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Nitroimidazole Hypersensitivity: A Retrospective Analysis of Clinical Management and Diagnostic Testing

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ABSTRACT

Objective: Nitroimidazoles, particularly metronidazole and ornidazole, are widely used in the treatment of anaerobic and protozoal infections. Although generally well tolerated, hypersensitivity reactions (HSRs) to nitroimidazoles have been increasingly recognized and may significantly limit antimicrobial options. The diagnosis of HSRs is often challenging due to overlapping clinical presentations, concomitant drug exposures, and the limited sensitivity of available diagnostic tests. This study aimed to characterize the clinical features, diagnostic methods, and causality assessment outcomes in patients evaluated for suspected nitroimidazole hypersensitivity.

Materials and Methods: Among 1,570 patients tested for drug allergy between January 2019 and October 2025, 30 for whom diagnostic testing with nitroimidazoles was planned were included. Demographic data, clinical characteristics, and laboratory findings were systematically reviewed. Diagnostic procedures included skin prick testing (SPT), intradermal testing (IDT), and drug provocation testing (DPT). Causality was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria and the Naranjo Adverse Drug Reaction Probability Scale.

Results: Of the 30 patients, 23 had a history consistent with nitroimidazole hypersensitivity. Most were middle-aged women (mean age 43.8 years, 82.6% female), and two-thirds had an atopic background. Immediate-type reactions predominated (87%), most commonly urticaria, angioedema, or both. Allergy testing was performed in 20 patients: all SPTs were negative, IDT was positive in one (4.3%), and DPT confirmed hypersensitivity in two (8.7%). Overall, two patients had confirmed metronidazole allergy and one had ornidazole allergy, whereas most were reclassified as non-allergic after testing. Causality assessments categorized the majority as unclassified (WHO-UMC, 69.6%) or possible (Naranjo, 65.2%).

Conclusion: Nitroimidazole hypersensitivity is rare but clinically important. Most reported allergies were unconfirmed upon systematic re-evaluation, underscoring the value of structured diagnostic algorithms. While causality tools aid interpretation, confirmatory DPT remains the cornerstone for accurate diagnosis and safe antimicrobial stewardship.

Keywords: Nitroimidazole, metronidazole, ornidazole, drug hypersensitivity

INTRODUCTION

Infectious diseases remain a major global health burden, responsible for millions of deaths each year. The rise of antimicrobial resistance further limits treatment options (1). Beyond resistance, drug hypersensitivity reactions (HSRs) and inaccurate allergy labeling pose additional challenges that compromise optimal antibiotic use. Although antibiotics are among the most commonly prescribed drugs and the leading cause of reported drug allergies, over 90% of these cases are not confirmed upon evaluation (2,3). Such mislabeling often results in avoidance of first-line agents, use of broad-spectrum alternatives, increased costs, and promotion of resistance.

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Nitroimidazoles, introduced into clinical practice in the 1950s, are five-membered heterocyclic compounds containing an imidazole ring with a nitro ($-NO_2$) substituent that defines their structural and pharmacologic characteristics (1,4). The 5-nitroimidazoles—metronidazole, tinidazole, ornidazole, and secnidazole— are the most commonly used members, effective mainly against anaerobic and microaerophilic organisms such as Bacteroides fragilis, Clostridium difficile, and Fusobacterium nucleatum. Metronidazole remains a first-line agent for bacterial vaginosis, trichomoniasis, giardiasis, and mild C. difficile infections, and is also used in Helicobacter pylori eradication regimens (1).

Ornidazole and tinidazole share a similar antimicrobial spectrum with metronidazole but offer longer elimination half-lives, improved tolerability, and comparatively lower resistance rates (5). These agents are preferred in single-dose treatments or in cases of metronidazole resistance, ornidazole is more commonly used for vaginitis and trichomoniasis, whereas tinidazole is frequently prescribed for giardiasis and amebiasis (5-8). The clinical choice among these agents depends on the site and type of infection, antimicrobial resistance patterns, and patient tolerability. Nevertheless, hypersensitivity reactions attributed to nitroimidazoles, although uncommon, are clinically relevant and warrant careful evaluation during antimicrobial selection and treatment planning.

Although diagnostic data for nitroimidazoles remain limited, available studies provide preliminary insights into test performance. Reported sensitivity and specificity for metronidazole and ornidazole skin testing are 33.3% and 16.6%, and 94.2% and 97.3%, respectively (9). The basophil activation test has demonstrated higher sensitivity—71.4% for metronidazole and 83.3% for ornidazole—at an optimal concentration of 5 mg/mL, whereas specific IgE assays remain unstandardized for these agents. Specific IgE testing lacks standardization for these drugs. For delayed-type reactions, patch testing or late-reading intradermal testing may provide supportive information, while in vitro tests such as the lymphocyte transformation test or ELISpot can be used as complementary tools (10,11). Given the limited sensitivity of skin tests for nitroimidazoles, drug provocation testing (DPT) is often required to establish the diagnosis (12). This procedure is most appropriate in patients with a low likelihood of true allergy, mild cutaneous symptoms, or uncertain histories, and should be performed under strict medical supervision in specialized centers (13). DPT may also be considered in cases involving multiple concomitant drug exposures, whereas in patients with severe or high-risk reaction histories, it should be restricted to settings with full resuscitation facilities.

Strengthening the identification, prevention, and reporting of adverse drug reactions (ADRs) is crucial for improving patient safety and reducing healthcare burden (14). Within this framework, causality assessment integrates clinical, temporal, and laboratory data to determine the likelihood that a drug caused a given reaction. Standardized tools such as the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system and the Naranjo Adverse Drug Reaction Probability Scale are widely used to ensure objective and reproducible evaluation of suspected drug-related events(15,16).

