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Review article

IMMEDIATE AND DELAYED HYPERSENSITIVITY REACTIONS TO PROTON PUMP INHIBITORS: A REVIEW ARTICLE

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Abstract: Proton pump inhibitors (PPIs) are among the most widely prescribed medications in clinical practice, primarily used for managing acid-related gastrointestinal disorders. While generally regarded as safe, with adverse effects being rare and typically mild, PPIs have been associated with hypersensitivity reactions. These reactions, which may be immediate or delayed, vary in severity from mild to potentially life-threatening.

This review provides an in-depth analysis of key aspects of PPI use, with a particular emphasis on the pathophysiological and clinical characteristics of both immediate and delayed hypersensitivity reactions. It also explores cross-reactivity among PPIs and offers a practical framework to assist clinicians in diagnosing and managing these conditions effectively. Additionally, the review highlights the critical need for further research to develop standardized diagnostic and therapeutic protocols, enabling personalized and evidence-based care for patients experiencing PPI-related hypersensitivity.

Keywords: Proton pump inhibitors, hypersensitivity reactions, immediate hypersensitivity, delayed hypersensitivity, prick test, patch test, lymphocyte activation test, cross-reactivity.

INTRODUCTION

Proton pump inhibitors (PPIs) are widely prescribed for managing acid-related gastrointestinal conditions such as gastric and duodenal ulcers, dyspepsia, gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, *Helicobacter pylori* (*H. pylori*) eradication, and the prevention and management of ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs) (1). These drugs suppress gastric acid production by irreversibly inhibiting the H^+/K^+-ATPase enzyme in gastric parietal cells (2). Although generally considered safe and effective, PPIs have been associated with a range of adverse effects (1). Among these, hypersensitivity reactions stand out as significant clinical concerns, encompassing a spectrum of manifestations from mild dermatological symptoms to severe systemic complications (3).

Immediate hypersensitivity reactions (HSRs) to PPIs are primarily IgE-mediated and occur rapidly after drug administration, presenting with symptoms such as urticaria, angioedema, and potentially life-threatening anaphylaxis. These reactions are driven by histamine release from mast cells and basophils and are further complicated by cross-reactivity among PPIs due to their structural similarities. This cross-re-

activity limits therapeutic options and necessitates careful diagnostic evaluation (4).

Delayed hypersensitivity reactions to PPIs are less common but often more severe, primarily mediated by type IV hypersensitivity mechanisms involving T-cell activation. These reactions present a broad spectrum of clinical manifestations, ranging from mild cutaneous symptoms to severe systemic involvement, including potentially fatal conditions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) (5).

This review integrates current evidence on the pathophysiology, clinical manifestations, diagnostic methods, and management strategies for both immediate and delayed PPI-induced HSRs, offering guidance to clinicians in addressing these uncommon but clinically significant challenges.

PPIs: Structure, Mechanism of Action, and Pharmacokinetics

The class of proton pump inhibitors (PPIs) includes six FDA-approved drugs: rabeprazole, lansoprazole, pantoprazole, esomeprazole, omeprazole, and dexlansoprazole (1). These weakly basic substituted benzimidazoles are specifically designed to accumulate in the highly acidic environment of parietal cell canaliculi, achieving high local concentrations and effectively inhibiting the H^+/K^+ATPase—the proton pump responsible for gastric acid secretion (6, 7). Administered as enteric-coated tablets or capsules to protect against gastric degradation, PPIs are absorbed in the proximal small intestine (6). Despite a short plasma half-life of approximately one to two hours, their duration of action is significantly extended due to their unique mechanism.

Once in the acidic canaliculus, PPIs are protonated and converted into their active sulfenamide form, which covalently binds to specific cysteine residues on the proton pump, causing irreversible inhibition of acid secretion. Recovery of acid production requires the synthesis of new proton pumps or the activation of resting ones (6). The activation kinetics and binding site preferences of individual PPIs, influenced by their chemical structures, determine their biological activity and duration of inhibition. Rapidly activated PPIs bind fewer cysteine residues, allowing for faster recovery of acid secretion, while delayed activation facilitates binding to additional sites, prolonging their effect (7).

PPIs are prodrugs requiring acid activation and are metabolized primarily by the cytochrome P450 system, with CYP2C19 and CYP3A4 playing key roles. Genetic polymorphisms, particularly in CYP2C19, significantly impact plasma levels and efficacy, underlining the importance of individual variability in therapeutic outcomes (8).

Clinical Applications of PPIs

Proton pump inhibitors are indispensable in the management of a range of acid-related disorders. They are the first-line therapy for gastroesophageal reflux disease (GERD), particularly in patients with erosive esophagitis, where they promote effective symptom relief, esophageal mucosal healing, and the prevention of complications such as stricture formation or Barrett's esophagus. In non-erosive GERD, PPIs are also highly effective in symptom control compared to H2 receptor antagonists (9).

