*

The concept of hypersensitivity to human sweat was first described in 1953 [48]. The issue of sweat allergy was not spotlighted again until 1989, when Adachi and Aoki [49] performed a radioallergosorbent test and detected IgE antibody to sweat in patients with atopic dermatitis. This immediate-type allergic reaction to sweat was also confirmed in

patients with CholU in 1994 [31]. That study also demonstrated that after transfer of the patient's serum into a normal subject, the ASwST showed positive results, indicating that these patients with CholU have a type I allergy to their own sweat. Hide et al. observed that basophils of patients with atopic dermatitis released histamine when mixed with sweat, and this reaction was inhibited by the removal of IgE from the basophils in 2002 [50]. Furthermore, we found in 2005 that 11 of 17 patients with CholU showed immediate-type skin reactions and confirmed that the level of histamine release from basophils in the response with autologous sweat was well correlated with response of the ASwST [24]. Takahagi et al. found that patients with CholU exhibited histamine release from basophils in response to semipurified sweat antigen, which induced histamine release from mast cells and basophils via antigen-specific IgE in patients with atopic dermatitis, in 2009. Hiragun et al. [33] identified a putative protein, MGL\_1304 of *Malassezia globosa*, as a major allergen in the sweat of humans with atopic dermatitis in 2013 and CholU in 2014 as described earlier in 2.2.1 section [34]. These findings suggest that MGL\_1304 in sweat is a major antigen for many patients with CholU who have a sweat allergy. We speculate that many of the patients with CholU enrolled in the above study had sweat allergy-type CholU, but whether the study included patients with the CholU-Anhd subtype is unclear. In contrast, we recently used this commercial histamine release test with semipurified sweat antigen to detect sweat allergy in a characteristic case series of patients with CholU-PA [17]. In that study, we found a positive correlation between IgE-radioallergosorbent test titers against *Malassezia* species and the histamine release test with semipurified sweat antigen. Moreover, we demonstrated that the basophil activation test using semipurified

sweat antigen displayed a higher sensitivity and negative predictive value and a lower number of non-responders than did the histamine release test in 47 patients (including 41 patients with CholU) whose symptoms worsened with sweating [35]. Our previous study revealed that only two of eight patients with AIGA had sweat allergy detected by the histamine release test on sweat or the skin test using autologous sweat, suggesting that sweat allergy is not involved in the pathogenesis of AIGA [10].

### *2.3.3 Cholinergic-related substances*

The sweat glands receive sympathetic innervation but express CHRM3, which is normally expressed in the parasympathetic nervous system. Ach induces sweating when injected intradermally, causing pinpoint wheals around the injection site (Fig. 2, left side) [24]. This is called the ACh test and is used as an adjunct diagnostic technique for CholU. The ACh test can also be used as a local sweating test when used in combination with the Minor method (Fig. 2, right side) [24]. In fact, recent European reports have shown that ACh injections elicit a wheal and flare in more than one-third of patients with CholU, although the subtype of CholU is unknown [22]. In our previous study, 6 (50%) of the 12 patients with CholU tested showed a positive response in the ACh test, and all 6 patients who developed satellite wheals after the ACh test showed hypersensitivity to sweat [24]. It is important to note that the positive ACh test result in this study reflected the appearance of the surrounding satellite wheal, not the injection site. Furthermore, the surrounding satellite wheal is known to coincide with the sweating point [24]. In other words, the positive ACh test result, which reflects the wheal of the surrounding satellites, indicates that ACh

promotes sweating from the secretory part of the sweat glands via CHRM3. It is highly possible that the positive ACh test result reflects the generated sweat leaks from the sweat duct to the dermis and degranulation of mast cells via sweat allergy around the sweat ducts. It has been reported that in atopic dermatitis, which is easily associated with CholU, sweat leaks into the dermis because of decreased expression of claudin-3 in the sweat ducts in the dermis [51].

In contrast, the CholU-Anhd subtype tends to be less frequently associated with the formation of satellite wheals after the ACh test (Fukunaga A et al., unpublished data). Sawada et al. [9] also reported that ACh injection induces no reaction at the anhidrotic site in patients with the CholU-Anhd subtype. The authors found that not only sweat glands but also mast cells express CHRM3. A schematic model was proposed in which ACh released from postganglionic sympathetic nerves cannot be trapped by the ACh receptors of eccrine glands because of decreased expression of these receptors and overflow of ACh to adjacent mast cells secondary to decreased expression of ACh esterase in the CholU-Anhd subtype [9, 25]. Based on their series of studies, Tokura et al. classified CholU into the ACh-direct, sweat allergic type and the ACh-indirect, depressed sweat type from the aspect of ACh involvement [52]. Thus, ACh and other cholinergic-related substances appear to play an important role in the development of CholU. However, we believe that further research is needed to determine the involvement of these substances in each subtype of CholU.