In this study, both tools were systematically applied to assess causality in nitroimidazole-associated hypersensitivity reactions and to explore their utility as complementary frameworks in retrospective evaluation. The study further aimed to characterize the clinical features, diagnostic testing outcomes, and causality assessment findings of patients evaluated for suspected hypersensitivity to nitroimidazole antibiotics, and to examine the applicability of these scales in clinical allergy practice.

MATERIALS and METHODS

Study Design, Patient Population, and Data Collection

This retrospective study was conducted between January 2019 and October 2025 at the Ege University Allergy and Clinical Immunology Outpatient Clinic, a tertiary referral center in İzmir, Türkiye. Among 1,570 patients who underwent drug allergy testing during this period, patients for whom diagnostic testing with nitroimidazoles was planned (including skin prick, intradermal, or drug provocation tests) were selected for inclusion. A total of 30 patients were included and defined as the overall testing cohort (Group 1) (Figure 1). Within this cohort, Group 2 was defined as the subset of patients whose clinical history suggested a possible or suspected hypersensitivity reaction to nitroimidazoles. Patients with unknown suspected drug names (n = 4) or with a history of hypersensitivity reactions to antibiotics other than nitroimidazoles (e.g., clindamycin) (n = 3) were excluded, and the remaining patients constituted Group 2, reflecting the clinically relevant population targeted by the primary objectives of this

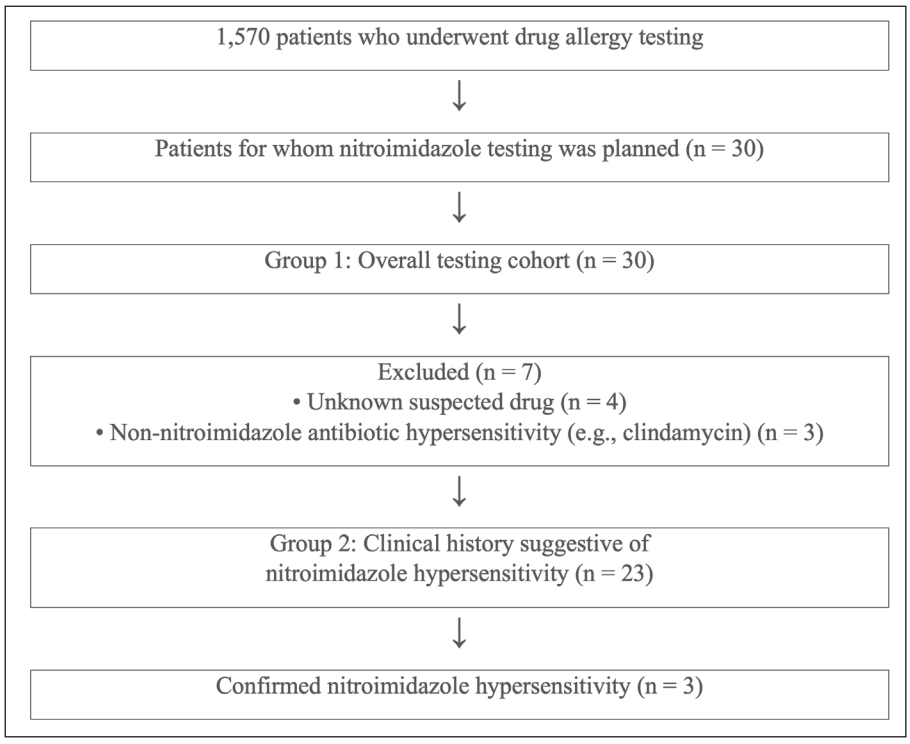

Figure 1: Patient selection and diagnostic flow.

study. This grouping approach aligns with real-world clinical practice, in which nitroimidazole testing may be performed both for suspected hypersensitivity and for alternative drug evaluation in complex or ambiguous scenarios. While descriptive data are presented for both groups, the main analyses focused on Group 2 (the nitroimidazole hypersensitivity group). For each patient, a standardized case report form was completed. Demographic data (age, sex, place of residence, access to emergency care), clinical history (comorbidities, history of drug and food allergies, anaphylaxis, mastocytosis), and laboratory findings (serum tryptase, total IgE, peripheral blood counts, liver and renal function tests) were recorded.

An atopic phenotype was defined as the presence of allergic diseases that were considered IgE-mediated, such as food allergy, allergic rhinitis, atopic dermatitis, or asthma. Information regarding the drug reaction history—including suspected drugs, route of administration, latency from exposure to symptom onset, clinical manifestations, severity of reaction, treatment, and hospitalization—was systematically documented. The timing of hypersensitivity reactions was classified according to the latency from drug exposure as follows: within 1 hour (immediate reactions), 1-6 hours (early accelerated reactions), 6-24 hours (late accelerated reactions), and after 24 hours (delayed/non-immediate reactions). The severity of type I hypersensitivity reactions was graded using the Updated WAO Grading System for Systemic Allergic Reactions (grades 1-5) (17). Grade 3-5 reactions were classified as anaphylaxis, consistent with the updated WAO diagnostic criteria, in which anaphylaxis is defined as a rapidly developing systemic hypersensitivity reaction involving more than one organ system and carrying the potential for severe or life-threatening outcomes (13,17).

Causality Assessment

Causality assessment was performed for all hypersensitivity reactions using two standardized pharmacovigilance tools: the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system and the Naranjo Adverse Drug Reaction Probability Scale. Both methods were independently applied by two experienced clinical allergists to ensure objectivity and consistency (14-16). The WHO-UMC system categorizes the causal relationship between a suspected drug and an adverse reaction into six levels (certain, probable, possible, unlikely, conditional/unclassified, and unassessable) based on the temporal association, dechallenge/rechallenge findings, exclusion of alternative causes, and overall clinical plausibility (14,16).

The Naranjo algorithm uses a structured 10-item questionnaire, generating a total score that defines the probability as definite (≥9), probable (5-8), possible (1-4), or doubtful (≤0) (14,15).