In the context of peptic ulcer disease, PPIs play a pivotal role in both healing and prevention. For ulcers associated with *Helicobacter pylori* infection, PPIs are an integral part of eradication regimens, as they suppress gastric acid, enhancing the efficacy of antibiotics like amoxicillin and clarithromycin. For NSAID-induced ulcers, PPIs reduce the risk of ulcer formation and facilitate healing, especially in high-risk individuals such as older adults or those with a history of ulcers (9, 10).

High-dose PPIs are essential in managing Zollinger-Ellison syndrome, a rare condition characterized by gastrin-secreting tumors that lead to excessive gastric acid production. PPIs effectively control acid hypersecretion, alleviating symptoms and preventing complications like severe peptic ulceration (11).

In critically ill patients, PPIs are commonly employed for stress ulcer prophylaxis, particularly in those with risk factors such as mechanical ventilation, coagulopathy, stroke, or burns. PPIs are also used in managing eosinophilic esophagitis, where they can reduce esophageal inflammation and improve symptoms in a subset of patients (9).

Additionally, functional dyspepsia—a common condition characterized by upper abdominal discomfort or pain—may respond to PPI therapy, particularly in cases associated with acid-related symptoms (12). Other less common indications include their use in treating gastric hypersecretory states and assisting in the management of conditions like laryngopharyngeal reflux, where acid plays a contributing role (9, 13).

Adverse Effects of PPIs

PPIs are generally well-tolerated, though their use can result in both short-term and long-term adverse effects. In the short term, common side effects include gastrointestinal symptoms such as diarrhea, constipa-

tion, nausea, and abdominal discomfort. Headaches are also frequently reported among users (14).

Long-term use of PPIs, however, has been associated with more significant complications. Chronic suppression of gastric acid can impair the absorption of essential nutrients, including vitamin B12, magnesium, and calcium, leading to conditions such as anemia, hypomagnesemia, and osteoporosis. Prolonged acid suppression has also been linked to a higher risk of infections, such as *Clostridioides difficile*-associated diarrhea and small intestinal bacterial overgrowth (SIBO) (15, 16). Moreover, there is an increased susceptibility to respiratory infections, including pneumonia.

Emerging evidence suggests a potential relationship between long-term PPI use and chronic kidney disease or acute interstitial nephritis. Cardiovascular risks have also been postulated, with some studies reporting a possible link to myocardial infarction in certain populations, though the data remain inconclusive (15). Neurological concerns, such as cognitive decline and dementia, have been noted in association with extended PPI use; however, causality has not been firmly established (17).

Additionally, gastrointestinal effects such as gastric hyperplasia and the development of fundic gland polyps have been observed, particularly in long-term users (18). While these polyps are generally benign, they warrant monitoring to ensure patient safety.

PPIs as a Risk Factor for Allergic Disease Development

Emerging evidence suggests that gastric acid suppression, including the use of PPIs, contributes to the development of allergic diseases (3). Maternal PPI use during pregnancy has been associated with an increased risk of asthma in offspring, highlighting the need for cautious prescribing during pregnancy to mitigate potential respiratory risks in children (19). Similarly, the use of acid-suppressive drugs within the first six months of infancy has been linked to a heightened likelihood of developing allergic diseases later in life, indicating a critical window during which such medications may influence immune development (20).

A large Swedish cohort study of 80,870 matched pairs of children and adolescents further supports this association, demonstrating that PPI use significantly increases the risk of incident asthma. This risk was particularly pronounced in infants and toddlers, with hazard ratios (HRs) of 1.83 for children under six months and 1.91 for those aged six months to two years. Variability in asthma risk among individual PPIs was observed, with pantoprazole exhibiting the highest HR of 2.33. These findings underscore the necessity of prescribing PPIs to children only when clearly indicated, carefully balancing the therapeutic benefits against the potential risks (21).

Mechanistically, PPIs suppress gastric acid secretion, permitting intact food allergens and protein-bound oral drugs to persist in the digestive tract, thereby enhancing their capacity to sensitize and trigger allergic reactions. Additionally, PPIs may promote Th2-biased immune responses, particularly in the offspring of sensitized mothers. Impaired gastric acid production, whether due to PPI use or conditions like atrophic gastritis, has been strongly associated with an elevated risk of sensitization to oral allergens and drugs (22).

HSRs to PPI: Underlying Mechanisms and Clinical Features

While generally safe, hypersensitivity reactions (HSRs) to PPIs, although infrequent, are increasingly recognized as significant adverse events. These reactions encompass a broad spectrum of clinical manifestations, ranging from mild cutaneous symptoms to severe systemic involvement, and may present early or delayed (23). The growing awareness of these adverse effects necessitates a detailed understanding of their underlying mechanisms and clinical features.

Immediate HSRs

The majority of HSRs to PPIs are immediate in onset and predominantly IgE-mediated, as confirmed through diagnostic methods such as skin prick tests (SPT), intradermal tests (IDT), oral provocation tests (OPT), and basophil activation tests (BAT) (4). These reactions occur when antigens bind to IgE molecules attached to high-affinity FcεRI receptors on mast cells, leading to the release of inflammatory mediators, including histamine, leukotrienes, and prostaglandins, which cause the characteristic symptoms of hypersensitivity (24). Immediate HSRs are more common in females, with reported rates ranging from 61% to 81.5%, and are primarily observed in adults, with a mean age between 43 and 54 years across multiple studies (25, 26, 27). Only a few cases have been reported in pediatric patients (28).

