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Review

Evaluation and management of hypersensitivity to proton pump inhibitors: comprehensive literature review

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ABSTRACT

Objective: Proton pump inhibitors (PPIs) are widely used for the treatment of gastroesophageal reflux disease and peptic ulcer disease. PPIs are well tolerated, but they can cause hypersensitivity reactions (HSRs). Although simply avoiding a PPI after an HSR is appropriate for most patients, there are clinical scenarios that require treatment with a PPI.

Data Sources: A comprehensive literature review was performed to propose an evidence-based approach to the evaluation and management of HSRs to PPIs.

Study Selection: Articles from June 1986 through September 2012 on PPI hypersensitivity were reviewed. Thirty-nine studies that met the search criteria were included in the review. HSRs to PPIs and skin testing protocols used to evaluate HSRs were analyzed from the 39 identified publications. For each case, the culprit drug and dose, the age and sex of the patient, and the symptoms and timing of the HSR were recorded. HSRs were classified into immune- or nonimmune-mediated categories.

Results: A total of 118 cases of immune-mediated HSRs to 5 PPIs were identified, most of which were suspected IgE-mediated HSRs. Omeprazole was the culprit PPI most frequently associated with HSRs. The most common clinical manifestations of PPI HSRs were cutaneous reactions. Nonirritating concentrations for skin prick and intradermal testing were identified. Skin testing showed variable cross-reactivity patterns among the different PPIs.

Conclusion: The HSRs to PPIs should be formally investigated, especially when reasonable alternative therapies do not exist. The reviewers propose an evidence-based algorithm for evaluating and managing patients with an HSR to a PPI.

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Introduction

Proton pump inhibitors (PPIs) represent a family of medications commonly used for the treatment of gastroesophageal reflux disease and peptic ulcer disease. Currently, there are 6 PPIs approved by the Food and Drug Administration available for use in the United States: omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole, and dexlansoprazole. Although PPIs are generally well tolerated, without significant side effect profiles, there are multiple case reports of hypersensitivity reactions (HSRs) to PPIs, ranging from mild to severe reactions, including anaphylaxis.^{1–9} An H₂ receptor blocker can sometimes be used instead of a PPI, but in some instances, such as *Helicobacter pylori* gastritis, treatment with a PPI is essential.⁴ Therefore, although simply avoiding PPIs after an HSR is appropriate for most patients, there are specific patients who require PPI therapy despite an HSR.

Based on an extensive review of the literature, the reviewers propose an evidence-based approach for the evaluation and management of patients with an HSR to PPIs.

Methods

A literature search in PubMed was performed using keywords and combination of keywords with the word *and*, including *proton pump inhibitor*, *PPI*, *hypersensitivity*, *drug allergy*, and *adverse reactions*. Through this search, 42 published articles related to PPI hypersensitivity from June 1986 through September 2012 were identified. These 42 publications included a multicenter case–control study, multiple case series, and several case reports. However, of these studies, only 39 publications were incorporated in this review because the search was limited to English-language publications only, including 1 Spanish-language publication by Garmendia Zallo et al,¹⁰ which had an English abstract.

From these 39 publications, all cases of hypersensitivity to a PPI and all skin testing protocols used to evaluate PPI hypersensitivity were reviewed in detail. For each case, the culprit drug and dose, the age and sex of the patient, and the symptoms, timing, and types

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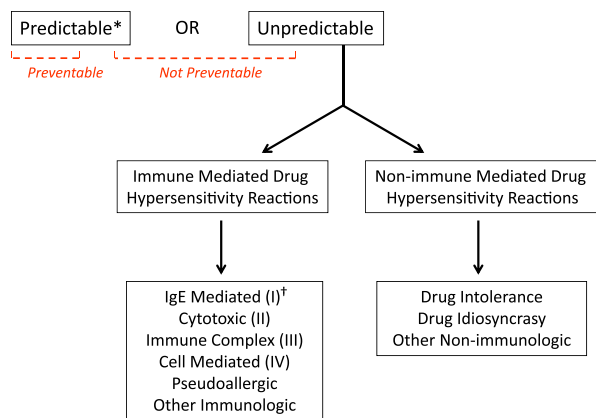


