Diagnosis approach to hypersensitivity reactions in Helicobacter pylori eradication

Abordagem diagnóstica das reações de hipersensibilidade na erradicação do Helicobacter pylori

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ABSTRACT

Background: Helicobacter pylori (HP) infection is treated with a combination of antibiotics and antisecretory agents. Hypersensitivity reactions (HSR) limit therapeutic options. This study characterizes the diagnostic approach of HSR to HP eradication therapy. **Methods:** Retrospective analysis (1/2011–6/2024) of patients with suspected HSR to HP eradication therapy (proton pump inhibitors (PPI) + amoxicillin + clarithromycin or PPI + amoxicillin + clarithromycin + metronidazole). Diagnosis was considered: 1) confirmed by a suggestive clinical history (CH) and positive specific IgE to β-lactams (βL sIgE) or positive skin tests [skin prick tests (SPT), intradermal tests (IDT), epicutaneous tests], or based on a positive drug provocation test (DPT); 2) probable based on suggestive CH and positive lymphocyte transformation test (LTT); or 3) excluded by negative DPT or non-suggestive CH. **Results:** Of 42 patients [88% female, mean (range) age 55 years old (22-85)], 10 had immediate HSR: five had anaphylaxis, five had urticarial rash. Amoxicillin HSR diagnosis was confirmed in seven of these patients (two based on βL sIgE, two on βL sIgE /SPTs, one on SPT, two on IDTs) and excluded by DPT in three. HSRs to clarithromycin, metronidazole, and PPIs were excluded

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in all patients. Non-immediate HSRs were reported in 32 patients. Amoxicillin HSRs diagnosis was confirmed in five of these patients based on DPT and considered probable in one (based on LTT). Clarithromycin HSR was confirmed in two patients by DPT, and PPI (omeprazole) HSR in one patient by DPT. **Conclusion:** Clinical history alone overestimates HSR. Amoxicillin was the most frequent etiology of immediate and non-immediate HSRs. Immediate HSRs were diagnosed using sIgE and skin tests, while non-immediate HSRs relied on DPT. In both groups, DPT was necessary to exclude hypersensitivity.

Key-words: Drug provocation test; eradication therapy; helicobacter pylori; hypersensitivity reactions; skin test.

RESUMO

Contexto: *A infeção por* Helicobacter pylori (HP) *é tratada com antibióticos e agentes anti secretores usados de forma concomitante. As reações de hipersensibilidade (RHS) limitam as opções terapêuticas. Este estudo caracteriza a abordagem diagnóstica das RHS à terapêutica de erradicação do HP.* ***Métodos:*** *Análise retrospetiva (1/2011–6/2024) de doentes com suspeita de RHS à terapêutica de erradicação do HP [inibidores da bomba de protões (IBP) + amoxicilina + claritromicina ou IBP + amoxicilina + claritromicina + metronidazol]. O diagnóstico foi considerado: 1) confirmado por história clínica (HC) sugestiva e IgE específica para β-lactâmicos (βL sIgE) positiva ou testes cutâneos [testes cutâneos por picada (TCP), testes intradérmicos (IDT), testes epicutâneos] positivos ou com base numa prova de provocação (PP) positiva; 2) provável com base em HC sugestiva e teste de transformação linfocitária (TTL) positivo; ou 3) excluído por PP negativa ou HC não sugestiva.* ***Resultados:*** *Dos 42 doentes [88% mulheres, média (âmbito) de idade 55 anos (22-85)], 10 apresentaram RHS imediatas: cinco anafilaxias, cinco erupções cutâneas urticariformes. O diagnóstico de RHS à amoxicilina foi confirmado em sete destes doentes (dois com base na βL sIgE, dois em βL sIgE/TCP, um em TCP, dois em IDT) e excluído por PP em três. RHS à claritromicina, metronidazol e IBP foram excluídas em todos os doentes. Foram reportadas RHS não imediatas em 32 doentes. O diagnóstico de RHS à amoxicilina foi confirmado em cinco doentes por PP e considerado provável em um (com base no TTL). O diagnóstico de RHS à claritromicina confirmou-se em dois doentes por PP e ao IBP (omeprazol) em um doente por PP.* ***Conclusão:*** *A história clínica isolada sobrestima as RHS. A amoxicilina foi a causa mais frequente de RHS imediatas e não imediatas. O diagnóstico de RHS imediata baseou-se nos resultados da sIgE e nos testes cutâneos, enquanto as RHS não imediatas dependeram da PP. Em ambos os grupos, a PP foi fundamental para excluir hipersensibilidade.*

