Case Report

# Rapid Onset of Cutaneous Adverse Drug Reaction to 2HPMZ/2HPM: A Case Report

*Pandu Satya Widiarto,[1] Farchan Azzumar,[1] Khansa Putriana,[1,2] Erlina Burhan[1,3]*

*[1]Respiratory Programmatic Implementation and Research Institute (RPRI), Jakarta, Indonesia*
*[2]Duren Sawit Public Health Center, Jakarta, Indonesia*
*[3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta, Indonesia*

## Abstract

**Background:** The World Health Organization (WHO) has endorsed the 4-month tuberculosis (TB) regimen, 2HPMZ/2HPM (Isoniazid, Rifapentine, Moxifloxacin, Pyrazinamide), as a non-inferior alternative to the standard six-month course, representing a major advancement in global TB control. While large clinical trials established its general safety, real-world data and management of its cutaneous adverse drug reactions (CADRs) remain limited.

**Case:** A case of a 19-year-old male initiated on the 2HPMZ/2HPM regimen for pulmonary TB. Within 30 minutes of treatment initiation, the patient developed a maculopapular erythematous rash on both arms and legs. Given the mild degree, the treatment was continued, along with administration of Cetirizine and Prednisone, for 7 days.

**Discussion:** This case demonstrates safe continuation of treatment following the emergence of mild CADR. CADR can manifest as early as 30 minutes following ingestion, as exhibited in this case. Showing the importance of close initial observation for the 2HPMZ/2HPM regimen. 7-days of antihistamine and corticosteroid administration also appeared to be sufficient when done promptly.

**Conclusion:** This case demonstrates the safety and feasibility of maintaining the full 2HPMZ/2HPM regimen despite mild cutaneous manifestations, thus avoiding treatment interruption, the need for complex re-challenge protocols, and potential treatment failure.

**Keywords:** 2HPMZ/2HPM, adverse effect, cutaneous adverse drug reaction, tuberculosis

**Corresponding Author:**
*Pandu Satya Widiarto* | Respiratory Programmatic Implementation and Research Institute (RPRI), Jakarta, Indonesia | pandu.satya@yayasanrpri.org

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## INTRODUCTION

Tuberculosis (TB) remains a persistent problem in infectious diseases globally. The duration of treatment is an important factor in a patient's compliance and treatment success.[1] A novel shorter regimen that consists of two months of Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinamide followed by nine weeks of daily Isoniazid, Rifapentine, and Moxifloxacin (2HPMZ/2HPM) combination for four months has been developed and yielded a non-inferior result compared to the current standard six-month regimen.[2]

Besides the patient aspect, a shorter 2HPMZ/2HPM regimen is also likely to be able to simplify the programmatic management and improve the equity of TB medication when the fixed-dose combination is made available.[3] However, adverse drug reactions (ADR) are the main concern to be answered in the current endeavour and to safeguard patients' trust.[4] Therefore, proper ADR management from the 2HPMZ/2HPM regimen, and all TB medication in general, is necessary.

As the regimen is new, impact data, such as ADRs from 2HPMZ/2HPM administration in a real-world clinical setting, are scarce. Generally, the clinical manifestations of drug allergy vary from mild symptoms (pruritus and rash) to life-threatening (DRESS syndrome involving multiple organs). Several pieces of evidence have identified the potential for hypersensitivity reactions with Rifapentine and Pyrazinamide.[5,6]

Unfortunately, the ADR occurrence report from the 2HPMZ/2HPM regimen is very high (81.8% to 100%).[5,6] Further, half of the patients dropped out and deferred to older and longer regimens instead.[5] Therefore, this case report aims to describe clinical manifestations of 2HPMZ/2HPM allergic reactions

and report the sufficient management practice in primary health care settings where resources are limited.

## CASE

A case of a 19-year-old HIV-negative male patient with a main complaint of persistent cough for four weeks despite initial management at the primary health center (PHC). Past medication, food, and dust allergy history were absent. The patient lived in the same house with his father, mother, and one sibling. No other family members experienced similar symptoms and no history of disease or allergy between family members was present. The patient was later diagnosed with Drug-Sensitive Tuberculosis (DS-TB) through bacteriological confirmation and initiated a four-month 2HPMZ/2HPM regimen. His weight was 60 kg, so his regimen consisted of 1200mg of Rifapentine, 400mg of Moxifloxacin, 300mg of Isoniazid, and 1500mg of Pyrazinamide.