Studies have identified differences in the prevalence of PPI-induced HSRs based on the specific PPI involved. Bose et al. reported omeprazole as the most frequently implicated PPI (45.76%), followed by lansoprazole (20.34%), pantoprazole (16.95%), esomeprazole (14.41%), and rabeprazole (2.54%) (25). Conversely, Bonadonna et al. identified esomeprazole as the most frequently involved (30%), followed by

lansoprazole (26.4%) and omeprazole (18.9%) (26). A 2013 study by Ozdemir et al. found lansoprazole to be the primary culprit in 80% of cases, with esomeprazole (16.9%), pantoprazole (13.8%), rabeprazole (3.1%), and omeprazole (1.5%) occurring less frequently (27). A subsequent analysis in 2020 by the same group, which included data from 12 studies involving 395 patients and 416 immediate HSRs, found lansoprazole to account for the highest proportion of cases (40.6%), followed by omeprazole (26.2%), pantoprazole (15.6%), esomeprazole (14.4%), and rabeprazole (3.1%) (5). The researchers suggested that regional prescribing practices may influence the distribution and prevalence of hypersensitivity reactions associated with specific PPIs. Notably, there are no reported cases of immediate HSRs to dexlansoprazole.

Across various studies, urticaria and/or angioedema were observed in 44.1% to 49.2% of patients, while anaphylaxis, the most frequently reported clinical presentation, occurred in 50.8% to 53.6% of cases (5, 27). Additional manifestations included generalized pruritus, hypotension, non-urticarial skin rashes, erythema, and dyspnea or shortness of breath (25), reflecting the diverse clinical spectrum of immediate hypersensitivity reactions to PPIs. Immediate hypersensitivity reactions most commonly occur within the first hour of medication intake (75.4%), but they can also present up to 24 hours later (24.6%) (27). A patient with a history of pantoprazole-induced anaphylaxis exhibited a 7-hour latency period, with a positive IDT supporting an immediate hypersensitivity mechanism (29). In another case, a 47-year-old Hispanic male was referred for recurrent idiopathic anaphylaxis, with the most recent episode occurring 3 hours after pantoprazole intake and previous episodes reported at 24, 10, and 4 hours post-intake. Positive IDT with pantoprazole confirmed an IgE-mediated hypersensitivity reaction (30). This delayed onset may be attributed to the enteric coating of PPIs, which can slow the release of the active compound. Additionally, polymorphisms in the CYP2C19 gene, associated with a poor metabolizer phenotype, have been hypothesized to influence the timing of reactions (29). Consequently, patients exhibiting symptoms consistent with immediate allergic reactions to PPIs, even when delayed up to 24 hours, may still involve an IgE-mediated mechanism. Such cases warrant further evaluation using immediate skin tests to confirm the underlying cause.

Delayed HSRs

Drug-induced delayed HSRs encompass a broad range of clinical manifestations, spanning from mild to severe presentations. Mild reactions, such as maculopapular exanthema (MPE) and fixed drug eruption (FDE), are typically self-limiting and resolve with appropriate management. In contrast, severe and potentially life-threatening cutaneous adverse reactions, including SJS, TEN, and DRESS, require urgent medical intervention due to their high morbidity and mortality risks. Although delayed HSRs are well-characterized for many drug classes, data specific to their association with PPIs remain limited (5).

Among hypersensitivity reactions to PPIs, non-IgE-mediated responses are relatively uncommon (14%) compared to IgE-mediated reactions (86%), of which 10% are type IV cell-mediated hypersensitivity responses (25). This finding suggests that type IV hypersensitivity, which includes reactions mediated by T cells and delayed in onset, is the most frequent mechanism underlying these reactions, as all hypersensitivity reactions beyond type II culminate in type IV responses.

A landmark 14-year case series has significantly advanced the understanding of PPI-related delayed cutaneous adverse reactions, reporting 69 cases—the largest dataset to date. The study identified a spectrum of clinical presentations, including 29 cases of MPE, 27 of SJS/TEN, 10 of DRESS, two of FDE, and one of acute generalized exanthematous pustulosis (AGEP). Esomeprazole emerged as the most commonly implicated PPI, particularly in severe cases such as SJS/TEN and DRESS (51%, 35/69), followed by omeprazole and lansoprazole. The latency period varied by reaction type, with an average of 18.6 days for MPE, 20.8 days for SJS/TEN, 7.0 days for AGEP, and 27.2 days for DRESS (31). These findings underscore the delayed nature of PPI-induced hypersensitivity and highlight the need for clinical vigilance in monitoring patients on PPI therapy.