Palavras-chave: *Prova de provocação com fármacos; terapêutica de erradicação;* helicobacter pylori*; reações de hipersensibilidade; testes cutâneos.*

INTRODUCTION

Helicobacter pylori (HP) infection is associated with various gastroduodenal diseases such as peptic ulcer, functional dyspepsia, MALT lymphoma, and distal gastric cancer. As a result, it remains one of the leading causes of morbidity and mortality worldwide, making its treatment crucial (1,2,3).

In the Portuguese clinical guidelines, the first-line treatment involves a triple therapy regimen with a proton pump inhibitor (PPI) in a standard dose twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily. For patients with a history of penicillin allergy, amoxicillin is replaced by 500 mg metronidazole twice daily in combination (3,4). Non-bismuth quadruple concomitant therapy (PPI standard dose twice daily, amoxicillin 1000 mg twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily) has superior outcomes when compared to triple therapy, with >90% successful eradication rates in all regions of Europe (5).

A drug hypersensitivity reaction (HSR) label represents a public health problem. It also has a significant financial burden for affected individuals and health systems, as the main consequence is the interruption of first-line treatment and the switch to second-line alternatives, which may be less effective, more toxic, and costlier, usually affecting quality of life (6). The rate of documented drug allergy is higher among women, individuals of european ancestry, adults, and hospitalized patients (7).

Diagnosing a drug HSR involves a combination of clinical history (CH), skin testing (ST), and, in some cases, *in vitro* testing such as serum-specific immunoglobulin E (sIgE) assays, basophil activation tests, or lymphocyte transformation test (LTT). The sensitivity of LTT for detecting delayed drug HSR has been reported to range from 27% to 74%, while its specificity has been estimated between 85% and 100% (8). Although LTT cannot establish a definitive diagnosis of drug allergy on its own, it may support the diagnosis in selected cases, particularly in severe non-immediate HSR, when interpreted in conjunction with clinical history (8). Drug provocation test (DPT) is the gold-standard method to confirm or exclude hypersensitivity.

Amoxicillin is a widely used β-lactam antibiotic that belongs to the penicillin class. In developed countries, it is estimated that 5% to 15% of patients report penicillin allergy, making it one of the most frequent drug allergy labels (9). Although many patients carry a penicillin allergy label, more than 95% can tolerate it after an appropriate evaluation. The penicillin ST is a validated and safe method used in the assessment of suspected IgE-mediated allergy, with a high negative predictive value (NPV) (>95%), making it more reliable than in vitro tests (10). Although sIgE for beta-lactams (βL sIgE) are available, they have poor positive and negative predictive values (11). Intradermal (IDT) and patch tests (PT) are reliable tools for diagnosing non-immediate hypersensitivity reactions (NI-HSR) to aminopenicillins with high sensitivity (10).

Macrolides, which are structurally characterized by their lactonic cycle structure, are effective antibiotics against gram-positive and gram-negative bacteria. Clarithromycin is preferentially used in the eradication therapy of HP infection (12).

HSRs associated with macrolides occur less frequently than those associated with β-lactams, sulfonamides, and fluoroquinolones. Approximately 1% of patients receiving macrolide treatment experience mild, delayed skin eruptions (13). IgE-mediated reactions are very rare, and anaphylaxis is uncommon (13). The effectiveness of ST with non-irritating concentrations of macrolides remains uncertain (13). Consequently, patients with a history of non-severe reactions to macrolides may be considered for a direct challenge (13).

