

# Association between proton pump inhibitors and respiratory infections: A systematic review and meta-analysis of clinical trials

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**BACKGROUND:** Proton pump inhibitors (PPIs) have become the mainstay of treatment for and prevention of many serious gastrointestinal diseases. Laboratory and clinical evidence suggests that the increase in gastric pH caused by PPIs may be linked to increased bacterial colonization of the stomach and may predispose patients to an increased risk for respiratory infections.

**OBJECTIVE:** To examine the association between PPI treatment and respiratory infections.

**METHODS:** A literature search was conducted using PubMed, MEDLINE and Cochrane databases of randomized, placebo-controlled trials evaluating the efficacy of PPIs. Studies that listed and quantified the specific adverse events of 'respiratory infection' or 'upper respiratory infection' (or equivalent), and compared their rates between PPIs and placebo were included. The  $\chi^2$  analysis was used to calculate the significance of association in individual studies and a meta-analysis of the selected studies was performed.

**RESULTS:** Of 7457 studies initially identified and 70 relevant randomized, controlled trials (RCTs) selected, seven studies met the inclusion criteria. A total of 16 comparisons for  $\chi^2$  analysis were possible given the multiple dosage arms used in several studies. PPIs included in the studies were esomeprazole, rabeprazole, pantoprazole and omeprazole. More than one-half of the studies showed a trend toward an association between PPI use and respiratory infections, although the majority of the studies failed to show a significant correlation. A single study using high-dose esomeprazole (40 mg) showed a significant association – 4.3% rate of respiratory infections in the active group compared with 0% in the placebo group ( $P < 0.05$ ). Meta-analysis showed a trend toward an association between PPIs and respiratory infections, although it failed to reach significance (OR 1.42, 95% CI 0.86 to 2.35;  $P = 0.17$ ).

**CONCLUSION:** Although a trend was evident in both a  $\chi^2$  analysis of individual studies and a meta-analysis, the present review and meta-analysis failed to show a conclusive association between PPIs and respiratory infections. Very few RCTs actively sought out respiratory infections, which excluded the majority of RCTs identified. A well-structured, placebo-controlled prospective study would be needed to determine whether a true association between PPIs and respiratory infections exists.

**Key Words:** Proton pump inhibitors; Respiratory infections

## L'association entre les inhibiteurs de la pompe à protons et les infections respiratoires : Une analyse systématique et une méta-analyse des essais cliniques

**HISTORIQUE :** Les inhibiteurs de la pompe à protons (IPP) sont devenus le pilier du traitement et de la prévention de nombreuses maladies gastro-intestinales graves. D'après des données de laboratoire et des données cliniques probantes, l'augmentation du pH gastrique attribuable aux IPP pourrait être reliée à une colonisation bactérienne accrue de l'estomac et prédisposer les patients à un plus grand risque d'infections respiratoires.

**OBJECTIF :** Examiner l'association entre le traitement aux IPP et les infections respiratoires.

**MÉTHODOLOGIE :** À l'aide des bases de données de PubMed, de MEDLINE et de la bibliothèque Cochrane, les auteurs ont effectué une recherche dans les publications afin de trouver les essais aléatoires et contrôlés contre placebo évaluant l'efficacité des IPP. Ils ont inclus les études qui énuméraient et quantifiaient les effets indésirables précis de « l'infection respiratoire » ou de « l'infection des voies respiratoires supérieures » (ou de l'équivalent) et qui comparaient leur taux entre les IPP et les placebos. L'analyse  $\chi^2$  a permis de calculer la signification de l'association dans les études individuelles et une méta-analyse d'études sélectionnée.

