

Levocetirizine and Prednisone Are Not Superior to Levocetirizine Alone for the Treatment of Acute Urticaria: A Randomized Double-Blind Clinical Trial

Caroline Barniol, MD; Emilie Dehours, MD; Jean Mallet, MD; Charles-Henri Houze-Cerfon, MD; Dominique Lauque, MD*;
Sandrine Charpentier, MD, PhD

*Corresponding Author. E-mail: lauque.d@chu-toulouse.fr.

Study objective: We evaluate the efficacy of a 4-day course of prednisone added to antihistamine for the management of acute urticaria in an emergency department (ED).

Methods: In this double-blind randomized clinical trial, patients were eligible for inclusion if aged 18 years or older and with acute urticaria of no more than 24 hours' duration. Patients with anaphylaxis or who had received antihistamines or glucocorticoids during the previous 5 days were not included. In addition to levocetirizine (5 mg orally for 5 days), patients were assigned to receive prednisone (40 mg orally for 4 days) or placebo. The primary endpoint of the study was itching relief 2 days after the ED visit, rated on a numeric scale of 0 to 10. Secondary endpoints were rash resolution, relapses, and adverse events.

Results: A total of 100 patients were included, 50 in each group. Seven patients in the prednisone group and 8 in the placebo group discontinued treatment. At 2-day follow-up, 62% of patients in the prednisone group had an itch score of 0 versus 76% of those in the placebo group (Δ 14%; 95% confidence interval -31% to 4%). Thirty percent of patients in the prednisone group and 24% in the placebo group reported relapses (Δ 6%; 95% confidence interval -23% to 11%). Mild adverse events were reported by 12% of patients in the prednisone group and 14% in the placebo group.

Conclusion: The addition of a prednisone burst did not improve the symptomatic and clinical response of acute urticaria to levocetirizine. This study does not support the addition of corticosteroid to H₁ antihistamine as first-line treatment of acute urticaria without angioedema. [Ann Emerg Med. 2017;■:1-7.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/\$-see front matter

Copyright © 2017 by the American College of Emergency Physicians.

<http://dx.doi.org/10.1016/j.annemergmed.2017.03.006>

INTRODUCTION

Background

Acute urticaria is a relatively common cause for consultation in the emergency department (ED). It accounts for 7% to 35% of dermatologic conditions presenting at the ED.¹⁻⁵ Of the symptoms of this condition, pruritus is the most bothersome because it may impair daily activities and cause sleep disturbances.⁶ ED management of acute urticaria without angioedema or wheezing is usually limited to avoidance of the allergen, when it can be identified, and to symptomatic treatment with H₁ antihistamines.^{7,8} The 2013 update of international guidelines for the definition, classification, diagnosis, and management of urticaria states that a short course of oral corticosteroids may be helpful to reduce disease duration and activity in acute urticaria.⁷

Importance

Only 2 studies have suggested that corticosteroids may be effective in the treatment of acute urticaria.^{9,10} Patient condition improved more quickly and more completely when corticosteroids were added to antihistamines. One study was a randomized controlled trial performed with 43 patients treated with old first-generation H₁ antihistamines,⁹ whereas the other was a nonrandomized cohort study on the causes and treatment of acute urticaria.¹⁰

Physicians use glucocorticoids as ancillary therapeutic agents in the treatment of acute urticaria. In Italy, 93% of patients attending an ED for this condition, most of them without angioedema, received corticosteroids in 2011.¹¹ The effect of corticosteroids as first-line ED treatment of acute urticaria needs to be studied in a randomized clinical trial of patients receiving a modern second-generation antihistamine.

Editor's Capsule Summary*What is already known on this topic*

The role for corticosteroids in urticaria is not clear.

What question this study addressed

Does adding prednisone to antihistamine therapy hasten itch resolution in simple urticaria?

What this study adds to our knowledge

In this double-blind, placebo-controlled trial of 100 adults, itch and rash relief at 2 days were similar with and without prednisone.

How this is relevant to clinical practice

Adding a corticosteroid to antihistamine therapy for simple urticaria appears unnecessary.

