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Patients with chronic cold urticaria may benefit from doxycycline therapy

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Bulleterd statements: Antibiotic treatment has been described to result in chronic cold urticaria (ColdU) remission in case reports and small case series. Here, we assessed the effects of antibiotic treatment in a sizeable population of patients with ColdU

DEAR EDITOR,

Chronic cold urticaria (ColdU) is a rare but severe and potentially life-threatening form of chronic urticaria characterized by the development of wheal and flare type skin reactions or angioedema after skin exposure to cold¹. Extensive cold contact (e.g. swimming in cold water) and low trigger thresholds (i.e. wheal responses to

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temperatures of 20°C or higher) may lead to systemic reactions including anaphylactic shock².

The diagnosis of ColdU is based on a detailed history and the results of provocation testing. For traditional provocation testing, a melting ice cube is applied to the skin for five minutes. Individual critical temperature thresholds (CTTs), i.e. the highest temperature that suffices to induce a wheal, can be determined by TempTest[®]³.

ColdU wheals result from skin mast cell activation in response to cold and rewarming, but the detailed pathomechanisms of ColdU wheal development are unknown. Activated mast cells release several proinflammatory mediators, most importantly histamine⁴. Histamine induces vasodilatation and increases vascular permeability, which lead to erythema and wheals⁵.

ColdU management includes cold avoidance and the prevention of signs and symptoms by antihistamines^{6,7}. In many cases, however, conventional antihistamine doses do not completely protect patients, and higher than standard doses of antihistamines are required^{8,9}. Up to 15% of patients with ColdU do not show any clinical improvement even on high dose antihistamines^{9,10}.

Antibiotic treatment has been described to result in ColdU remission in case reports and small case series^{11,12}. Here, we assessed the effects of antibiotic treatment with doxycycline in a sizeable population of ColdU patients.

26 patients (6 male and 20 female) with a confirmed diagnosis of ColdU were analysed retrospectively particularly in relation to their response to antibiotic treatment. The mean [SD] age of patients was 41 [17] years and the mean [SD] disease duration was 7.2 [6] years. The mean [SD] CTT, as assessed by TempTest[®] 3.0, was 14°[6] C.

All patients were treated with doxycycline 200 mg/d for 7 to 28 days (mean [SD] 18.5 [5] days). One, 4, 2, 18, and 1 patient received doxycycline for 7, 10, 14, 21, and 28 days, respectively. In 2 (8%) patients doxycycline was used as a monotherapy and 24 (92%) patients received doxycycline in combination with an H1 antihistamine. Assessment of the

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response before and after antibiotic therapy was conducted after discontinuation of antihistamines for min. 48h. Treatment responses were assessed by cold provocation tests done with TempTest® 3.0 (n = 24), ice cube test (n = 1), or 15°C hand bath (n = 1) before and after therapy. Test sites were read for wheal development (= positive response) at 10 minutes after testing. The highest temperature at which a wheal reaction was observed was recorded as CTT. Patients were categorized according to their CTT response to treatment as “complete responders”, i.e. no wheal to the lowest temperature tested (4°C), “partial responders” i.e. reduction in CTT $\geq 4^\circ\text{C}$ compared to baseline, and “non-responders”, i.e. a CTT reduction $< 4^\circ\text{C}$ in comparison with baseline. The Student’s *t* test was used for statistical analyses, and a *p* of <0.05 was considered to indicate a statistical difference.

Doxycycline treatment did not significantly reduce CTTs of ColdU patients (baseline [SD]: 14 [6]°C versus post treatment [SD]: 12 [8] *p* = 0.5). However, a subpopulation of ColdU patients (5 of 26, 19%) showed full remission in response to therapy, i.e. no wheal development after provocation with 4°C after treatment. Another 4 patients (15%) showed partial responses, i.e. a CTT reduction of $\geq 4^\circ\text{C}$ after therapy (Fig. 1). Treatment responses to doxycycline were not linked to disease duration or severity, age of the patients or duration of the treatment.

Further analyses showed no differences between pre-treatment CTTs of responders and non-responders (Fig 2A). However, complete responders had lower pre-treatment CTTs as compared to partial responders (*p* = 0.01) (Fig. 2B).

Successful treatment of ColdU with antibiotics has been reported earlier in case reports and small case series¹³⁻¹⁵. *Moeller* et al, in 1996, described remission of ColdU in 5 of 10 patients after treatment with tetracycline¹¹. In our study, 34% of ColdU patients benefited from the treatment with doxycycline, half of them showed full remission. A possible explanation for the discrepancy between our results and previous findings could be the larger and thus more representative number of included patients (n=26) in our study. Also, response to therapy in our study was assessed by standardized provocation testing (TempTest® 3.0, ice-cube test or cold hand bath) in each patient versus baseline, while *Moeller* et al performed provocation testing after therapy only in

isolated cases. The exact method of response assessment is, unfortunately, not reported in the *Moeller et al* paper.

In our study, CTTs did not predict whether or not patients benefit from antibiotic treatment. In those patients who do respond to treatment, lower CTTs were linked to better responses to treatment than high CTTs. We do not presently know why. The more important and interesting question, however, is why some patients show a benefit and even complete remission, whereas most patients do not. Our present studies address this question. It appears unlikely that those patients who show complete remission do so because of placebo effects or due to spontaneous remission. The identification of the mechanism of action of antibiotic treatment in ColdU could help to better understand the pathomechanisms of ColdU and to predict the outcome of doxycycline therapy. This would help clinicians to conduct targeted therapy and individualized management of ColdU patients.

The strength of this study is the use of CTT assessments of disease activity and the response to therapy in a sizable patient population. The weakness of the study is that no long-term follow up was done to assess the duration of therapeutic benefit. Also, bacterial infections were checked for only by history and physical examination, and no laboratory tests for bacterial infections were conducted.

The therapeutic effects of doxycycline in ColdU could be explained by its effects on underlying chronic subclinical bacterial infections that cause and maintain ColdU. However, there is very little evidence from the literature that bacterial infections are a relevant cause of ColdU¹⁶. The effects of doxycycline could also be due to its immune-regulatory activity and its impact on cytokine production. Tetracyclines and particularly doxycycline suppress cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin- (IL-) 1 β , and IL-6, involved in inflammatory skin disorders¹⁷. Furthermore, doxycycline inhibits the IgE-mediated degranulation and inflammatory cytokine production of mast cells and histamine-induced vascular permeability¹⁸.

Treatment with doxycycline can be beneficial for patients with ColdU. Further studies should be done to investigate the mechanism of action and the duration of treatment responses, and to identify markers that allow for treatment outcome prediction.

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