Figure 1. Classification of adverse drug reactions. Listed are all unintended pharmacologic effects of a drug, except therapeutic failures, intentional overdosage, abuse of drug, or errors in administration. *Usually dose dependent and related to the known pharmacologic actions of the drug. †Often referred to as drug hypersensitivity reactions and includes patients with anaphylaxis. From Weiss et al.¹³

of HSRs were recorded. Two studies, by Bonadonna et al¹¹ and Razzak et al,¹² were not incorporated in this subanalysis and categorization of reactions owing to a lack of specific patient demographics. However, data from these 2 studies were used to report cases of HSRs to PPIs.

Hypersensitivity reactions were categorized into a new model, using the drug allergy practice parameters classification system as a guide (Fig 1).¹³ Immune-mediated HSRs were subdivided according to the Gell–Coombs classification into type I, II, III, and IV HSRs.¹³ IgE-mediated reactions were considered type I reactions; cytotoxic reactions were labeled type II reactions; immune-complex-mediated reactions were classified as type III reactions; and cell-mediated or delayed-type reactions were considered type IV reactions. Immune-mediated HSRs also included pseudoallergic reactions and “other immunologic” reactions that did not fit into the Gell–Coombs classification. Pseudoallergic reactions were defined as systemic reactions that mimic anaphylaxis but are triggered by non-IgE-mediated release of cellular components from mast cells and basophils.¹³ “Other immunologic” reactions comprised hypersensitivity vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS), and blistering disorders, including Stevens-Johnson syndrome or toxic epidermal necrolysis.¹³ Nonimmune-mediated HSRs were subdivided into reactions owing to drug intolerance, drug idiosyncrasy, or other non-immunologic phenomenon. All PPI HSRs were independently reviewed and categorized by 2 allergy and immunology physicians, and no discrepancies were found.

Results

Patient Characteristics

This comprehensive literature review identified 118 cases of immune-mediated HSRs to 5 different PPIs (Table 1).^{1–12,14–39} Almost all cases of reported PPI HSRs were described in adults with a mean age of 46 ± 13 years. One case report described anaphylaxis secondary to omeprazole in a 14-year-old boy.¹⁴ Most HSRs to PPIs occurred in female patients (61%).

Clinical Symptoms and Types of PPI HSRs

Omeprazole was identified as the most frequent cause of HSRs to PPIs ($n = 54$). The other reported cases were related to lansoprazole ($n = 24$), pantoprazole ($n = 20$), esomeprazole ($n = 17$), and rabeprazole ($n = 3$). There were no reported cases of HSRs to dexlansoprazole. Most cases (86%) were type I IgE-mediated HSRs, and the

other cases were type IV HSRs (9%) or “other immunologic” reactions (5%).^{1–12,14–39} The most frequent clinical manifestations of HSRs were urticaria (54%), generalized itching or pruritus (52%), angioedema (38%), hypotension (23%), skin rash other than urticaria (21%), erythema (20%), and dyspnea or shortness of breath (20%).

Non-IgE-mediated HSRs (14%) to PPIs were reported less frequently than IgE-mediated HSRs (86%).^{1–12,14–39} DRESS syndrome, which is a delayed-type severe hypersensitivity syndrome with life-threatening cutaneous manifestations, was reported with esomeprazole. Patch testing was performed in this case scenario and confirmed a type IV HSR, supporting the diagnosis of DRESS syndrome.¹⁹ Contact dermatitis with lansoprazole was described in a 58-year-old man who worked at a lansoprazole manufacturing pharmaceutical company. Patch testing was positive to lansoprazole, and strict avoidance of lansoprazole led to the resolution of symptoms.²⁵ There also were documented cases of contact dermatitis to omeprazole in an occupational environment.^{20,23} A case describing hypersensitivity vasculitis to omeprazole and a case of pseudoallergic reaction to pantoprazole also were documented.^{22,24}