**RÉSULTATS :** Parmi les 7 457 études repérées au départ et les 70 essais aléatoires et contrôlés (EAC) sélectionnés, sept études respectaient les critères d'inclusion. Il a été possible de procéder à un total de 16 comparaisons pour les besoins de l'analyse  $\chi^2$ , en raison des multiples groupes de posologie utilisés dans plusieurs études. L'esomeprazole, le rabeprazole, le pantoprazole et l'oméprazole étaient les IPP inclus dans les études. Plus de la moitié des études ont révélé une tendance vers une association entre le recours aux IPP et les infections respiratoires, même si la majorité des études ne démontraient pas de corrélation significative en ce sens. Une seule étude faisant appel à de l'esomeprazole à forte dose (40 mg) a indiqué une association significative, soit un taux d'infections respiratoires de 4,3 % dans le groupe actif par rapport à 0 % dans le groupe prenant un placebo ( $P < 0,05$ ). La méta-analyse a révélé une tendance vers une association entre les IPP et les infections respiratoires, sans pour autant être significative (RRR 1,42, 95 % IC 0,86 à 2,35,  $P = 0,17$ ).

**CONCLUSION :** Même si une tendance était évidente à la fois dans l'analyse  $\chi^2$  des études individuelles et la méta-analyse, les présentes analyse et méta-analyse n'ont pu démontrer d'association concluante entre les IPP et les infections respiratoires. Très peu d'EAC évaluaient les infections respiratoires, ce qui excluait la majorité des EAC repérés. Il faudrait entreprendre une étude prospective bien structurée contrôlée contre placebo pour déterminer s'il existe une véritable association entre les IPP et les infections respiratoires.

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Proton pump inhibitors (PPIs) have become the mainstay of treatment and prophylaxis for gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), and are one of the most prescribed classes of medications in North America because of both their excellent efficacy and safety profiles (1-3).

The most commonly reported side effects of PPIs include headache, nausea and diarrhea, which occur only slightly more frequently than with placebo in randomized, controlled trials (RCTs). Long-term safety issues with PPIs have become progressively less discussed in recent years, with no long-term complications reported in up to 11 years of continuous use (4). Initial concerns regarding the possible increased risk for atrophic gastritis in *Helicobacter pylori*-positive patients receiving PPIs and the potential for cancer risk have been refuted by a clinical trial (4). Dosage reduction of PPIs is not necessary, even in patients with compromised renal or hepatic function; all of this has contributed to the soaring popularity of PPI use in the general population.

While initial investigations into complications of PPI use focused on dysplasia and cancer, there has been growing evidence that PPI use may not be completely free of risk. Recent cohort and case-control studies investigating the risk for *Clostridium difficile* infection with in-hospital PPI use have shown a positive association, with ORs ranging from 2.4 to 2.7 (5,6,7). More recent data suggest that the association may even extend into the community setting (8).

Laboratory and clinical evidence suggests that a less acidic gastric pH may be linked to increased bacterial colonization of the stomach (9). This colonization is thought to be an important source of pathogens that could cause pneumonia by translocating to the lungs via the upper digestive and upper respiratory tracts (10). Until recently, studies looking specifically at clinical outcomes such as ventilator-associated pneumonia in the critical care setting have not been definitive in either demonstrating or entirely refuting a link to acid suppressive drugs (ASDs) (11,12). Although it accounts for 60,000 deaths annually in the United States alone, until recently, virtually no attention has been paid to any association between community-acquired pneumonia (CAP) and ASD use. Over the past few years, European population-based studies (13-15) have suggested that an association may exist.

The objective of the present study was to examine the association between the outpatient use of PPIs and respiratory infections, including CAP.

## METHODS

### Study identification

Relevant articles evaluating the efficacy of PPIs published before August 2007 were identified through PubMed, MEDLINE and Cochrane databases. Individual searches using the key words "proton pump inhibitors", "PPI", "esomeprazole", "rabeprazole", "lansoprazole", "pantoprazole" and "omeprazole" were conducted. Studies identified by this method were used to identify additional citations.

