Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

Tolerance induction in a drug-induced fever case due to trimethoprim-sulfamethoxazole in a cystic fibrosis patient

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Received 19 May 2025; Accepted 26 September 2025
Available online 1 January 2026

KEYWORDS
desensitization;
drug fever;
septrim;
trimethoprim-sulfamethoxazole

Abstract
Drug-induced fever is a probably an under/misdiagnosed condition. The onset of drug-induced fever is highly variable among drugs and patients, usually occurring after 7–10 days of treatment, with rapid resolution after discontinuation. However, it sometimes appears at any time during treatment, even after stopping the drug. The estimated prevalence is 10%, and early diagnosis avoids hospitalizations, expensive treatments, and techniques, favoring the sustainability of the Health System. We report a 40-year-old woman diagnosed with Cystic Fibrosis and drug-induced fever due to trimethoprim-sulfamethoxazole. She was referred to the Allergy Department by the Pulmonology Department because of *Pandoraea sputorum* sputum colonization, which was only sensitive to TMP-SMX. After confirming the diagnosis and given the absence of therapeutic alternatives, obtaining informed consent, and informing her Pulmonology specialist, desensitization was decided upon, following the therapeutic scheme described in Table 1, using premedication with Acetaminophen and Prednisone to improve comfort and reaching a dose of 320/1600 mg in 8 days. This is a unique case of successful desensitization in TMP-SMX-induced fever in a young patient with Cystic Fibrosis. In summary, we believe that in Medicine, the most important thing is to individualize treatments based on each patient's needs and assessing risks and benefits.
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https://doi.org/10.15586/aei.v54i1.1418
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Introduction

Drug-induced fever is a probably an underdiagnosed or misdiagnosed condition. It is a febrile response that chronologically coincides with the administration of a drug and disappears after stopping it. It is suspected with an adequate temporal relationship and when other causes are excluded.[1]

The onset of drug-induced fever is highly variable among drugs and patients, usually occurring after 7–10 days of treatment, with rapid resolution after discontinuation. However, drug-induced fever can occur at any time after starting the medication, and even after it has been discontinued.[2]

The fever usually reappears a few hours after re-exposure, confirming the diagnosis.[3] This is controversial and should be performed with caution due to the possibility of a more severe reaction.[1]

Case report

We report a 40-year-old woman diagnosed with Cystic Fibrosis in childhood who received Trimethoprim-Sulfamethoxazole (TMP-SMX) for a urinary infection in 2013; she developed a fever (39°C) after 7 days. Not suspecting a relation with the drug, in 2021 she was prescribed TMP-SMX again for a respiratory infection and had a 39°C fever 2 days later, discontinuing the treatment on her own.

She was referred to the Allergy-Department by Pulmonology-Department because *Pandorae sputorum* sputum colonization only sensitive to TMP-SMX.

The allergy workup included prick and intradermal skin testing, which were negative in immediate and delayed readings. These tests were performed despite knowing that their usefulness is very limited in cases of drug-induced fever, but it was important to rule out any possibility of IgE-mediated or delayed hypersensitivity.[4] The oral challenge was performed over 2 days; on the first day, she received a total dose of 80/400 mg TMP-SMX with no reaction. On the second day, she received 160/800 mg. After 24 hours, she developed a 39°C fever without other symptoms. The blood test was normal.

After confirming the diagnosis and given the absence of therapeutic alternatives, obtaining informed consent, and informing her Pulmonology specialist, desensitization was decided upon, following the therapeutic scheme described in Table 1, using premedication with Acetaminophen and Prednisone to improve comfort and reaching a dose of 320/1600 mg in 8 days. She remained afebrile during the protocol and continued with 320/1600 BID for 3 weeks. Regarding premedication, she took 1 g Acetaminophen and 25 mg Prednisone daily during the first week, 1 g/10 mg during the second, and 1 g/5 mg during the third (except for the dose increase days when she took 50 mg of Prednisone). Blood testing was performed during the second and third weeks, without blood, liver, or kidney abnormalities. The desensitization protocol used in this patient was individualized based on her specific reaction (drug-induced fever), the total required dosage (320/1600 mg), and the total treatment duration (3 weeks). Therefore, it differs from the protocols described in the literature. Premedication with paracetamol and prednisone was used to achieve drug tolerance during the protocol in this patient without therapeutic alternatives, considering that paracetamol controls symptomatic expression (central thermoregulation) and prednisone reduces underlying immune activation.

