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**Successful desensitization in a child with delayed cotrimoxazole hypersensitivity: a case report**

**Running title:** Desensitization in a delayed reaction

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**To the editor:**

Sulfonamides are effective drugs for the treatment of infectious diseases caused by a number of pathogens including gram-positive bacteria, gram-negative bacteria and protozoa. The probability of severe allergic reactions to this group of drugs and the development of different families of antimicrobials have caused a limited usage to a few specific indications in certain groups of patients. Trimethoprim is a bacteriostatic agent which is commonly used in combination with sulfamethoxazole due to their synergic effect, known as cotrimoxazole. Several allergic reactions to cotrimoxazole, ranging from mild to potentially fatal syndromes such as Steven Johnson's or Toxic Epidermal Necrolysis, have been described<sup>1</sup>. According to literature, sulfamethoxazole is the culprit of most of the allergic reactions induced by the association of trimethoprim-sulfamethoxazole<sup>2</sup>.

We present the case of a 6-year-old boy with an atopic history of grass pollen-induced rhinoconjunctivitis ongoing treatment with specific sublingual immunotherapy. He had history of transient, moderate eosinophilia (up to 1850 cells/ $\mu$ L) during grass pollen season in 2011 and 2012. The patient was diagnosed with right calcaneus chronic osteomyelitis in October 2010 and received different antimicrobials with recurrence of the disease. He presented for the first time in our hospital in May 2011 with a chief complaint of right heel pain. Imaging studies showed an inflammatory focus that suggested a recurrence of the disease. Treatment with ceftriaxone and vancomycin were empirically started. A fine needle aspiration cytology reported the presence of *Staphylococcus warneri*, methicillin sensitive. He underwent surgical cleaning a month later followed by amoxicillin-clavulanic acid treatment for four weeks. The patient was apparently well until January 2013 when he was brought back to the hospital due to heel pain associated with impairment in walking. He was diagnosed with recurrence of the infection and started treatment with cotrimoxazole and rifampicin, for 12 weeks duration. Eight days later, the patient presented

with a papular pruritic rash in both his upper and lower extremities. Rifampicin was discontinued and was maintained with cotrimoxazole and antihistamines. The rash reappeared after four days, now observed in photo-exposed areas (figure 1). He was then referred to Allergology Department for further evaluation and management.

Skin prick tests (SPT) with sulfamethoxazole (100 mg/ml), trimethoprim (32 mg/ml) and rifampicin (60 mg/ml) and intradermal skin tests (ID) with sulfamethoxazole (10 mg/mL) and rifampicin (1 mg/mL) were performed according to the European Academy of Allergy and Clinical Immunology guidelines. Laboratory tests including liver function parameters were also performed. Skin tests (SPT and ID) with sulfamethoxazole and trimethoprim were repeated at the previously referred concentrations, followed by ultraviolet (UV) photopatch tests (UltraVitalux 300W quartz lamp, Osram®, Madrid) with both drugs individually [trimethoprim 32 mg/ml (10% petrolatum) and sulfamethoxazole 100 mg/ml (10% petrolatum)] according to the European Academy of Dermatology and Venereology recommendations. Drug challenge and drug desensitization were performed. Finally SPT, ID and UV photopatch test were repeated six months after the completion of treatment.

The patient showed negative SPT and ID with the tested drugs. Blood test revealed normal white blood cell count with mild lymphocytosis without eosinophilia; C reactive protein and liver function studies were both normal. The working diagnosis was photo-induced, delayed drug reaction due to the clinical history. Thus, photopatch tests were done which turned out to be negative. Drug challenge test with cotrimoxazole was performed, achieving a total dose of 600/120mg of trimethoprim/sulfamethoxazole respectively. The patient showed immediate good tolerance, but developed intense facial rash two hours after the final dose.

Cotrimoxazole became the only oral available antimicrobial to treat the severe and recurrent reaction of our patient, allowing him to maintain his normal activities and avoiding a long-term hospitalization as well, hence, drug desensitization to cotrimoxazole was indicated and performed using the protocol described in *Table I*.

The final dose of cotrimoxazole was reached and maintained for the next three months, without any adverse reaction. The patient showed also a good tolerance to sun exposure during the treatment. Six months after completion of the treatment, SPT and ID remained negative but the photopatch test with trimethoprim was positive.

Outpatient follow-up with Infectious Disease and Orthopedic departments were performed during duration of the treatment. Blood tests and liver function were strictly performed every 15 days with no evidence of alterations except a variable hypereosinophilia ranging from 780 to 2430 cells/ $\mu$ L

(normal value: 0-400 cells/ $\mu$ L) without symptoms nor signs of organ involvement. The treatment with cotrimoxazole was maintained until the complete remission of the infection despite the hypereosinophilia which normalized two months after the completion of the treatment (figure 2). Two years after the end of the treatment, he was seen in the Alergollogy Department for follow-up wherein the patient was apparently doing well –asymptomatic, able to play football, walk without impairment and no signs of infection-.

