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Malassezia infection associated with chronic spontaneous urticaria without angioedema: a report on five cases

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Abstract

Introduction: Chronic spontaneous urticaria (CSU) is a challenging condition to treat and it significantly affects quality of life. Bacterial, viral, parasitic, and fungal infections have been associated with triggering and/or perpetuating urticaria in certain individuals. There is a paucity of literature on CSU associated with *Malassezia* infection.
Methods and results: We present a case series of five patients with CSU without angioedema in whom we observed temporal association of *Malassezia* infection with CSU. The presence of *Malassezia* was confirmed by clinical examination, Wood's lamp, and KOH examination. The patients with CSU experienced improvement after specific antifungal therapy.
Conclusion: *Malassezia* infection may be associated with recurrent and chronic urticaria in a certain group of susceptible patients and thus specific targeted therapy against it might result in complete remission of urticaria along with clearing of the infection.

Keywords: *Malassezia*, chronic urticaria, association, antifungals

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Introduction

Chronic spontaneous urticaria (CSU) is defined as the occurrence of itchy wheals, angioedema, or both over a 6-week period independent of external stimuli (1). It is thought to have a more significant impact on patients' quality of life than any other allergic disease because it affects the activity of daily life and causes sleep disturbances, emotional problems, loss of energy, work absenteeism, and frustration in social relations (2). Activation of cutaneous mast cells, which contain preformed mediators such as histamine, plays a major role in the pathogenesis of urticaria. Many etiological factors have been implicated in the pathogenesis of CSU, including bacterial and viral infections, parasites, fungi, food and food additives, and autoantibodies directed against IgE receptors. Fungal infections are a less-recognized and less-reported cause of urticaria. There are isolated reports mentioning *Candida* and dermatophytes in association with urticaria (1, 3, 4). Tang et al. (5) observed the role of *Malassezia furfur* in the prevalence of chronic urticaria among a ship's crew. We report a case series of five patients with CSU without angioedema possibly induced by *Malassezia* infection.

Methods and results

Five patients with CSU were identified with coexisting *Malassezia* infection: four males and one female (median age: 32 yrs, range: 16–40 yrs). The clinical data for the patients are summarized in Table 1. Investigations such as complete blood cell count, ESR, CRP, blood sugar, urine and stool analysis, liver, renal, and thyroid function test, anti-thyroid peroxidase antibodies, anti-thyroglobulin, autologous serum skin test, HIV antibody, autoantibodies (ANA, ds-DNA), and IgE were either normal or negative. The *Helicobacter pylori* profile and latex-IgE were negative. Serum tryptase and C3, C4 levels could not be studied due to a lack of resources.

All five patients presented with recurrent pruritic, evanescent, erythemato-edematous papules and plaques of prolonged duration (> 6 weeks) with fluctuating severity of symptoms suggestive of CSU with a significant compromise to their quality of life (Figs. 1–5).