Figure 1. Patient's Left Arm

Figure 2. Patient's Right Arm

During treatment initiation, the patient developed cutaneous adverse drug reactions (CADR), shown by rash on both arms and legs, along with moderate pruritus thirty minutes after ingesting the drugs. No mucosal manifestations or other systemic symptoms (such as fever or angioedema) occurred. Vital signs were within normal limits. The CADR manifestations were grade 2 maculopapular rash and grade 2 urticaria (Figure 1 and 2).

After being closely observed in the PHC for possible immediate life-threatening ADR, the patient was later discharged and was given Prednisone 3x5 mg and Cetirizine 1x10 mg for 7 days with no treatment interruption. Upon online follow-up, the CADR had completely disappeared during the first 24 hours after Prednisone and Cetirizine. No subsequent ADR occurred until the end of the 2HPMZ/2HPM regimen course without dosage adjustment.

## DISCUSSIONS

The 2HPMZ/2HPM has recently been proposed as a shorter (four-month) regimen alternative for TB medication. Despite the promising efficacy, each drug component has its own allergy property associated with CADR occurrences. Isoniazid and Moxifloxacin are known to cause Mild CADR (Rash) in 6% of patients. Further, serious ADR requiring treatment interruption occurs in 7% of patients receiving Isoniazid and 15% of patients receiving Moxifloxacin. On the other hand, Rifampicin (precursor of Rifapentine, which has a similar profile) and Moxifloxacin, though possible, only cause rash in a small number of patients.[7]

The overall incidence rate of CADR associated with TB medication is unavailable due to a wide variability of investigative study design, baseline patients' characteristics, manifestation, case definition, and grading.[7] However, the impact of CADR should not be underestimated as it is often reported as the most common ADR and is proven to cause treatment interruption in 8–13% of CADR cases.[5,7]

That patient developed a grade 2 maculo-papular rash and grade 2 urticaria 30 minutes after ingesting the initial 2HPMZ/2HPM regimen. The dermatological manifestation in this case is similar to

other findings in which maculopapular rash is the most common adverse reaction of the HMPZ regimen and most of the CADR is mild (grade 2 and lower).[2,6,8] The moderate-to-severe adverse reactions from HMPZ are dominated by blood, lymphatic, and hepatobiliary disorders, which were not present in this case.[2]

In this case, the CADR has a rapid onset, that is, within 30 minutes after HMPZ administration. This onset of manifestation is similar to the older first-line regimen in which the CADR most often occurs in less than an hour.[4] Other, more latent or delayed types of CADR, such as lichenoid rash, occur within the first two months of treatment initiation.[8] Symptoms generally resolve spontaneously in the first few weeks.

The underlying pathophysiology of CADR is primarily immune-mediated, most commonly involving type IV hypersensitivity reactions driven by T-cell activation against drug-related antigens or haptens. However, rapid-onset reactions, as observed in this case, may also involve type I hypersensitivity mechanisms mediated by IgE and mast cell activation, resulting in urticaria and pruritus. Non-IgE-mediated pathways, such as direct mast cell activation or pharmacological interaction with immune receptors, may further contribute to the variability in clinical presentation and onset.[9]

Determining the causality between CADR and TB medications in a limited resource setting, such as a PHC, is challenging. One alternative to determine the causality of adverse drug reaction (not limited to cutaneous manifestation) is using a scoring method such as the Naranjo score.[10] However, this score is not thoroughly applicable to a wide range of clinical settings, where 4 questions on the Naranjo Score are not applicable in 85% of patients in the USA.[11] This situation is consistent with this case, where questions 6, 7, and 8 were not applicable (Table 1). Therefore, clinical judgement from the treating physician should be relied on more.

Several differential diagnoses should also be considered in patients presenting with acute rash following anti-tuberculosis drug administration, including viral exanthema, non-allergic drug reactions, contact dermatitis, and early manifestations of severe cutaneous adverse reactions.[12] In primary healthcare settings with limited resources, differentiation relies predominantly on clinical assessment. The clear temporal relationship between drug ingestion and symptom onset, as seen in this case within 30 minutes, strongly supports a drug-related reaction. The absence of systemic features such as fever, mucosal involvement, blistering, or epidermal detachment makes severe manifestations unlikely, while the lack of prodromal symptoms reduces the likelihood of viral exanthema. Contact dermatitis is also improbable given the distribution and timing unrelated to external exposure.