Other cutaneous reactions associated with PPIs include symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), also referred to as drug-related baboon syndrome. A recent study reported three cases of SDRIFE linked to PPIs, with two cases caused by omeprazole and one by pantoprazole. The latency period for these reactions ranged from 3 to 7 days after drug administration (32). Additionally, cases of severe exfoliative dermatitis have been documented, including an 82-year-old male who developed symptoms two weeks after initiating esomeprazole therapy (33) and a 41-year-old male who experienced persistent dermatitis for 18 months after discontinuing omeprazole (34).

PPIs have also been identified as potential triggers for occupational exposure-related contact dermatitis, particularly in individuals frequently handling these medications (5, 35). In a study by Ghatan et al., ap-

proximately one-third of 96 individuals with suspected occupational exposure-related symptoms were diagnosed with omeprazole-specific allergy. The diagnosis was confirmed using patch testing or the lymphocyte transformation test (LTT), demonstrating the utility of these diagnostic tools in occupational settings (36). Additional reports have documented contact dermatitis linked to omeprazole in a horse breeder (37) and similar reactions associated with pantoprazole and lansoprazole (38, 39).

Another recognized immunological adverse reaction to PPIs is subacute cutaneous lupus erythematosus (SCLE), which typically manifests within the first year of treatment, though cases have been reported with latencies ranging from 1 week to 3–5 years. SCLE predominantly affects women (89%) and is associated with antibodies such as anti-Ro/SSA (73%) and antinuclear antibodies (61%). Lansoprazole and omeprazole are the most frequently implicated PPIs, with cross-reactivity documented among these medications. Individuals with a history of cutaneous lupus erythematosus appear to have an elevated risk of developing PPI-induced SCLE (40).

In addition to dermatological reactions, hematological adverse effects such as neutropenia, thrombocytopenia, and hemolytic anemia have been linked to PPI use (41,42,43). These conditions are thought to be mediated through type II hypersensitivity mechanisms, suggesting immune involvement in their pathogenesis (35).

This growing body of evidence highlights the diverse clinical spectrum of PPI-induced hypersensitivity reactions, emphasizing the importance of accurate diagnosis, awareness of underlying immune mechanisms, and tailored management strategies to mitigate associated risks.

Diagnostic Approaches

Immediate HSRs

The evaluation of HSRs to PPIs requires a multifaceted approach, incorporating clinical history, physical examination, and targeted diagnostic procedures. For IgE-mediated reactions, the preferred methods for confirming sensitization include SPT, IDT, and OPT. Advanced techniques, such as the BAT, can further aid diagnosis in ambiguous cases (4). Two pivotal multicenter studies, conducted by Bonadona et al. (26) and Ozdemir et al. (27), assessed the diagnostic utility of SPT and IDT compared to OPT in patients with PPI-induced HSRs.

In the Bonadona et al. study, 53 patients were analyzed, with 12 demonstrating positive skin test results, predominantly in cases of severe reactions. Skin tests exhibited high diagnostic accuracy, with 100% specificity, 100% positive predictive value, and 91.9% negative predictive value, though sensitivity was moderate at 50–61.3%. These findings highlight the value of skin testing in minimizing the need for OPT in patients with positive test results (26). Similarly, the Ozdemir et al. study evaluated 65 patients with suspected immediate HSRs to PPIs and 30 control subjects. SPT and IDT displayed high specificity (100%) and positive predictive value (100%), but sensitivity was moderate (58.8%). In 12 patients with negative diagnostic skin test results, OPTs with the suspected PPIs were conducted, yielding a positive result in eight cases (66.7%). This study concluded that skin tests are highly specific and valuable for diagnosing PPI-induced hypersensitivity, but OPT remains indispensable for confirming negative skin test findings (27).

SPTs were conducted using both undiluted commercial oral and injectable PPI formulations. Tablets and capsules were crushed and diluted in saline, and the tests were performed on the volar forearm. A wheal at least 3 mm larger than the negative control after 20 minutes was considered positive. For patients with negative SPT results, IDTs were conducted using serial dilutions of injectable PPI preparations. A small volume of the test solution was injected intradermally, and an increase in wheal size of at least 3 mm accompanied by erythema after 15 minutes was deemed positive. Patients with negative skin test results subsequently underwent single-blind, placebo-controlled OPTs with alternative PPIs. Doses were administered incrementally at 30-minute intervals until the full dose was reached or a reaction occurred. Vital parameters, including blood pressure, pulse, and FEV1, were closely monitored throughout. A positive OPT was defined by objective signs of hypersensitivity, such as urticaria, angioedema, bronchospasm, or a 20% reduction in FEV1 (27).

These studies collectively emphasize the critical role of skin tests in the diagnostic evaluation of immediate PPI-induced HSRs, while underscoring the complementary importance of OPT in confirming cases with negative skin test results. The dosages of PPIs utilized in these studies for skin testing and OPT are detailed in Table 1.

Currently, there are no studies on the detection of specific IgE antibodies for PPIs. The BAT has emerged as a promising diagnostic tool for immediate PPI allergic reactions, offering a sensitivity of 73.8% and specificity of 100% in studies involving omeprazole. Combining the BAT with skin tests increases diagnostic accuracy, enabling confident diagnoses of PPI HSRs in 85.7% of cases, though research on other PPIs remains limited (4).