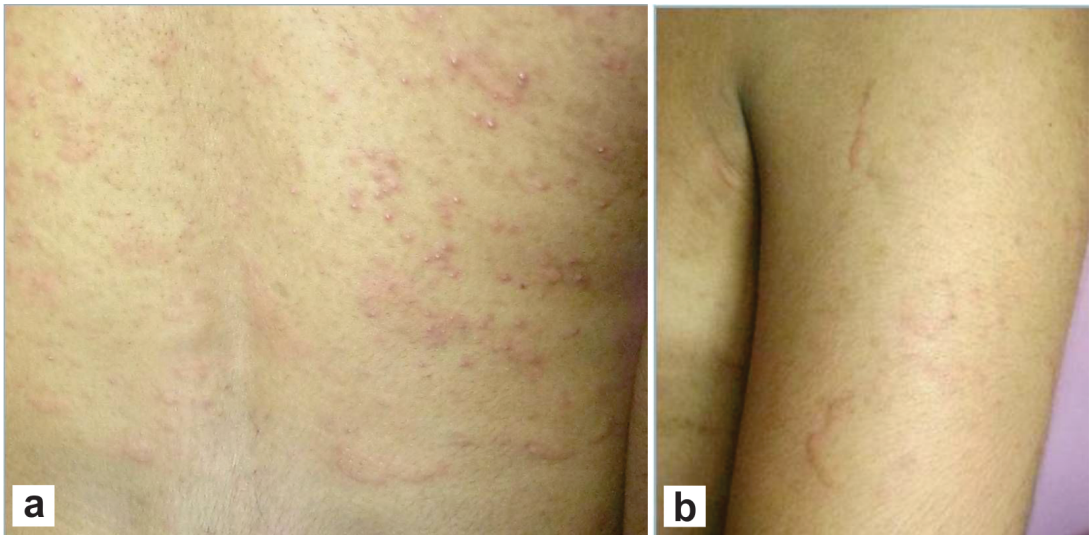

Figure 1 | *Malassezia* folliculitis: erythematous papules and pustules with urticarial wheals a) over trunk and b) left arm (Patient no. 3).

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Table 1 | **Clinical profile and other relevant findings of the patients.**

Variable	Case no.				
	1	2	3	4	5
Age (yrs) / Sex	38/male	16/female	28/male	40/male	32/male
Duration of urticaria	10 weeks	8 weeks	12 weeks	20 weeks	26 weeks
DLQI and UAS7 on first visit	19, 26	18, 24	20, 27	21, 28	25, 35
Treatment received before consultation	Oral levocetrizine 10 mg OD and topical calamine lotion	Oral desloratidine 5 mg OD and topical calamine lotion, iron supplements	Oral levocetrizine 5 mg and montelukast 10 mg OD	Oral combination of desloratidine 5 mg and montelukast 10 mg OD, oral ebastine and short course of oral steroid	Oral combination desloratidine 5 mg OD and montelukast 5 mg, short course of oral steroid, topical calamine lotion
Presenting complaints	Hyperpigmented, scaly macules over axillae and trunk	Erythematous dome-shaped comedo-papules over trunk	Erythematous papules and pustules over trunk and left arm	Hyperpigmented scaly macules over axillae and back	Hypopigmented, scaly macules over back
Clinical diagnosis	Pityriasis versicolor	*Malassezia* folliculitis	Chronic urticaria with: *Malassezia* folliculitis	Pityriasis versicolor with symptomatic dermographism	Pityriasis versicolor with symptomatic dermographism
Predisposing factor for *Malassezia* infection	None	Atopic familial background	Hyperhidrosis	History of pityriasis versicolor in brother and mother	None
KOH smear / Wood's lamp	*Malassezia* spores and hyphae, Wood' lamp: yellowish-white fluorescence	Spores and hyphae consistent with *Malassezia*	Wood' lamp: yellowish-white fluorescence	*Malassezia* spores and hyphae	*Malassezia* spores and hyphae
Other findings	Prick test for extracts of pityriasis versicolor scales: negative	–	–	Prick test for extracts of pityriasis versicolor scales: negative	Prick test for extracts of pityriasis versicolor scales: negative
Treatment received	Oral fluconazole 400 mg once and repeated at weekends for 4 weeks with continuous topical sertaconazole cream for 2 months	Oral itraconazole, 200 mg/day for 2 weeks plus topical sertaconazole lotion for 2 months	Oral itraconazole, 200 mg/day for 2 weeks plus topical sertaconazole lotion for 2 months	Oral fluconazole 400 mg once and repeated on weekends for 4 weeks with continuous topical sertaconazole cream for 2 months	Oral fluconazole 400 mg once and repeated on weekends for 4 weeks with continuous topical sertaconazole cream for 2 months
	Plus oral levocetrizine 10 mg OD for 6 weeks				
Outcome	Complete resolution of pityriasis versicolor and remission of attacks of urticaria 2 weeks after addition of antifungal agents	Complete resolution of *Malassezia* folliculitis and remission of attacks of urticaria after 3 weeks	Complete resolution of *Malassezia* folliculitis and remission of attacks of urticaria after 4 weeks	Complete resolution of pityriasis versicolor and remission of attacks of urticaria after 6 weeks	Complete resolution of pityriasis versicolor and remission of attacks of urticaria after 4 weeks
DLQI and UAS7 at 8th week of follow-up	1, 1	0, 0	1, 2	2, 3	4, 5

yrs = years, DLQI = Dermatology Life Quality Index, UAS7 = Weekly Urticaria Activity Score, OD = once daily.