#### *2.3.4 Poral occlusion*

Several reports have suggested that CholU is caused by poral occlusion. Kobayashi et al. [53] documented that biopsy specimens from two patients with CholU and hypohidrosis showed occlusion of the superficial acrosyringium. Rho [54] reported that patients with CholU, most of whom develop symptoms only in the winter season, is relatively high complication rate of hypohidrosis and that topical application of antikeratolytic agents to the affected area may be helpful. These reports suggest that poral occlusion is also involved in the etiology of CholU accompanied by hypohidrosis. We also reported a patient with AIGA accompanied by CholU whose histopathology showed occlusion of the superficial acrosyringium [55]. Moreover, firm keratotic plugs suggesting poral occlusion were observed in a patient with acquired idiopathic partial anhidrosis, and the application of adapalene gel (which is reportedly effective for reduction of keratotic plugs in patients with porokeratosis) improved sweating function within 3 weeks [56]. Based on these reports, whether poral occlusion is the cause of the CholU-Anhd subtype or the result of decreased sweating remains unclear.

### *2.3.5 Hypohidrosis/anhidrosis*

The various etiologies of decreased sweating in patients with CholU include autoimmunity to sweat glands or ACh receptors, degeneration of post-ganglionic sympathetic skin nerve fibers, and poral occlusion [26, 40, 53, 57, 58]. In contrast, there is little information about the pathomechanism by which CholU occurs in the CholU-Anhd subtype (i.e., AIGA accompanied by CholU). As explained in the above section on cholinergic-related substances, Sawada et al. [9, 25] proposed that ACh cannot be trapped by the ACh

receptors of eccrine glands because of decreased expression of these receptors and decreased expression of ACh esterase in the CholU-Anhd subtype, and overflow of ACh acts on adjacent mast cells to form CholU. Indeed, research has shown that mast cells express CHRM3 [9]. In contrast, whether ACh can induce degradation of human mast cells *in vivo* remains unclear. The clinical picture of CholU associated with hypohidrosis may be a goosebump-like punctate rash either with or without an erythematous halo, and further research is required to elucidate the pathophysiology of the CholU-Anhd subtype. A recent study showed that an elevated serum carcinoembryonic antigen concentration might be a marker of disease activity of AIGA [59].

The herein-described categorization and pathophysiological features of each subtype of CholU are illustrated in Table 1 and Figure 3.

### **3. Disease burden of CholU**

Specific tools for CholU had been missing until the recent development of the first disease-specific health-related quality-of-life instrument for CholU: the Cholinergic Urticaria Quality of Life Questionnaire (CholU-QoL) [11]. This report described correlations between the CholU-QoL scores, the Dermatology Life Quality Index (DLQI) scores and urticaria control test scores. Moreover, it showed that the domain “emotions” of CholU-QoL scores was most strongly affected in patients with CholU [11], although the subtype of CholU was not mentioned. Our previous study also did not focus on the subtypes of CholU, but it showed that the total DLQI score was  $10.1 \pm 5.5$  and that patients with refractory CholU unresponsive to H1RA had quite impaired quality of life [8]. Munetsugu et al. [60]

reported that the DLQI impairment in patients with AIGA was equivalent to or more severe than that in patients with atopic dermatitis. Steroid pulse therapy alleviated the anhidrosis of all eight patients with AIGA, and the symptomatic improvement was clearly linked to improved quality of life [10].

#### **4. Diagnosis of CholU**

##### **4.1 Provocation test and disease severity/activity score**

The clinical diagnosis of CholU is usually not difficult, as the symptoms of CholU develop only after an increased body temperature has been stimulated in a repetitive manner and the appearance of the eruption is characteristic. However, a provocation test should be performed to accurately diagnose and rule out other types of urticaria and EIA. Provocation tests for the diagnosis of CholU are performed by raising the body temperature through exercise (treadmill or stationary bicycle) or the use of a hot bath (42°C for 15 min) [6, 61, 62]. The EAACI/GA<sup>2</sup>LEN/EDF/UNEV consensus panel recommends the following criterion to confirm the diagnosis of CholU: the core body temperature has increased by >1.0°C over the baseline as indicated by a passive warming test involving sitting for up to 15 min in a bath filled with water at 42°C [6]. Although the use of an esophageal or rectal thermometer to measure core body temperature is more accurate than the use of an oral thermometer, the former is invasive and unsuitable for outpatients. Therefore, a standardized protocol for diagnosing and measuring CholU thresholds using pulse-controlled ergometry has been proposed [63]. Pulse-controlled incremental ergometry for 30 min (stationary bicycle) increasing their pulse rate by 15 beats every 5 min with an