In cases where multiple drugs were administered simultaneously and the specific suspected agent could not be determined, reactions were categorized as conditional/unclassified according to the WHO-UMC criteria. When the exact name or formulation of the suspected drug was unknown, reactions were classified as unassessable/unclassifiable by the WHO-UMC system and as doubtful by the Naranjo algorithm. In this study, both causality assessment scales were retrospectively applied based on detailed clinical documentation, without performing additional diagnostic testing. These frameworks were implemented to provide a transparent and standardized evaluation of causality, complementing clinical judgment within the context of allergy diagnostics.

Diagnostic Procedures

Diagnostic procedures included skin tests and, when required, drug provocation tests. Skin prick testing (SPT) and intradermal testing (IDT) were carried out at least 4-6 weeks after the index reaction, provided there was no contraindication. For metronidazole, the intravenous solution (500 mg/100 mL) was used. SPTs were performed with undiluted solutions (1/1), while IDTs were performed with dilutions of 1/100 and 1/10 of the injectable preparations (18). In all SPTs, histamine (10 mg/mL) was used as the positive control and saline as the negative control. A skin prick test result was considered positive when the wheal diameter exceeded the negative control by ≥3 mm. For IDTs, positivity was defined as an increase of at least 3 mm in the initial wheal size accompanied by surrounding erythema after 20 minutes, and at least 3 mm larger than the reaction produced by the negative control.

In our study, metronidazole DPT was performed only in patients without contraindications for drug provocation testing (19). Metronidazole and ornidazole were administered orally in 500 mg tablet form. An initial 250 mg dose was given, followed by an observation period of at least 2 hours, and extended up to the latency of the index reaction. If no symptoms developed, a second 250 mg dose was administered. Patients were monitored for at least two additional hours, with a total observation time of 8 hours on the test day, and were re-evaluated after 24 hours. Written informed consent was obtained from all patients before skin testing and drug provocation procedures. All procedures were undertaken in a hospital environment with immediate access to resuscitation facilities. Drugs that could mask or aggravate hypersensitivity were discontinued in advance after consultation with the relevant clinical departments.

Ethical approval was obtained from the Ege University Clinical Research Ethics Committee (approval no: 25-10.2T/17). The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables were expressed as absolute numbers and percentages. Descriptive statistics were primarily used to illustrate the demographic characteristics, clinical features, diagnostic testing outcomes, and causality assessment results. Given the retrospective design and limited sample size, analyses were primarily descriptive and no formal hypothesis testing was performed.

RESULTS

A total of 30 patients for whom nitroimidazole allergy testing was planned were included as the overall testing cohort (Group 1). The mean age was 46.1 ± 15.8 years (range: 19-73), and 26 (86.7%) were female (Table I). Twenty patients (66.7%) were classified as having an atopic phenotype, most commonly allergic rhinitis (33.3%). A history of drug allergy was reported in 15 patients (50%), and seven (23.3%) had a previous episode of anaphylaxis, predominantly drug-induced. Laboratory findings, including serum tryptase, total IgE, and basic hematologic and biochemical parameters, were within normal limits in most patients.

The nitroimidazole hypersensitivity group (Group 2, n=23) included patients with a clinical history suggesting a possible or suspected hypersensitivity reaction to nitroimidazoles (Table I), and this group represents a subset of Group 1. This group had a mean age of 43.8 ± 15.7 years, and 19 (82.6%) were female. Fifteen patients (65.2%) were classified as having an atopic phenotype, most commonly

allergic rhinitis (39.1%) and asthma (13%). Ten patients (43.5%) had a history of drug allergy, and three (13%) reported previous anaphylaxis. The median total IgE level was 70.1 IU/mL (IQR 22.5-189.0), and the median serum tryptase level was 5.79 µg/L (IQR 5.40-7.51), comparable to those of the overall cohort. Other hematological and biochemical parameters showed no significant deviation from normal ranges (Supplementary Table I).

In the nitroimidazole hypersensitivity group (Group 2, n=23), the most frequently suspected drugs were metronidazole (60.9%) and ornidazole (34.8%), with a single case of tinidazole (4.3%) (Table II). These agents were mainly prescribed for genital tract (30.4%) and *H. Pylori* infections (30.4%), followed by odontogenic (17.4%) and protozoal infections (13.0%). Concomitant drug exposure was reported in 91.3% of patients, while only two had a single suspected agent (one metronidazole and one ornidazole). The median latency to presentation was 2 months (range 0.25-144). Oral administration predominated (69.9%). Most reactions were immediate (87.0%), particularly early accelerated (47.8%) and <1 h (34.8%). Cutaneous manifestations were common, with urticaria (34.8%), urticaria with angioedema (26.1%), and isolated angioedema (21.7%) (Figure 2). Multisystem involvement occurred in 30.4%, including respiratory (21.7%) and cardiovascular symptoms (13%). According to WAO grading, 56.5% of reactions were mild-to-moderate (Grades 1-2), while 26.0% were severe (Grades 3-4). Acute treatment was administered in 82.6%, mainly with corticosteroids and antihistamines, epinephrine was required in 8.7%. Over half were treated in the emergency department, and 8.7% required hospitalization. Causality assessment showed frequent uncertainties, with most cases classified as unclassified by WHO-UMC (69.9%) and possible by Naranjo (65.2%).