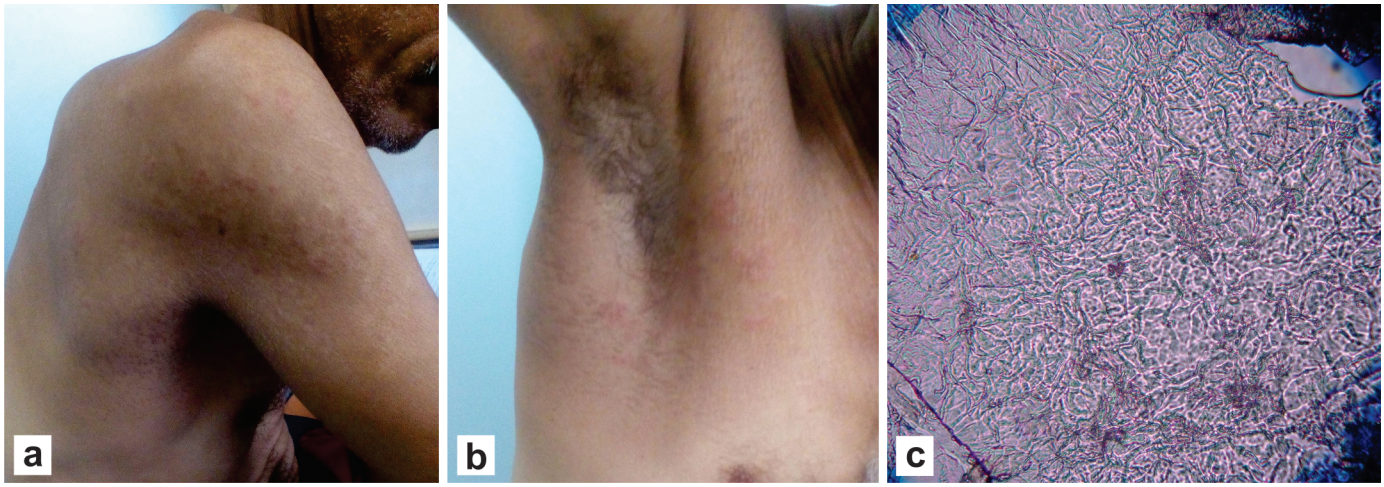


Figure 2 | Pityriasis versicolor: a) hyperpigmented scaly macules over the upper back and right shoulder; b) over the right axilla with urticarial weals; c) KOH examination of scales showing spores and hyphae (Patient no. 1).