Use of modern nonsedative H₁ antihistamines is recommended because they have a better safety profile than first-generation sedative H₁ antihistamines.⁷

Goals of This Investigation

We designed a prospective, randomized, placebo-controlled, double-blind, parallel-group study on the efficacy of a short course of prednisone in addition to levocetirizine for the treatment of acute urticaria in ED patients. The primary outcome variable was complete resolution of itching, defined by an itch score of 0 of 10 at 2-day follow-up. Secondary endpoints were rash resolution, relapses, and adverse events.

MATERIALS AND METHODS**Study Design**

Enrollment in this prospective, randomized, double-blind, controlled trial began in February 2012 and finished when the desired number of patients was reached in January 2014. The French National Agency of Medicine and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé) and the regional ethics committee approved this study in October and November 2011, respectively. A standard statement that explained the nature of the study was read to eligible patients, and if they agreed to participate they filled out an informed consent form and were enrolled.

Setting

The study was conducted at a multifacility academic hospital that has 2 tertiary care academic EDs, which

together treated more than 98,000 patients aged 15 years or older in 2013. The patients were prospectively enrolled by their treating emergency physician. Before the study, physicians underwent a comprehensive education program concerning the ethical conduct of research and the study protocol, including data collection and signs and treatment of acute urticaria. Shorter refresher sessions were provided throughout the study period.

Selection of Participants

Patients were eligible for inclusion if they were aged 18 years or older and presented to the ED with acute generalized rash of no more than 24 hours' duration that was characterized by fleeting wheals and itching. The exclusion criteria were angioedema; anaphylaxis; fever; use of antihistamines or glucocorticoids during the 5 days before ED admission; known allergy to the study drugs or formulation ingredients; patient-reported history of diabetes, chronic respiratory failure, or cardiac or renal failure; active peptic ulcer disease; pregnancy or breastfeeding; and inclusion in another clinical trial. Patients were enrolled by emergency physicians working clinically.

Interventions

Eligible patients were treated with either levocetirizine (5 mg orally once daily for 5 days) and prednisone (40 mg orally once daily for 4 days) or levocetirizine at the same dosage and placebo. Both the prednisone and the placebo doses were prepared in identical capsules by the hospital's pharmacy department so that neither the treating emergency physician nor the patient could discern which study medication was administered. Randomization was performed by the hospital pharmacy. The allocation list was generated by a computer random-number generator and was equilibrated by blocks of 10 for each ED. Levocetirizine tablets and prednisone or placebo capsules were placed in 2 packs in sealed envelopes that were sequentially numbered and stored in the ED. The patient was assigned the upcoming envelope. The first dose of levocetirizine and prednisone or placebo was given during the patient's ED visit. Patients were observed for 1 hour in the ED after initiation of treatment. Before discharge, they were instructed to receive the medications in the envelope on the subsequent 4 days.

Data Collection and Processing

All baseline data, including age, sex, height, weight, medical history, eliciting factors, baseline itch score, extent of urticaria, pulse rate, and blood pressure, were collected

prospectively and recorded directly in a case report form by the treating physicians. Patient condition was reassessed clinically in the ED 1 hour after initiation of treatment, and itch scores, rash scores, and adverse events were recorded. Patients were contacted by telephone 2, 5, 15, and 21 days after ED discharge by the same investigator, who was blinded to the patient group. They were asked to rate their itch score, to describe any remaining rash or relapse, to confirm compliance with medications, and to state any adverse effects. Patients were asked specifically about general, gastrointestinal, muscular, and neuropsychiatric symptoms, dry mouth, and tendon rupture. Itching was assessed by asking patients to rate their pruritus with an integer between 0 and 10, 0 being “itching free” and 10 being “worst itching ever.” We chose to use a verbal numeric rating scale rather than a visual analog scale to ease data collection by telephone. The percentage of total body surface area affected by urticaria was estimated with the rule of 9s.¹² Patients were asked at follow-ups about relapses. Fleeting relapses occurring at follow-up intervals were recorded even if the itch scores and the rash scores measured at the call were improved compared with the previous scores. Accuracy of data collected, consistency with source documents, and missing data were controlled by a research assistant throughout the study.

