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Proton pump inhibitors in allergy: benefits and risks

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Abstract

Proton pump inhibitors (PPIs) are widely prescribed and are indicated for the treatment of several GI disorders. Allergists may prescribe PPIs due to the co-incidence of gastroesophageal reflux disease (GERD) with asthma or rhinitis, or when GERD presents as chronic cough. Further, long-term high-dose PPI therapy is a recommended option for management of eosinophilic esophagitis, resulting in histologic remission in approximately 40% of patients. Here, we discuss current recommendations for PPI use, de-escalation, and their side effect profile. We review evidence supporting the epidemiologic link between use of acid-suppressant medication and subsequent development of allergic disorders.

Keywords

proton pump inhibitor; asthma; eosinophilic esophagitis; hypersensitivity; adverse events

Introduction

Acid-suppressant medications are a class of medication that inhibit gastric acid secretion and include histamine-2 receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs). Approximately 15 million U.S. adults, or 7.8% of the American population are estimated to use PPIs.[1] They are standard treatment for several conditions including gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter* pylori infection (in combination with antibiotics), upper gastrointestinal (GI) bleeding prophylaxis, and hypersecretory conditions like Zollinger-Ellison Syndrome.[2] Proton pump inhibitors are frequently prescribed, available over the counter, and commonly continued for longer than may be clinically indicated. Use in pregnancy, infancy and early childhood is common despite guidance to avoid unnecessary use of PPIs and little data to support PPI efficacy for many indications.[3,4] Over time, there has been increasing focus on potential side effects attributable to PPI use.[5–7] Care should be taken to limit PPI use to indications where benefit is expected, and to consider de-escalation of therapy when feasible.[8] In this review, we discuss data supporting use of PPIs in allergic conditions, risks of chronic PPI use, and potential impact of PPIs on development of allergic disorders.[9]

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Role of proton pump inhibitor treatment in allergic disorders

Gastroesophageal reflux disease frequently occurs together with rhinitis, asthma, and eosinophilic esophagitis (EoE), and can exacerbate these conditions. The symptoms of GERD, in particular cough,[10] can mimic uncontrolled asthma. Approaches to address this concern have been reviewed in depth elsewhere.[11] There has been significant interest in the potential role of PPI as a primary or adjunctive treatment for atopic conditions, in particular asthma and eosinophilic esophagitis. We will review the data for these below.

Asthma—GERD frequently coexists with asthma, however the results of trials regarding the role of acid suppression in the management of asthma have been inconsistent. While several trials have demonstrated improved patient-reported asthma symptoms following acid suppression therapy for GERD,[12–17] there is less evidence to support objective improvement in asthma control with reflux therapy.[18–20] A recent Cochrane-review concluded there was moderate-certainty evidence for improved forced expiratory volume in one-second (FEV1, mean difference 0.1 L 95% CI 0.05 to 0.15, 1333 participants, 7 studies) and decreased use of rescue medications (−0.71 puffs per day, 95% CI −1.20 to −0.22; 239 participants, 2 studies) following GERD therapy.[19] However, the authors identified no studies focused on their targeted primary outcomes including hospital admissions, emergency room visits, or unscheduled doctor visits. Therefore, the impact of PPI treatment on asthma exacerbation risk and hospital utilization remains unclear.

Similarly, a recent meta-analysis reported no discernable benefit with PPI treatment for GERD on morning peak-expiratory flow across fourteen randomized clinical trials including a total of 2,182 participants.[20] A separate study reported limited clinical benefit in patients who have symptomatic GERD and nighttime asthma symptoms,[15] and these patients may represent the group most likely to see improvement in asthma symptoms with PPI treatment.

