

Acute urticaria treated with systemic glucocorticoids: An evidence-based review

Andreia Lasca, Juliana Gomes, Ana Teresa Gorgulho de Pinho, Raquel Filipa Martins, Daniela Moreira

Background and objective

Systemic glucocorticoids (GCs) are frequently used in the treatment of acute urticaria (AU) to reduce its duration and intensity. AU is a self-limited transient condition and might not require treatment in mild cases. This review aims to evaluate the most recent evidence on the benefit of using GCs in the treatment of uncomplicated AU.

Methods

Evidence-based research was conducted on clinical guidelines published in The National Institute for Health and Care Excellence, meta-analyses, systematic reviews and randomised controlled clinical trials (RCCT) in The Cochrane Library and PubMed. The medical subject headings (MeSH) terms used were 'urticaria' and 'glucocorticoids'.

Results

The initial research resulted in a total of 23 articles, of which two RCCT met all inclusion criteria.

Discussion

The included studies do not recommend the combination of GCs in short-course treatment with H1 antihistamines for uncomplicated AU.

URTICARIA IS A SKIN RASH condition (also commonly known as hives) characterised by the sudden development of typical skin lesions, with or without angioedema. Urticarial lesions are pruritic erythematous or pale papules with well-defined edges. They disappear upon digital pressure and resolve spontaneously in less than 24 hours.^{1,2} In approximately 9% of cases, angioedema is present, which is a sudden, painful and erythematous oedema that involves subcutaneous tissue, lasting up to 72 hours.

Urticaria is classified as acute when its duration is less than or equal to six weeks. Usually, the diagnosis is clinical and does not require other tests. Urticaria is often a self-limited condition that does not need treatment.

The pathophysiology of urticaria involves the activation of mast cells that releases histamine, the main mediator of the response. Histamine, leukotrienes and prostaglandins in circulation cause vasodilation and the activation of several processes.^{1,2}

Regarding treatment, it is essential to eliminate possible underlying causes, avoid precipitating factors (eg medications, specific triggers, stress or food) and induce tolerance through controlled exposure. Second-generation, non-sedating H1 antihistamines are considered first-line therapeutic options for acute urticaria (AU). The latest European guideline

(The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria) describes that the daily dose can be quadrupled in situations of poor therapeutic response.³ Currently, first-generation antihistamines are not recommended, as they do not have an antipruritic effect in addition to the sedative effect.³

Compared with glucocorticoids (GCs), there are few studies that evaluate the benefit of their association in the treatment of AU itself. The 2013 update of the international guidelines for the definition, classification, diagnosis and management of urticaria suggests considering a short course in AU treatment or in chronic urticaria exacerbation.⁴ There are two previous studies that support this recommendation; however, these studies had controversial results and limitations to their methodology.^{5,6}

AU is a frequent reason for visits to general practitioners and emergency departments (EDs) and is associated with significant morbidity and healthcare costs.^{7,8} In this context, the aim of this article is to review and analyse the current evidence on the benefit of using GCs to treat AU.

Methods

A review of the literature was carried out for clinical guidelines published in The National

Institute for Health and Care Excellence (NICE), meta-analyses, systematic reviews and randomised controlled clinical trials (RCCT) in The Cochrane Library and PubMed. The research included studies involved humans and published in the last decade, in Portuguese and English. The medical subject heading (MeSH) terms were 'urticaria' and 'glucocorticoids'.

The inclusion criteria were defined based on the patient/population, intervention, comparison and outcomes (PICO) criteria. The target population was adults aged ≥ 18 years with AU and in whom the intervention was the treatment with GCs, compared to the absence of this intervention or placebo. The outcome studied is better symptomatic control and a reduction in the duration of AU. Inaccessible or duplicate articles were excluded from the review.