ambient temperature of 20-22°C is sensitive and specific for diagnosing CholU. The median time to induce wheals using this technique was 27 min, and the four of ten CholU patients had their symptoms after the end of the exercise. This report revealed that sweating itself is more important in the development of CholU than the rise in core body temperature [63]. A foot bath thermal sweating test (43°C for 30 min, room temperature of approximately 25°C, relative humidity of 40%–50%, and use of lower leg) is standardly performed in Japan as a systemic sweating test (Fig. 4). A foot bath thermal sweating test may also serve as a whealing provocation test for CholU-Anhd (i.e., AIGA accompanied by CholU).

Assessment scores for disease severity and activity specific to CholU have been developed. The Cholinergic Urticaria Severity Index (CholUSI) is used to assess the severity of CholU [63]. The CholUSI is a sum score that takes into account the frequency of CholU symptoms, eliciting factors, duration of skin lesions and itch. Accordingly, the CholUSI score ranges from 0 to 21 points: <5 points: very mild CholU; 5–9 points: mild CholU; 10–15 points: moderate CholU; >15 points: severe CholU. The Weekly Cholinergic Urticaria Activity Score (CholUAS7) is used to assess the disease activity of CholU; it is calculated as the 7-day sum of [(Whealday + Itchday) × Intensity of elicitor day], and the maximum score is 168 points [64].

#### 4.2 Differential diagnosis

CholU needs to be differentiated from other types of inducible urticaria and anaphylaxis in terms of clinical episodes and the rash shape (Table 2). CholU must be differentiated from

EIA and heat urticaria (HU) based on whether the clinical episode has developed secondary to exercise and/or heat stimulation. EIA includes four types: food-independent EIA, food-dependent EIA with IgE sensitivity, food-dependent EIA without IgE sensitivity, and drug-dependent EIA [28]. Strenuous exertion may provoke both EIA and CholU, but passive warming will induce solely CholU and not EIA. The wheals in EIA are typically large, could also be small or even absent and appear as diffuse erythematous change in EIA but the wheals are typically small in CholU. HU is a rare type of physical (inducible) urticaria that is characterized by itchy erythema and well-demarcated wheals appearing soon after heat exposure, and the wheals are restricted to the heated area [65]. HU can be differentiated from CholU by the characteristic clinical presentation that develops after the provocation tests [6].

CholU should be differentiated from aquagenic urticaria and adrenergic urticaria with a similar clinical presentation of a punctate rash. Aquagenic urticaria is a rare form of chronic inducible urticaria in which contact with any source of water, regardless of its temperature or pH, evokes small pruritic wheals surrounded by flare [37, 66]. The diagnosis is based on the clinical history and water provocation test result. In the water provocation test, a compress or towel soaked with 35°C to 37°C water or physiological saline is placed on the patient's trunk. Adrenergic urticaria is a rare type of stress-induced physical urticaria characterized by widespread pruritic punctate wheals triggered by stress, trauma, and emotional upset [36]. Adrenergic urticaria can be distinguished from CholU by the presence of a white halo of vasoconstriction surrounding small red or pink wheals [67]. Adrenergic urticaria can be diagnosed by intradermal injection of adrenaline or

noradrenaline, which causes the characteristic rash [68]. A positive noradrenaline test result and negative ACh skin test result can be useful for the differential diagnosis of adrenergic urticaria and CholU, although these test results are not definitive because CholU may result in a negative ACh skin test [68].

Finally, the subjective symptom of CholU is a feeling of stinging or tingling pain and/or itching during sweating. A recent study focusing on dermal pain triggered by sweating stimuli showed that 10 of 30 patients with dermal pain triggered by sweating stimuli did not develop eruptions [69]. In other words, because there is a group of patients without eruptions that show subjective symptoms similar to those of CholU, this pathological condition should be differentiated.