Current asthma guidelines do not recommend empiric treatment of GERD for patients with asthma.[21,22] Rather, current recommendations support treatment of reflux guided by patient symptoms.[21]

One use of PPI relevant to asthma care is for stress ulcer prophylaxis in the setting of systemic corticosteroid use or critical illness. Patients in the ICU can have multiple additive risks for GI bleeding including lack of enteral intake, poor GI perfusion, coagulopathy, and anticoagulant use. An open-label crossover study of 26,828 adult patients requiring mechanical ventilation in the intensive care unit showed no significant difference in the rates of in-hospital mortality, GI bleeding, or *C.difficile* infection in patients receiving a PPI or H2RB.[23] In the setting of critically ill patients, guidelines recommend PPI over histamine-2 receptor blocker (H2RB) and assessment of individual patient bleeding risk.[24]

Recently, increasing data suggest that the risk for stress ulcers in asthma patients who are receiving corticosteroids may relate to patient-specific risk factors including comorbidities and concurrent medication use. A recent retrospective study of 30,177 pediatric patients admitted to the ICU for critical asthma found that whereas medical prophylaxis to prevent stress ulcers has been increasingly prescribed over time, there were no episodes of GI bleeding noted over a 10-year period.[25] Compared with children, adult patients may have

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multiple risks for GI bleeding including use of nonsteroidal anti-inflammatory drugs and anticoagulants. Studies have indicated that GI prophylaxis with PPI may be underutilized in older adults at sustained risk of GI bleeding owing to therapy with these classes of medications.[26–28]

Eosinophilic Esophagitis—Uniquely among atopic disorders, PPIs are recommended as a treatment for eosinophilic esophagitis. Importantly, a trial of PPI therapy is no longer included as a necessary step for diagnosis in most recent EoE guidelines.[29,30] EoE can be confirmed in a patient with symptoms of esophageal dysfunction who has at least 15 eosinophils per high powered field (~60 eosinophils per mm^2) on esophageal biopsy and no other identifiable causes of esophageal eosinophilia on medical evaluation. When used for treatment of EoE, the current twice-daily dosing recommendations are not explicitly addressed by the US Food and Drug Association (FDA) in PPI packaging inserts (Table 1).

Multiple studies have evaluated the efficacy of PPIs in EoE, however there have been no randomized controlled studies comparing the efficacy of PPI monotherapy to other EoE therapies like swallowed corticosteroids or dietary exclusion. In prior meta-analyses, the overall percentage of adults who achieved histologic remission on PPI therapy was approximately 50%.[31–33] The American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters recently published a joint guideline on EoE treatment reviewing 23 clinical studies of PPI treatment in EoE patients using Grading of Recommendations, Assessment, Development, and Evaluations methodology.[34] That review found an unweighted histologic response of 42% to PPI, with a high level of observed intertrial variability owing to inconsistent patient selection criteria, dosing, and therapy duration across PPI trials.[34] Additional concerns the contributed to an assessment of very low quality metric of evidence in the Grading of Recommendations, Assessment, Development, and Evaluations study were that a significant portion of PPI trials were retrospective, single-arm studies without comparison to other types of EoE therapy. The risk ratio for PPI treatment compared to placebo (RR 0.66, 95% CI, 0.61–0.72) was consistent with the likely benefit of PPI for a subset of patients. Proton pump inhibitors are relatively inexpensive, have a long-standing safety profile, and are they are easily administered. Proton pump inhibitor treatment should be discussed with patients along with risks and benefits of other forms of EoE therapy when choosing initial therapy or reevaluating therapy options owing to persistent disease activity.[29,34] There are no validated biomarkers to predict the subgroup of EoE patients that will maximally benefit from PPI or other EoE therapy, therefore a shared decision making approach regarding the choice of EoE therapy options with the individual patient is recommended. An additional consideration is that GERD and EoE can co-exist, and some EoE patients derive additional symptomatic relief with use of PPI while on another form of EoE therapy.