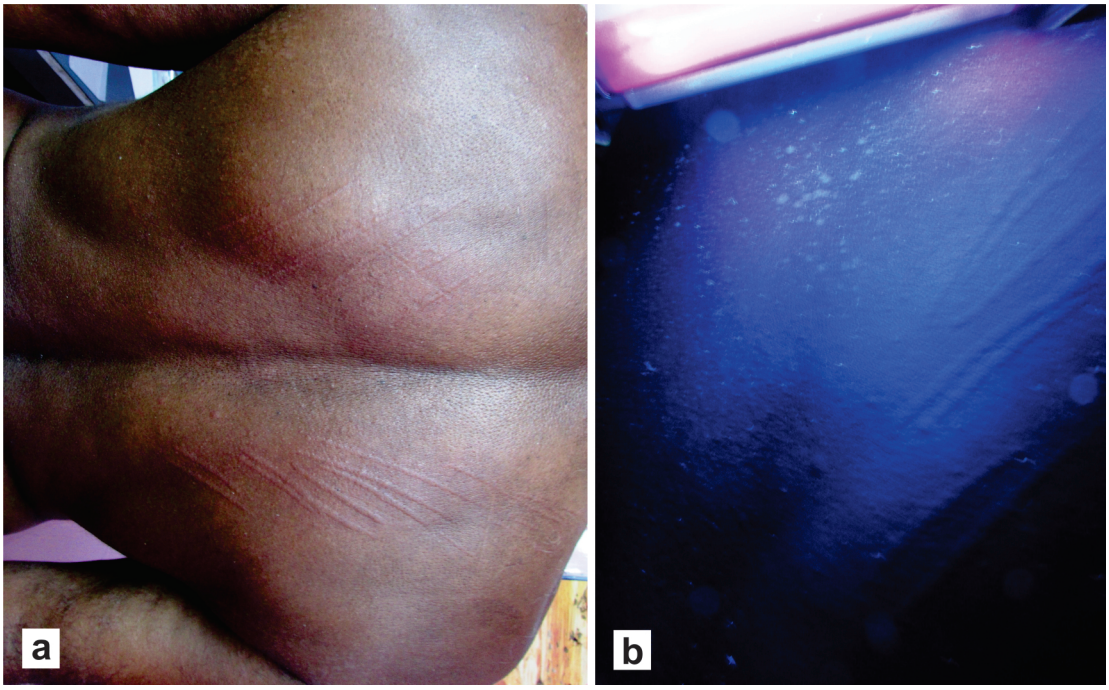


Figure 3 | Pityriasis versicolor: a) hypopigmented scaly macules over the left flank region with symptomatic dermographsim; b) Wood's lamp of the same showing bright yellow fluorescence (Patient no. 5).

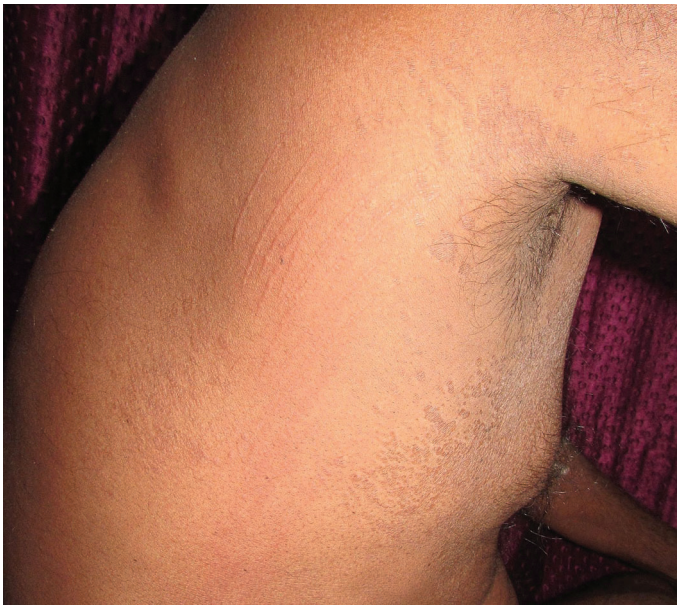


Figure 4 | Pityriasis versicolor: hyperpigmented scaly macules over the axilla and back with symptomatic dermographsim (Patient no. 4).

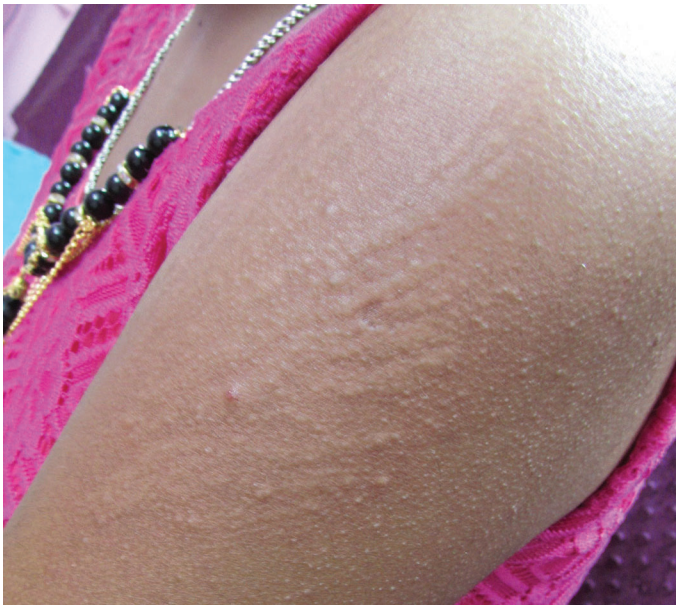
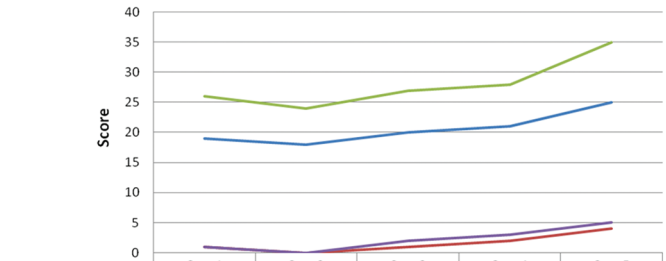


Figure 5 | *Malassezia* folliculitis over the left arm with transient edematous plaques suggestive of urticaria (Patient no. 2).