Table 1. *Recommended nonirritant skin test concentrations and provocation doses for diagnosis of immediate HSRs to PPIs*

PPIs	SPT	IDT	OPT	References
Omeprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	**Bonadonna P, 2012** (26)
Pantoprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	
Esomeprazole	40 mg/ml	0.4, 4 mg/ml	5, 5, 10, 20 mg	
Rabeprazole	40 mg/ml	/	5, 5, 10, 20 mg	
Lansoprazole	30 mg/ml	/	5, 10, 15 mg	
Omeprazole	20 mg/ml 0.4, 4 mg/ml	0.004, 0.04, 0.4 mg/ml	5, 10, 20 mg	**Kepil Ozdemir S, 2013** (27)
Pantoprazole	40 mg/ml 0.4, 4 mg/ml	0.004, 0.04, 0.4 mg/ml	5, 10, 20 mg	
Esomeprazole	20 mg/ml 0.8, 8 mg/ml	0.008, 0.08, 0.8 mg/ml	5, 10, 20 mg	
Rabeprazole	20 mg/ml	/	5, 10, 20 mg	
Lansoprazole	30 mg/ml	/	7.5, 15, 30 mg	

*PPIs = Proton Pump Inhibitors; SPT = Skin Prick Test; IDT = Intradermal Test; OPT = Oral Provocation Test

Table 2. *Patch test preparations for the diagnosis of delayed HSRs to PPIs*

PPIs	Concentration	Solvent	Form	References
Omeprazole	30%	petrolatum	granules/tablets	**Bavbek S, 2024** (4)
Pantoprazole	30%	petrolatum	granules/tablets	
Esomeprazole	30%	petrolatum	granules/tablets	
Rabeprazole	30%	petrolatum	granules/tablets	
Dexlansoprazole	30%	petrolatum	granules/tablets	
Lansoprazole	30%	petrolatum	granules/tablets	
Pantoprazole	10%	petrolatum	powder	
Esomeprazole	10%	petrolatum	powder	

*PPIs = Proton Pump Inhibitors

Delayed HSRs

Diagnosing delayed HSRs to PPIs relies on a combination of detailed clinical history and patch testing, which is regarded as an effective and reliable approach. Patch testing offers a non-invasive method to confirm the involvement of PPIs in hypersensitivity reactions and is particularly useful when other diagnostic tools are limited (4). PPIs have been tested at concentrations ranging from 0.1% to 50%, using various vehicles such as petrolatum, saline, and occasionally alcohol (23). Patch tests are typically performed on the upper back or other suitable sites by applying small amounts of the prepared PPI mixture in specialized chambers. Reactions are assessed after a designated period, often 96 hours, to detect positive responses indicative of delayed hypersensitivity mechanisms (31). Lin et al. conducted patch testing 3–8 months after the resolution of delayed HSR episodes, using a panel of suspected drugs administered within one month of the onset. Powders were diluted to a 10% concentration in petrolatum, and 57% (4/7) of the patients exhibited a positive reaction, confirming the PPI's role in delayed HSR causation (31). Bavbek et al. recommend reducing PPI granules or tablets to a fine powder, diluting the material to a 30% concentration in petrolatum, and documenting the active ingredient concentration. For injectable formulations like esomeprazole and pantoprazole, they propose a 10% dilution in petrolatum (Table 2) (4).

The LTT is a widely used in vitro diagnostic tool for detecting delayed HSRs. This assay measures the

proliferation of drug-specific T cells upon stimulation with suspected offending drugs. In a study by Lin et al., LTT was performed on 27 patients with PPI-related delayed HSRs and 7 healthy controls. Peripheral blood mononuclear cells were cultured with the suspected PPIs and a solvent control for one week. The granulysin-based LTT demonstrated a sensitivity of 59.3% (16/27) and a specificity of 96.4% (27/28), with significantly higher granulysin release in the PPI-delayed HSRs group compared to controls. In contrast, the IFN-γ-based LTT showed a lower sensitivity of 29.2% (7/24) while maintaining a high specificity of 95.0% (19/20), with no significant differences in IFN-γ release between groups (31). Ghatan et al. examined occupational hypersensitivity reactions to omeprazole using LTT. Among 96 symptomatic individuals, 31 (32%) tested positive, compared to 2 of 21 control subjects (9.5%). Patch testing identified positive results in 33% (28/84) of symptomatic individuals, with a strong correlation between patch test and LTT results. Among those with positive patch tests, 82% (23/28) also had positive LTT results, demonstrating its high sensitivity and specificity. Combining patch testing with LTT identified an additional eight individuals with omeprazole allergy, underscoring the value of integrating these methods for improved diagnostic accuracy, particularly in cases of occupational hypersensitivity (36). These findings highlight the complementary roles of patch testing and LTT in diagnosing delayed hypersensitivity reactions to PPIs and their importance in managing drug-induced allergies.