Outcome Measures

The primary endpoint of the study was itching relief 2 days after the ED visit. Itching relief was defined as a numeric rating scale score equal to 0 of 10. Secondary endpoints were rash resolution, defined as 0% of total body surface area covered by urticaria, percentage of patients with relapses, and adverse events.

Primary Data Analysis

Descriptive statistics are reported as medians with interquartile ranges (IQRs) and proportions with exact binomial 95% confidence intervals (CIs). Proportions were compared by using χ^2 tests or Fisher's exact test when appropriate. Data were analyzed with Stata (StataCorp, College Station, TX).

The sample size was calculated on the basis of previous data showing that complete remission of acute urticaria occurred within 3 days of treatment in 66% of patients treated with antihistamine and 94% of patients treated with corticosteroid.¹⁰ Most of the difference between corticosteroid and histamine alone occurred within the first 2 days of treatment in another trial.⁹ The approach for the study design was a superiority design, so a sample size of 41 was therefore calculated with a 2-sided test with a 0.05 type

I error and a power of 80%. We decided nevertheless to include 100 patients to offset those who were noncompliant or lost to follow-up. All participants who underwent random assignment were analyzed according to group assignment in an intention-to-treat fashion. We performed a post hoc sensitivity analysis to determine the robustness of the results to the inclusion of data from participants who deviated from the protocol. The main outcome, itch score at 2-day follow-up, was analyzed per protocol after exclusion of participants who discontinued treatment.

RESULTS

Characteristics of Study Subjects

Figure 1 shows the trial profile. Among the 710 eligible patients, 412 had the following exclusion criteria: angioedema or anaphylaxis (142), use of antihistamines or glucocorticoids before their ED visit (116), rash of greater than 24 hours' duration (103), younger than 18 years (33), pregnancy (8), fever (5), chronic disease (4), and previous inclusion (1). One hundred sixty eligible patients were not included because the treating emergency physician was not available or not included in the trial. One hundred patients were randomly assigned to treatment.

Seven patients in the prednisone group and 8 in the placebo group showed poor compliance and discontinued treatment, mainly because they experienced no improvement. One patient in the placebo group had vomiting and abdominal pain in the ED 1 hour after initiation of treatment. These symptoms were related to anaphylaxis, and the patient rapidly improved after a steroid injection. Twelve patients discontinued early, during the first 2 days of treatment. Three of the 8 subjects who withdrew from treatment in the placebo group received a corticosteroid during the treatment period. Follow-up data were available at days 2, 5, 15, and 21 after entry for 100, 88, 85, and 92 patients, respectively. Overall, 41 patients (82%) in the prednisone group and 39 (78%) in the placebo group complied with the treatment and were available for follow-up at 21 days.

The baseline characteristics of the 100 patients are reported in Table 1. Median itch scores at entry were 7 (IQR 5 to 8) for both the placebo group and the prednisone group. The median percentages of total body surface area affected by urticaria were 33 (IQR 10 to 49) for the placebo group and 30 (IQR 10 to 54) for the prednisone group.

Main Results

Both treatments proved to be effective, with cessation of symptoms within 2 days in the majority of patients. At