## **5. Management of and therapeutic approach to CholU**

The therapeutic approach to CholU vary greatly based on the presence of sweating dysfunction (CholU-Anhd subtype and other subtypes). Therefore, differential diagnosis of subtypes based on the presence of sweating abnormality is very important before treatment. However, few studies have evaluated therapeutic approaches focusing on the subtypes of CholU.

Many patients in studies conducted before the consideration of CholU subtypes showed only a mild to moderate response to standard H1RA doses [8, 46, 70]. Increasing the dose of an H1RA in 32 patients with CholU that is refractory to standard doses may improve the disease activity, but this occurs in fewer than half of all patients, although there is no description regarding CholU subtype [46]. Adding an H2RA was reportedly effective in

patients with refractory CholU that was unresponsive to up-dosing of an H1RA, although there is no description regarding CholU subtype [8]. There are also reports on the efficacy of scopolamine butylbromide (an anticholinergic agent) [71]; combinations of propranolol (a  $\beta$ 2-adrenergic blocker), antihistamines, and montelukast [72]; and injection of botulinum toxin [73]. Although the side effect profile of danazol limits its use, high doses of danazol (600 mg daily) have been reported to be effective. [6]. Several studies have shown that omalizumab is effective for severe CholU cases [74, 75], but cases of omalizumab treatment failure has also been reported [76-78]. Desensitization protocols involving regular physical exercise and/or bathing or treatment with autologous sweat in patients with sweat allergy-type CholU have been reported [19, 20, 79]. A more recent report showed that regular sweating activity is effective in alleviating the symptoms of CholU with or without hypohidrosis [80].

Regarding the CholU-Anhd subtype, systemic administration of corticosteroids such as intravenous high-dose (500–1000 mg) steroid pulse therapy for AIGA appears to merit recommendation based on the findings presented in numerous case reports despite an insufficient level of research-based evidence [10, 30, 81]. A recent report stated that the treatment response rate of steroid pulse therapy in 57 patients with AIGA was 73%, and the recurrence rate was 48%. Furthermore, it is interesting that the effectiveness was reduced when the steroid pulse therapy was given in the autumn before it became cold [82]. A trial of oral immunosuppressants is worthwhile in patients who do not respond to steroid pulse therapy, although only one case is reported in Japan [30]. In patients with AIGA, H1RAs can be administered at increased doses appropriate to the symptoms experienced [83].

Topical application of keratolytic agents is reportedly effective in treating hypohidrotic CholU, which is associated with the occlusion of sweat ducts [54]. Oral pilocarpine is reportedly effective for alleviation of the symptoms of AIGA [84]. Omalizumab was shown to be effective in a patient with CholU-Anhd with atopic dermatitis [85]. Medications acting on nervous systems transiently attenuates dermal pain triggered by sweating stimuli including CholU-Anhd [69]. Takahagi et al. reported that  $\text{Ca}^{2+}$  channel  $\alpha 2\delta$  ligands and anti-anxiety agents might be effective for dermal pain (Response Ratio, 33% and 60%) [71].

Overall, however, the currently available treatments for CholU-Anhd are not satisfactorily effective with the exception of steroid pulse therapy, and symptomatic recurrence often occurs even after steroid pulse therapy. Thus, the development of better treatment methods is expected.

These recommended therapeutic management approaches are summarized in Figure 5.

## **6. Conclusions**

This review focused primarily on the subtypes of CholU. Although many unclear points remain in the pathophysiology of CholU, subtype classification is essential for an accurate understanding of this disease because the pathophysiology of each subtype is likely to be different. In addition, subclassing CholU, which is relatively resistant to conventional treatments and significantly impairs quality of life, leads to the provision of better treatments. In the future, it is expected that the pathophysiology and therapeutic management of CholU will be established with a focus on specific CholU subtypes.

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## Figure Legends

### **Fig. 1** Diversity of clinical picture of CholU

(a) Typical appearance of CholU: pinpoint-sized, highly pruritic red wheals occur after sweating. (b) CholU-PA: angioedema associated with cholinergic urticaria. (c) Follicular-type CholU: CholU matching hair follicles. (d) Goosebump-like punctate rash with surrounding erythematous halo.

CholU, cholinergic urticaria; CholU-PA, cholinergic urticaria with palpebral angioedema

### **Fig. 2** Satellite urticarial response induced by intradermal acetylcholine injection (Ovisot<sup>®</sup>; Daiichi Sankyo, Tokyo, Japan)

Arrowhead: small satellite wheal. Arrow: intradermal injection site of acetylcholine.

### **Fig. 3** Pathophysiology of each subtype of CholU

(a) Conventional sweat allergy-type CholU (i); Follicular-type CholU (ii); CholU-PA (iii).