Metronidazole is a nitroimidazole with structural similarities to tinidazole, clotrimazole, ketoconazole, miconazole, and albendazole. Metronidazole is one of the main drugs for treating anaerobic infections; it can also be used for protozoal infections and gastrointestinal in-

fections. HSRs to metronidazole are rare, with only a few case reports in the literature (14). However, a variety of different reaction types, both immediate (I-HSR) and NI-HSRs, have been reported (15,16). A potential for cross-reactivity exists between metronidazole and other imidazoles (16).

PPIs are usually well-tolerated, leading to overprescription and consumption, with a risk of side effects of approximately 1%–3% (17). Their widespread use has been associated with I-HSRs and NI-HSRs, some of which might be life-threatening. STs are useful in diagnosing I-HSRs to PPIs, with a high specificity and a positive predictive value; however, their sensitivity is low (17). There is a substantial cross-reactivity between PPIs, which can be assessed first by ST and subsequently by DPT in I-HSR (17). Data regarding PPI NI-HSRs are limited. In non-severe delayed HSRs, DPT is recommended in cases of a doubtful history and negative ST to exclude PPI hypersensitivity (17).

The clinical manifestations of I-HSR or NI-HSR that develop during HP eradication therapy may considerably impact the future prescription of antibiotics and PPI. Consequently, allergological work-up is crucial to ensure an accurate diagnosis and avoid mistakenly labeling patients with a drug allergy to multiple medication classes.

The aim of this retrospective analysis was to characterize the diagnostic allergological approach and the main culprits of suspected HSR to HP eradication therapy.

METHODS

Study design

The authors performed a retrospective, observational, descriptive, and inferential review of patients with a history of HSRs to HP eradication therapy.

Patients and data collection

From 01/2011 to 06/2024, all patients older than 18 years evaluated in our drug allergy outpatient clinic with a suspected HSR to HP eradication therapy (therapy A: PPI + amoxicillin + clarithromycin, or therapy B: PPI + amoxicillin + clarithromycin + metronidazole) were included. Suspected HSR were classified based on chronology as immediate (<1 hour after drug exposure) or NI-HSR (>6 hours) (13). Diagnosis was classified as: 1) confirmed, based on a suggestive CH and positive βL sIgE (penicilloyl G, penicillolyl V, amoxicillin or ampicillin) or positive ST [skin prick tests (SPT), IDT, PT] or based on a positive DPT/Prolonged DPT; 2) probable, based on suggestive CH and positive LTT; and 3) excluded, based on a negative DPT or CH (well-known non-allergic adverse drug effects or subsequent tolerance to a drug involved in the reaction) (8,13). Prolonged DPT was performed in non-immediate reactions (after a minimum washout period of 48 h, for 2 to 4 days at the daily therapeutic dose) (18). Skin tests, βL sIgE, LTT, and DPT were performed at least 4 weeks after the symptoms of the index reaction had subsided (19). The concentrations and dilutions used in the skin tests are described in Table 1.

Table 1. Concentrations/dilutions used in skin tests (11,14,17,20,21)

Drugs	SPT	IDTs	PT
Amoxicillin	20 mg/mL (1/1)	1/10; 1/1	5-10% pet.
Clarithromycin	10 - 50 mg/ml (1/1)	1/100	0,1- 1%; 10% pet.
Metronidazole	–	5 mg/mL	1% pet.
PPI	–	4 mg/ml	1-10% pet.

IDT – intradermal test; pet. – petrolatum; PPI – proton pump inhibitors; PT – patch test; SPT – skin prick test.

Ethics

This study was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki of 1946. All participants provided written informed consent prior to allergological evaluation.

Data analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 28®. Descriptive statistics were used to characterize the sample. Categorical variables were described as absolute and relative frequencies. For variables with normal distribution, we present the mean (standard deviation), and for variables without normal distribution, the median (minimum-maximum).