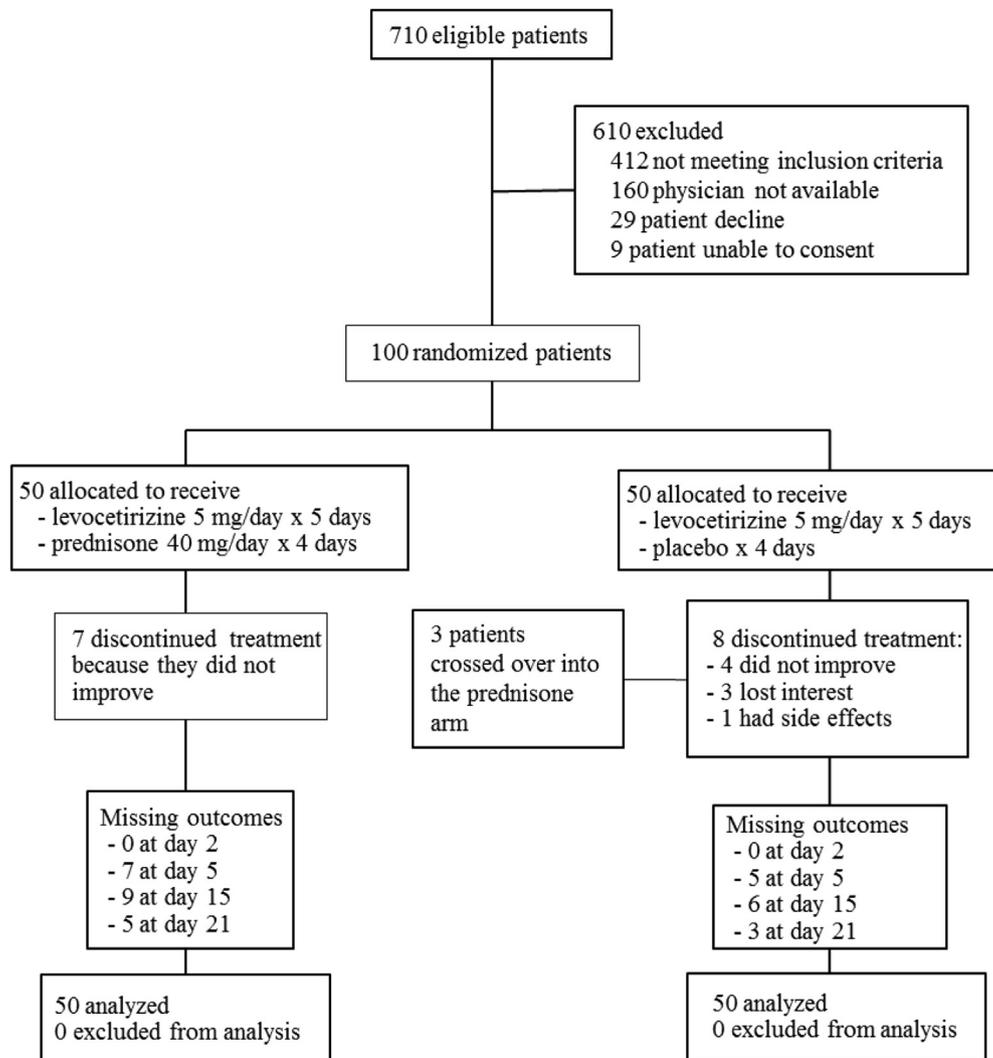


Figure 1. Flow chart of the study.

follow-up 2 days after entry into the study, 62% of the patients in the prednisone group had an itch score of 0 versus 76% of those in the placebo group (Δ -14% ; 95% CI -31% to 4%). The sensitivity analysis performed after exclusion of the 15 patients who violated the protocol found similar results: 67% of patients in the prednisone group and 79% in the placebo group had an itch score of 0 at 2-day follow-up (Δ -11% ; 95% CI -29% to 8%). After 2 days' treatment, the rash resolved in 70% of patients in the prednisone group versus 78% of those in the placebo group (Δ -8% ; 95% CI -25% to 9%).

Other assessments performed 1 hour after ED treatment, at 5 days when treatment was discontinued, and at later dates did not show better itching relief with prednisone than with placebo (Figure 2). Median itch scores were 2 (IQR 1 to 5) for the prednisone group and 2 (IQR 0 to 5) for the placebo group at 1 hour after entry

into the study, and 0 for both groups at 2-day follow-up. Figure 3 presents the changes in itch score as parallel line plots for each patient from baseline to 2 days, showing a similar pattern of decrease for both groups. Itch score increased at day 2 in only 4 patients in the prednisone group and 2 patients in the placebo group. The improvement of rash score for each patient in both groups from baseline to 2 days is shown in Figure E1, available online at <http://www.annemergmed.com>.