	Case 1	Case 2	Case 3	Case 4	Case 5
DLQI -On 1st visit	19	18	20	21	25
DLQI- At 8th week	1	0	1	2	4
UAS7- On 1st visit	26	24	27	28	35
UAS7 -At 8th week	1	0	2	3	5

Figure 6 | Graphic description of DLQI and UAS-7 scores on first visit and at 8th week showing a sharp decline in DLQI and UAS-7 scores at the 8th week after the addition of antifungal therapy. DLQI = Dermatology Life Quality Index, UAS7 = Weekly Urticaria Activity Score.

All patients had coexisting *Malassezia* infection (either in the form of pityriasis versicolor or *Malassezia* folliculitis), which was confirmed by Wood's lamp and 10% potassium hydroxide (KOH) mount. They were treated with specific therapy directed against *Malassezia* with the addition of a systemic antihistaminic. After 6 weeks of therapy, all of the patients experienced remission of attacks of urticaria in addition to the elimination of *Malassezia* infection. None of the patients required further treatment with antihistaminics for the next 6 months of follow-up, and all of them remained symptom free with much improved quality of life.

Discussion

Almost 50% of cases of CSU are idiopathic and up to 31% of cases are associated with infections (1, 3). An association between CSU and occult infection has been proposed, but with little evidence. Microorganisms such as *Helicobacter pylori* and *Streptococcus*, *Staphylococcus*, and *Yersinia* infections have been recognized as the cause of urticaria (1). Most reported infections in CSU are related to the gastrointestinal tract, and to the dental and ear, nose, and throat region (1). Fungi implicated in CSU are *Candida* spp. and dermatophytes (3, 4). Hiragun et al. (6) demonstrated elevated levels of IgE against MGL_1304, a protein component of *Malassezia* contained in sweat, which is an important antigen for patients with atopic dermatitis and cholinergic urticaria.

Pathogenic forms of *Malassezia* are linked with pityriasis versicolor (PV), seborrhoeic dermatitis, and *Malassezia* folliculitis, and they have also been implicated in exacerbation of atopic dermatitis and psoriasis in certain patients. Because of their affinity to lipids, sebum-rich areas of the skin such as the face, scalp, and upper trunk are predominantly affected (7). Two metabolic pathways—phospholipase production and indole pigment synthesis—are associated with strains isolated from diseased human skin. The latter pathway produces potent indolic arylhydrocarbon receptor ligands such as indirubin and indolo carbazole, which potentially modify the epidermal cells' functions and thus play a major role in the pathogenesis of *Malassezia* infections (8). Indoles produced by *Malassezia* also downregulate the production of inflammatory mediators and antigen-presenting capacity (8).

The mechanism of causation of urticaria in our patients is unclear. The protein components of *Malassezia* include 67-kDa, 37-kDa, and 17-kDa. The 17-kDa component (i.e., MGL_1304) has a high histamine-releasing property and it is also an important antigen for patients with atopic dermatitis and cholinergic urticaria. In contrast, the glycoprotein Malg46b component of *M. globosa* acts as a major antigen for IgE antibodies in patients with atopic dermatitis (9). It can be speculated that the protein components of *Malassezia* may act as haptens under specific environmental conditions of stimulation.