Current consensus guidelines recognize EoE as an indication for long-term PPI treatment.[8] When PPI monotherapy is used for EoE, empiric trials of PPI deprescribing are not indicated and PPI should be continued unless there is shared decision making to switch to another form of EoE therapy. There have been few studies of the long-term efficacy of PPI use in EoE patients. A recent retrospective analysis of 138 adult EoE patients observed for a mean follow up time of 3.6 ± 2.9 years demonstrated that 60% of patients with long-term follow

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up maintained histologic remission on high-dose PPI therapy.[35] Patient demographics, symptoms, atopic status, endoscopic findings and PPI doses were similar between the groups but there was a trend for pre-PPI dilation being more common in patients who did not respond to PPI therapy (60% vs 33%, *P*=0.06). A separate retrospective analysis of a cohort of 75 adult EoE patients indicated a higher long-term response rate of 87% after 1–2 years' time.[36] Recurrence of esophageal eosinophilia while on PPI were more likely to occur in those with rhinoconjunctivitis as compared to those without it (40% vs. 13%, respectively, P = 0.007) and with a cytochrome P450 family 2 subfamily C member 19 (CYP2C19) rapid metabolizer genotype as compared to those without (36% vs. 6%, respectively, P = 0.01).[36] This CYP2C19 rapid metabolizer genotype the has been associated with lower serum PPI levels and in a prospective clinical trial of high-dose PPI therapy in 92 pediatric patients. Binary logistic modeling in a study of 92 pediatric patients demonstrated that the CYP2C19 rapid metabolizer genotype was associated with a PPI-nonresponsive EoE phenotype (odds ratio (OR) [95% confidence interval (CI)] = 7.71 [1.21, 49.11], P = 0.031).[37] These findings raise the question of if patient genotype could predict the therapeutic efficacy of high-dose PPI in EoE. The association of CYP2C19 polymorphisms with PPI response in EoE patients requires further prospective validation to determine if this strategy could predict patients' response to PPI therapy across a diverse population.

Potential Adverse Effects

The short-term effects of PPIs have been extensively studied in randomized controlled studies for GERD, and PPIs have proven quite safe for short-term use. Side effects are reversible with discontinuation of therapy and include headache (<5%) and diarrhea (<5%).[6,19,38] With the increasing prevalence of long-term PPI use, there has been growing scrutiny of potential long-term adverse events with these medications. Most studies were performed as case-control or cohort studies with risk for bias and potential effects from residual confounding,[7] and have had low effect sizes which call into question their clinical significance. This evidence was rated low to very low quality by expert panels.[5]

Data from multiple prospective studies has indicated little independent risk of bone mineral density loss or fracture from isolated PPI use.[39–42] Additional prospective data on the long-term safety of PPI has come from a randomized controlled trial of 17,598 participants with stable cardiovascular disease randomized to either pantoprazole 40 mg daily or placebo and one of four anticoagulant regimens over three years.[43] The data from this study were examined for a variety of long-term side effects seen in prior population-based studies. No significant differences were seen in pneumonia, cardiovascular disease, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cancer, hospitalizations, and all-cause mortality. Current guidelines do not recommend routine screening labs for renal function, bone health, or nutritional status in patients receiving long-term PPI.[5]

Of the outcomes of interest, the only finding was a significant increase in enteric infections in pantoprazole compared to placebo groups (1.4% versus 1.0% in the placebo group; odds ratio, 1.33, 95%CI: 1.01 to 1.75, *P*=0.04). These included *Salmonella, E.coli, Shigella*, and Campylobacter infections, and were observed at a lower rate than had been reported in

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prior review of observational studies.[44] There was a nonsignificant increase in *Clostridium difficile* infection in thirteen individuals in the pantoprazole treated groups.[43] Gastric acid is bactericidal and plays an important role in host defense against enteric pathogens. Acid suppression has been confirmed to increase susceptibility to enteric pathogens in murine models, which confirms this suspected mechanism.[45,46]

Idiosyncratic adverse events: There have been case reports of idiosyncratic adverse events with PPI use. By definition, these events are unpredictable and nonspecific. For PPI, these events are rare and include acute interstitial nephritis[47,48] and subacute cutaneous lupus.[49,50]