Fifteen patients (30%) in the prednisone group and 12 patients (24%) in the placebo group reported one or more relapses (Table 2) (Δ 6% ; 95% CI -11% to 23%). Most of these relapses (89%) occurred during the first 5 days of the protocol. Nine patients in the prednisone group were treated with another corticosteroid, 6 after premature discontinuation of the study treatment and 3 after completing the 5-day treatment period. Three patients in

Table 1. Baseline clinical and demographic characteristics.*

Group	Prednisone, n=50	Placebo, n=50
Age, y	27 (23–41)	27 (23–44)
Male patients	23 (46)	24 (48)
Body mass index, kg/m ²	23 (21–27)	23 (21–25)
Eliciting factors	27 (54)	30 (60)
Food	13 (26)	6 (12)
Drug	6 (12)	8 (16)
Contact urticaria	3 (6)	5 (10)
Insect bite	1 (2)	1 (2)
Itch score on numeric rating scale	7 (5–8)	7 (5–8)
Rash		
% of total body surface	30 (10–54)	33 (10–49)
<10% of total body surface, No. (%)	12 (24)	9 (18)
10%–50% of total body surface, No. (%)	21 (42)	28 (56)
>50% of total body surface, No. (%)	17 (34)	13 (26)
Pulse rate, beats/min	80 (70–83)	80 (71–90)
Systolic blood pressure, mm Hg	129 (120–140)	130 (120–140)

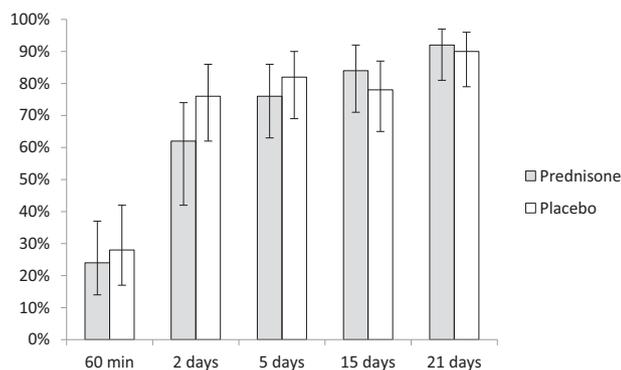
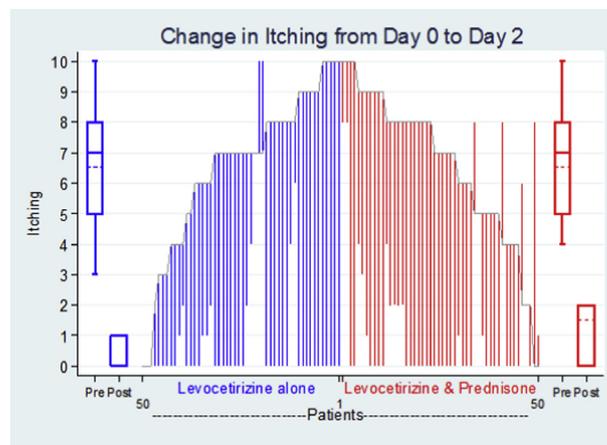
*Results are expressed median (IQR) unless otherwise indicated.

the placebo group were treated with a corticosteroid during the study treatment period and 2 later.

Seven patients (14%) in the prednisone group and 7 (14%) in the placebo group reported mild adverse effects of treatment that did not warrant its discontinuation (Table 2). The most common were fatigue (7 patients), sedation (3), insomnia (2), and dyspepsia (2). No serious or severe adverse effect of the treatment was reported.

LIMITATIONS

First, patients in our study were followed up by telephone and not clinically. To improve outcome reporting accuracy, all patients were called by the same investigator and a scoring system was used to assess itching

**Figure 2.** Percentage and CIs of patients with an itch score of 0 of 10 in the prednisone and placebo groups.**Figure 3.** Changes in each patient's itch score from baseline to 2 days, contrasted between groups. For each treatment group, the day 0 itch score is sorted from highest (patient 1) to lowest (patient 50) and displayed along the gray line. For each patient, a line extends from that value to the day 2 value. The box plots show the overall group changes in itch score between both groups.