Stratification scales used for RCCTs included the Jadad scale to evaluate the included RCCT⁹ and the Strength of Recommendation Taxonomy (SORT) scale from the American Academy of Family Physicians to assign levels of evidence (LE).¹⁰

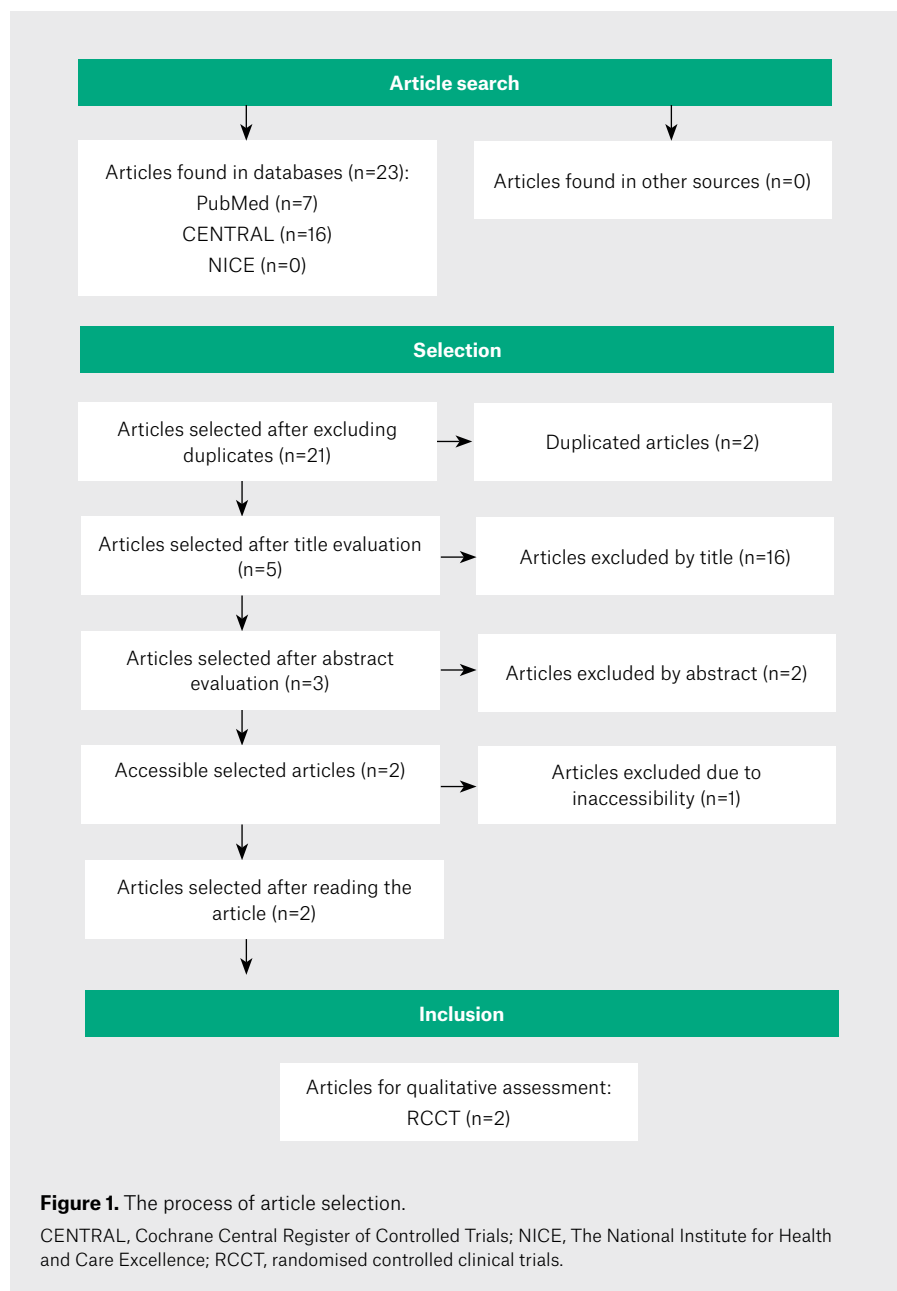
The current study authors independently included and classified the articles according to the SORT scale. A discussion of these findings follows.