RESULTS

A total of 42 patients (37 female and 5 male) with suspected HSRs to HP eradication therapy were included in the analysis. All patients were referred by healthcare professionals, i.e., general practitioners, consultants, or allergists.

The mean age of the subjects at the time of the first appointment in our Drug Allergy outpatient clinic was 55 years (ranging from 22 to 85 years). A history of atopy was confirmed in 10 (24%) patients: rhinitis in seven patients and asthma in five (50%).

In most cases (79%, n=33), therapy A was used, while therapy B was administered to nine patients (21%).

Clinical data, including latency of the reaction (i.e., time interval between start of treatment and onset of symptoms), are summarized in Table 2. Depending on the latency between therapy administration and clinical symptoms, we classified the reactions as immediate in 10 (24%) patients and as non-immediate in 32 (76%) patients.

The suspected PPI included omeprazole in 18 patients (three I-HSR; 15 NI-HSR), pantoprazole in 12 (three I-HSRs; nine NI-HSRs), esomeprazole in nine (two I-HSRs; seven NI-HSRs), lansoprazole in two (one I-HSRs; one NI-HSR), and rabeprazole in one patient (one NI-HSR).

Immediate reactions

In 24% of cases (n=10), IHRs were observed, seven (70%) with therapy A and three (30%) with therapy B.

The clinical manifestations were classified as anaphylaxis in five (50%) patients.The remaining patients (n=5,50%) presented with urticaria and/or angioedema.

HSRs to clarithromycin could be excluded in two (20%) patients, and to PPI in eight (80%), only by anamnesis. HSR to metronidazole was excluded by anamnesis in one patient (33% of those using therapy B).

Suspected drugs were amoxicillin in 10 (100%) patients, clarithromycin in eight (80%), metronidazole in two (20%), and PPI in two (20%).

Table 2. Clinical data of the 42 patients studied.

	Mean (range)	
Age, years	55	(22-85)
	n	**(%)**
Sex		
Female	37	(88%)
Therapy*		
A	33	(79%)
B	9	(21%)
Timing of onset		
Immediate reaction	10	(24%)
A	7	(70%)
B	3	(30%)
No immediate reaction	32	(76%)
A	26	(81%)
B	6	(19%)
After 1-3 days	13	(41%)
After 4-6 days	6	(19%)
After 7-9 days	10	(31%)
After 10-12 days	3	(9%)

* Therapy A: proton pump inhibitors + amoxicillin + clarithromycin; Therapy B: proton pump inhibitors + amoxicillin + clarithromycin + metronidazole

Table 3. Allergy work-up of immediate hypersensitivity reactions

Amoxicillin n=10	**βL sIgE** n=9	**SPT (20 mg/mL)** n=6	**IDT (1/10-1/1)** n=3	**DPT** n=3
Positive (+)	4	3	2	0
Negative (-)	5	3	1	3
Clarithromycin n=8		**SPT (10-50 mg/mL)** n=5	**IDT (1/100)** n=5	**DPT** n=8
Positive (+)		0	0	0
Negative (-)		5	5	8
Metronidazole n=2				**DPT** n=2
Positive (+)				0
Negative (-)				2
PPI n=2				**DPT** n=2
Positive (+)				0
Negative (-)				2

DPT – drug provocation test; IDT – intradermal test; LTT – lymphocyte transformation test; PPI – proton pump inhibitors; PT – patch test, SPT – skin prick test.

The results of the diagnostic approach and allergy study are summarized in Table 3.

Amoxicillin

βL sIgE testing was performed in nine patients and was positive in four (44%). STs with amoxicillin were performed in six patients: six SPTs [amoxicillin 20 mg/mL (1/1)] and three IDTs (dilutions 1/10 - 1/1) were performed, being positive in three (17%) and two (67%) patients, respectively. DPT was performed in three patients, and all were negative.

Clarithromycin

STs were performed with clarithromycin in five patients, with SPTs [clarithromycin 10 - 50 mg/ml (1/1)] and IDTs (1/100) being negative in all patients. DPTs were performed in eight patients, and all were negative.