and rash extent. Second, 7 patients in the prednisone group and 8 in the placebo group discontinued treatment, and 3 of them crossed over from the placebo to the prednisone arm. These protocol deviations may have biased results and decreased the odds of demonstrating an effect of prednisone in the intention-to-treat analysis. However, the sensitivity analysis performed after these patients were excluded confirmed that the addition of prednisone did not improve urticaria resolution compared with antihistamine alone. Third, all patients attended the ED with untreated acute urticaria of recent onset. The purpose of our study was to test the use of prednisone in first-line ED management of acute urticaria without angioedema. Therefore, our results may not be relevant to more severe urticaria that persists for days or weeks and resists a first line of treatment. Fourth, data on use of topicals for relieving itching were not

Table 2. Relapses and adverse effects.*

Group	Prednisone, n=50	Placebo, n=50	Absolute Risk Difference, % (95% CI)
Relapses	15 (30)	12 (24)	6 (–11 to 23)
One	12 (24)	10 (20)	4 (–12 to 20)
Two	2 (4)	2 (4)	0
Three	1 (2)	0	2 (–5 to 10)
Adverse effects			
Fatigue	4 (8)	3 (6)	2 (–9 to 14)
Sedation	0	3 (6)	–6 (–16 to 21)
Insomnia	2 (4)	0	4 (–4 to 13)
Dyspepsia	1 (2)	1 (2)	0

*Results are expressed as No. (%) unless otherwise indicated.

collected. Randomization presumably distributed these treatments equally between the 2 groups of patients.

DISCUSSION

In this randomized, double-blind study of patients with acute urticaria, the addition of a 4-day prednisone burst to levocetirizine did not increase or accelerate the rate of resolution observed with the antihistamine alone. The rash resolved in most patients in the prednisone group and in the placebo group after 2 days of treatment. In addition, we found no difference in the incidence of relapses or adverse effects during and after the treatment period. These data suggest that prednisone does not increase the effectiveness of a first-line treatment with antihistamine in patients presenting to the ED with recent urticaria without anaphylaxis.

In conflict with our results, 2 previous studies suggested that a burst of corticosteroid in addition to antihistamine could be beneficial to patients with acute urticaria. Pollack and Romano⁹ performed a randomized, double-blinded trial on the addition of a 4-day prednisone burst to standard treatment with antihistamines in 43 patients attending an ED for acute urticaria of no more than 24 hours' duration. Patients in the prednisone group had greater improvement in rash and itch score than those in the placebo group at 2- and 5-day follow-up. The authors concluded that the addition of prednisone improved the symptomatic and clinical response of acute urticaria to antihistamines, without any apparent adverse effects. The discrepancies observed with our negative results could be related to differences in sample size or in antihistamines. The first-generation antihistamines used in their study, diphenhydramine and hydroxyzine, may be less potent H₁ antagonists and be less effective in relieving the symptoms of acute urticaria than newer second-generation antihistamines.^{13,14}

The second study was a nonrandomized prospective cohort study of 109 patients who attended a dermatology consultation for acute urticaria, received an antihistamine (loratadine) or prednisolone for 3 days, and were followed up until complete remission.¹⁰ Both treatment regimens were effective in controlling whealing, but symptoms ceased earlier in corticosteroid-treated patients, with 94% experiencing complete remission within 3 days of treatment compared with 66% of patients treated with loratadine. This study was not randomized and was not carried out in an ED setting.

Based on these 2 early studies, in 2004 a best evidence topic report on acute urticaria concluded that the addition of oral corticosteroid to an antihistamine resulted in decreased itch and more rapid rash resolution in patients presenting to the

ED with acute urticaria.¹⁵ More recently, the 2013 revision of the international guidelines for the definition, classification, diagnosis, and management of urticaria suggested that a short course of oral corticosteroids may be useful for acute urticaria and acute exacerbation of chronic spontaneous urticaria to reduce disease duration and activity.⁷ Nevertheless, the low level of evidence of this recommendation, related to the lack of well-designed randomized clinical trials, was emphasized. In 2014, a review recommended oral corticosteroid for a few days in patients with acute urticaria associated with marked symptoms or angioedema to shorten the duration of attacks.⁸