In the sweat allergy type [(i) and (iii)], wheals are formed around sweat glands due to leakage of sweat into the dermis and IgE-mediated reaction of surrounding mast cells. In follicular-type CholU (ii), serum factor and acetylcholine stimulate mast cells around the hair follicles to form wheals consistent with the hair follicles.

(b) CholU with acquired anhidrosis and/or hypohidrosis (iv).

In CholU-Anhd, CHRM3 expression (ACh receptor) is decreased in the sweat glands, and ACh overflows to promote degranulation from the adjacent mast cells. There may be

infiltration of inflammatory cells such as lymphocytes and mast cells around the sweat glands. Sweat leakage and/or palmar occlusion may also be involved.

CholU, cholinergic urticaria; CholU-Anhd, cholinergic urticaria with acquired anhidrosis and/or hypohidrosis; CholU-PA, cholinergic urticaria with palpebral angioedema

**Fig. 4** Appearance of foot bath thermal sweating test

**Fig. 5** Proposed therapeutic algorithm for CholU with and without hypohidrosis (opinion of authors)

CholU, cholinergic urticaria; H1RA, histamine H1 receptor antagonist; H2RA, histamine H2 receptor antagonist Solid lines indicate strong recommendations and dashed lines are conditional recommendations.

Table 1. Subtype categorization and pathophysiological features of ChoIU

Subtype	Histamine	Sweat allergy	Cholinergic-related substances	Autologous serum skin test	Sex predominance	Atopic predisposition	Hypohidrosis	Pathology	Severity (author's opinion)
Conventional sweat allergy-type ChoIU	Deeply involved	Positive	Acetylcholine test: positive	Negative	None	ND	None	Sweat allergy, sweat leaking	Moderate
Follicular-type ChoIU	Involved	Negative	Acetylcholine test: negative	Positive	None	ND	ND	Serum factor	Mild
ChoIU-PA	Deeply involved	Positive	ND	Negative	Female	Strong	None	Sweat allergy, preexistence of eczema	Severe
ChoIU-Anhd	Less involved	Negative	Acetylcholine test: negative	ND	Male	Weak	Always	Excess acetylcholine following decrease of CHRM3 expression on sweat gland, CHRM3 expression on mast cells, poral occlusion, carcinoembryonic antigen	Severe

ChoIU, cholinergic urticaria; ChoIU-Anhd, cholinergic urticaria with acquired anhidrosis and/or hypohidrosis; ChoIU-PA, cholinergic urticaria with palpebral angioedema; CHRM3, cholinergic/acetylcholine receptor M3; ND, not determined

Table 2. Differential diagnosis of cholinergic urticaria

	Characteristics	Provocation test
Exercise-induced anaphylaxis	Flushing, increased warmth, malaise, diffuse itching, urticaria, angioedema, gastrointestinal symptoms (nausea, vomiting, abdominal cramps, and diarrhea), hypotension, syncope, laryngeal edema, anaphylaxis, and rarely asthma. Wheals are large and may converge.	Standard treadmill exercises for approximately 30 min after specific food or drug intake.
Heat urticaria	Itchy erythema and well-demarcated wheals appearing soon after heat exposure, restricted to the heated area.	Skin testing with metal/glass cylinders filled with hot water, hot water baths, or TempTest® measurements.
Aquagenic urticaria	Small pruritic wheals surrounded by flare after contact with any source of water, regardless of its temperature or pH.	A compress or towel soaked with 35°C to 37°C water or physiological saline is placed on the patient's trunk. The compress or towel can be taken off within 20 min if the patient reports pruritus and first wheals are seen at the skin test site.
Adrenergic urticaria	Small red or pink pruritic wheals surrounded by a white halo of vasoconstriction, triggered by stress, trauma, or emotional upset.	Intradermal injection of adrenaline or noradrenaline (1 µg/mL), which produces the characteristic rash.