### Study selection

The meta-analysis inclusion criteria included randomized, single- or double-blinded, placebo-controlled studies investigating PPIs in various gastrointestinal diseases. Unblinded studies were excluded. Most studies identified had evaluated the use of PPIs in patients with GERD or PUD. Selected studies were required to have clearly presented the prevalence of

the specific adverse events of respiratory infection, upper respiratory infection or pneumonia in both treatment and placebo arms. Studies stating no difference in adverse events without explicit mention of respiratory infections were excluded.

### Data extraction

Data regarding adverse events were required to be given explicitly, including clearly stating the adverse events of respiratory infections and upper respiratory infections (or equivalent), with quantification of both active and placebo arms.

### Data analysis

$\chi^2$  analyses evaluating active and placebo arms, as well as their association with respiratory infections, were performed to assess the significance of association. A meta-analysis of outcomes was performed by combining trials using the Mantel-Haenszel method (RevMan 4.2; The Cochrane Collaboration, United Kingdom). Statistical heterogeneity was evaluated and  $P < 0.1$  was considered significant. Primary outcomes were summarized.

## RESULTS

The initial key word search identified 7457 studies. The majority were excluded because they were either not RCTs or because the control group did not receive a placebo. Most studies identified evaluated the use of PPIs in patients with GERD or PUD. Only 70 RCTs met the major inclusion criteria. Of these 70 studies, 63 were excluded because it was not possible to isolate the adverse events of respiratory infection, upper respiratory infection or pneumonia for the active group, control group or both.

Seven studies (16-22) met all predefined inclusion criteria. All seven studies were peer-reviewed publications. Three studies used esomeprazole, two used omeprazole, one used pantoprazole and one used rabeprazole. All studies compared PPIs with placebos. They ranged in duration from four weeks to six months. A total of 2586 patients (1943 active treatment, 643 placebo) were included in all of the studies. Table 1 summarizes the characteristics of the trials.

Table 2 summarizes the prevalence of respiratory infections in the included studies. The mean prevalence of respiratory infections in the active treatment groups was 4.2% (range 0% to 6.6%) and in the placebo groups was 2.9% (range 0% to 8%).

$\chi^2$  analyses (Table 3) revealed that the majority of trials showed no statistically significant association between PPIs and respiratory infections, although five of seven studies did demonstrate a greater number of infections in the active treatment arm. Only a single treatment arm in one study showed a significant association; this occurred in the esomeprazole 40 mg arm when tested against placebo in a study by Vakil et al (17), revealing a P-value of 0.05.

A meta-analysis of included studies (Figure 1) revealed no significant association between PPI use and respiratory infection. A total of 84 respiratory infections (of 1943 subjects) occurred in treatment groups and 22 (of 643 subjects) occurred in placebo groups; 4.3% and 3.4%, respectively. The total OR for developing a respiratory infection with PPI treatment was found to be 1.42 (95% CI 0.86 to 2.35). The test for overall effect revealed a P-value of 0.17 (deemed insignificant), and the test for heterogeneity revealed a P-value of 0.51.

## DISCUSSION

The present study failed to show a significant association between the use of PPIs and respiratory tract infections over the course of use during which these medications are normally initially prescribed. While statistically insignificant, the absolute incidence of respiratory infections was estimated to be 1.3% higher in patients receiving PPIs than in those receiving placebo. This would translate into a number needed to harm of approximately 77, suggesting that even if a true association exists, it may have limited clinical significance, except possibly in the most vulnerable patients.

Only a minority of the 70 trials identified actually tracked respiratory infections such as pneumonia. Another limitation of our study is that most studies used the term 'respiratory infections' without clearly defining the diagnostic criteria used (history, radiological, positive cultures, antibiotic use, etc) for those events and, as a result, there may have been a significant degree of subjectivity related to those outcomes. We could not determine the proportion of viral infections in each study, which would be important given that the hypothesis forwarded is that ASDs may cause bacterial respiratory infections through bacterial translocation. There are no randomized trials of PPIs investigating respiratory infections as an end point and we therefore identified respiratory infections followed in RCTs as adverse events. Reporting bias may have influenced the results because only a minority of studies reported the presence or absence of respiratory infections. Despite these limitations, we were able to pool the results of more than 2000 patients from placebo-controlled trials, the strongest level of evidence available.