Skin Testing and Cross-Reactivity

Skin prick testing (SPT) and intradermal testing (IDT) protocols were described, with subtle dosage differences.^{2,4–8,11,15,16} Table 2 summarizes some published skin testing protocols for PPIs. Multiple case reports described potential cross-reactivity among PPIs confirmed by skin test results.^{2,3,5–7,11,15,16,27} Three general patterns of cross-reactivity were found among members of the PPI family:

1. Hypersensitivity to omeprazole showed cross-reactivity with all other PPIs.^{5,16,27}
2. Hypersensitivity to omeprazole showed cross-reactivity with pantoprazole, but not with lansoprazole.^{6,16}
3. Hypersensitivity to lansoprazole showed cross-reactivity with rabeprazole, but not with omeprazole, pantoprazole, and esomeprazole.^{7,15,16}

Desensitization Protocol

Only 1 published case report in the literature described a successful PPI desensitization protocol. A 44-year-old man with a history of duodenal ulcer underwent gastroscopy for recurrent and persistent heartburn. He was found to have *H pylori* gastritis, but treatment with triple therapy had failed twice. Because the patient was still symptomatic, he underwent another trial of triple therapy with 40 mg of omeprazole, amoxicillin, and clarithromycin. Forty minutes after taking the omeprazole dose, the patient developed an anaphylactic reaction with symptoms of sweating, generalized itching, diffuse erythema, angioedema of the face and hands, and hypotension. He recovered after being treated with subcutaneous epinephrine, dexamethasone, and intravenous fluids. This patient's ongoing heartburn prompted a repeat gastroscopy, disclosing persistent *H pylori* gastritis. Despite a severe HSR to omeprazole, the patient had no reasonable alternative therapies for his gastritis and underwent skin testing for omeprazole and pantoprazole.⁴

The patient was found to have positive IDT results to omeprazole (0.04 and 0.4 mg/mL) and pantoprazole (0.02 and 0.2 mg/mL). As a result, inpatient desensitization to omeprazole was performed. Granules from the omeprazole capsule were dissolved in bicarbonate solution to create serial 10-fold dilutions, starting with a concentration of 0.002 mg/mL. The oral desensitization protocol was started at a 0.001-mg dose and each follow-up dose was doubled and administered at 20-minute intervals. The final dose of 16 mg was achieved after 5.6 hours and a cumulative dose of 32.665 mg was administered. After completion of the

Table 1Summary of all reported reactions to proton pump inhibitors and skin testing results^a