In all five patients, there was a temporal relationship of CSU with active *Malassezia* infection. Symptomatic dermographism was also seen in patients 4 and 5. Although symptomatic dermographism is present in 4 to 5% of the normal population, its prevalence in CSU is reported to be 22% (10). Anti-histamine treatment was only partially effective and urticaria readily recurred after it was discontinued. There was significant deterioration of quality of life, as evident by high Dermatology Life Quality Index (DLQI) (11) and Weekly Urticaria Activity Scores (UAS7) (12, 13) on the first visit. Interestingly, 7 to 10 days after the addition of oral fluconazole/itraconazole and topical sertaconazole, a sharp decline in the DLQI and the UAS7 was observed (Fig. 6), which was maintained for the next 4 weeks, and all patients showed complete resolution and recurrences were stopped for next 6 months with drastic improvement in their quality of life.

Malassezia yeast is susceptible to topical and oral antifungal agents. Commonly used topical agents include azoles, hydroxypyridones, allylamines, benzylamines, tacrolimus, and pimecrolimus. We preferred oral itraconazole and fluconazole in patients with extensive involvement and in those with topical treatment failure (7).

Unfortunately, we could not identify the subspecies of *Malassezia* spp., evaluate the anti-*Malassezia* IgE antibodies, or perform a radioallergosorbent test, which may provide more insight into the link of urticaria with *Malassezia*. More detailed, multicentric, and larger studies on *Malassezia* infection and its specific association with CSU will be of more value.

The literature on urticaria in association with *Malassezia* is scant. To the best of our knowledge, only one study is available in PubMed, in which the authors found the carrier rates of *Malassezia furfur* to be significantly higher in a ship's crew suffering from urticaria than in normal control subjects (5).

Conclusion

We report five cases of chronic spontaneous urticaria associated with *Malassezia* infection. All of them showed significant remission of urticaria, especially after antifungal therapy directed against *Malassezia* infection in addition to oral levocetrizine, and they remained free of disease for the following 6 months.

References

1. Wedi B, Raap U, Wieczorek d, Kapp A. Urticaria and infections. Allergy Asthma Clin Immunol. 2009;5:10.
2. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197–201.
3. Ergon MC, Ilknur T, Yucesoy M, Ozkan S. Candida spp. colonization and serum anticandidal antibody levels in patients with chronic urticaria. Clin Exp Dermatol. 2007;32:740–3.

4. Godse K, Zawar V. Chronic urticaria associated with tinea infection and success with antifungal therapy—a report of four cases. Int J Infect Dis 2010;Suppl 3:e364–5.
5. Tang XP, Zeng K, Chen GH, Bi LY, Fan LZ, Shao CF. Study of the association of Malassezia furfur with chronic urticaria among the ship crews. Di Yi Jun Yi Da Xue Xue Bao. 2003;23:870–2.
6. Hiragun M, Hiragun T, Ishii K, Suzuki H, Tanaka A, Yanase Y, et al. Elevated serum IgE against MGL_1304 in patients with atopic dermatitis and cholinergic urticaria. Allergol Int. 2014;63:83–93.
7. Gupta A, Batra R, Bluhm R, Boekhout T, Dawson TL. Skin diseases associated with Malassezia species. J Am Acad Dermatol. 2004;51:785–98.
8. Elegraki A, Cafarchia C, Gaitanis G, Iatta R, Boekhout T. Malassezia infections in humans and animals: pathophysiology, detection, and treatment. PloS Pathog. 2015;11:e1004523.
9. Kanbe T, Koyama T. Atopic dermatitis and Malassezia species: a study of antigenic components of Malassezia species for immunoglobulin E of patients with atopic dermatitis. Nihon Ishinkin Gakkai Zasshi. 2003;44:71–5.
10. Soter NA, Kaplan AP. Urticaria and angioedema. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in general medicine. 6th ed. New York: McGraw-Hill; 2003. p. 1129–43.
11. Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? Allergy. 2008;63:777–80.
12. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210–6.
13. Stull D, McBride D, Gimenez-Arnau A, Grattan C, Khalil S, Balp M-M. Validation of chronic spontaneous/idiopathic urticaria (CSU/CIU) health states using weekly Urticaria Activity Score (UAS7) and Dermatology Life Quality Index (DLQI) [poster]. American Academy of Dermatology Annual Meeting, San Francisco, March 2015. RTI Health Solutions. 2015 [cited 2017 Oct 4]. Available from: https://www.rtihs.org/publications/validation-chronic-spontaneousidiopathic-urticaria-csuciu-health-states-using-weekly.