In Group 2, allergy testing was performed in 20 of 23 patients (87.0%), while three were lost to follow-up. The main indication was diagnostic evaluation (69.6%) or assessment of a potential alternative drug (17.4%). In four patients, nitroimidazole testing was performed for alternative purposes—most commonly due to first-line use in acute dental abscesses, a history of severe reaction, or lack

Table I: Baseline characteristics of the study population, presented for the overall testing cohort (Group 1) and patients with suspected nitroimidazole hypersensitivity (Group 2)

Characteristics		Group 1 n=30	Group 2 n=23	Characteristics		Group 1 n=30	Group 2 n=23
Age (year)	Mean	46.1 ± 15.8	43.8±15.7	**Sex, n (%)**	Female	26 (86.7)	19 (82.6)
	Min-max	19-73	19-73		Male	4 (13.3)	4 (17.4)
	Median	47.5	46				
Place of residence, n (%)	Urban	10 (33.4)	10 (43.5)	**Emergency care access, n (%)**	Easy	14 (46.7)	13 (56.5)
	District	20 (66.7)	13 (56.5)		Moderate	11 (36.7)	6 (26.1)
	Village	0	0		Difficult	5 (16.7)	4 (17.4)
Allergic rhinitis, n (%)	Yes	10 (33.3)	9 (39.1)	**Atopic dermatitis, n (%)**	Yes	1 (3.3)	1 (4.3)
	No	20 (66.7)	14 (60.9)		No	29 (96.7)	22 (95.7)
Venom allergy, n (%)	Yes	2 (6.7)	2 (8.7)	**Chronic urticaria, n (%)**	Yes	4 (13.3)	3 (13)
	No	28 (93.3)	21 (91.3)		No	26 (86.7)	20 (87)
Atopic phenotype, n (%)	Yes	20 (66.7)	15 (65.2)	**Asthma, n (%)**	Yes	3 (10)	3 (13)
	No	10 (33.3)	8 (34.8)		No	27 (90)	20 (87)
Suspected MCAS, n (%)	Yes	1 (3.3)	1 (4.3)	**Contact dermatitis, n (%)**	Yes	2 (6.7)	2 (8.7)
	No	29 (96.7)	22 (95.7)		No	28 (93.3)	21 (91.3)
Drug allergy, n (%)	Yes	15 (50)	10 (43.5)	**Anaphylaxis, n (%)**	Drug-induced	5 (16.7)	3 (13)
	No	15 (50)	13 (56.5)		Venom-induced	1 (3.3)	1 (4.3)
History of drug allergy, n (%)	NSAIDs	3 (10)	2 (8.7)	**History of drug allergy symptoms, n (%)**	Urticaria	6 (20)	5 (17.4)
	Beta-lactams	6 (20)	3 (13)		Urticaria+Angioedema	2 (6.7)	2 (8.7)
	Other antibiotics	1 (3.3)	1 (4.3)		Anaphylaxis	5 (16.7)	2 (8.7)
	NSAIDs+antibiotics	4 (13.3)	3 (13)		Erythema	1 (3.3)	1 (4.3)
	PPI + antibiotics	1 (3.3)	1 (4.3)		Localized bullous eruptions	1 (3.3)	0

MCAS: mast cell activation syndrome, **NSAIDs:** nonsteroidal anti-inflammatory drugs, **PPI:** proton pump inhibitor.

of other available options—and all results were negative (Table III). Metronidazole was the most frequently tested agent (69.6%), followed by ornidazole (17.4%). The tested preparations included Biteral® (13%), Flagyl® (56.5%), and Turkfleks® (13%). Skin prick tests were performed in 60.9% of patients and were uniformly negative. Intradermal testing was undertaken in 56.5% and yielded one positive result (4.3%). Drug provocation testing was conducted in 56.5%, with two positive challenges (8.7%) and 13 negative results, four patients (17.4%) did not complete the test. Overall, two patients (8.7%) were confirmed to have metronidazole allergy and one (4.3%) had ornidazole allergy, while the remaining cases were either negative or untested. In Group 2 (n=23), final allergy testing confirmed metronidazole allergy in 2 patients (8.7%), while 10 (43.5%) were classified as non-allergic. Ornidazole allergy was identified in 1 patient (4.3%), whereas 3 (13.0%) were confirmed as tolerant. Three patients (13.0%) were not tested due to loss to follow-up. In the remaining cases, causality assessment categorized 3 (13.0%) as unlikely and 1 (4.3%) as probable.

Two patients were confirmed with metronidazole allergy. A 28-year-old male developed a delayed maculopap-

Table II: Suspected Drug Reaction Characteristics

Characteristics		Group 1 n=30	Group 2 n=23	Characteristics		Group 1 n=30	Group 2 n=23
Suspected Drug, n (%)	Metronidazole	14 (46.7)	14 (60.9)	**Associated infections, n (%)**	Odontogenic Inf.	7 (23.3)	4 (17.4)
	Ornidazole	8 (26.7)	8 (34.8)		Genital tract Inf.	9 (30.0)	7 (30.4)
	Tinidazole	1 (3.3)	1 (4.3)		H. pylori Inf.	8 (26.7)	7 (30.4)
	Clindamycin	3 (10.0)			Periop. Inf.	3 (10.0)	2 (8.7)
	Unknown	4 (13.3)			Intestinal protozoal Inf.	3 (10.0)	3 (13)
Concomitant drug, n (%)	Yes	25 (83.3)	21 (91.3)	**Latency to presentation (month)**	Mean ± SD	31.7 ± 67.8	13.8 ± 31.1
	No	5 (16.7)	2 (8.7)		Min-max	0.25-300	0.25-144
					Median	2	2
Route of administration, n (%)	Oral	22 (73.3)	16 (69.6)	**Type of hypersensitivity rxns, n (%)**	Immediate rxns,	24 (80.0)	20 (87)
	Intravenous	3 (10)	3 (13)		Non-immediate rxns	6 (20.0)	3 (13)
	Other routes	5 (16.7)	4 (17.4)				
Timing of Reactions, n (%)	Immediate rxns	10 (33.3)	8 (34.8)	**WHO Adverse Event Grades, n (%)**	Grade 1	12 (40.0)	10 (43.5)
	Early accelerated	13 (43.3)	11 (47.8)		Grade 2	4 (13.3)	4 (17.4)
	rxns	4 (13.3)	2 (8.7)		Grade 3	4 (13.3)	3 (13)
	Late accelerated rxns	3 (10)	2 (8.7)		Grade 4	4 (13.3)	3 (13)
	Delayed rxns						
Treatment, n (%)	No	3 (10)	3 (13)	**Treatment setting, n (%)**	ED	13 (43.3)	12 (52.2)
	Yes	25 (83.3)	19 (82.6)		Home	10 (33.3)	7 (30.4)
	Unknown	2 (6.7)	1 (4.3)		Inpatient	3 (10)	2 (8.7)
Treatment given, n (%)	Epi + IV + H1 + CS	3 (11.1)	2 (8.7)	**Hospitalization, n (%)**	Yes	3 (10)	2 (8.7)
	IV + H1 + CS	7 (25.9)	7 (30.4)		No	27 (90)	21 (91.3)
	IV H1 + CS	5 (18.5)	4 (17.4)				
	PO H1	8 (29.6)	6 (26.1)				
	PO H1 + CS	2 (7.4)	1 (4.3)				
	Unknown	2 (7.4)	1 (4.3)				
WHO-UMC causality categories, n (%)	Probable	4 (13.3)	2 (8.7)	**Naranjo algorithm causality assessment, n (%)**	Probable	8 (26.7)	7 (30.4)
	Possible	1 (3.3)	1 (4.3)		Possible	17 (56.7)	15 (65.2)
	Unlikely	4 (13.3)	3 (13)		Doubtful	5 (16.7)	1 (4.3)
	Unclassified	16 (53.3)	16 (69.9)				
	Unclassifiable	5 (16.7)	1 (4.3)				