Adverse events associated with polypharmacy—Many patients taking PPI are receiving other medications This is thought to be a contributing factor in certain types of adverse events. There have been reports of rhabdomyolysis in patients concurrently using PPI and β-hydroxy-β-methylglutaryl-CoA reductase inhibitors (statins).[51,52] However, these events are rare and rhabdomyolysis is a known complication with statin therapy. Further study is needed to understand whether PPI increases the risk for rhabdomyolysis with statin therapy. Hypomagnesemia has been reported with long-term PPI use. In the absence of other medications, PPI use is associated with low urinary magnesium, which implies that there is reduced uptake of magnesium from the GI tract.[53–56] Loop and thiazide diuretics promote urinary magnesium excretion, and the combination of PPI with these medications can increase the risk of hypomagnesemia. Prolonged QT interval and torsades de pointes have been associated with severe hypomagnesemia attributed to PPI use.[57,58] Torsades de pointes has also been reported in patients taking both PPI and drugs that prolong the QT-interval.[59–61] While reports of these reactions are rare, thorough medication review and discontinuing unnecessary medications can reduce the potential risk for harm.

Drug allergy—Awareness of potential drug hypersensitivity reactions are of particular importance to the practicing allergist. Although PPIs are generally well-tolerated, there have been cases of both immediate- and cell-mediated hypersensitivity to oral and IV forms of PPI, including omeprazole, esomeprazole, rabeprazole, lansoprazole, and pantoprazole. There have been rare reports of severe cutaneous reactions to PPI.[62,63] A recent review of case reports and small case series describing hypersensitivity reactions to PPI found that most were immediate reactions (309 out of 443, 69%), with anaphylaxis described in 53.6% of patients and angioedema or urticaria in 44.1% of patients.[64] PPIs triggered 0.8% of anaphylaxis cases in the Uppsala Monitoring Centre database of suspected adverse drug reactions.[65] In a study of 2119 patients in the French pharmacovigilance database, PPI elicited and urticaria or angioedema in 6 patients and anaphylaxis in 14 patients.[66]

The validity of skin prick testing for evaluation of immediate hypersensitivity to PPIs has been evaluated and varying non-irritating concentrations for skin prick and intradermal testing have been reported.[67–71] Recommendations for nonirritating testing concentrations have been reviewed in detail elsewhere, including current recommendations to maximize sensitivity and specificity.[72] Intradermal testing should only be performed using injectable intravenous preparations of PPIs, as crushed tablets and oral solutions can be irritating.[72] Recent prospective study of skin testing for PPI in 65 patients with history suggestive of

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immediate hypersensitivity to PPI and 30 controls was performed using standardized skin prick and intradermal concentrations for omeprazole (SPT: 20mg/mL, 4mg/mL, 0.4 mg/mL; IDT: 0.004 mg/ml, 0.04 mg/ml, 0.4 mg/ml), lansoprazole (SPT: 30 mg/ml), pantoprazole (SPT: 40 mg/ml, 4 mg/ml, 0.4 mg/ml; IDT: 0.004 mg/ml, 0.04 mg/ml, 0.4 mg/ml), rabeprazole (SPT: 20 mg/ml), and esomeprazole (SPT: 20 mg/ml, 8 mg/ml, 0.8 mg/ml; IDT: 0.008 mg/ml, 0.08 mg/ml, 0.8 mg/ml).[68] Oral provocation tests with the suspected culprit PPI (n=12) and other PPIs (n=61) were performed. Calculated sensitivity was 58.8%, specificity 100%, negative predictive value 70.8 %, and positive predictive value 100 %.[68] The observed sensitivity and negative predictive value was slightly lower than what had been observed with a prior study of 53 patients in which 41 patients completed challenge.[67] Those authors performed SPT using the undiluted commercial preparation (40 mg/mL) for omeprazole, esomeprazole, and pantoprazole, and rabeprazole (40 mg/mL) and lansoprazole (30 mg/mL) were prepared by dissolving the powder in saline. IDT were performed with the injectable preparations of omeprazole, esomeprazole, and pantoprazole at 0.4 and 4 mg/mL. In this study, only 1 of 9 patients with a prior grade III hypersensitivity reaction consented to oral challenge, therefore patients participating in oral challenge had more mild reactions. The sensitivity of skin testing was 61.3%, specificity was 100%, negative predictive value was 91.9%, and positive predictive values was 100%.[67]