Metronidazole

The two patients with suggestive CH underwent DPTs, and both were negative.

PPI

The two patients with suggestive CH underwent DPTs (omeprazole and esomeprazole), which were negative in both patients.

Non-immediate reactions

NI-HSRs were reported in 32 (76%) patients: therapy A was administered in 26 (81%) patients, and therapy B in six (19%) patients. Most of these patients presented maculopapular exanthema (n=15, 47%), followed in frequency by late urticaria (n=9, 28%), angioedema (n=5, 16%), and other nonspecific symptoms (n=3, 9%).

Amoxicillin allergy was excluded in 2 (6%) patients, clarithromycin in 6 (19%), PPI in 22 (69%), and metroni-

dazole in 2 (33% of those treated with therapy B), solely by anamnesis.

The suspected drugs were amoxicillin in 30 (94%) patients, clarithromycin in 26 (81%), metronidazole in four (13%), and PPI in 10 (31%).

The results of the diagnostic approach and allergy study of NI-HSRs are summarized in Table 4.

Amoxicillin

STs with amoxicillin 20mg/ml (1/1), with delayed readings at 48 hours, were conducted in 15 patients, including 10 IDTs (1/10-1/1) and 15 PTs [5-10% petrolatum (pet.)]. None of these tests yielded positive results. LTTs were performed in two patients with skin reactions lasting > 7 days, affecting > 50% of the body surface and requiring systemic corticosteroids, returning a positive result in one (50%). Additionally, DPTs were performed with amoxicillin in 29 patients, and were positive in 5 (17%).

In our sample with NI-HSRs, the calculated NPV for the IDT with amoxicillin was 73% and for the PT with amoxicillin was 67%.

Clarithromycin

Eleven patients underwent STs with clarithromycin 10-50 mg/ml (1/1), with delayed readings at 48 hours, including seven IDTs (1/100) and 11 PTs (0,1-1% and 10% pet.), and all were negative. DPTs were carried out in 26 (100%) patients, and two (8%) of them had positive reactions.

Metronidazole

One patient underwent STs, which included IDTs with metronidazole at 5 mg/mL and PTs with metronidazole

Table 4. Allergy work-up of non-immediate hypersensitivity reactions

Amoxicillin n=30	**IDT (1/10-1/1) n=10**	**PT (5-10% pet.) n=15**	**LTT n=2**	**DPT n=29**
Positive (+)	0	0	1	5†
Negative (-)	10	15	1	24
Clarithromycin n=26	**IDT (1/100) n=7**	**PT (0,1-1% and 10% pet.) n=11**		**DPT n=26**
Positive (+)	0	0		2‡
Negative (-)	7	11		24
Metronidazole n=4	**IDT (5mg/mL) n=1**	**PT (1% pet.) n=1**		**DPT n=4**
Positive (+)	0	0		0
Negative (-)	1	1		4
PPI n=10	**IDT (4mg/mL) n=4**	**PT (1-10% pet.) n=4**		**DPT n=10**
Positive (+)	0	0		1
Negative (-)	4	4		9

† Three of these 5 DPTs were positive in subsequent administrations (prolonged DPT)
‡ These 2 DPTs were positive in subsequent administrations (prolonged DPT)
DPT – drug provocation test; IDT – intradermal test; LTT – lymphocyte transformation test; pet. – petrolatum; PPI – Proton pump inhibitors; PT – patch test.

at 1% pet.; both tests were negative. DPT was performed in four patients, and all were negative.

PPI

STs (with delayed readings at 48 hours) were conducted in four patients, including IDTs with PPI at 4 mg/mL and PT with PPI at 1-10% pet.; all results were negative. Ten patients underwent DPT with PPI, and one patient (10%) tested positive for omeprazole.