Reference	Culprit drug	Classification	Clinical symptoms	Timing of reaction	ST results
Aksu and Kurt ²⁹	Lansoprazole	Type I	Flushing, urticarial plaques, angioedema	2 h	ST–
Bowlby and Dickens ³⁰	Omeprazole	Type I	Mild angioedema, urticaria, pruritus	1–3 h	NA
Caboni et al ¹⁹	Esomeprazole	Other immunologic (DRESS)	Erythematous skin rash, followed by desquamation of skin	20 d	NA
Choi et al ²⁸	Lansoprazole	Type I	Hypotension, facial and neck swelling	Immediately	NA
Choi et al ²⁸	Omeprazole	Type I	Urticaria, periorbital swelling, hypotension	30 min	NA
Conde-Salazar et al ²⁰	Omeprazole ^b	Type IV	Pruritic lesions involving face, neck, hands	6 wk	NA
Conde-Salazar et al ²⁰	Omeprazole ^b	Type IV	Dermatitis involving eyelids, nose, perioral area	6 mo	NA
Confino-Cohen and Goldberg ⁴	Omeprazole	Type I	Angioedema of face and hands, hypotension	40 min	ST+
Demirkan et al ³¹	Lansoprazole	Type I	Flushing, hypotension	20 min	ST+
Elfau et al ¹⁶	Omeprazole	Type I	Urticaria, hypotension, loss of consciousness	5 min	ST+
Elfau et al ¹⁶	Omeprazole	Type I	Urticaria	2 h	ST+
Elfau et al ¹⁶	Omeprazole	Type I	Pruritic erythema, urticaria	45 min	ST+
Elfau et al ¹⁶	Omeprazole	Type I	Erythema, angioedema of hands	30 min	ST+
Elfau et al ¹⁶	Omeprazole	Type I	Pruritic erythema, urticaria, facial angioedema	10 min	ST+
Fardet et al ³²	Pantoprazole	Type I	Urticaria, swollen tongue and eyes, hypotension	Within few minutes	NA
Galindo et al ⁸	Omeprazole	Type I	Itching, dyspnea, hypotension	Within few minutes	ST+
Gamboa et al ¹⁸	Omeprazole	Type I	Pruritus, lip angioedema, disseminated wheals	15 min	ST+
Garmendia Zallo et al ¹⁰	Omeprazole	Type I	Pruritus, urticaria, facial angioedema	1–2 h	ST+
Garrido et al ⁵	Omeprazole	Type I	Itching, diffuse erythema	1 h	ST+
Gonzalez et al ¹	Omeprazole	Type I	Urticaria, facial edema	30 min	ST+
Gratacós et al ³³	Pantoprazole	Type I	Severe hypotension	4 h	NA
Haeney ²⁶	Omeprazole ^c	Type I	Angioedema, urticaria	2 h	NA
Heaton et al ²¹	Lansoprazole	Other immunologic (TEN)	Rash with erythematous plaques involving 60% of total BSA	7 d	NA
Kaatz et al ²²	Pantoprazole	Type I	Flushing, dyspnea, hypertensive reaction	2 h	ST–
Kollmeier et al ³⁴	Pantoprazole	Type I	Urticaria, angioedema, impaired consciousness	3 h	ST+
Lai et al ³⁵	Pantoprazole	Type I	Erythema, hypotension	5 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	45 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	30 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	60 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria	4 h	ST–
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	45 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	60 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria	30 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria, angioedema	30 min	ST+
Lobera et al ⁶	Omeprazole	Type I	Urticaria	30 min	ST+
Meding ²³	Omeprazole ^b	Type IV	Eczema on eyelids	During occupational setting	NA
Meding ²³	Omeprazole ^b	Type IV	Eczema on eyelids, itching	During occupational setting	NA
Natsch et al ⁹	Omeprazole	Type I	Periorbital edema, pruritus	45 min	NA
Natsch et al ⁹	Lansoprazole	Type I	Pruritus, urticaria, facial edema	45 min	NA
Natsch et al ⁹	Pantoprazole	Type I	Pruritus, urticaria, swelling of tongue and eye	Within hours	NA
Odeh et al ²⁴	Omeprazole	Other immunologic (hypersensitivity vasculitis)	Palpable skin rash, pruritus	4 wk	NA
Ottervanger et al ³⁶	Omeprazole	Type I	Urticaria, angioedema, hypotension	Within a few minutes	ST+
Pérez-Ezquerro et al ²	Omeprazole	Type I	Swelling of hands, severe shortness of breath	30 min	ST+
Pérez Pimiento et al ¹⁵	Lansoprazole	Type I	Pruritic erythema, swelling of palms and soles, loss of consciousness	30 min	ST+
Pérez Roldán et al ³⁸	Lansoprazole	Type I	Glottis edema	45 min	NA
Porcel et al ⁷	Lansoprazole	Type I	Cutaneous rash, edema of eyelids	30 min	ST+
Ricciardi et al ³⁷	Pantoprazole	Type I	Itching, urticaria, angioedema of lips	2 h	NA
Ricciardi et al ³⁷	Pantoprazole	Type I	Urticaria, facial edema	45 min	NA
Stefanaki et al ²⁷	Omeprazole	Type I	Itching, facial angioedema, urticaria	15 min	ST+
Tayman et al ¹⁴	Omeprazole	Type I	Itching, diffuse erythema, facial edema	2 h	ST+
Vilaplana and Romaguera ²⁵	Lansoprazole ^b	Type IV	Pruritic papules on face, neck, upper arms	5 d	NA
Vlahos et al ¹⁷	Lansoprazole	Type I	Itching, erythematous rash, facial edema	10 min	ST+
Vovolis et al ³⁹	Rabeprazole	Type I	Itching, angioedema of upper lip	30 min	ST+
Vovolis et al ³	Omeprazole	Type I	Itching, facial angioedema, urticaria	15 min	ST+
Vovolis et al ³	Omeprazole	Type I	Urticaria	1 h	ST+
Vovolis et al ³	Pantoprazole	Type I	Itching, shock, loss of consciousness	5 min	ST+