Rxns: Reactions, **Periop:** Perioperative, **Inf:** Infection, **Epi:** intramuscular epinephrine, **IV:** intravenous fluids, **PO:** per os, **H1:** antihistamine, **CS:** corticosteroid, **ED:** Emergency Department, **Home:** At home, **Inpatient:** Hospitalized, **MPE:** Maculopapular exanthema, **WHO-UMC:** World Health Organization-Uppsala Monitoring Centre.

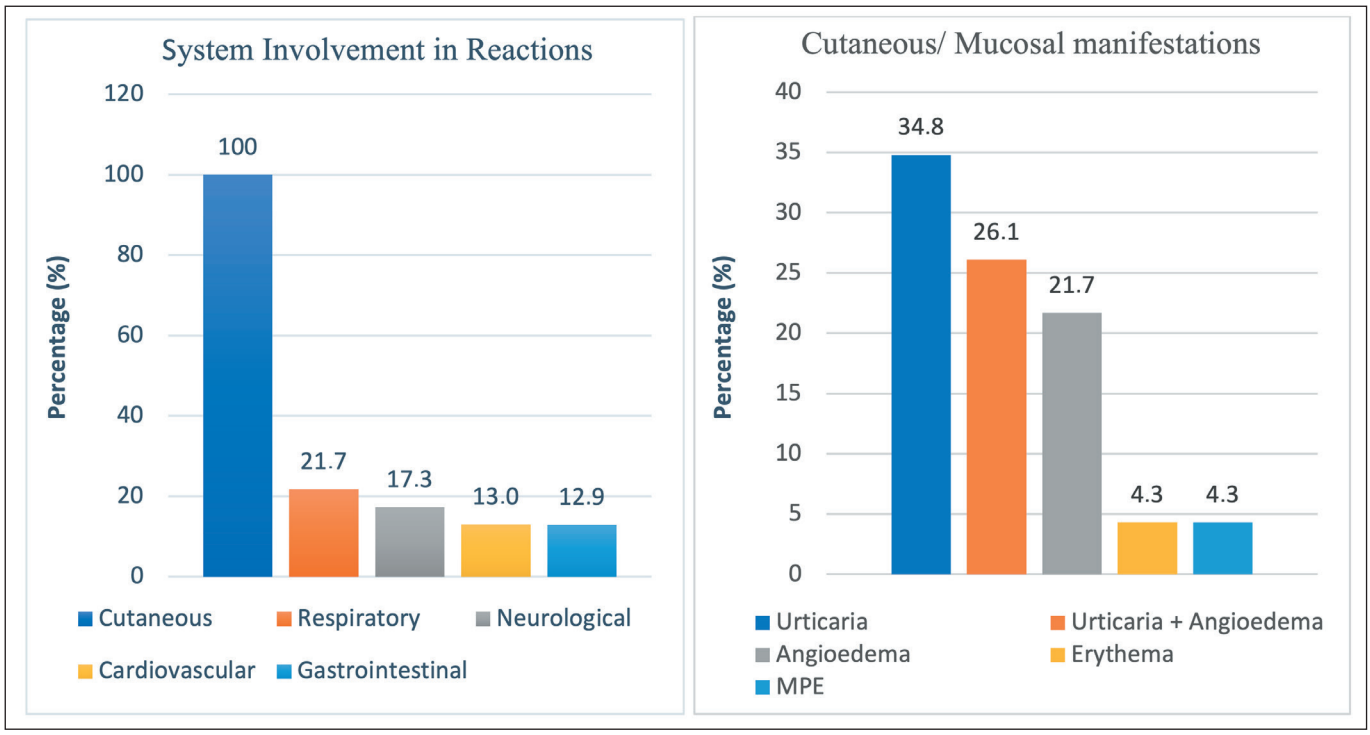

Figure 2: Cutaneous and Systemic Involvement in Group 2.