Discussion

Drug-induced fever is frequently underdiagnosed, especially during infections.[3] The estimated prevalence is 10%, and early diagnosis helps avoid hospitalizations and expensive treatments and techniques, favoring the sustainability of the health system.[2]

It usually resolves within 48–72 h after discontinuing the culprit drug. If fever reappears a few hours after re-exposure, it confirms the diagnosis.[3]

Table 1 Eight-day desensitization protocol to trimethoprim/sulfamethoxazole for drug fever.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Premedication[1]	Paracetamol 1g Prednisone 50mg	Paracetamol 1g Prednisone 25mg	Paracetamol 1g Prednisone 50mg	Paracetamol 1g Prednisone 25mg	Paracetamol 1g Prednisone 50mg	Paracetamol 1g Prednisone 25mg	Paracetamol 1g Prednisone 25mg	Paracetamol 1g Prednisone 50mg
Rising dose[2]	0.4/2 mg 0.8/4 mg 1.6/8 mg 3.2/16 mg	3.2 / 16 mg	8/40 mg 16/80 mg 32/160 mg 64/329 mg	64/320 mg	80/400 mg	80/400mg	80/400 mg	160/800 mg 160/800 mg
Total accumulated dose[3]	***6/30 mg***	***3.2/16mg***	***120/600 mg***	***64/320 mg***	***80/400 mg***	***80/400 mg***	***80/400 mg***	***320/1600 mg***[4]

[1]Premedication with Paracetamol and Prednisone 1 hour before taking.
[2] One hour intervals between each dose.
[3]Dose increase on days 1,3,5 and 8.
[4]Subsequently maintenance with a dose of 320/1600 mg for 3 weeks.

Our patient developed fever after 7 days of treatment during the first reaction, after 2 days during the second, and after 24 hours during the third; the fever resolved after discontinuation of TMP-SMX treatment TMP-SMX treatment.

A maculopapular rash may appear in a minority of patients; although this does not rule out the diagnosis, it forces the clinician to evaluate other causes of drug reaction (DRESS, SJS, AGEP, etc.).

Sometimes, blood tests show mild hypertransaminasemia and elevated erythrocyte sedimentation rate without eosinophilia.[2] Our patient did not show skin lesions or analytical abnormalities.

The mechanisms causing drug-induced fever are unknown, but five categories are postulated: alteration of thermoregulation mechanisms (as occurs with thyroid hormone, sympathomimetics, or anticholinergics); fever related to drug administration (contamination with endotoxins or other exogenous pyrogenic substances); fever related to the mechanism of action of the drug (common in oncology chemotherapy); idiosyncratic reactions such as neuroleptic malignant syndrome, malignant hyperthermia, or serotonin syndrome; and the most common hypersensitivity reactions, especially antimicrobials, allopurinol, and anticonvulsants.[2]

There is no evidence that TMP-SMX alters thermoregulation or releases pyrogenic substances; therefore, in our case, these options are highly unlikely. Capsule contamination seems unlikely on three remote occasions. The absence of other symptoms rules out idiosyncratic reactions. In our case, the most probable mechanism is a hypersensitivity reaction.

The drug-challenge test should only be performed on very selected patients, given the risk of developing fever again, as these are reproducible reactions in most cases.[6] Therefore, if re-exposure is carried out, it must be performed in an appropriate setting, with patient monitoring and blood testing availability. It must not be performed in severe cases with organ damage, skin peeling, or blistering lesions. If fever reappears with re-exposure, the diagnosis is confirmed, and the drug should be avoided.[7,8]

Our patient scored 7 on the Naranjo Scale for causality assessment of drug reactions; this is equivalent to "probable" causality.[9]

We performed the challenge to confirm the diagnosis, as the previous reactions occurred in the context of infections, and a drug reaction was not suspected.

Sulfonamides are, after beta-lactams, the most frequent antibiotics to cause reactions, with TMP-SMX affecting 34/1000 exposed patients. Among them, skin reactions are the most frequent (3% in immunocompetent patients and 30% in HIV patients). A rash is the most frequent skin reaction described.[4]

Desensitization protocols are used for IgE-mediated hypersensitivity reactions (type 1) and mild type 4 hypersensitivity reactions when there are no therapeutic alternatives. Most of the TMP-SMX desensitization protocols described in the literature have been performed in HIV patients with maculopapular rashes or HS type 1 Reactions.[4] Desensitization is contraindicated in severe type 4 hypersensitivity reactions such as SJS, TEN, DRESS, and AGEP, as well as in type 2 and type 3 hypersensitivity reactions.[5]

Our patient had *Pandorae sputorum* sputum colonization, which was only sensitive to TMP-SMX, necessitating the use of this antibiotic. We did not find any report in the literature on desensitization or tolerance induction in drug-induced fever reactions; therefore, with the agreement of the patient and her pulmonologist, we carried out the desensitization/tolerance induction protocol as described in Table 1, premedicating with acetaminophen and prednisone, and successfully completing the 3-week treatment, thereby eradicating the germ.

Conclusion

The mechanisms of desensitization are not yet well understood, nor are the specific causes of drug-induced fever.[1,2] Therefore, we do not know the exact reason for our success in this case, but we managed to improve the patient's condition and prevent future complications.

We want to emphasize that even if it has never been done before, and despite not knowing the mechanism, this should not be a limitation to performing the procedure when a patient truly needs treatment, provided the reaction is not severe. This is a unique case of successful desensitization in TMP-SMX-induced fever in a young patient with cystic fibrosis. In summary, we believe that in medicine, the most important thing is to individualize treatments based on each patient's needs while carefully assessing risks and benefits which is the real precision Medicine..

Author's Contribution

All authors have contributed equally.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Funding

The authors declare that no funding was received for the present study.

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