

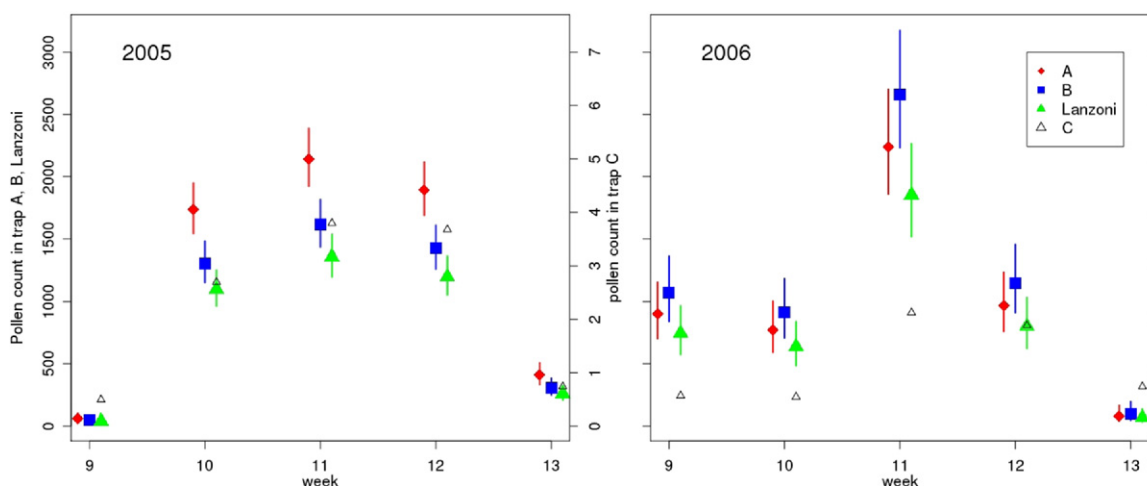


Figure 1. Weekly pollen counts in the traps during the 2 study years. Error bars indicate 95% confidence intervals.

parts of the hedge were similar, confirming the impact of the trimming.

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TWO PATIENTS WITH ANAPHYLACTIC SHOCK DUE TO FOSFOMYCIN

Fosfomycin is an antibiotic belonging to the phosphonic acid family, structurally dissimilar to other antibiotic groups, and generally well tolerated. It is a common alternative for patients allergic to β -lactam or other antibiotics, particularly in urinary tract infections, and

allergic reactions to fosfomycin are considered to be extremely rare.^{1,2} We report 2 cases of anaphylaxis after fosfomycin intake, with positive skin test results in both cases and a positive basophil activation test (BAT) result in 1 case.

Case 1 occurred in a 39-year-old woman with a history of allergic rhinoconjunctivitis and no other clinical records. She experienced a generalized rash, angioedema, dyspnea, and loss of consciousness just minutes after consuming a single oral dose of fosfomycin trometamol (Monurol, 3 g; Pharmazam, Santa Perpetua De Mogoda, Spain) for a urinary tract infection. On admission, her heart rate was 150/min and her oxygen saturation was 80%. Her clinical manifestations resolved with subcutaneous epinephrine and intravenous steroids and antihistamines. The results of skin tests included in our protocol for idiopathic anaphylaxis (including various food allergens, *Anisakis*, and latex) were negative. The results of skin tests with aeroallergens were positive only to *Parietaria judaica* pollen—a fact that we consider related to rhinitis and unrelated to the episode. The results of skin prick tests with fosfomycin were positive at a concentration of 10 mg/mL (12 × 15-mm wheal size). Given its potential utility in the diagnosis of immediate reactions to a number of drugs,^{3–5} a BAT was performed with different concentrations of fosfomycin, with negative results (Table 1).

Case 2 occurred in a 40-year-old woman with a history of allergic rhinoconjunctivitis and no other clinical records. The patient received a single dose of fosfomycin trometamol (Monurol, 3 g; Pharmazam) for a urinary tract infection and immediately experienced generalized redness of the skin involving the soles of her feet, dyspnea, and nausea, all of which evolved to rapid resolution after intravenous steroid and antihistamine administration at the emergency department. Again, the results of skin tests in our protocols were negative, except for tests for *Dermatophagoides pteronyssinus* and *Lolium perenne*. The results of skin prick tests with fosfomycin were negative at a concentration of 10 mg/mL, but the results of intradermal tests were positive at a concentration of 5 mg/mL (13 × 22-mm wheal size). Saline solution and histamine, 10 mg/mL, were used as negative and positive controls, respectively. A BAT with fosfomycin yielded positive results, but only to the 0.1-mg/mL concentration of fosfomycin. Both skin tests and BAT were performed on 10 atopic controls, with negative results (Table 1).

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Table 1. Basophil Activation Test With Fosfomycin^a

	Patient No.		Control No.									
	1	2	1	2	3	4	5	6	7	8	9	10
Baseline activation	0.4	0.9	0.6	1.7	2.2	1.3	3.1	1.1	2.4	0.9	1.6	2.7
Anti IgE (positive control)	49.3	52.7	39	35.4	41.7	36.3	53.2	46.9	61.2	29.4	60.9	36.9
Fosfomycin, 0.1 mg/mL	0.7	9	0.5	1.2	0.4	1	0.9	3.1	0.3	1.8	0.8	2.1
Fosfomycin, 1 mg/mL	2.3	0.8	1.1	2.1	1.2	0.5	2.1	3	1.1	2.1	1.1	2.8
Fosfomycin, 10 mg/mL	3.2	0	0.2	2.6	2.2	1.9	2.5	2.6	0.9	0.9	1.9	2.5

^a The data in the table correspond to the percentages of basophils activated. Test results were considered positive when activation was equal to or greater than the double of baseline activation in at least 5% of the basophils activated.

To the best of our knowledge, allergic reactions to fosfomycin are extremely infrequent. A MEDLINE search of the literature (from 1966 on) revealed only 2 previous reports of anaphylactic shock due to this antibiotic. In the first one,¹ the skin test results were positive with fosfomycin, but the results of the histamine release test used for in vitro diagnosis were negative. In the second one,² the results of BAT with fosfomycin were positive in a patient with anaphylaxis after ingestion of this antibiotic. In this patient the skin test results were negative, but the diagnosis was confirmed by oral challenge test. Our patients had a suggestive history and positive skin test results to fosfomycin. In addition, 1 patient had a positive BAT result. BAT is limited by its sensitivity in drug allergies to approximately 50% in general for drugs studied.⁶ Depending on the cutoff point, significant variations in specificity are obtained. The cutoff point applied by our group in these cases is the same as those reported by other authors with the same drug.²

Skin tests are the chosen diagnostic technique (75% sensitivity in the 4 cases published) in IgE-mediated allergic reactions. Nevertheless, it is advisable to have an in vitro diagnostic technique available to confirm the results of the in vivo tests and particularly to avoid the challenge tests in patients with symptoms compatible with IgE-mediated reactions but with negative skin test results. BAT is a reliable in vitro diagnostic technique for rare fosfomycin-induced reactions, with a 66% sensitivity (2 of 3 cases). These 2 cases confirm the difficulty in making a firm diagnosis of this rare reaction. Our data coupled with the existing literature show that both in vivo and in vitro testing may be needed to document fosfomycin sensitization.

In summary, we describe 2 patients with anaphylaxis due to fosfomycin, a rare cause. Both patients had positive skin test results and 1 of them had a positive BAT result. This is the

second case report in which an in vitro test confirmed fosfomycin sensitization.

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