Abbreviations: BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; NA, not applicable; ST, skin testing; ST–, negative skin test result; ST+, positive skin test result; TEN, toxic epidermal necrolysis.

^aData from Bonadonna et al¹¹ and Razzak et al¹² are not included in this table because of unavailability of patient demographics.

^bPatient did not have oral or intravenous administration of the drug but had contact with the drug in an occupational setting.

^cPatient found to be allergic to capsule shell containing omeprazole granules.

desensitization process, the patient ingested 1 20-mg capsule of omeprazole and tolerated it without any reaction. Thereafter, the patient was started on 20 mg of omeprazole twice daily for treatment purposes. Follow-up skin testing performed 24 hours after the desensitization protocol showed a weaker IDT response to omeprazole and pantoprazole.⁴

Discussion

This comprehensive literature review suggests that immune-mediated HSRs to PPIs are more common than nonimmune-mediated HSRs, although it is likely that several cases of PPI HSRs have not been reported in the literature. Among immune-mediated

Table 2

Skin testing protocols used for evaluation of proton pump inhibitor hypersensitivity

Reference	Esomeprazole (mg/mL)	Lansoprazole (mg/mL)	Omeprazole (mg/mL)	Pantoprazole (mg/mL)	Rabeprazole (mg/mL)
Elfau et al ¹⁶					
Patients, n = 5					
Controls, n = 14					
SPT	40	15	40	40	10
IDT	0.04, 0.4, 4	0.015, 0.15, 1.5	0.04, 0.4, 4	0.04, 0.4, 4	0.01, 0.1, 1
Galindo et al ⁸					
Patients, n = 1					
Controls, n = 6					
SPT	NT	NT	4, 40	NT	NT
IDT	NT	30	4, 20	NT	NT
Garrido et al ⁵					
Patients, n = 1					
Controls, n = 5					
SPT	20	30	40	40	20
IDT	0.02, 0.2, 2	0.03, 0.3, 3	0.04, 0.4, 4	0.04, 0.4, 4	0.02, 0.2, 2
Pérez-Ezquerro et al ²					
Patients, n = 1					
Controls, n = 10					
SPT	NT	15	40	20	20
IDT	NT	0.15, 1.5	NT	0.2, 2	0.2, 2
Pérez Pimiento et al ¹⁵					
Patients, n = 1					
Controls, n = 5					
SPT	NT	30	20	20	20
IDT	NT	NT	0.8, 8	0.8, 8	NT
Porcel et al ⁷					
Patients, n = 1					
Controls, n = 5					
SPT	20	30	40	40	20
IDT	0.02, 0.2, 2, 20	0.03, 0.3	0.04, 0.4, 4, 40	0.04, 0.4, 4, 40	0.02, 0.2, 2
Stefanaki et al ²⁷					
Patients, n = 1					
Controls, n = 5					
SPT	20	30	4, 20	40	10
IDT	NT	NT	0.04, 0.004	NT	NT
Vovolis et al ³⁹					
Patients, n = 1					
Controls, n = 5					
SPT	40	30	20	40	20
IDT	2	NT	4	4	NT

Abbreviations: IDT, intradermal testing; NT, not tested; SPT, skin prick testing.