Several desensitization protocols to cotrimoxazole have been described, mostly among HIV-patients as prophylaxis for opportunistic pathogens. Pyle et al recently reported the safety and efficacy of outpatient-graded administration of cotrimoxazole in immunocompetent subjects with a history of sulfonamide adverse drug reaction<sup>3</sup>. We performed the protocol described by Caumes<sup>4</sup> for the graded administration of increasing doses of cotrimoxazole until reaching the final recommended dose in the third day of desensitization which allowed the completion of the treatment.

On the other hand, we consider that the eosinophilia seen in our patient could have been secondary to his atopic history. However, the progressive resolution after completion of treatment and the persistence of mild to moderate eosinophilia beyond grass pollen season may support the hypothesis of its relation with the treatment, as other authors have reported the presence of eosinophilia in HIV patients ongoing long-term treatment with cotrimoxazole (5), although this finding was not confirmed through a control group such as HIV patients without cotrimoxazole.

We consider that the clinical relevance of this case lies in the fact of performing drug desensitization in a delayed photo-induced reaction, of which we have not found any such cases reported in the existing literature. The exclusive sensitization observed to trimethoprim emphasizes the importance of testing each component separately in order to identify the culprit drug. In connection with this, it would be interesting to perform a drug challenge with sulfamethoxazole in order to confirm the clinical relevance of the observed results in the near future. In conclusion, this case of oral drug desensitization to cotrimoxazole in an immunocompetent child with a photo-induced reaction, allowed him to successfully complete the definitive treatment.

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**Table I.** Oral desensitization to trimethoprim-sulphamethoxazole (Caumes, 1997)<sup>4</sup>.

| Day 1              | Day 2              | Day 3              |
|--------------------|--------------------|--------------------|
| 0,8/4 mg (9 h AM)  | 16/80 mg (9 h AM)  | 80/400 mg (9 h AM) |
| 1,6/8 mg (11 h AM) | 32/160 mg (3 h PM) |                    |
| 4/20 mg (1 h PM)   | 40/200 mg (9 h PM) |                    |
| 8/40 mg (5 PM)     |                    |                    |



**Figure 1.** Facial rash in photo-exposed areas.

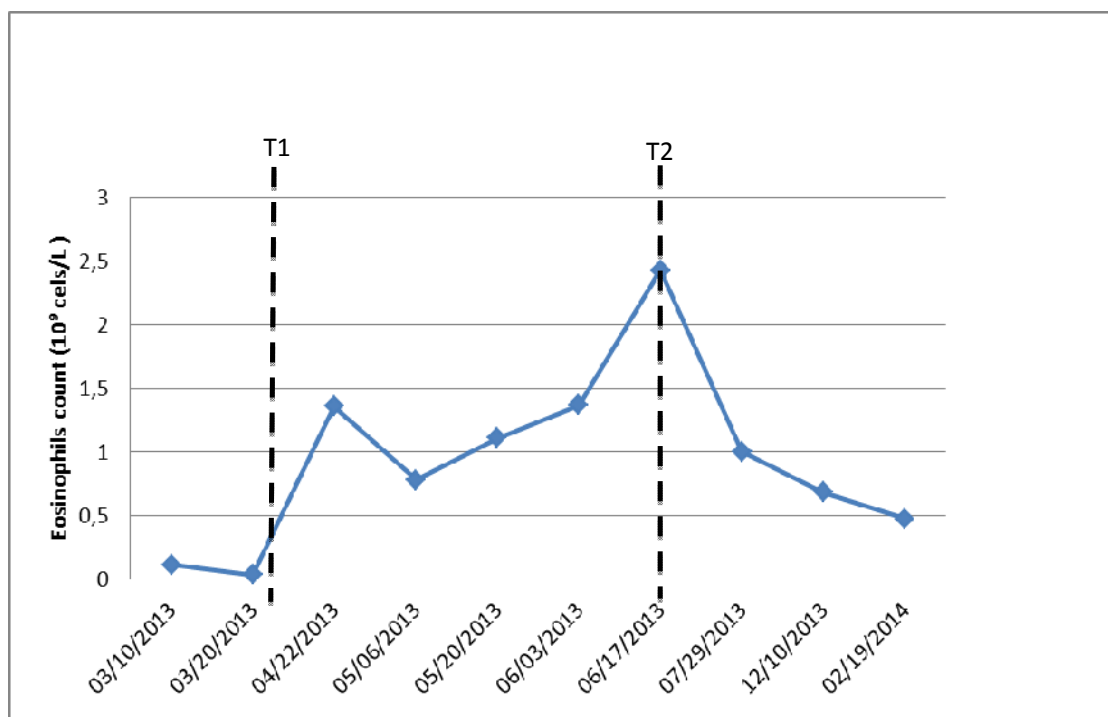


**Figure 2.** T1: Start of desensitization; T2: End of desensitization. Normal value of eosinophils count: 0-0.4x10<sup>9</sup> cells/L).