Results

The initial literature research yielded a total of 23 articles (seven articles in PubMed, 16 in CENTRAL and zero in NICE), of which two were excluded due to duplication. Among the 21 remaining articles, 16 were excluded based on title screening as they did not align with the objective of this review. In the subsequent phase, two articles were excluded after abstract review, and one due to inaccessibility. The process of selection is shown in Figure 1. Following consensus between reviewers, two studies were identified for inclusion (Table 1). Regarding methodological robustness, Jadad Scale application was used to assess quality (1–5 [max quality]) (Table 2).

Randomised controlled clinical trials

In January 2018, Barniol et al published a prospective, randomised, placebo-controlled, double-blind, parallel-group study aiming to assess the efficacy of a short course of



prednisone combined with levocetirizine for AU treatment in an ED.¹¹ The primary objective was to evaluate complete resolution of pruritus, scored from 0 to 10 (in this study, 0 means no itch), over a period of two days. Secondary objectives included assessing resolution of rash, relapses and adverse effects. The study was conducted from February 2012 to January 2014, involving 100 participants, randomised into two groups: placebo (levocetirizine 5 mg/day

for five days + placebo for four days) and prednisone (levocetirizine 5 mg/day for five days + prednisone 40 mg/day for four days). Both treatments demonstrated efficacy, with complete resolution of pruritus at two days observed in 62% of the prednisone group and 76% of the placebo group. In this randomised control trial (RCT), the addition of steroids to antihistamines had a worse resolution on skin rash (urticaria) than antihistamines and placebo (Table 1).¹¹

Table 1. RCCTs included in the present review

Reference	Methodology	Intervention	Outcome	LE
Barniol et al (2018) ¹¹	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≥18 years • AU without angioedema or anaphylaxis <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Habitual use of antihistamines • Fever • Pregnancy • Chronic illness • Previous inclusion (n=100) 	<p>(1) Levocetirizine 5 mg/day, 5 days + placebo (n=50)</p> <p>(2) Levocetirizine 5 mg/day, 5 days + prednisone 40 mg/day, 4 days (n=50)</p>	<p>Resolution of pruritus:</p> <ul style="list-style-type: none"> • (1) 76% • (2) 62% <p>Resolution of skin rash:</p> <ul style="list-style-type: none"> • (1) 78% • (2) 70% <p>Relapse:</p> <ul style="list-style-type: none"> • (1) 24% • (2) 30% <p>Adverse effects:</p> <ul style="list-style-type: none"> • (1) 14% • (2) 14% 	2
Palungwachira et al (2021) ¹²	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • 18–60 years • Uncomplicated AU with <24 h evolution • Itching score (visual analogue scale) >5 <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Angioedema or anaphylaxis • Use of GCs or antihistamines in the previous 5 days • Known allergy to the drugs used in the study • Pregnancy or breastfeeding • Chronic urticaria (n=75) 	<p>(1)</p> <ul style="list-style-type: none"> • CFM 10 mg IV • Cetirizine 10 mg/day, 7 days (n=25) <p>(2)</p> <ul style="list-style-type: none"> • CFM 10 mg IV • Dexamethasone 5 mg IV • Cetirizine 10 mg/day, 7 days (n=25) <p>(3)</p> <ul style="list-style-type: none"> • CFM 10 mg IV • Dexamethasone 5 mg IV • Cetirizine 10 mg/day, 7 days • Prednisolone 20 mg/day, 5 days (n=25) 	<p>Response to pruritus up to 60 min:</p> <ul style="list-style-type: none"> • (1) 84% • (2) 90% <p>Relapse at 7 days:</p> <ul style="list-style-type: none"> • (1) 4.2% • (2) 0% • (3) 29.2% <p>Monthly relapse:</p> <ul style="list-style-type: none"> • (1) 8.3% • (2) 0% • (3) 25.0% <p>Minor adverse effects:</p> <ul style="list-style-type: none"> • (1) 0% • (2) 17.4% • (3) 4.2% <p>Patient satisfaction with treatment:</p> <ul style="list-style-type: none"> • (1) 100% • (2) 95.7% • (3) 87.5% 	2

AU, acute urticaria; CFM, chlorpheniramine maleate; GCs, glucocorticoids; h, hours; IV, intravenous; LE, level of evidence; n, number; RCCT, randomised controlled clinical trials.