Acute urticaria is a self-limited transient condition. Mild cases may not require treatment. Pharmacologic therapy is initiated to relieve itching. Most attacks settle within 2 to 3 weeks and further relapses are prevented by avoidance of the inducing stimulus. The proportion of patients progressing from acute urticaria to anaphylaxis is not documented but appears low. Only 1 of our 100 patients underwent anaphylaxis, confirming that acute urticaria is most frequently a self-limited disorder. Emergency physicians must observe the patient for 1 to 2 hours in the ED after treatment to ascertain that an anaphylactic reaction is not developing. Patients whose condition has not progressed beyond simple urticaria to angioedema or systemic symptoms within a few hours of onset of pruritic rash are unlikely to experience worsening once treatment is initiated.¹⁶

Second-generation antihistamines are recommended as first-line medications for both children and adults because of their good safety profile.^{7,17} Older first-generation H₁ antihistamines have pronounced adverse effects, including anticholinergic and sedative effects that impair quality of life.¹⁸ H₁ antihistamines reduce the wheal and pruritus mediated primarily by the actions of histamine on H₁ receptors located on endothelial cells and on sensory nerves. The dosage of second-generation antihistamines may be increased up to 4-fold as second-line treatment in patients who do not respond to a single dose.^{7,19}

Despite the evidence that second-generation H₁ antihistamines treat acute urticaria without disturbing adverse effects, many physicians believe that corticosteroids are still the most effective treatment to obtain rapid symptom relief. Corticosteroids were used in 93% of 459 subjects attending an ED for acute urticaria, most of them without angioedema.¹¹ Emergency physicians may be concerned that patients worsen after discharge and return to the ED with more severe symptoms or anaphylaxis. However, corticosteroids are no longer drugs of choice in initial anaphylaxis treatment.^{20,21} Our results do not support the addition of corticosteroid to antihistamine as a first-line treatment of uncomplicated acute urticaria. Even if short-term treatment with corticosteroids does not cause

clinically significant toxicity, recurrent or long-term treatment may have deleterious effects. Refractory cases must be referred to a dermatologist or allergist.

In conclusion, the addition of a 4-day burst of prednisone to levocetirizine was not superior to levocetirizine alone for relieving itching or improving the time course of resolution of acute urticaria. This study does not support the addition of corticosteroids to H₁ antihistamine as first-line treatment of acute urticaria without angioedema. Other randomized controlled studies should address the role of corticosteroids in the management of acute urticaria as a second-line treatment or when angioedema is present.

The authors acknowledge the sponsors, Toulouse University Hospital and the French Society of Emergency Medicine; Dr. Vanina Bongard for advice on study design; the clinical research assistants for their help in conducting this study; and Nina Crowte for translation services.

Supervising editor: Steven M. Green, MD

Author affiliations: From the Pôle de Médecine d'Urgences, Centre Hospitalier Universitaire, Toulouse, France (Barniol, Dehours, Mallet, Houze-Cerfon, Lauque, Charpentier); the Université Paul Sabatier Toulouse III, Toulouse, France (Lauque, Charpentier); and INSERM UMR 1027 Equipe 5, Toulouse, France (Charpentier).

Author contributions: CB and SC conceived the study, designed the trial, and obtained research funding. CB, ED, JM, C-HH-C, and SC supervised the conduct of the trial, recruitment of patients, and data collection. CB, DL, and SC managed the data, including quality control. DL and SC provided statistical advice on study design and statistical methodology and analyzed the data. DL had full access to all the data and had final responsibility for the decision to submit for publication. CB drafted the article, and all authors contributed substantially to its revision. DL takes responsibility for the paper as a whole.

All authors attest to meeting the four [ICMJE.org](http://www.icmje.org) authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. This work was sponsored by Toulouse University Hospital for regulatory and ethical submission. Support was solely institutional. The study was supported by a grant from the French Society of Emergency Medicine and a local grant from Toulouse University Hospital, 2011, number 1122102.

Publication dates: Received for publication December 31, 2016. Revision received February 26, 2017. Accepted for publication March 1, 2017.

Trial registration number: NCT02565680

The sponsor of the study had no role in study design, data collection, analysis and interpretation, or writing of this report.