HSRs to PPIs, suspected IgE-mediated HSRs were the most prevalent. These suspected IgE-mediated HSRs presented most commonly with cutaneous symptoms and likely occurred because of mast cell degranulation. Clinical manifestations of HSRs, such as these cutaneous reactions, were assessed with skin testing protocols. Results from skin tests showed different patterns of cross-reactivity among members of the PPI family. Nonetheless, omeprazole was found to be the most common culprit PPI causing suspected IgE-mediated HSRs. One possible explanation for this trend is that omeprazole was the first PPI introduced in the drug market and remains the most widely used drug in its class.¹⁶ In most instances, PPIs should be avoided, and alternative drug therapy should be used if an HSR to a PPI is identified. However, in rare cases in which no alternative therapy is available and the need for a PPI is documented, desensitization is a reasonable option.

Skin testing is the first step in the evaluation of patients who experience mild to moderate immune-mediated HSRs to PPIs. The reviewers recommend SPT with solutions of nonirritating concentrations of 40 mg/mL of omeprazole (60 negative controls),^{2,5–8,16} 40 mg/mL of esomeprazole (19 negative controls),^{16,39} 30 mg/mL of lansoprazole (25 negative controls),^{5,7,15,27,39} 40 mg/mL of pantoprazole (34 negative controls),^{5,7,16,27,39} and 20 mg/mL of rabeprazole (30 negative controls).^{2,5,7,15,39} If the SPT reaction is negative, IDT should be pursued. IDT can be performed with 1:1,000, 1:100, and 1:10 diluted solutions of these medication concentrations.¹⁶ According to the published protocol,¹¹ SPT and IDT

are read 15 to 20 minutes after testing is initiated, and a positive or negative skin test result is determined.

Cross-reactivity exists among the various PPIs, as indicated by skin testing; however, the patterns of cross-reactivity are variable. Cross-reactivity within the PPI family is likely related to their similar organic structure.^{5–8,11,15,16,28} All PPIs are composed of a benzimidazole ring and a pyridine ring. Omeprazole and pantoprazole have a methoxy chain and a difluoromethoxy chain on their benzimidazole rings, respectively, and their pyridine rings also have different substitutions. Therefore, the basic skeleton of the benzimidazole and pyridine rings likely accounts for the cross-reactivity between omeprazole and pantoprazole. In contrast, lansoprazole and rabeprazole have the basic benzimidazole and pyridine skeleton with no substitutions on the benzimidazole ring. The only difference in the structures of these 2 PPIs is that lansoprazole has a trifluoroethoxy substitution on the pyridine ring and rabeprazole has a methoxypropoxy chain on the pyridine ring.⁶ Overall, lansoprazole and rabeprazole have more similarity in their structures compared with omeprazole and pantoprazole, accounting for their cross-reactivity. This selective hypersensitivity among members of the PPI family may be dictated by the similarity among their side chain groups.⁸ Moreover, dexlansoprazole is the R-enantiomer of lansoprazole.⁴⁰ The reviewers suspect that dexlansoprazole has similar properties to lansoprazole, and people with a hypersensitivity to lansoprazole also may react to dexlansoprazole. However, this is speculation.