Table III: Summary of Allergy Tests with Nitroimidazoles

Characteristics		Group 1 n=30	Group 2 n=23			Group 1 n=30	Group 2 n=23
Allergy testing, n (%)	Allergy tests performed Patient lost to follow-up	27 (90.0) 3 (10.0)	20 (87) 3 (13)	**Purpose of testing, n (%)**	Diagnostic Alternative Diagnostic+Alternative	16 (59.3) 7 (25.9) 4 (14.8)	16 (69.6) 4 (17.4) 0
Tested drug contents, n (%)	Ornidazole Metronidazole	4 (14.8) 23 (85.2)	4 (17.4) 16 (69.6)	**Tested drug, n (%)**	Ornisid ® Biteral ® Flagyl ® Turkfleks 0.5% ®MET	1 (3.3) 3 (10.0) 19 (63.3) 4 (13.3)	1 (4.3) 3 (13) 13 (56.5) 3 (13)
SPT, n (%)	Performed but negative No test performed	12 (44.4) 15 (55.6)	9 (39.1) 11 (47.8)	**IDT, n (%)**	Performed but negative Performed and positive No test performed	11 (40.7) 1 (3.7) 15 (55.6)	10 (43.5) 1 (4.3) 9 (39.1)
DPT, n (%)	Performed but negative Performed and positive Lost to follow-up No test performed	19 (65.5) 2 (6.9) 5 (16.7) 4 (13.8)	13 (56.5) 2 (8.7) 4 (17.4) 4 (17.4)	**Final Allergy Test, n (%)**	MET allergy - No MET allergy -Yes ORN allergy - No ORN allergy - Yes Not tested MET Unlikely MET Probable	16 (55.2) 2 (6.9) 3 (10.3) 1 (3.4) 3 (10) 4 (13.8) 1 (3.4)	10 (43.5) 2 (8.7) 3 (13) 1 (4.3) 3 (13) 3 (13) 1 (4.3)

SPT: Skin Prick Test, **IDT:** Intradermal Test, **DPT:** Drug Provocation Test, **MET:** Metronidazole, **ORN:** Ornidazole.
Bold entries represent key diagnostic outcomes (SPT/IDT/DPT results and final diagnostic classifications) highlighted

ular exanthema, and a 26-year-old female experienced an early urticarial eruption after metronidazole use for Helicobacter pylori infection. In both, skin tests were negative, but oral provocation reproduced the reactions. Causality was classified as unclassified (WHO-UMC) and possible (15). One patient was confirmed with ornidazole allergy.

A 28-year-old female developed immediate angioedema after oral intake. Skin prick testing was negative, intradermal testing positive, and oral provocation omitted. Causality was probable by both scales.

One patient was identified as a probable hypersensitivity case. A 66-year-old female with β-lactam allergy developed a Grade 3 reaction during multidrug therapy including metronidazole. Skin tests were negative, and provocation was not performed due to severity. Causality was unclassified by WHO-UMC and probable by Naranjo et al. (15). Three patients were ultimately considered unlikely cases due to alternative explanations. One showed a nocebo response on provocation, another had a positive levofloxacin skin test indicating an alternative culprit, and the third was later confirmed with β-lactam allergy. Accordingly, all were categorized as unclassified by WHO-UMC and possible by Naranjo but deemed unlikely in terms of nitroimidazole causality. Four patients had reactions with unknown suspected drugs, all involving concomitant therapies for H. pylori, odontogenic, genital tract, or perioperative infections. Causality was unassessable by WHO-UMC and doubtful by Naranjo et al. (15). Drug provocation with metronidazole was negative in all, confirming safe tolerance.

In Group 2, three patients had a history of grade 3 anaphylaxis and three had grade 4 anaphylaxis (WAO classification) (Table II). All six patients were female, with a mean age of 53.50 ± 12.99 years (median 53, range 36-68). Atopic comorbidities were present in five patients (allergic rhinitis n=3, venom allergy n=1, drug allergy n=3, β-lactam allergy n=3, including one with previous β-lactam anaphylaxis). The suspected drug was metronidazole in four patients and ornidazole in two, and all reported concomitant medication exposure. Two reactions occurred after intravenous administration, two after oral intake, and two with combined ovule and oral forms. Four patients presented to the emergency department, and one was hospitalized. One patient was lost to follow-up, among the remaining five, diagnostic testing was performed in four and alternative challenge in one. Skin tests (SPT/IDT) in two patients and oral provocation testing in four were negative.

In Group 1, three patients experienced hypersensitivity reactions to clindamycin, however, none were suspected nitroimidazole allergy and therefore were not included in Group 2, and nitroimidazole testing was performed solely to identify a safe alternative agent for anaerobic coverage. Two patients developed delayed cutaneous reactions to clindamycin—one with maculopapular exanthema during odontogenic infection and another with a localized bullous lesion during genital tract infection, the latter reproduced identical findings during clindamycin provocation, and the former declined clindamycin re-exposure, so metronidazole was evaluated as the alternative in both cases. The third patient developed an immediate Grade 1 urticarial reaction with cough in the setting of odontogenic infection and had known β-lactam allergy and chronic urticaria, because the patient did not consent to clindamycin retesting, metronidazole was also used as the alternative. Causality assessment classified these clindamycin reactions as probable/possible in two cases and unlikely/possible in one, and all three patients had negative metronidazole provocations, confirming its safe use.

DISCUSSION

In this retrospective cohort, we present one of the few detailed real-life analyses of nitroimidazole-associated HSRs, systematically integrating standardized causality assessment tools (WHO-UMC and Naranjo algorithms) into clinical allergy evaluation. Although nitroimidazoles such as metronidazole and ornidazole are widely prescribed and generally well tolerated, true allergic reactions remain exceedingly rare. However, the frequent use of these agents for polymicrobial and anaerobic infections, often in combination with other antibiotics, poses a diagnostic challenge in determining the responsible drug. Our findings highlight that while most reported cases were clinically mild and limited to cutaneous symptoms, objective confirmation of true allergy was established in only a small fraction of patients through provocation testing. This underscores the importance of systematic re-evaluation and structured causality analysis to prevent unnecessary drug avoidance and maintain effective antimicrobial options.