Our investigation was stimulated in part by the results of two Dutch studies by Laheij et al (14,15). The first, a retrospective questionnaire (15) of 700 outpatients, suggested that ASD users were 2.3 times more likely to have had symptoms of a respiratory infection in the month preceding assessment. In the second, a large cohort of nearly one million patients was studied (14). In this study, the retrospective cohort analysis revealed that ASD users were nearly 4.5 times more likely to develop pneumonia than non-users. A case-control analysis of the same cohort, in an attempt to control for confounders, revealed an adjusted OR of 1.89 for PPIs and 1.63 for histamine-2 receptor antagonists; both values were statistically significant. The authors estimated an attributable risk of one extra case of pneumonia for every 100 years of PPI use.

In the present systematic review and meta-analysis, we have not been able to demonstrate a causal relationship between PPIs and pneumonia. However, the link is, without question, plausible. There is an impressive volume of literature supporting several facets of a possible physiological connection. It is clear that ASDs, and especially PPIs, are effective in raising gastric pH (23-30). Both basic science and clinical data show that higher gastric pH is associated with gastric bacterial colonization (30-32) and critical care studies have demonstrated an association between ASDs and increased bacterial colonization (25,27-30,33-37). Studies have gone on to show that ASDs are associated with increased translocation of gastric pathogens and secondary respiratory colonization (25,29-30,32,38-40). Furthermore, several studies have shown evidence that specific pathogens causing pneumonia in the critical care setting were of gastric origin (28,32,33,41).

The association is also not without precedence. There has been considerable evidence of an association between

**TABLE 1**  
Studies meeting inclusion criteria for the present study

Study	Study arms	Duration of study	Total patients, n (active, placebo)
Talley et al (16)	Esomeprazole 20 mg (on demand: mean 7.8 mg/day) Placebo	6 months	342 (170, 172)
Vakil et al (17)	Esomeprazole 40 mg Esomeprazole 20 mg Esomeprazole 10 mg Placebo	6 months*	373 (281, 92)
Miner et al (18)	Rabeprazole 20 mg Rabeprazole 10 mg Placebo	4 weeks	203 (133, 70)
Johnson et al (19)	Esomeprazole 40 mg Esomeprazole 20 mg Esomeprazole 10 mg Placebo	6 months*	315 (238, 77)
Richter and Bochenek (20)	Pantoprazole 40 mg Pantoprazole 20 mg Pantoprazole 10 mg Placebo	8 weeks	603 (521, 82)
Valenzuela et al (21)	Omeprazole 40 mg Omeprazole 20 mg Placebo	8 weeks	520 (416, 104)
Sontag et al (22)	Omeprazole 40 mg Omeprazole 20 mg Placebo	8 weeks	230 (184, 46)
Total patients			2586 (1943, 643)

\*Adverse events reported only at one month

histamine-2 receptor antagonists, the most studied form of ASDs in the critical care setting, and ventilator-associated pneumonia (25-26,28,33). Several studies have also shown non-significant trends supporting the association (11,27,29,41). The evidence, however, has been mixed, with other studies failing to show any association (34,42-49). Meta-analyses of trials testing ASDs versus sucralfate have supported a possible association, with some showing a significant association between ASDs and pneumonia (50-53), and others showing a nonstatistically significant trend (11,53-55). In these and other studies, the use of ASDs was associated with late, as opposed to early, pneumonia (33,41), possibly accounting for the time required for gastric colonization, translocation and infection (56).