The diagnostic utility of SPT and IDT with delayed readings for identifying delayed HSRs to PPIs remains poorly investigated. To date, the only available data comes from a study by Ghatan et al., which reported that all 18 individuals who underwent prick testing showed negative results (36). Similarly, the role of OPT in diagnosing T cell-mediated delayed reactions to PPIs is not well-defined. Although no studies have specifically evaluated the effectiveness of DPTs in PPI-induced delayed hypersensitivity, their use may be justified in cases with inconclusive clinical histories and negative skin test results. In nonsevere delayed reactions, DPTs could serve as a valuable tool to rule out PPI hypersensitivity (4). This approach ensures a more comprehensive assessment of delayed hypersensitivity to PPIs.

Cross-Reactivity Between PPIs

Cross-reactivity among PPIs is well-documented and primarily attributed to their structural similarities, particularly the modifications in the benzimidazole and pyridine rings (5). Four distinct patterns of cross-reactivity have been observed. In some cases, patients exhibit hypersensitivity to all available PPIs, a phenomenon known as whole group hypersensitivity. Others may experience allergic reactions specifically to omeprazole, esomeprazole, and pantoprazole, while tolerating lansoprazole and rabeprazole. Conversely, some patients show hypersensitivity exclusively to lansoprazole and rabeprazole but tolerate omeprazole, esomeprazole, and pantoprazole. Additionally, a pattern of selective hypersensitivity has been identified, where patients react to only one specific PPI while tolerating all others (1). Skin testing and oral provocation testing (OPT) are crucial for identifying safe alternatives for patients with hypersensitivity. Studies indicate that 61.6% of patients with immediate HSRs to one PPI may exhibit cross-reactivity to another (4). Comprehensive testing across all available PPIs is essential for accurately identifying safe options for affected patients.

Data on cross-reactivity in delayed HSRs to PPIs is more limited. A study by Lin et al. highlights the challenges of managing cross-hypersensitivity reactions due to the structural similarities among PPIs. In a cohort of 27 patients with PPI-related delayed HSRs, 13 patients were able to tolerate structurally different PPIs, while others exhibited cross-hypersensitivity, particularly within two structurally similar groups: the omeprazole-esomeprazole-pantoprazole group and the lansoprazole-dexlansoprazole-rabeprazole group. These findings underscore the importance of structural differences, such as side chain substitutions, in determining tolerability (31).

Management of HSRs to PPIs

Immediate HSRs

The first step in managing immediate hypersensitivity reactions (HSRs) to PPIs is to identify the suspected PPI as the causative agent and discontinue its use until the diagnostic process is complete. In cases of acute reactions, emergency interventions such as the administration of epinephrine, antihistamines, fluids, airway management, and corticosteroids are essential for stabilizing the patient (44). Skin testing should be performed on the suspected PPI, and if the results are positive, the implicated PPI should be avoided. If skin tests for the suspected PPI are negative and the reaction was mild, an oral provocation test (OPT) can be conducted. A negative OPT result excludes hypersensitivity, while a positive result confirms the need to avoid the specific PPI. In cases where skin tests are negative but there is a history of severe reactions to the suspected PPI, the drug should be avoided regardless.

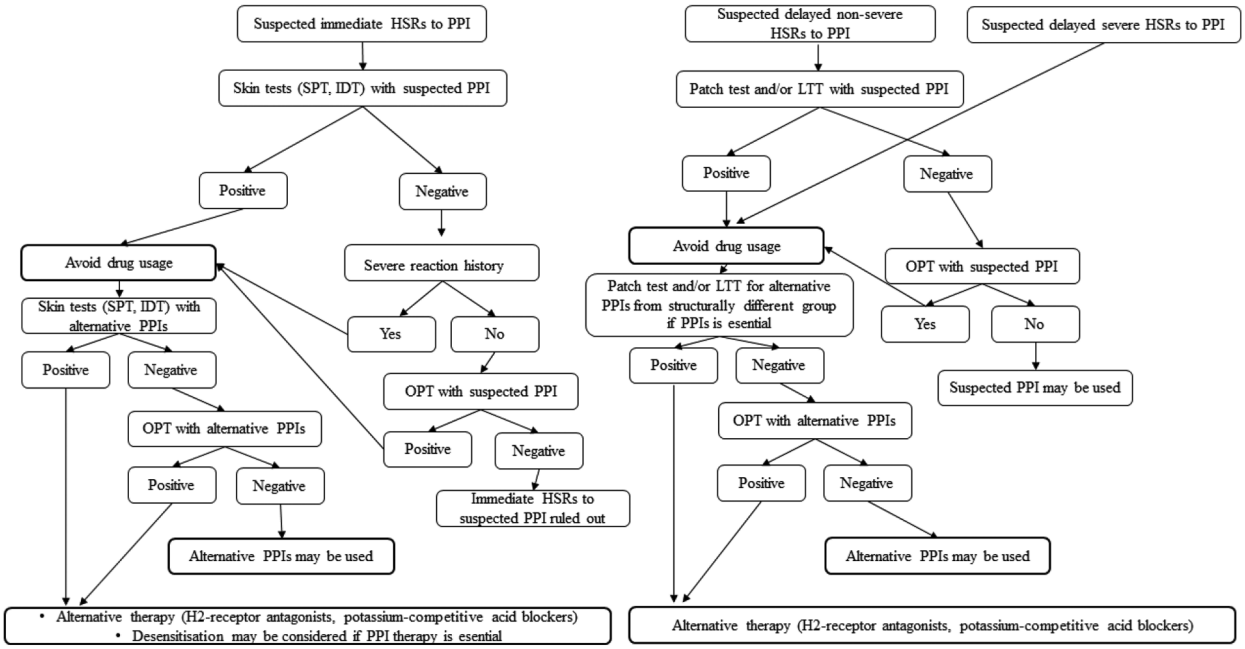
When PPI therapy is essential, skin testing and OPT should be performed on alternative PPIs within the same class to evaluate cross-reactivity. An alternative PPI with negative skin and OPT results may be safely used. If cross-reactivity is identified across all PPIs, alternative acid-suppressing medications such as histamine (H2)-receptor antagonists or potassium-competitive acid blockers (e.g., vonoprazan fumarate) should be considered (45). If PPI therapy is deemed essential, desensitization may be a viable therapeutic option (Figure 1); however, current data on desensitization protocols are limited, with only two documented case reports involving omeprazole and rabeprazole in immediate HSRs.