In the present study, most patients evaluated for suspected nitroimidazole hypersensitivity were middle-aged females, consistent with previous reports indicating a higher prevalence of antibiotic allergy among women (63-75%) and a typical age range of 40-50 years. The likelihood of antibiotic allergy labeling has also been shown to increase with age, particularly after the fourth decade of life (20). Approximately two-thirds of our patients exhibited an atopic phenotype, most commonly allergic rhinitis and asthma. This finding is consistent with previous reports indicating that atopic individuals have a significantly

higher risk of developing drug allergies compared with non-atopic individuals, and that allergic rhinitis and asthma are the most frequent coexisting allergic conditions among adults with antibiotic hypersensitivity (21). In our cohort, 43.5% of patients reported a history of drug allergy, most commonly to β-lactam antibiotics (13%), NSAIDs (8.7%), or a combination of both (13%). Antibiotics—particularly β-lactams—and NSAIDs remain the leading triggers of drug hypersensitivity in adults, and are frequently implicated in multiple drug hypersensitivity syndrome, conditions defined by allergic reactions to two or more chemically unrelated drugs. These syndromes pose significant diagnostic and therapeutic challenges by limiting safe treatment options. Female sex, older age, chronic comorbidities, and an atopic background are recognized predisposing factors (22). In line with these findings, the predominance of middle-aged atopic women in our study likely reflects a population intrinsically more susceptible to multiple or cross-reactive drug allergies. In our study, baseline laboratory parameters, including serum tryptase and total IgE, remained within normal limits in most patients. This finding is consistent with previous reports suggesting that these biomarkers alone are insufficient for diagnosing drug allergy (23). The most commonly reported symptoms associated with prior drug allergy were urticaria (17.4-20%), urticaria with angioedema (6.7-8.7%), and anaphylaxis (8.7-16.7%). These results align with the established literature indicating that urticaria and angioedema represent the predominant cutaneous manifestations of antibiotic-induced HSRs, often accompanied by respiratory symptoms in more severe cases. Collectively, these findings reflect the typical demographic and clinical characteristics of patients referred to tertiary allergy centers for antibiotic hypersensitivity evaluation and form the basis for a more focused analysis of nitroimidazole-associated hypersensitivity, a rare but clinically significant entity presenting unique diagnostic and therapeutic challenges.

Among nitroimidazole derivatives, metronidazole has been most frequently reported as the suspected agent in HSRs, primarily due to its widespread prescription and clinical use both globally and in Turkey (1,9,24). Frequent exposure is a well-recognized factor contributing to sensitization risk. In our study, metronidazole was the most commonly self-reported suspected drug, followed by ornidazole, consistent with their predominant clinical use in genitourinary, odontogenic, and *H. pylori* infections. HSRs to nitroimidazoles—including metronidazole, tinidazole, ornidazole, and benznidazole—are most often mild and cutaneous, typically presenting as maculopapular exanthema or fixed drug eruptions (11,25,26). However, severe reactions, though rare, have been reported, including mucosal erosions, widespread eruptions, angioedema, and exceptionally life-threatening conditions such as Stevens-Johnson syndrome or anaphylaxis (11,25). In our cohort, self-reported suspected drug reactions most frequently manifested as immediate-type hypersensitivity (87%), primarily early accelerated reactions with urticaria or urticaria accompanied by angioedema, whereas delayed reactions accounted for only 13%. Approximately one-third of patients exhibited multisystem involvement, most commonly respiratory (21.7%) and cardiovascular (13%) manifestations during moderate-to-severe reactions. According to WAO grading, over half of the reactions were mild to moderate (Grades 1-2), whereas severe reactions (Grades 3-4) represented nearly one-quarter of cases. These findings are consistent with prior reports indicating that nitroimidazole-induced hypersensitivity typically presents with cutaneous and mucosal symptoms, while systemic involvement remains less frequent but clinically significant. Treatment was required in over 80% of patients, and more than half presented to the emergency department, reflecting the acute and sometimes unpredictable nature of these reactions. Epinephrine use remained limited (8.7%), underscoring the low rate of true anaphylaxis. Among patients who underwent diagnostic evaluation, three were confirmed to have true nitroimidazole allergy. Two were reactive to metronidazole and one to ornidazole. The reactions included a delayed maculopapular exanthema, an immediate urticarial eruption (Grade 2), and an immediate angioedema (Grade 1). All were mild, self-limited reactions, consistent with the typically benign clinical spectrum of nitroimidazole hypersensitivity reported in the literature.

Nitroimidazole-induced HSRs are thought to result from the interaction between the drug's structural properties and its metabolic transformation. The nitro ($-NO_2$) group attached to the imidazole ring is believed to generate reactive intermediates during biotransformation, thereby triggering immune activation (27). In addition, certain side chains and metabolites may enhance antigenicity and contribute to allergic sensitization. Cross-reactivity has been reported both among 5-nitroimidazole derivatives (e.g., metronidazole-tinidazole, ornidazole-secnidazole) and between structurally related imidazole compounds (28-30). Furthermore, potential cross-reactivity between metronidazole and other agents such as ke-

toconazole, fluconazole, bifonazole, tioconazole, albendazole, and esomeprazole has been described (31-34). In our study, four patients with concomitant exposure to multiple drugs—including two involving ornidazole and one involving tinidazole—underwent alternative drug testing with metronidazole (n=2) and ornidazole (n=1), all results were negative. These findings suggest that alternative nitroimidazoles may be safely tolerated in patients with suspected hypersensitivity when cross-reactivity is uncertain, provided that testing is conducted under controlled clinical conditions (9). Nonetheless, published reports have indicated that in patients with confirmed metronidazole allergy and no viable therapeutic alternatives—particularly in the treatment of *Trichomonas vaginalis* infections—metronidazole desensitization can be considered a safe and effective clinical option (29).