a



c



b



d

Fig. 1

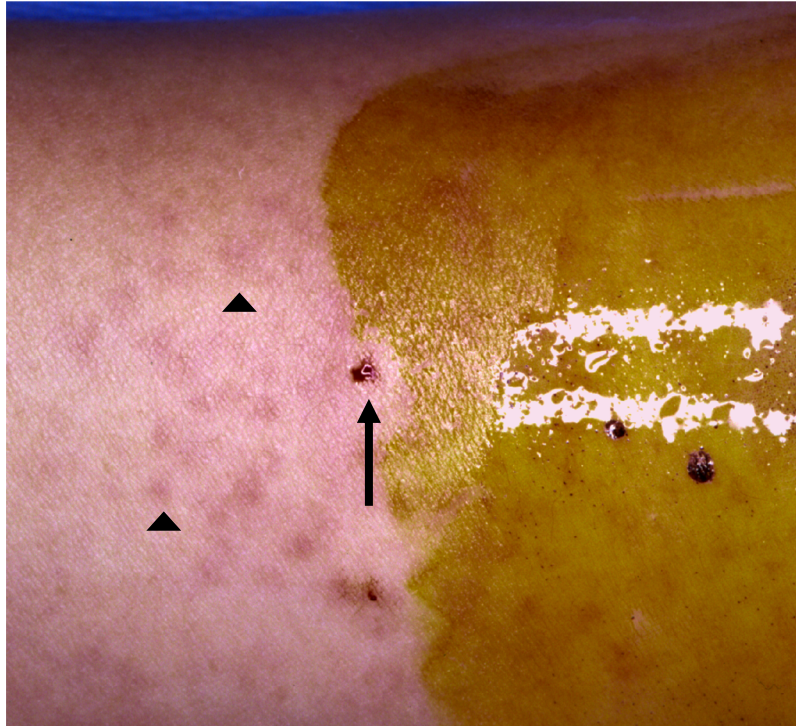


Fig. 2

- (i) Conventional sweat allergy-type ChIU
- (ii) Follicular-type ChIU
- (iii) ChIU with palpebral angioedema (ChIU-PA)

