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Drug Provocation Testing as the Cornerstone for Diagnosing Antituberculosis Drug Hypersensitivity

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Abstract

Drug hypersensitivity reactions (DHRs) remain an important challenge in everyday clinical practice, especially in conditions that require prolonged multidrug treatment such as tuberculosis. Hypersensitivity to anti-tuberculosis therapy (ATT) can disrupt ongoing treatment, reduce adherence, and ultimately compromise therapeutic outcomes. For this reason, an accurate and structured diagnostic approach is crucial to identify drug-related hypersensitivity and non-immunologic adverse reactions is therefore crucial to support safe clinical decision making. A 52-year-old male patient with pulmonary tuberculosis developed recurrent hypersensitivity manifestations during the continuation phase of ATT. The patient experienced two episodes of generalized pruritus, soft tissue swelling, and dyspnea, both of which required hospitalization. Similar symptoms recurred after ATT was substituted with levofloxacin. He was subsequently referred for allergy evaluation and underwent drug provocation testing (DPT) performed as a graded drug challenge with performed sequentially with isoniazid, rifampicin, ethambutol, and pyrazinamide under close clinical supervision. No immediate reactions were observed during in-hospital monitoring. No immediate hypersensitivity reactions were observed during in-hospital monitoring; however, delayed cutaneous symptoms developed after discharge following exposure to each tested agent, supporting the diagnosis of delayed-type hypersensitivity reactions. This case underscores the clinical challenges associated with delayed hypersensitivity reactions to multiple first-line anti-tuberculosis drugs. Drug provocation testing, when applied in a controlled and risk-stratified setting, provides valuable diagnostic clarification and assists in selecting alternative therapeutic strategies. A systematic diagnostic strategy is key to guiding individualized and safe treatment decisions in tuberculosis patients with suspected drug hypersensitivity.

INTRODUCTION

Drug hypersensitivity reactions (DHRs) represent a major challenge in clinical management. In many cases, they lead to interruption or modification of ongoing therapy (Bavbek et al., 2022; Bavbek & PhDv, 2025; Borrás Cuartero et al., 2024; Buhari et al., 2024; Pallardy et al., 2024; Pichler, 2022). This issue is particularly relevant in conditions requiring prolonged or combination pharmacotherapy, such as infectious and chronic inflammatory

diseases, where hypersensitivity reactions may adversely affect treatment outcomes and patient safety. Clinically, DHRs present with highly variable manifestations, spanning from mild cutaneous symptoms to severe systemic reactions, thereby complicating timely recognition and appropriate clinical management. In more severe cases, marked skin involvement, angioedema, or respiratory symptoms may lead to recurrent hospital admissions (Blanca et al., 2009; Lehloenya & Dheda, 2012).

Among antimicrobial agents, anti-tuberculosis therapy (ATT) is frequently implicated in drug hypersensitivity due to the need for long-term multidrug regimens and the involvement of complex drug metabolism pathways (Dartois & Rubin, 2022; Sharma et al., 2025; Singha et al., 2024; Zade, 2024). Hypersensitivity reactions associated with ATT may arise through immediate or delayed immunological mechanisms and are commonly associated with treatment discontinuation, poor adherence, and unfavorable therapeutic outcomes (Shin et al., 2021). The World Health Organization (WHO) has recognized adverse drug reactions, including hypersensitivity, as a major obstacle to successful tuberculosis treatment, emphasizing the necessity of accurate identification and appropriate management of drug-related reactions to preserve both safety and treatment effectiveness (World Health Organization, 2025).

To address these challenges, current guidelines issued by the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO) advocate a structured, stepwise diagnostic approach based on comprehensive clinical evaluation and, when indicated, confirmatory procedures such as drug provocation testing (DPT) or drug desensitization (DSENS) (Barbaud et al., 2024). This case report presents a patient with suspected delayed hypersensitivity reactions to multiple first-line anti-tuberculosis agents and underscores the importance of a systematic diagnostic strategy in achieving safe and effective tuberculosis management.

The novelty of this case report lies in four aspects. First, it documents the first reported case in Indonesia of DPT-confirmed delayed hypersensitivity to all four first-line ATT drugs in a single patient. Second, it provides a detailed, reproducible graded challenge protocol with tables showing the stepwise administration of each drug. Third, it clearly demonstrates the distinction between immediate (in-hospital, negative) and delayed (post-discharge, positive) reactions, supporting the T-cell-mediated mechanism. Fourth, it describes successful alternative treatment planning (macrolide-based regimen) based on DPT results.

The primary objective of this case report is to describe the diagnostic approach, DPT protocol, and clinical outcomes in a patient with suspected delayed hypersensitivity to multiple first-line ATT drugs. The specific objectives are: (1) to present the graded challenge protocol for isoniazid, rifampicin, ethambutol, and pyrazinamide; (2) to distinguish immediate from delayed reactions based on temporal patterns; (3) to discuss the immunological mechanisms (Gell and Coombs Type IV) underlying the observed reactions; and (4) to provide practical guidance for clinicians considering DPT in similar cases.