Patients with suspected drug allergy often experience uncertainty regarding their diagnosis, therapeutic options, and future risk of reactions, while clinicians in real-world allergy practice face additional challenges in identifying the suspected drug due to multiple concomitant medication exposures, alternative clinical explanations, and incomplete medical histories (35). Among patients undergoing nitroimidazole testing for clinical indications, 13.3% could not accurately recall the drug associated with the reaction. Most patients (91.3%) were taking multiple concomitant medications beyond their routine treatments. Additionally, 13% had chronic urticaria and 3.3% had suspected mast cell activation syndrome—conditions that can mimic or confound the clinical presentation of drug allergy. Nearly all patients also had concurrent infectious diseases, further complicating causal interpretation. Collectively, these factors highlight the challenges in assigning causality in hypersensitivity evaluations under real-world conditions. Pharmacovigilance-based causality assessment tools—particularly the WHO-UMC system and the Naranjo algorithm—may provide a structured preliminary framework for evaluating suspected drug-related hypersensitivity reactions. However, among patients evaluated for suspected drug hypersensitivity and undergoing allergy testing, 69.9% of reactions were categorized as "unclassified" by the WHO-UMC system and 65.2% as "possible" by the Naranjo algorithm, with no cases rated as "certain" or "definite." Among the 23 patients evaluated for suspected nitroimidazole hypersensitivity, diagnostic testing confirmed true drug allergy in three cases, while the suspected agent was excluded in thirteen. Four patients were lost to follow-up and therefore untested, and four were ultimately classified as unlikely—three due to identification of an alternative suspected drug and one because of a nocebo reaction. These findings indicate that while such systems contribute to standardized documentation and interpretation, they are insufficient as standalone diagnostic methods. In clinical allergy practice, confirmatory testing—particularly SPT/IDT and DPT—remains the decisive step, enabling the accurate identification or exclusion of true HSRs that cannot be resolved through retrospective causality scoring alone.

The principal strength of this study is that it reflects the realities of clinical allergy practice by integrating patient histories, causality assessment tools, and confirmatory testing, thereby bridging the gap between guidelines and real-world practice. In this context, the "gap" refers to the discrepancy between guideline-based diagnostic pathways—which generally assume clearly defined culprit drugs, isolated medication exposure, and access to standardized testing—and the complexities of real-life clinical scenarios, where patients often present with multiple concomitant medications, overlapping infectious symptoms, incomplete or unreliable histories, and comorbid conditions such as chronic urticaria or mast-cell-related disorders. Nevertheless, diagnostic challenges—such as incomplete or confounded patient histories, limited sensitivity of available tests, and the absence of standardized in vitro assays—remain significant, leaving provocation testing as the only definitive but risk-bearing method. Along with the retrospective design, small sample size, and single-center setting that may introduce referral bias, these limitations restrict generalizability but also emphasize the practical difficulties in diagnosing nitroimidazole hypersensitivity.

In conclusion, nitroimidazole hypersensitivity remains an uncommon but clinically important condition, particularly given the widespread use of these agents. Our findings demonstrate that the majority of patients with a history suggestive of nitroimidazole hypersensitivity were not confirmed to have true allergy when systematically evaluated. This highlights the importance of structured diagnostic algorithms—particularly the integration of skin testing and drug provocation testing—to accurately distinguish true hypersensitivity from non-allergic or uncertain reactions. While pharmacovigilance-based causality tools provide supportive frameworks, confirmatory testing remains essential for ensuring safe antimicrobial steward-

ship and preventing unnecessary drug avoidance. Future prospective studies with larger cohorts and standardized in vitro diagnostics are needed to refine current strategies and improve patient care.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Supplementary Table I: Baseline Laboratory Findings

Characteristics		Normal ranges	Group 1 n=30	Group 2 n=23
Triptaz (µg/L), Median (IQR, min-max)	n=11 (36.7%)	<11.4	5.4 (4.2-6.9, 3.8-23.0)	5.79 (5.40-7.51, 3.83-23.0)
Total IgE (IU/mL), Median (IQR, min-max)	n= 20 (66.7%)	<100	76.7 (25.2-301.3, 0.8-1318)	70.1 (22.5-189.0, 0.8-1318.0)
ALT (U/L) Mean ± SD	n=23 (76.7%)	0-41	16.3 ± 7.5	16.6 ± 7.9
Creatinine Median (mg/dL) (IQR, min-max)	n=23 (76.7%)	0.6-1.2	0.68 (0.65-0.73, 0.52-0.90)	0.68 (0.64-0.73, 0.52-0.90)
WBC $\times 10^3/\mu L$ Median (IQR, min-max)	n= 24 (80%)	4.0-10.0	7.7 (6.8-10.0, 3.9-19.0)	7.82 (6.81-10.91, 3.91-19.02)
Neutrophil $\times 10^3/\mu L$ Median (IQR, min-max)	n= 24 (80%)	2.0-7.0	4.5 (3.9-6.3, 1.8-14.8)	4.56 (3.97-6.28, 1.77-14.78)
Lymphocyte$\times 10^3/\mu L$ Mean ± SD	n= 24 (80%)	1.0-3.0	2.46 ± 0.72	2.41 ± 0.70
Monocyte $\times 10^3/\mu L$ Median (IQR, min-max)	n= 24 (80%)	0.2-1.0	0.59 $\times 10^3/\mu L$ (0.53-0.76, 0.40-1.28)	0.58 (0.46-0.76, 0.40-1.28)
Eosinophil $\times 10^3/\mu L$ Median (IQR, min-max)	n= 24 (80%)	0.0-0.5	0.18 (0.11-0.31, 0.00-0.79)	0.16 (0.09-0.24, 0.00-0.79)
Basophil $\times 10^3/\mu L$ Mean ± SD	n= 24 (80%)	0.0-0.2	0.041 ± 0.022	0.043 ± 0.020
Hemoglobin g/dL Median (IQR, min-max)	n= 24 (80%)	12-16	13.25 (12.60-14.45, 10.90-15.60)	13.3 (12.7-14.35, 1.5-15.6)
Platelet $\times 10^3/\mu L$ Mean ± SD	n= 24 (80%)	150-450	296.8 ± 98.1	298.9 ± 91.9

ALT: Alanine aminotransferase, **IgE:** Immunoglobulin E, **NSAIDs:** Nonsteroidal anti-inflammatory drugs, **WBC:** White blood cell count.