In one case, a 44-year-old man with immediate HSRs to omeprazole and Helicobacter pylori infection underwent oral desensitization using serial dilutions of omeprazole, starting at 0.001 mg and escalating over 5.6 hours to a final dose of 16 mg, successfully tolerating a 20 mg capsule thereafter. Post-desensitization skin tests showed significantly reduced reactivity, and the patient tolerated subsequent treatment with levofloxacin, tetracycline, and omeprazole (20 mg twice daily) for a 14-day therapy regimen without hypersensitivity, effectively managing his condition (46). In another case, a 26-year-old woman diagnosed with a duodenal ulcer experienced anaphylaxis after taking pantoprazole and esomeprazole. Skin testing confirmed hypersensitivity to all tested PPIs, leaving no alternative treatments. As a result, a desensitization protocol with rabeprazole was successfully implemented, enabling the patient to tolerate rabeprazole therapy without further hypersensitivity reactions (47).

These cases highlight the potential efficacy and safety of desensitization protocols for patients requiring PPIs despite a history of immediate HSRs. However, further research is needed to establish standardized desensitization approaches.

Delayed HSRs

The initial step in managing delayed HSRs to PPIs is to identify the suspected PPI as the causative agent and discontinue its use immediately. For non-severe delayed HSRs, patch testing, with or without an LTT, should be performed on the suspected PPI. A positive test result confirms hypersensitivity, and the implicated PPI should be avoided. If the patch test and/or LTT results are negative, an OPT can be conducted (4). A negative OPT excludes hypersensitivity, allowing for the continued use of the suspected PPI. However, if the OPT is positive, the specific PPI must be avoided, and alternative PPIs from a structurally different group should be evaluated using patch testing, LTT, and OPT. If all tests for the alternative PPI are negative, it may be safely used. If any of these tests are positive, alternative acid-lowering treatments should be used (45). In cases with a history of severe delayed HSRs, the suspected PPI should be avoided without testing. If PPI therapy is essential, the diagnostic steps for alternative PPIs mentioned above should be followed (Figure 1).



*HSRs = Hypersensitivity Reactions; PPIs = Proton Pump Inhibitors; SPT = Skin Prick Test; IDT = Intradermal Test; OPT = Oral Provocation Test; H2-Receptor Antagonists = Histamine Type 2 Receptor Antagonists; LTT = Lymphocyte Transformation Test

***Figure 1**. Schematic representation of the diagnostic and therapeutic approach for immediate and delayed HSRs to PPIs (authors archive)*

Management of severe delayed hypersensitivity reactions involves the immediate withdrawal of the causative drug, maintenance of proper hydration and electrolyte balance, regulation of body temperature, and meticulous care of damaged skin. Advanced strategies, such as autoclaved banana leaves, porcine xenografts, and stem cell therapies, have been explored to enhance wound healing. Pharmacological treatments, including corticosteroids, cyclosporine, intravenous immunoglobulins (IVIg), and newer agents like tacrolimus and biologics, have demonstrated varying levels of efficacy. Among these, cyclosporine has shown particularly promising results in reducing mortality rates. Emerging therapies, such as plasmapheresis and intravenous N-acetylcysteine, also show potential benefits, though their broader application is often limited by cost and accessibility (48).

Further research is required to refine these therapeutic strategies and establish standardized protocols for the diagnosis and management of delayed HSRs to PPIs, ensuring optimal patient outcomes.