Out of all the patients referred to our department with suspected HSRs to HP eradication therapies, 15 (36%) were confirmed (seven I-HSRs, eight NI-HSRs), and one was classified as probable (NI-HSR). This data is depicted in Table 5. In this study, HSRs to amoxicillin were confirmed in 12 (29%) patients (seven I-HSRs, five NI-HSRs), to clarithromycin in two (5%) (two NI-HSRs), to PPI in one (2%) (NI-HSR), and none to metronidazole. The presence of atopy was not statistically associated with the positivity of the allergy work-up (p=0,08). However, out of the seven confirmed I-HSR, four (57%) reported atopy (Table 5). On the other hand, out of the nine confirmed NI-HSRs, only one patient presented atopy (Table 5).

The diagnosis of I-HSR was confirmed in all patients who presented a history of anaphylaxis.

Table 5. Patients with a positive allergy work-up to at least one of the tested HP eradication drugs

Patient (gender, age in years)	Allergic comorbidities	Culprit	Reaction timing	Reaction manifestation	Confirmation test
f, 67	No	Amoxicillin	I	Anaphylaxis	IDT
m, 64	No	Amoxicillin	I	Anaphylaxis	SPT
m, 49	No	Amoxicillin	I	Anaphylaxis	βL sIgE
f, 61	R	Amoxicillin	I	Anaphylaxis	βL sIgE / SPT
f, 56	R	Amoxicillin	I	Anaphylaxis	IDT
f, 73	A	Amoxicillin	I	Urticaria	βL sIgE / SPT
f, 32	A + R	Amoxicillin	I	Urticaria/AE	βL sIgE
f, 74	No	Amoxicillin	NI	AE/MPE	DPT
f, 52	No	Amoxicillin	NI	MPE	DPT
f, 54	No	Amoxicillin	NI	MPE	DPT
f, 29	No	Omeprazole	NI	MPE	DPT
f, 52	No	Amoxicillin	NI	Urticaria/AE	DPT
f, 47	No	Amoxicillin †	NI	Urticaria/AE	LTT
f, 66	No	Amoxicillin	NI	Urticaria	DPT
f, 26	No	Clarithromycin	NI	Urticaria/AE	DPT
f, 54	A	Clarithromycin	NI	Urticaria/AE	DPT

† Probable, positive LTT
AE – angioedema; A – asthma; βL sIgE – beta-lactam specific IgE; I – immediate; IDT – intradermic test; MPE – maculopapular exanthema; NI – non immediate; DPT – drug provocation test; LTT – lymphocyte transformation test; SPT – skin prick test; R – rhinitis; f – female; m – male

DISCUSSION AND CONCLUSIONS

Eradication of HP is the first-line treatment of HP-infected patients as it can reduce dyspeptic symptoms, minimize the risk of serious complications of the infection, and reduce gastric cancer risk (1). This type of treatment is generally well tolerated; however, HSR can occur (1,3). In our study, women were the predominant reporters of adverse reactions to HP eradication therapies, consistent with findings from previous studies (7). We noticed that anamnesis alone leads to an overestimation of HSR. After the complete allergic work-up, true HSRs were confirmed in only 36% (n=15) of the patients.

In our sample, the most common clinical manifestation was generalized maculopapular rash (n=15; 36% of the total), similar to that described in previous studies (13,22,23). The major causes of skin eruptions during antibiotic therapy are infections, in particular viral exanthemas (22,23). It is often difficult to identify the etiology of skin lesions, with an overestimation of HSR to drugs. Cutaneous eruptions associated with HP eradication therapy can be caused by HP itself, especially eruptions that occur three or more days after completion of HP eradication therapy (22). On the other hand, the most common clinical features of a cutaneous adverse drug reaction are generalized and progressively confluent macular and papular lesions (6,13,22,23).

Regarding the latency of the reaction, in this study, NI-HSRs were the most frequent, such as maculopapular exanthema, and late urticaria or angioedema, which is in accordance with the literature (13). Phenotypically, I-HSR may present with urticaria, angioedema, bronchospasm, or, in severe cases, anaphylaxis. In this study, the most frequent manifestations of I-HSRs were urticaria/angioedema and anaphylaxis (13, 24).