Table 2. Methodological robustness of the RCCTs included, according to the Jadad scale

	Barniol et al (2018) ¹¹	Palungwachira et al (2021) ¹²
Is it randomised?	1	1
Is it double blind?	1	1
Is there a description of abandonments (losses or exclusions)?	1	1
Is the randomisation method described?	1	1
Is it appropriate?		
Is the concealment method described? Is it adequate?	1	1
Total	5	5

0, no; 1, yes.

RCCT, randomised controlled clinical trials.

A randomised, double-blind and placebo-controlled trial published in 2021 by Palungwachira et al¹² evaluated the immediate effect of intravenous (IV) GCs in combination with chlorpheniramine maleate (CFM) for the treatment of severe pruritus caused by AU in ED patients. Resolution of rash, intensity of pruritus (assessed in terms of urticaria activity score for seven days, which is the standard used by the European Academy of Allergy and Clinical Immunology) and adverse effects were also evaluated. The study was conducted between October 2017 and February 2019, involving 75 patients randomised into three groups: CFM 10 mg IV and cetirizine 10 mg/day for seven days treatment group (G-CFM); CFM 10 mg IV, dexamethasone 5 mg IV and cetirizine 10 mg/day for seven days treatment group (G-CFM/Dex); and CFM 10 mg IV, dexamethasone 5 mg IV, cetirizine 10 mg/day for seven days and prednisolone 20 mg/day for five days treatment group (G-CFM/Dex/Pred). Past studies indicate that the combination of GCs with antihistamines might induce faster remission of AU; therefore, they are frequently prescribed for AU patients.^{5,6} Findings from this study included the following:

- Dexamethasone made no significant difference to pruritus at 60 minutes compared to antihistamines alone.
- Regarding the secondary objectives,

addition of prednisolone was associated with a higher rate of recurrent urticaria. And regarding adverse effects, such as transient blurred vision, dry mouth, dyspepsia, dizziness, headache, palpitations, perineal itching and urinary retention, these were reported only in the two groups treated with dexamethasone.

- All patients were satisfied with their treatment in the G-CFM group, contrasting with 87.5% in the G-CFM/Dex/Pred group; this reflects whether these patients would or would not like to be treated with the same regimen if they experienced a similar situation¹² (Table 1).

Discussion

Analysing the two RCCTs included in this review, some similarities are identified that contradict the evidence from previous studies;^{5,6} both studies suggest that there is no benefit in the association of a short course of GCs in uncomplicated AU treatment.

Two previous studies contradict this statement; however, these had controversial results and methodological limitations.^{5,6} One of these was a randomised and double-blind study, by Polaco and Romano published in 1995.³ It evaluated the association of a prednisone dose for four days with standard antihistamine treatment in 43 patients

with AU with <24 hours of evolution in an ED. The group of patients who received prednisone achieved a rash improvement and better itching score at the two- and five-day follow-up. In the study by Pollack and Romano, the authors assumed benefit, without apparent adverse effects. These results, unlike recent studies, might be due to the use of first-generation H1 antihistamines, less potent and less effective H1 antagonists in the symptomatic relief in AU compared to second-generation H1 antagonists.⁵

The other study was a prospective, non-randomised cohort study by Zuberbier et al.⁶ It involved 109 patients seen at a dermatology appointment for AU, treated with loratadine or prednisolone for three days and followed until complete remission. In this study, both treatment regimens were effective in controlling the rash, but symptoms resolved faster in patients treated with GCs (94% vs 66%). It should be noted that this study was non-randomised and was not carried out in an emergency or acute situation.⁶

Although a protocol published by Javaud et al¹³ was excluded from this research study, it was a protocol of a prospective, double-blind, multicentre study. It will be the largest study to test the hypothesis that treatment with a combination of GCs and antihistamine might not reduce the urticaria activity score. A further study on this is being undertaken.¹³

The use of GCs as an adjuvant therapy for AU continues to be a common practice. For this reason, it is important to evaluate their benefit with modern second-generation, non-sedating medications and the associated better safety profile shown in RCCTs.