Cross reactivity patterns between PPIs have been described, and likely relate to the structures of the drugs.[72] Patients with hypersensitivity to pantoprazole have been shown to have positive SPT or reactions to omeprazole or esopmeprazole.[67,70,73]

Of note, enteric coatings on delayed-release formulations of PPI can contain gelatin.[74] Full ingredient lists and other prescribing information of FDA-approved medications can be checked at dailymed.nlm.nih.gov. There have been reports of anaphylaxis induced by gelatin in enteric coatings in gelatin-sensitized individuals,[75] and it may be necessary to perform skin testing or challenge to both gelatin and the drug to differentiate the cause of anaphylaxis.[65]

Risk of allergic disease following PPI use—The development of atopic disease is complex and is thought to result from a combination of genetic predisposition and prenatal and early life environmental exposures.[76] Exposure to acid suppressant medications, both prenatally and in childhood, have been linked to the development of multiple atopic diseases including asthma, food allergy and eosinophilic esophagitis (Table 2).[77]

The most well-studied association described to date is between exposure to ASMs and PPI and subsequent development of asthma. In 2009, the first association between prenatal exposure to PPIs and H2RAs increased risk of asthma in childhood was described.[78] Subsequently, two meta-analyses confirmed these initial findings and reported that prenatal PPIs were associated with an overall increased risk of asthma in childhood (RR = 1.34; 95% CI 1.18–1.52; I^2 = 46% and HR 1.30; 95% CI, 1.07–1.56; I^2 = 45.2%).[79,80]

A large cohort study found children prescribed PPIs during infancy (first 6 months of life) had an increased risk for multiple atopic conditions including asthma (aHR for PPI 1.41,95%CI:1.31–1.52), food allergy (aHR for PPI 2.59,95%CI: 2.25–3.00) and allergic

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rhinitis (aHR for PPI 1.44,95%CI: 1.36–1.52.).[81] More recently the relationship between childhood exposure to PPI and development of asthma was confirmed among a large cohort of children in Sweden.[82] This study found that PPI exposure during childhood was associated with increased risk of incident asthma (HR of 1.57 [95% CI, 1.49–1.64]). The highest risk of asthma was among those exposed as infants and toddlers (HR of 1.83 [95% CI, 1.65–2.03]).

While these studies included large numbers of patients, the effect sizes seen were relatively small. Further, the studies were retrospective and may fail to account for all potential biases due to confounding. One particular concern for exposure during childhood is protopathic bias; where symptoms of cough may be attributed to reflux and treated with PPI but in time manifest more completely as asthma.

Less is known about the association between PPI exposure and the specific risk of IgE-mediated food allergy, however several studies have found an increased risk of food allergy. A small cross-sectional study found an increased risk of food allergy following childhood exposure to PPI and all other ASM (adjusted prevalence ratio 1.70, 95%CI 1.10–2.50).[83] Another smaller case control study found a large increased risk of subsequent development in eosinophilic esophagitis (EoE) in those exposed to ASM during infancy (aOR 6.05 95%CI: 2.55–14.0).[84]

Several mechanisms have been suggested as the potential causal link between PPI use and development of atopy. These possible mechanisms include allergic sensitization, type 2 (T2) cytokine skewing and alterations in the microbiome. Mouse models suggest that ASM exposure increases formation of IgE to dietary antigens, type 2 cytokines, and clinical food allergy.[85] In a subsequent study of adults treated with 3 months of either PPI or H2RA for dyspepsia or chronic gastritis, food allergen sensitization was examined before and after ASM use.[86] Of the patients with pre-existing food specific IgE, 10% were noted to have a rise in serum food-specific IgE levels. However, 15% of the subjects developed *de novo* allergen sensitization, suggesting that ASM use could contribute to food-allergen sensitization in patients who may be at risk of food allergy.