In I-HSR, the diagnosis of drug hypersensitivity was confirmed in seven patients, with the culprit drug being amoxicillin. The diagnosis was established by sIgE and STs [two based on βL sIgE, two on βL sIgE/SPT, three on ST (SPT (n=1); IDT (n=2)]. All DPTs performed in I-HSRs were negative, supporting STs and laboratory test results.

In NI-HSRs, the diagnosis of drug hypersensitivity was established by DPT in eight patients (amoxicillin (n=5), clarithromycin (n=2), PPI (omeprazole, n=1)). Besides, diagnosis of amoxicillin hypersensitivity was considered probable in one additional patient, based on suggestive anamnesis together with positive LTT.

In both groups, I-HSRs and NI-HSRs, DPT was the gold standard to exclude drug hypersensitivity diagnosis (n=76).

This study confirmed that amoxicillin represents the main causative agent of HSR, as previously described (7,9). Regarding I-HSRs, amoxicillin was responsible for all HSRs. The most frequent clinical manifestation was anaphylaxis (in five patients), followed by urticaria/angioedema (in two patients). sIgE and STs have been successfully applied in the assessment of IgE-mediated reactions to penicillin, avoiding DPT, which carries an additional risk for the patient. In NI-HSRs, IDT and PT are reliable tools for the diagnosis of delayed drug hypersensitivity with a high sensitivity, particularly for aminopenicillins (10,20). In a study by *Iuliano et al*., which included 576 patients (260 with a history of I-HSR, 131 NI-HSR, and 114 unknown reaction mechanism), the authors reported that STs for penicillin antibiotics have a NPV of 96.3% and 91.9% for I-HSRs and NI-HSRs, respectively (25). The sensitivity of ST for penicillins was 90.7% for I-HSR and 84.2% for NI-HSR (25). A recent meta-analysis reported a summary sensitivity of 26.2% (18.7%–35.3%) for sIgE in patients with I-HSR to penicillin / β-lactam antibiotics (26).

Allergic reactions associated with macrolides are rare, and anaphylaxis is exceedingly uncommon. In a previously published study, a sub-analysis of twenty-eight patients with suspected HSRs to HP treatment identified only one patient with clarithromycin allergy (12). Our data showed two patients with a confirmed NI-HSRs to clarithromycin, presenting with urticaria/angioedema skin lesions as a clinical manifestation.

No confirmed cases of hypersensitivity to metronidazole were found in this study, in accordance with the

literature, where HSRs to metronidazole are rarely reported (15,16).

The rate of positive reactions to PPIs was low, with only one patient having a confirmed reaction to omeprazole with maculopapular exanthema as a clinical manifestation. Other studies suggest that, although rare, allergic reactions to PPIs can occur and are often underdiagnosed due to a lack of specific tests (16). The PPIs involved in the HSRs vary among countries: lansoprazole in studies from Turkey, esomeprazole and lansoprazole in Italy, and omeprazole in Spain, probably reflecting the prescription profile (17,27,28).

The diagnostic investigation to diagnose I-HSR or NI-HSR includes *in vivo, in vitro,* and DPT tests. Considering that *in vitro* and ST lack 100% negative predictive value, DPT is the gold standard for diagnosis (18).

This study has some limitations: firstly, the small number of patients and selection bias, as only patients evaluated in a drug allergy outpatient clinic were included; secondly, the lack of validated *in vivo* and *in vitro* tests to diagnose allergies to clarithromycin, metronidazole, and PPI.

To conclude, an allergic work-up is crucial for patients with suspected HSR to HP eradication therapy. A multi-drug HSR study protocol allows patients to benefit from better clinical guidance, resulting in an accurate diagnosis of confirmed or excluded hypersensitivity to each drug involved in the reaction. The importance of accurate diagnosis is reinforced to avoid unnecessary restrictions on essential drugs and to avoid patient mislabeling. Future studies should include larger samples and involve multiple centers, providing more robust evidence on this issue.

Conflict of interest

The authors have no conflicts of interest to declare.

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