The study by Barniol et al¹¹ suggested that the addition of a short four-day course of prednisone to levocetirizine did not increase or accelerate the rate of resolution of AU, compared to antihistamine alone. Furthermore, no significant difference was found 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 first-line antihistamine treatment in patients with AU without anaphylaxis or angioedema. Therefore, this study does not support the addition of GCs to H1 antihistamines as first-line treatment for AU patients.¹¹

Another RCT by Palungwachira et al observed a greater recurrence of itching and rashes in the oral prednisolone group compared to the antihistamine group.¹² Several publications report rebound dermatitis in patients treated with GCs.^{14,15} Furthermore, the combination of IV dexamethasone did not provide a significant clinical improvement in pruritus at 60 minutes. Therefore, this study did not support the combination of either IV or oral GCs with H1 antihistamines in the treatment of AU without angioedema.¹²

Using the SORT scale, the authors assigned the RCCTs analysed an evidence level of two. These are controlled and randomised RCCTs with adequate follow-up, but with a small sample size (between 75 and 100 participants). Additionally, they all include studies evaluating the efficacy and safety of the use of GCs in uncomplicated AU cases.

Limitations and strengths

Limitations to the first RCCT (by Barniol et al¹¹) should also be highlighted: the follow-up was carried out via a phone call at days 2, 5, 15, and 21; and only patients with untreated and recent onset AU were included. Their results might not be applicable to severe urticaria that persists for days or weeks and resists the first-line treatment.¹¹

Regarding the second study (by Palungwachira et al¹²), the limitations were: it was a single-centre study; self-assessment of an itching score might have resulted in exaggerated scores; the optimal dose of GCs for AU treatment has not been determined; there was an inability to instruct all patients to avoid trigger factors and to confirm that the patient had medication compliance at home.¹²

A limitation of this current review is the inclusion of two articles, reinforcing that they were the only studies to meet the criteria and objective of this work.

The authors add the application of the SORT scale as a positive point, as it values patient-oriented results. The definition of AU according to the MedDRA classification was taken into account through the description of signs and symptoms, instead of obtaining the diagnosis through complementary tests.

Despite evidence that second-generation H1 antihistamines treat AU without marked adverse effects, many physicians believe that GCs are still the most effective treatment for rapid symptom relief. GCs were used in the treatment of 93% of 459 patients attending an ED for acute urticaria, most of them without angioedema.¹⁶ This practice might be associated with the doctor's concern that the patient will return to the ED due to more severe symptoms or anaphylaxis; corticosteroids are no longer drugs of choice in anaphylaxis initial treatment.^{17,18}

Our study found that there is no benefit from the addition of GCs to the treatment of patients with uncomplicated AU.

Conclusion

In conclusion, the RCCTs included in this review showed that the combination of a short course of GCs with H1 antihistamines in the treatment of AU was not superior to antihistamines alone. Both studies do not support this practice as a first-line treatment for AU in patients without angioedema or anaphylaxis. It should be noted that the RCCTs analysed had a small sample size, as well as a short follow-up time, which does not evaluate the risk of developing recurrent urticaria when short-course GCs are used in the treatment of AU.

This evidence-based review has the scarce bibliographic evidence as its main limitation. Given the limited evidence available, it is not possible to confidently conclude whether there is effectively a clinical benefit in the use of GCs in the treatment of AU. Given this, the authors suggest that additional, methodologically robust, multicentre studies with longer follow-up will be necessary.