Currently, the most compelling potential mechanism is the alteration of the microbiome leading to dysbiosis (Figure 1). It is increasingly recognized that the gut and airway microbiome play a key role in the pathobiology of allergic disease and dysbiosis increases risk of allergic disorders[87,88] PPIs alter the gut and possibly even the airway microbiome leading to dysbiosis including a decrease in microbial diversity, lower abundance of gut commensal, and an increase in abundance of oral and upper gastrointestinal commensals.[89,90] These deleterious alterations may have lasting impacts when exposure occurs during the critical window for immune development (prenatal and early life).

There is a growing body of evidence suggesting that there is a true association between exposure to ASMs and the risk for developing allergic disease, but we must consider the possibility that the results are affected by unmeasured confounding or by cofounding by indication. For example, failure to thrive or vomiting in young infants may be attributed to reflux and treated with PPI, but ultimately are early signs of other underlying

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conditions such as EoE or milk protein intolerance. Further replication of results in multiple populations and using detailed prospective data will help to answer this important clinical question. For now, it is wise to carefully consider the risks and benefits of acid suppressant medication therapy during pregnancy, infancy and childhood and to restrict use of these medications to indications for which they are clinically indicated.

Conclusions:

Although PPI have a demonstrated role for the treatment of both short- and long-term conditions, they are frequently over-prescribed and are available without a prescription in many countries. Within the context of routine allergy care, PPIs are used to treat patients with comorbid GERD and in management of EoE.[31,34] EoE is considered an indication for continuous long-term PPI therapy.[8]

PPI have been extensively studied in short-term randomized controlled studies and have a well-described and acceptable short term safety profile. Care should be exercised when beginning PPI therapy in individuals on multiple medications due to the risk for adverse drug-drug interactions. The potential long-term adverse effects of PPIs have been scrutinized, with many initial associations identified. However, the current body of evidence does not entirely support a strong association between PPIs use and many potential long term adverse effects. Prospective studies of PPI have demonstrated an increased risk for enteric infection, including *C.difficile* infections.[43]. Data regarding long-term adverse effects is particularly lacking among pediatric and young-adult populations, which has relevance to long-term use in EoE.

Epidemiologic data suggests that PPI exposure during pregnancy and childhood is associated with risk of childhood allergic disease including asthma, food allergy and EoE. The most compelling potential causal mechanism is alteration of the microbiome. However, the possibility of uncontrolled cofounding remains, and additional prospective studies would be beneficial to clarify the magnitude of this effect.

Concurrent with national guidelines, allergists should use PPIs only when clinically indicated and therefore most likely to have clinical benefit.[5] Risks and benefits can be discussed with patients. Choosing the lowest effective dose for the shortest required duration of therapy is an effective option to minimize the risk of harm. For patients on chronic PPI, a trial of PPI de-escalation use should be considered in patients if there is not an indication for continuous long-term PPI therapy.[8]

Conflict of Interest:

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Abbreviations:

aHR	adjusted hazard ratio
ASM	acid suppressant medications
aOR	adjusted odds ratio
CI	confidence interval
CYP2C19	Cytochrome P450 family 2 subfamily C member 19
EoE	eosinophilic esophagitis
FEV1	Forced expiratory volume in the first second
FDA	Food & Drug Association
GERD	gastroesophageal reflux disease
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
H2RA	histamine-2 receptor antagonist
HR	hazard ratio
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
IgE	immunoglobulin E
PPI	proton pump inhibitor
T2	type 2
RR	relative risk