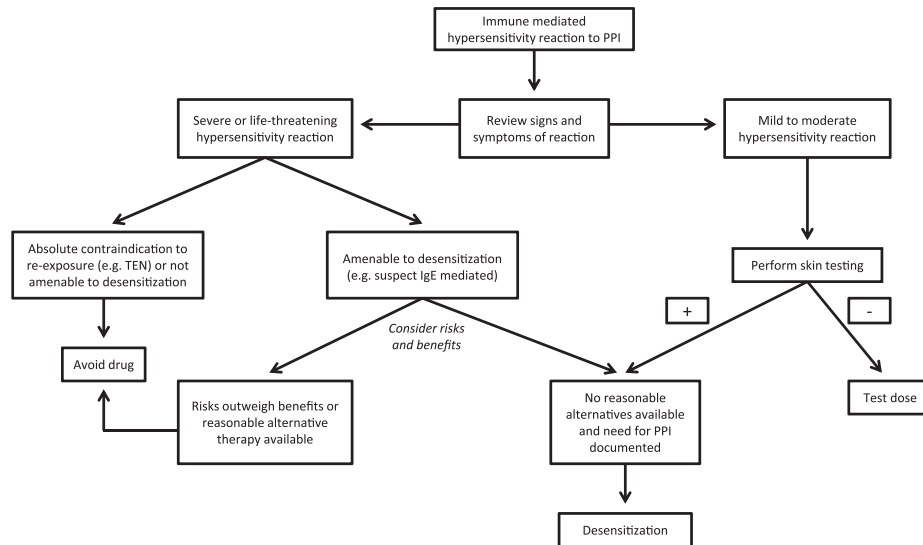


Figure 2. A stepwise approach to management of proton pump inhibitor hypersensitivity.

Owing to the risk of cross-reactivity, an HSR to one member of the PPI family can sometimes lead to avoidance of all members of this medication class in clinical practice. However, this may not be necessary, especially if a PPI is the treatment of choice. In cases in which a PPI is necessary for treatment, desensitization may be a reasonable approach. The only published desensitization protocol, described earlier, if used in a carefully monitored setting, is a safe and acceptable way of inducing tolerance in a patient with a suspected IgE-mediated HSR to a PPI.⁴

The reviewers propose a novel, stepwise approach to the evaluation and management of PPI HSRs. When an immune-mediated HSR to PPI is identified, it should be classified as a mild to moderate or severe reaction. If the reaction is mild to moderate, skin testing should be performed. With a positive skin test reaction and no alternative therapy to a PPI, desensitization should be considered. With a negative skin test reaction, a test dose of the PPI can be administered. Conversely, when a severe or life-threatening reaction is recognized and there is an absolute contraindication to re-exposure to the drug, the PPI should be avoided. However, if a severe HSR occurs and an IgE-mediated reaction is suspected, desensitization may be reasonable (Fig 2).

To the reviewers' knowledge, this study is the largest to date discussing HSRs to PPIs and their eventual management. However, there are some limitations to this study. It is not completely clear whether each identified HSR to a PPI occurred after the first dose or several doses after administration of the culprit drug. This information is presented for some cases, but is not available for all case scenarios. This limitation may have led to overdiagnosis of IgE-mediated HSRs. In addition, there is only 1 published case report of successful desensitization to a PPI. Although the desensitization protocol described in this study was carried out without any complications, further studies are needed to validate the safety and efficacy of desensitization to a PPI.

In conclusion, PPIs are commonly prescribed medications used for the treatment of gastrointestinal diseases. Given the need for PPI therapy in certain clinical situations, avoidance of this class of drugs owing to a history of HSR can be difficult. Although most HSRs to PPIs are mild, there are several documented cases of severe, anaphylactic reactions. Most reported cases of PPI hypersensitivity are IgE-mediated type I HSRs. However, there are also cases of type IV HSRs in individuals exposed to PPIs in an occupational setting, in addition to cases of other immune-mediated drug HSRs, including DRESS and toxic epidermal necrolysis. Therefore, HSRs to a PPI

should be formally investigated. Based on a comprehensive review of the literature on PPI hypersensitivity, the reviewers propose an evidence-based algorithm for evaluating and managing patients presenting with a history of an HSR to a PPI.

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