The theoretical contribution of this case report is to reinforce the understanding that delayed hypersensitivity to ATT is T-cell-mediated and can be safely diagnosed through graded drug challenge when severe immediate reactions are excluded. The practical contribution includes providing a template DPT protocol that can be adapted by other hospitals, as well as guidance on patient selection, monitoring requirements, and interpretation of results. The expected benefits are: (1) for patients: avoiding unnecessary avoidance of all first-line drugs;

(2) for clinicians: a structured approach to diagnosing ATT hypersensitivity; (3) for tuberculosis programs: reducing treatment interruptions and preventing drug resistance; and (4) for researchers: a foundation for larger studies on DPT for ATT hypersensitivity in Indonesia.

METHOD

A 52-year-old male with pulmonary tuberculosis was referred to Wangaya Hospital for further evaluation of suspected drug-induced hypersensitivity reactions. At the time of referral, the patient was in the third month of anti-tuberculosis therapy (ATT) and was receiving medications in the continuation phase. In July 2025, he experienced two episodes of moderate hypersensitivity reactions occurring approximately two weeks apart. Both episodes were characterized by generalized pruritus, soft tissue edema, and dyspnea, necessitating hospital admission on each occasion. Following the second hospitalization, given the close temporal relationship between ATT administration and symptom recurrence, anti-tuberculosis medications were temporarily withheld.

Subsequently, the patient was switched to an alternative antimicrobial agent, levofloxacin. However, similar hypersensitivity manifestations recurred during levofloxacin treatment, including pruritus affecting the upper extremities and facial edema. In light of recurrent reactions to multiple antimicrobial agents, the patient was referred to the Allergy and Clinical Immunology unit for comprehensive evaluation.

A structured diagnostic approach was planned, incorporating drug provocation testing (DPT) performed as a graded drug challenge (GDC) with first-line anti-tuberculosis agents. The objective was to identify the responsible drug(s) and to determine a safe and effective anti-tuberculosis treatment strategy. Drug provocation testing was sequentially conducted using isoniazid (400 mg), ethambutol (750 mg), rifampicin (450 mg), and pyrazinamide (1000 mg). Each challenge was performed at one-week intervals and only when the patient was clinically stable. Written informed consent was obtained prior to each procedure, and the patient was admitted to a dedicated infectious intensive care unit for eight hours of close monitoring during each provocation session.

Each drug was administered according to a graded challenge protocol in which the total therapeutic dose was divided into ten equal fractions and delivered over four consecutive stages at 30-minute intervals. The administered doses consisted of 1/10 of the total dose during the first stage, followed by 2/10, 3/10, and 4/10 during subsequent stages. Throughout the provocation process, the patient was carefully monitored for changes in vital signs and the development of hypersensitivity symptoms, including pruritus, angioedema, or respiratory complaints.

No immediate hypersensitivity reactions were observed during in-hospital monitoring, which extended for up to eight hours following drug administration. The patient was scheduled for outpatient follow-up five days later. At follow-up, he reported the onset of delayed hypersensitivity symptoms involving all four anti-tuberculosis agents, occurring approximately three hours after discharge following the final provocation session. These symptoms were limited to generalized pruritus and a sensation of warmth, without dyspnoea or other systemic allergic manifestations.

Based on these findings, delayed hypersensitivity reactions to all four first-line anti-tuberculosis agents were diagnosed. Alternative therapeutic options, including macrolide-based

regimens, were subsequently discussed with the pulmonology team to guide further management of tuberculosis.

Table 1. Graded challenges of ATT Isoniazid 400 mg

Steps	Time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	Immediate DHR (in Hospital)			Delayed DHR
					Vital sign	Cutaneous symptoms	Respiratory symptoms	
1	0	1/10	40	40	Stable	None	None	+ (rash after 3 hours out hospital)
2	30	2/10	80	120				
3	30	3/10	120	240				
4	30	4/10	160	400				

Table 2. Graded challenges of ATT Ethambutol 750 mg

Steps	Time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	Immediate DHR (in Hospital)			Delayed DHR
					Vital sign	Cutaneous symptoms	Respiratory symptoms	
1	0	1/10	75	75	Stable	None	None	+ (rash after 3 hours out hospital)
2	30	2/10	150	225				
3	30	3/10	225	450				
4	30	4/10	300	750				

Table 3. Graded challenges of ATT Rifampicin 450 mg

Steps	Time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	Immediate DHR (in Hospital)			Delayed DHR
					Vital sign	Cutaneous symptoms	Respiratory symptoms	
1	0	1/10	45	45	Stable	None	None	+ (rash after 3 hours out hospital)
2	30	2/10	90	135				
3	30	3/10	135	270				
4	30	4/10	180	450				