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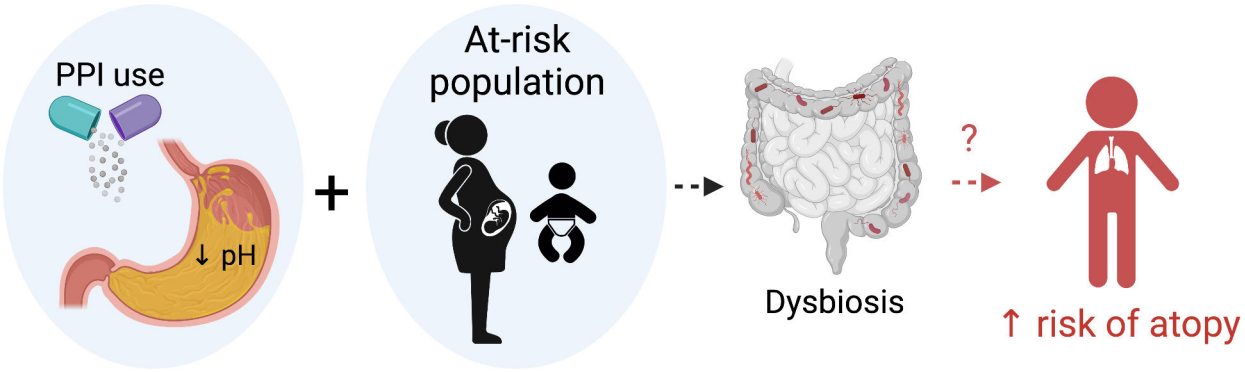

Figure 1:

Schematic of hypothesis of mechanistic link between early life PPI exposure and risk of subsequent atopy. In susceptible individuals, prenatal or early life PPI exposure reduces gastric acid. While this mechanism is not fully understood, microbial dysbiosis and later atopic disease may occur in a subset of patients. Figure created with biorender.com.

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Table 1.

US Food and Drug Administration-approved indications of proton pump inhibitors[91,92]

- Erosive esophagitis
- Gastric Ulcer Disease
- Gastroesophageal Reflux Disease
- Zollinger-Ellison Syndrome (pathological hyper-secretory conditions)
- Duodenal Ulcer
- NSAID-associated ulcers
- Eradication of *Helicobacter pylori*

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Table 2.

Proton pump exposure and risk for allergic disease

Author, Year	Study Type	Exposure	Allergic Outcome and Finding
Devine, et al., 2017[80]	Meta-analysis	Prenatal PPI	Asthma: HR 1.30 (95%CI:1.07–1.56)
Lai et al., 2018[79]	Meta-analysis	Prenatal PPI	Asthma: RR 1.34 (95%CI 1.18–1.52)
Mitre et al., 2018[81]	Cohort study	PPI during infancy (age <6 months)	Asthma aHR 1.41 (95%CI: 1.31–1.52) Food Allergy aHR 2.59 (95%CI: 2.25–3.00) Allergic Rhinitis aHR 1.44 (95%CI: 1.36–1.52)
Wang et al., 2021[82]	Cohort study	PPI during childhood (age < 18 years)	Asthma: HR 1.57 (95%CI: 1.49–1.64)
DeMuth, et al., 2013[83]	Cross-sectional	PPI and other ASM during childhood	Food Allergy aPR 1.70 (95%CI 1.10–2.50)
Jensen et al., 2018[84]	Case Control	PPI exposure during infancy	EoE aOR 6.05 (95%CI: 2.55–14.0)

ASM: acid suppressant medications, CI: confidence interval; EOE: eosinophilic esophagitis, aHR, adjusted hazard ratio, HR: hazard ratio, aOR: adjusted odds ratio, PPI: proton pump inhibitor, aPR: adjusted prevalence ratio