Authors

Andreia Lasca MD, Integrated Master's degree in Medicine, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; Medical training (residency), Family and General Medicine, USF Viriato, ACeS Dão Lafões, Viseu, Portugal

Juliana Gomes MD, Integrated Master's degree in Medicine, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; Medical training (residency), Family and General Medicine, USF A Ribeirinha, ULS Guarda, Guarda, Portugal

Ana Teresa Gorgulho de Pinho MD, Integrated Master's degree in Medicine, Faculty of Medicine at the University of Coimbra, Coimbra, Portugal; Medical training (residency), Family and General Medicine, USF Viriato, ACeS Dão Lafões, Viseu, Portugal

Raquel Filipa Martins MD, Integrated Master's degree in Medicine, Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal; Medical training (residency), Family and General Medicine, USF A Ribeirinha, ULS Guarda, Guarda, Portugal

Daniela Moreira MD, Integrated Master's degree in Medicine, Faculty of Medicine at the University of Coimbra, Coimbra, Portugal; Family Doctor, USF Viriato, ACeS Dão Lafões, Viseu, Portugal

Competing interests: None.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Correspondence to:

a32080@fcsaude.ubi.pt

References

- Zuberbier T, Aberer W, Asero R; Endorsed by the following societies: AAAAI, AAD, AAAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SDeMaSt, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73(7):1393-1414. doi: 10.1111/all.13397.
- Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: Definition, classification and diagnosis of urticaria. *Allergy* 2009;64(10):1417-26. doi: 10.1111/j.1398-9995.2009.02179.x.
- Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* 2022;77(3):734-66. doi: 10.1111/all.15090.
- Zuberbier T, Aberer W, Asero R, et al; European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. 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(7):868-87. doi: 10.1111/all.12313.
- Pollack CV Jr, Romano TJ. Outpatient management of acute urticaria: The role of prednisone. *Ann Emerg Med* 1995;26(5):547-51. doi: 10.1016/S0196-0644(95)70002-1.
- Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: Clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996;76(4):295-97. doi: 10.2340/0001555576295297.
- Rubegni P, Cevenini G, Lamberti A, et al. Dermatological conditions presenting at the emergency department in Siena University Hospital from 2006 to 2011. *J Eur Acad Dermatol Venereol* 2015;29(1):164-68. doi: 10.1111/jdv.12513.
- Ryan D, Tanno LK, Angier E, et al. Clinical review: The suggested management pathway for urticaria in primary care. *Clin Transl Allergy* 2022;12(10):e12195. doi: 10.1002/ct2.12195.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17(1):1-12. doi: 10.1016/0197-2456(95)00134-4.
- Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69(3):548-56. doi: 10.3122/jabfm.171.59.

11. Barniol C, Dehours E, Mallet J, Houze-Cerfon CH, Lauque D, Charpentier S. Levocetirizine and prednisone are not superior to levocetirizine alone for the treatment of acute urticaria: A randomized double-blind clinical trial. *Ann Emerg Med* 2018;71(1):125–131.e1. doi: 10.1016/j.annemergmed.2017.03.006.
12. Palungwachira P, Vilaisri K, Musikatavorn K, Wongpiyabovorn J. A randomized controlled trial of adding intravenous corticosteroids to H1 antihistamines in patients with acute urticaria. *Am J Emerg Med* 2021;42:192–97. doi: 10.1016/j.ajem.2020.02.025.
13. Javaud N, Soria A, Maignan M, et al. Glucocorticoids for acute urticaria: Study protocol for a double-blind non-inferiority randomised controlled trial. *BMJ Open* 2019;9(8):e027431. doi: 10.1136/bmjopen-2018-027431.
14. Ives TJ, Tepper RS. Failure of a tapering dose of oral methylprednisolone to treat reactions to poison ivy. *JAMA* 1991;266(10):1362. doi: 10.1001/jama.1991.03470100054031.
15. Brink D, McCabe J. What is the best dose and duration of prednisone for widespread contact dermatitis from poison ivy. *Evid Based Pract* 2018;21(8):22–23. doi: 10.1097/01.EBP.0000544884.27209.64.
16. 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(2):147–50. doi: 10.1016/j.ejim.2013.11.003.
17. Choo KJ, Simons FE, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Evid Based Child Health* 2013;8(4):1276–94. doi: 10.1002/ebch.1925.
18. Simons FE, Arduzzo LR, Dimov V, et al; World Allergy Organization. World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013;162(3):193–204. doi: 10.1159/000354543.