Table 4. Graded challenges of ATT Pyrazinamide 1000 mg

Steps	Time (min)	Drug concentration (mg)	Dose (mg)	Cumulative dose (mg)	Immediate DHR (in Hospital)			Delayed DHR
					Vital sign	Cutaneous symptoms	Respiratory symptoms	
1	0	1/10	100	100	Stable	None	None	+ (rash after 3 hours out hospital)
2	30	2/10	200	300				
3	30	3/10	300	600				
4	30	4/10	400	1000				

RESULTS AND DISCUSSIONS

Drug hypersensitivity reactions (DHRs) occur in susceptible individuals and continue to pose considerable diagnostic and therapeutic challenges, particularly in patients who require prolonged multidrug regimens, such as those receiving anti-tuberculosis therapy. Antimicrobial agents are among the drug classes most frequently implicated in DHRs, with reactions arising from immune responses directed against the administered drug or its reactive metabolites, leading to immune sensitization and subsequent clinical manifestations (Khan et al., 2022).

According to the Gell and Coombs classification, hypersensitivity reactions are divided into four distinct immunological types. Type I hypersensitivity reactions are immediate and mediated by immunoglobulin E (IgE), resulting in mast cell and basophil activation and presenting clinically as urticaria, angioedema, bronchospasm, or anaphylaxis. Type II hypersensitivity involves antibody-mediated cytotoxic mechanisms, whereas Type III hypersensitivity is caused by immune complex formation with subsequent complement activation. Type IV hypersensitivity, also known as delayed-type hypersensitivity, is mediated by T lymphocytes and typically develops hours to days following exposure to the offending drug. Among drug-induced hypersensitivity reactions, Type IV mechanisms are the most frequently observed, particularly in association with anti-tuberculosis medications (Abbas et al., 2025; Demoly et al., 2014).

Delayed-type (Type IV) hypersensitivity reactions are initiated by the activation of drug-specific T cells following antigen presentation through major histocompatibility complex pathways. Upon re-exposure, these primed T cells secrete pro-inflammatory cytokines, including interferon-γ and tumor necrosis factor-α, which promote the recruitment of inflammatory cells and subsequent tissue inflammation (Abbas et al., 2025). Clinically, delayed hypersensitivity reactions most often manifest more than 24 hours after drug administration and predominantly present with cutaneous symptoms such as pruritus, maculopapular eruptions, or a burning sensation, typically in the absence of severe systemic involvement. In the present case, the delayed onset of symptoms, their recurrence upon re-exposure, and the predominance of cutaneous manifestations strongly support a T-cell–mediated hypersensitivity mechanism rather than an immediate IgE-mediated reaction (Abbas et al., 2025; Collado-Chagoya et al., 2018).

The diagnostic evaluation of suspected drug hypersensitivity is primarily based on a thorough clinical history and careful assessment of the temporal relationship between drug exposure and symptom onset. When uncertainty persists, confirmatory procedures such as drug provocation testing (DPT) or drug desensitization (DSENS) may be considered. Drug provocation testing involves the administration of gradually increasing doses of a drug under close medical supervision to assess tolerance and establish or exclude hypersensitivity. This approach is indicated in patients with non-severe reactions or when delayed hypersensitivity is suspected. In contrast, DSENS aims to induce temporary immunological tolerance through incremental drug administration over a short period and is reserved for patients with confirmed drug hypersensitivity when no effective alternative therapy is available (Cernadas et al., 2010). Importantly, both drug provocation testing and desensitization are contraindicated in patients with a history of severe delayed hypersensitivity reactions, including Stevens–Johnson syndrome, toxic epidermal necrolysis, and other life-threatening cutaneous adverse drug reactions.

In the present case, graded drug challenge was considered more appropriate than desensitization due to the absence of severe immediate reactions and the predominance of delayed- onset cutaneous symptoms. Furthermore, the primary objective was to identify the offending anti- tuberculosis agents rather than to induce tolerance to a specific indispensable drug. The delayed manifestation of symptoms occurring more than 24 hours after drug exposure further supported the use of GDC as a safer and more informative diagnostic strategy.

CONCLUSION

Drug hypersensitivity reactions remain unpredictable and pose a major challenge in patients receiving multidrug anti-tuberculosis therapy. Careful monitoring and structured diagnostic pathway are essential to distinguish true hypersensitivity from other adverse drug reactions. In selected patients, drug provocation testing may provide valuable diagnostic clarification and support safer modification of tuberculosis treatment. Further studies involving larger cohorts are needed to better define the safety and clinical utility of graded drug challenge in anti-tuberculosis drug hypersensitivity.

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