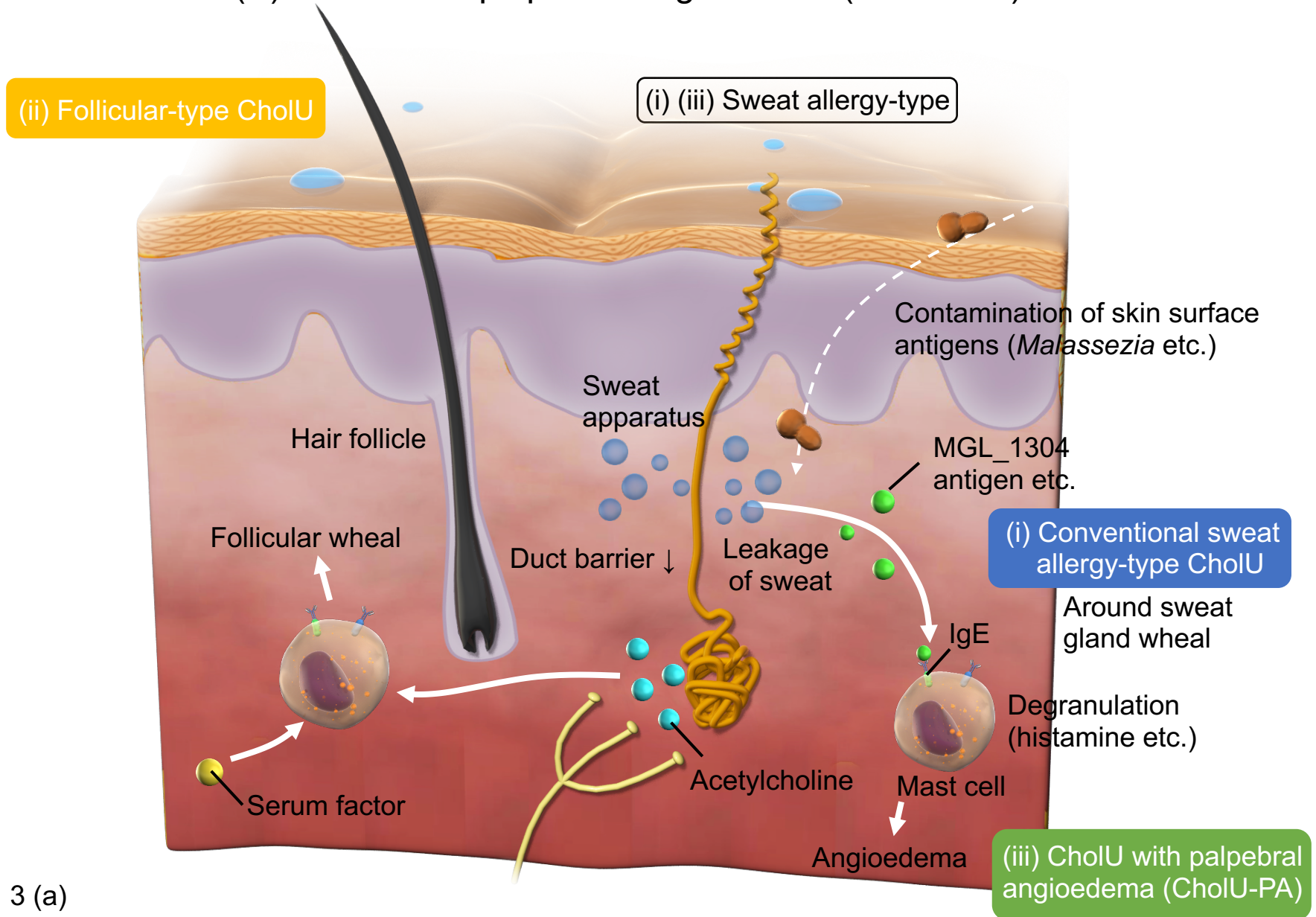


Fig. 3 (a)

(iv) CholU with acquired anhidrosis and/or hypohidrosis (CholU-Anhd)

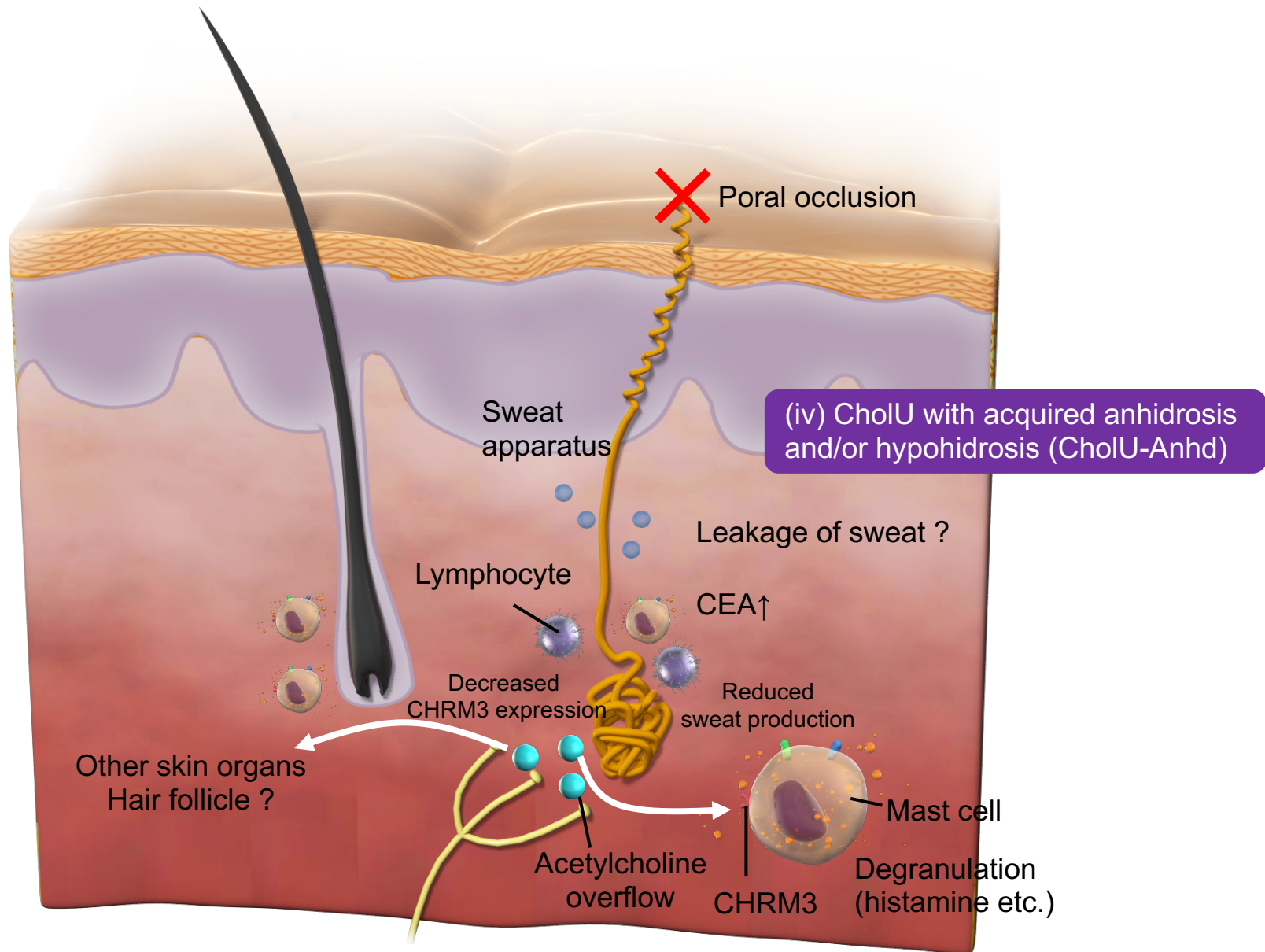


Fig. 3 (b)