Table 1. Naranjo Score

| No | Question | Yes | No | Don't Know | Score |
|---|---|---|---|---|---|
| 1 | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | +1 |
| 2 | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | +2 |
| 3 | Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | +1 |
| 4 | Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0 | 0 |
| 5 | Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 | 0 |
| 6 | Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | Not applicable |
| 7 | Was the drug detected in blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | Not applicable |
| 8 | Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | Not applicable |
| 9 | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | 0 |
| 10 | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | +1 |
| | Total | | | | +5 |

Furthermore, the favourable response to antihistamines and corticosteroids without clinical deterioration supports the diagnosis of mild CADR. Therefore, despite the absence of laboratory confirmation or allergy testing, a clinical diagnosis of CADR can be reasonably established in this primary care setting.

The CADR severity varies from mild (rash, pruritus, etc.) to severe (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, etc.). Established standards such as the Common Terminology Criteria for Adverse Events (CTCAE) should be utilized by clinicians to assign the severity grades.[13] While the occurrence of adverse events is high in 2HPMZ/2HPM recipients, most of those are mild (grade 2 and lower).[5,6] Grade 3 or higher adverse event from 2HPMZ/2HPM is similar with current six-month standard-of-care regimen, as well as the all-cause mortality.[2]

The management of CADR is generally guided by severity grading. Mild reactions (grade 1–2), such as limited maculopapular rash without systemic involvement, can be managed with continuation of anti-tuberculosis therapy along with symptomatic treatment, including antihistamines. In selected cases, corticosteroids, accompanied by close monitoring to detect any progression.[14]

In contrast, moderate-to-severe reactions (grade ≥3), particularly those involving mucosal lesions, systemic symptoms, or laboratory abnormalities, require prompt discontinuation of the suspected drugs and further evaluation. Severe CADR, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, necessitates permanent drug cessation and urgent referral. This grading-based approach allows clinicians to balance treatment continuation with patient safety, especially in resource-limited settings.[14]

There is a difference in CADR management between Indonesia's National TB Guideline and existing journals. According to Indonesia's National TB Guideline, treatment interruption and drug desensitisation are indiscriminately mandated when itch is accompanied by rash. That is because an itch is categorized as a severe reaction when rash is also present.[15] In contrast, a consensus from 65 experts said that treatment continuation, observation, and symptomatic antihistamine administration are sufficient for mild CADR, especially for a localised manifestation.[12] Additionally, the experts' consensus recommends desensitisation for a rapid onset mild CADR, which is absent from that patient's case management.

Adverse event monitoring should be done throughout the entire course of the regimen. In an outpatient setting, weekly monitoring is recommended in the first two months. Afterwards, monthly monitoring is recommended in the second half of the regimen. Additionally, daily monitoring is still recommended for the treatment supporter, along with prompt reporting to the healthcare worker.[3] In case any adverse event occurs, it must be documented on the health facility's medical record and reported on the drug side effect monitoring section (i.e., MESO Harian menu) of the national TB registry website.

As this case of CADR event occurs in PHC, there are some limitations to this case management due to resource constraints. No laboratory examination, allergy test, drug desensitization, and drug provocation test protocol was able to be conducted other than the TB confirmation test only. Continuing the course of the regimen despite mild CADR and limited examinations in this case was also proven to be safe and well-received by the patient. Invasive examination (such as skin biopsy, blood analysis, etc.) was not done as it may be excessive and impose unnecessary risk for that patient.

This practice is consistent with current guidelines from the International Union Against Tuberculosis and Lung Disease that only recommend treatment interruption on serious ADR, such as Stevens-Johnson Syndrome or Lyell Syndrome.[13] Serious ADR requiring treatment interruption only occurs in 1.9% of patients receiving the HMPZ regimen.[2] Also in accordance with the guideline, that patient was given oral Cetirizine and oral Prednisone during outpatient monitoring.

Despite the limited resource, this case demonstrates sufficient responses toward mild CADR without the need for treatment interruption.

## CONCLUSION

The CADR from the novel 2HPMZ/2HPM regimen can have a rapid onset as early as 30 minutes. CADR, in this case, falls under the mild category and does not require treatment interruption. That clinical evidence is vital for healthcare providers in resource-limited settings (including PHC or other primary health care) as a firm reference to conduct a sufficient measure and to safeguard patient trust toward the regimen, supporting patient compliance and treatment success.

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## CONFLICT OF INTEREST

The author declares no conflict of interest in the reporting of this case management.

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