REFERENCES

- Wang E, Lim BL, Than KY. Dermatological conditions presenting at an emergency department in Singapore. *Singapore Med J*. 2009;50:881-884.
- Alpalhão M, Uva L, Soromenho G, et al. Dermatological emergencies: one-year data analysis of 8,620 patients from the largest Portuguese tertiary teaching hospital. *Eur J Dermatol*. 2016;26:460-464.
- Martínez-Martínez ML, Escario-Travesedo E, Rodríguez-Vázquez M, et al. [Dermatology consultations in an emergency department prior to establishment of emergency dermatology cover]. *Actas Dermosifiliogr*. 2011;102:39-47.
- Baibergenova A, Shear NH. Skin conditions that bring patients to emergency departments. *Arch Dermatol*. 2011;147:118-120.
- Simonart T, Askenasi R, Lheureux P. Particularities of urticaria seen in the emergency department. *Eur J Emerg Med*. 1994;1:80-82.
- Poon E, Seed PT, Greaves MW, et al. The extent and nature of disability in different urticarial conditions. *Br J Dermatol*. 1999;140:667-671.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.
- Sabroe RA. Acute urticaria. *Immunol Allergy Clin North Am*. 2014;34:11-21.
- Pollack CV, Romano TJ. Outpatient management of acute urticaria: the role of prednisone. *Ann Emerg Med*. 1995;26:547-551.
- Zuberbier T, Iffländer J, Semmler C, et al. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol*. 1996;76:295-297.
- Losappio L, Heffler E, Bussolino C, et al. Acute urticaria presenting in the emergency room of a general hospital. *Eur J Intern Med*. 2014;25:147-150.
- Wallace AB. The exposure treatment of burns. *Lancet*. 1951;1:501-504.
- Juhlin L. A comparison of the pharmacodynamics of H₁-receptor antagonists as assessed by the induced wheal-and-flare model. *Allergy*. 1995;50(24 suppl):24-30.
- Grant JA, Danielson L, Rihoux JP, et al. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. *Allergy*. 1999;54:700-707.
- Poon M, Reid C. Best evidence topic reports. Oral corticosteroids in acute urticaria. *Emerg Med J*. 2004;21:76-77.
- Paul Tran T, Muelleman RL. Allergy, hypersensitivity, and anaphylaxis. In: Marx JA, Hockberger RS, Walls RM, eds. *Rosen's Emergency Medicine: Concepts and Clinical Practice*, 6th ed. Philadelphia, PA: Mosby Elsevier; 2006:1818-1837.
- Simons FE. Advances in H1-antihistamines. *N Engl J Med*. 2004;351:2203-2217.
- Staevska M, Gugutkova M, Lazarova C, et al. Night-time sedating H1-antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomized controlled trial. *Br J Dermatol*. 2014;171:148-154.
- Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676-682.
- Choo KJ, Simons FE, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Evid Based Child Health*. 2013;8:1276-1294.
- Simons FE, Arduzzo LR, Dimov V, et al. World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol*. 2013;162:193-204.

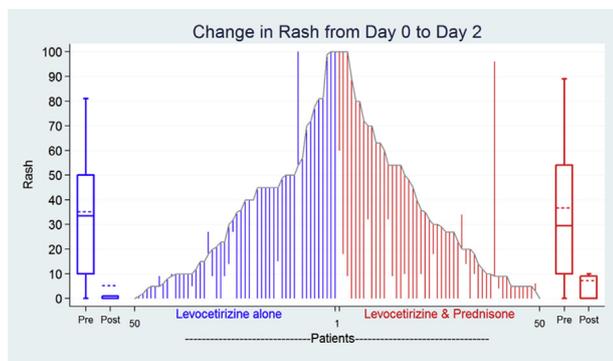


Figure E1. Changes in the percentage of total body surface area affected by urticaria (rash score) for each patient from baseline to day 2, contrasted between groups. For each treatment group, the day 0 rash score is sorted from highest (patient 1) to lowest (patient 50) and displayed along the gray line. For each patient, a line extends from that value to the day 2 value. The box plots show the overall group changes in rash score between both groups.