With respect to dose-response, the results of Laheij et al (14) showed that "more than one defined daily dose (DDD)" of PPI has a significantly higher OR for pneumonia than "less than one DDD" (OR 2.63 versus 1.21, respectively). While our study could not provide any conclusive evidence for a dose-response relationship, one study (17) did find a statistically significant association between PPIs and respiratory infections in  $\chi^2$  testing, using higher dose esomeprazole (40 mg versus 10 mg or 20 mg). However, other trials comparing different doses of PPI failed to show any association across all doses.

Although diseases such as nonvariceal upper gastrointestinal bleeding have a significant case fatality rate of approximately 5% (57), the case fatality rate of CAP is not insignificant. Of the one million CAP patients requiring hospitalization in the United States annually (58), 2% to 21% will

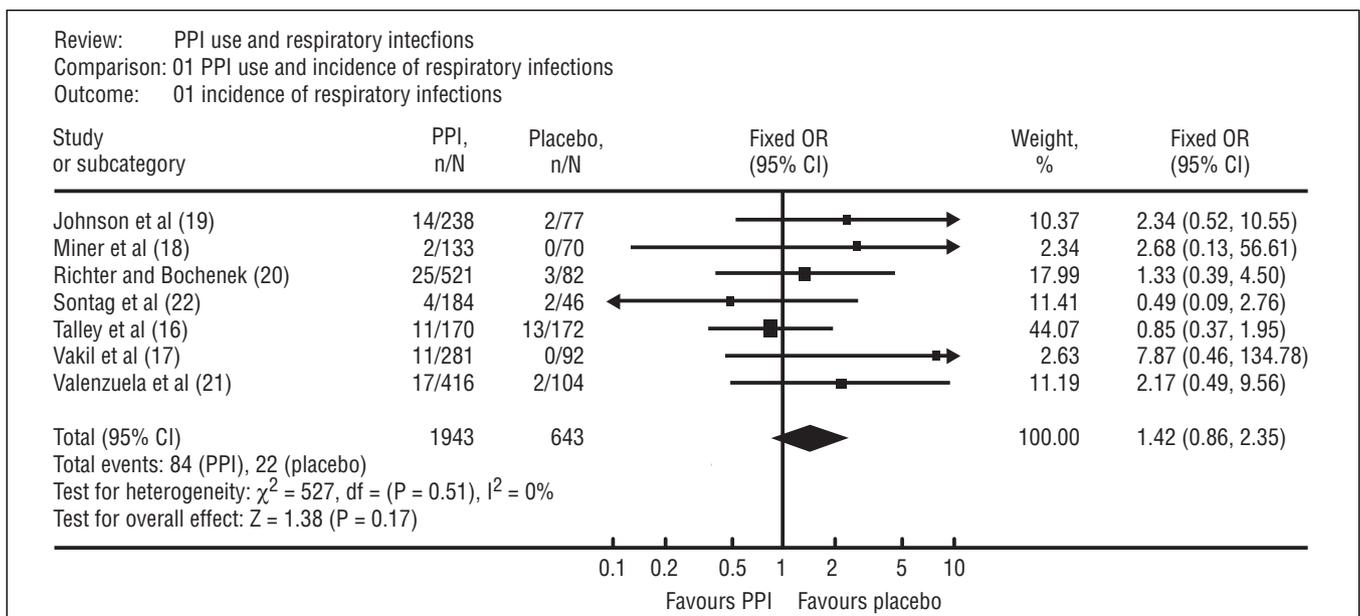
**TABLE 2**  
Prevalence of respiratory infections in included studies