Future Perspectives

The future of diagnosing and managing immediate and delayed hypersensitivity reactions (HSRs) lies in advancing diagnostic precision, leveraging personalized medicine, and developing innovative therapies. Emerging diagnostic tools, such as in vitro tests and biomarkers, are set to revolutionize accuracy, with the cytokine release enzyme-linked ImmunoSpot (ELISpot) assay gaining attention. This assay detects cytokine release, typically IFN-γ, when a patient's peripheral blood mononuclear cells are stimulated with suspected drugs, offering a reliable method to identify triggers. Pharmacogenomics, particularly the identification of genetic markers like human leukocyte antigens, is poised to play a pivotal role in personalizing treatment, enabling the identification of at-risk patients and optimizing drug selection (49).

On the therapeutic front, immunomodulatory treatments, including biologics that target specific inflammatory cytokines, show great promise for managing severe hypersensitivity reactions while minimizing side effects (50). Additionally, refined desensitization protocols will enhance the ability of patients to tolerate essential medications, even in cases of confirmed hypersensitivity. These advancements collectively aim to improve patient outcomes through safer, more precise, and individualized approaches to diagnosis and treatment.

Improved understanding of drug cross-reactivity will facilitate safer alternative therapy selection, particularly for structurally similar medications like PPIs. Alternative therapies, such as potassium-competitive acid blockers (45), will continue to evolve, offering safer options for affected patients. Challenges remain in establishing standardized diagnostic and treatment protocols and ensuring cost-effective, accessible solutions. Ongoing research into immune mechanisms and genetic factors is essential to advance the field. These advancements aim to deliver more accurate, efficient, and tailored care, improving outcomes and quality of life for patients with HSRs.

CONCLUSION

Hypersensitivity reactions to PPIs represent a significant clinical challenge due to their potential severity and the widespread use of these medications. A thorough understanding of the immunological mechanisms, clinical presentations, and appropriate diagnostic and therapeutic strategies is essential for optimal management. Future research should focus on improving diagnostic accuracy and exploring innovative approaches to minimize the risk of hypersensitivity while maintaining the therapeutic benefits of PPIs.

Abbreviations

PPIs - Proton Pump Inhibitors
GERD - Gastroesophageal Reflux Disease
H. pylori - Helicobacter pylori
NSAIDs - Nonsteroidal Anti-Inflammatory Drugs
HSRs - Hypersensitivity Reactions
SJS - Stevens-Johnson Syndrome
TEN - Toxic Epidermal Necrolysis
DRESS - Drug Reaction with Eosinophilia and Systemic Symptoms
SIBO - Small Intestinal Bacterial Overgrowth
SPT - Skin Prick Test
IDT - Intradermal Test
OPT - Oral Provocation Test
BAT - Basophil Activation Test
MPE - Maculopapular Exanthem
FDE - Fixed Drug Eruption
AGEP - Acute Generalized Exanthematous Pustulosis
SDRIFE - Symmetrical Drug-Related Intertriginous and Flexural Exanthema
LTT- Lymphocyte Transformation Test
SCLE - Subacute Cutaneous Lupus Erythematosus

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the study, performing the literature review, analyzing the data, and writing the manuscript. V.A., M.D.Z, K.Ć.,L.S. and S.V. assisted in the study design, data analysis, and manuscript writing. A.G., E.Ć.L., V.Z., H.P., M.M. and F.Dž. aided in data collection, interpretation, and manuscript preparation. L.S., E.Ć.L., and S.V. provided critical revisions and intellectual contributions to the manuscript. M.S. offered expert guidance and critical revisions.

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

RANE I ODLOŽENE HIPERSENZITIVNE REAKCIJE NA INHIBITORE PROTONSKE PUMPE: PREGLEDNI ČLANAK

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Inhibitori protonske pumpe su među najčešće propisivanim lekovima u kliničkoj praksi, prvenstveno se koriste za lečenje gastrointestinalnih poremećaja povezanih sa povećanim lučenjem hlorovodonične kiseline. Iako se generalno smatraju bezbednim, sa retkim i obično blagim neželjenim dejstvima, inhibitori protonske pumpe mogu biti povezani sa pojavom hipersenzitivnih reakcija. Ove reakcije, koje mogu biti rane ili odložene, variraju u težini od blagih do potencijalno životno ugrožavajućih. Ovaj pregled literature pruža detaljnu analizu ključnih aspekata primene inhibitora protonske pumpe, sa posebnim naglaskom na patofiziološke i kliničke karakteristike trenutnih i odloženih hipersenzitivnih reakcija. Takođe, rad istražuje ukrštenu reaktivnost među samim inhibitorima protonske pumpe i pruža praktičan vodič koji može pomoći lekarima u kliničkoj praksi u dijagnostikovanju i lečenju ovih stanja. Dodatno, rad ističe ključnu potrebu za daljim istraživanjima kako bi se razvili standardizovani dijagnostički i terapijski protokoli, omogućavajući personalizovanu i na dokazima zasnovanu negu za pacijente sa hipersenzitivnošću na inhibitore protonske pumpe.

Ključne reči: Inhibitori protonske pumpe, hipersenzitivne reakcije, trenutna hipersenzitivnost, odložena hipersenzitivnost, prick test, patch test, test aktivacije limfocita, ukrštena reaktivnost.

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