Fig. 4

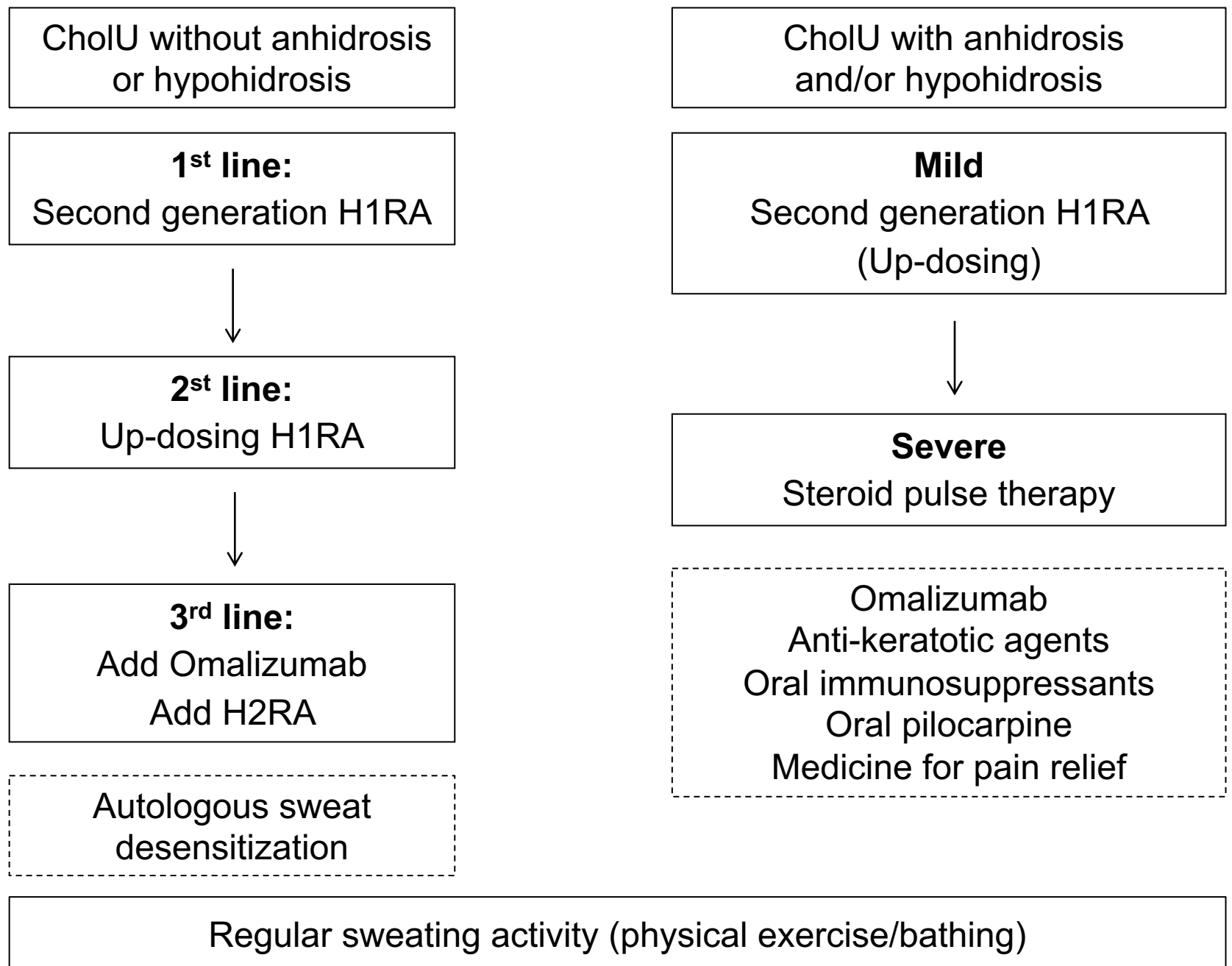


Fig. 5