Study	Adverse event quoted	Prevalence of adverse event, % (absolute number)				
		Active group A	Active group B (if present)	Active group C (if present)	Total prevalence (in sum of all active patients)	Placebo
Talley et al (16)	Respiratory infection	6 (11 of 170)	NA	NA	6 (11 of 170)	8 (13 of 172)
Vakil et al (17)	Respiratory infection	4.3 (4 of 92)	4.1 (4 of 98)	3.3 (3 of 91)	3.9 (11 of 281)	0 (0 of 92)
Miner et al (18)	Upper respiratory infection	0 (0 of 68)	3.1 (2 of 65)	NA	1.5 (2 of 133)	0 (0 of 70)
Johnson et al (19)	Respiratory infection	6.2 (5 of 81)	4.9 (4 of 81)	6.6 (5 of 76)	5.9 (14 of 238)	2.6 (2 of 77)
Richter and Bochenek (20)	Respiratory disorders	5.8 (10 of 173)	3.5 (6 of 174)	5.2 (9 of 174)	4.8 (25 of 521)	3.7 (3 of 82)
Valenzuela et al (21)	Upper respiratory infection	3.3 (7 of 214)	5.0 (10 of 202)	NA	5.1 (17 of 416)	1.9 (2 of 104)
Sontag et al (22)	Upper respiratory infection	2.2 (2 of 91)	2.2 (2 of 93)	NA	2.2 (4 of 184)	4.3 (2 of 46)

NA Not applicable

**TABLE 3**  
 $\chi^2$  testing for an association between proton pump inhibitor use and respiratory infections in individual studies, and their treatment arms

Study	Active intervention	Prevalance of respiratory infection in active intervention	Prevalence of respiratory infection in placebo	P
Talley et al (16)	Esomeprazole 20 mg	11 of 170	13 of 172	<1.0
Vakil et al (17)	Esomeprazole 40 mg	4 of 92	0 of 94	<0.05
	Esomeprazole 20 mg	4 of 98	0 of 94	<0.1
	Esomeprazole 10 mg	3 of 91	0 of 94	<0.1
	Esomeprazole 10 mg	3 of 91	0 of 94	<0.1
Miner et al (18)	Rabeprazole 20 mg	0 of 68	0 of 70	Not applicable
	Rabeprazole 10 mg	2 of 65	0 of 70	<0.2
Johnson et al (19)	Esomeprazole 40 mg	5 of 81	2 of 77	<1.0
	Esomeprazole 20 mg	4 of 81	2 of 77	<1.0
	Esomeprazole 10 mg	5 of 76	2 of 77	<1.0
Richter and Bochenek (20)	Pantoprazole 40 mg	10 of 173	3 of 82	<1.0
	Pantoprazole 20 mg	6 of 174	3 of 82	<1.0
	Pantoprazole 10 mg	9 of 174	3 of 82	<1.0
Valenzuela et al (21)	Omeprazole 40 mg	7 of 214	2 of 104	<1.0
	Omeprazole 20 mg	10 of 202	2 of 104	<0.2
Sontag et al (22)	Omeprazole 40 mg	2 of 91	2 of 46	<1.0
	Omeprazole 20 mg	2 of 93	2 of 46	<1.0



**Figure 1)** Results of a meta-analysis testing the association between proton pump inhibitors (PPIs) and respiratory infections. *df* Degrees of freedom

succumb to their illness; this figure rises to 50% among patients with severe disease (59). If PPIs do cause some cases of CAP, the risk-benefit ratio of chronic PPI administration clearly needs to be taken into account, particularly when administered to asymptomatic individuals for prophylactic indications such as the prevention of nonsteroidal anti-inflammatory-induced ulcers. This concern is highlighted by recent evidence that up to 60% of primary care PPI prescriptions may not be fulfilling established PPI indications (60), and by other data showing the explosive growth of the PPI market, with a British study (61) showing a growth of 456% in PPI prescriptions from 1992 to 1997.

The development and use of PPIs has led to a revolution in the management and prophylaxis of some of the most serious and debilitating diseases of the upper gastrointestinal tract over the past two decades. While it is not always possible to perform placebo-controlled trials to answer every clinical question, particularly those pertaining to relatively rare adverse events, the indications for the use of PPIs are sufficiently common that such a trial is likely feasible. Such a study would aid physicians and their patients in making informed decisions regarding the chronic administration of ASD therapy.

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