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## RISK OF COMMUNITY ACQUIRED PNEUMONIA WITH PROTON PUMP INHIBITORS: A SYSTEMIC REVIEW

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### ABSTRACT

**Background:** Proton pump inhibitors (PPIs) are widely used over-the-counter drugs for treatment of acid peptic disease. Irrational use of PPIs without proper indication has exposed patients to unnecessary risks. Currently, PPIs are under scrutiny by U.S.FDA to determine risk of community acquired pneumonia (CAP) as conflicting results have been obtained from various studies.

**Aim:** The aim of our study was to evaluate the risk of CAP with use of PPIs in adults.

**Methods:** We searched PUBMED and MEDLINE databases to identify studies meeting the inclusion criteria. All titles and abstracts were screened independently and in duplicate by authors for eligibility. The primary outcome was first episode of CAP. Only observational studies with a comparison arm were included. **Results :** Based on eligibility criteria, five observational studies were included for analysis. **Conclusion:** Further randomised controlled trials are needed to clarify the risk of CAP with PPI therapy .

**Keywords:** Proton pump inhibitors, Omeprazole, Pneumonia, community acquired pneumonia , CAP.

### INTRODUCTION

Proton pump inhibitors (PPIs) are potent suppressors of gastric acid secretion by inhibiting gastric H<sup>+</sup>K<sup>+</sup>-ATPase. Omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole are five PPIs available for clinical use. In typical doses, these drugs diminish the daily production of acid (basal and stimulated) by 80–95%. Since the discovery, PPIs are widely used to treat gastric and duodenal ulcers, gastroesophageal reflux disease (GERD) including erosive esophagitis, that is either complicated or unresponsive to treatment with H<sub>2</sub> receptor antagonists and for Zollinger-Ellison Syndrome. Lansoprazole is approved for treatment and prevention of recurrence of nonsteroidal anti-inflammatory drug (NSAID) associated gastric ulcers in patients who continue NSAID use and for reducing the risk of duodenal ulcer recurrence

associated with *H. pylori* infections. PPIs are known to cause remarkably few adverse effects like nausea, abdominal pain, constipation, flatulence, and diarrhoea, subacute myopathy, arthralgia, headache, and rashes. However, they are associated with various drug interactions.<sup>[1]</sup>

PPIs have enjoyed worldwide use without the emergence of major safety concerns until recently when the Food and Drug Administration (FDA) issued safety alert regarding increased risk of osteoporosis (hip fracture) with PPIs. U.S.FDA has also advised label changing to include new safety information about a possible increased risk of fractures of the hip, wrist, and spine<sup>[2]</sup>. This is based on the FDA's review of several epidemiological studies. Majority of this studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group. Other concerns

include increased rates of *Clostridium difficile* infection, decrease effectiveness of clopidogrel and risk of pneumonia associated with PPIs. Despite a growing number of studies that have shown PPIs could increase the risk pneumonia, the role of PPIs in pneumonia is still a matter of debate. So, we carried out a systemic review of five observational studies to find out the possible risk of community acquired pneumonia (CAP) in adults with PPIs use as compared with non users.

## METHODS

**Search strategy:** We performed computerized electronic search in PUBMED, MEDLINE using the following terms: anti-ulcer agent, proton pump inhibitor, PPI, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, antacid, pneumonia, community-acquired pneumonia and CAP. Abstracts, letters, case reports, and review articles were excluded from the search. Our search was restricted to studies involving human subjects and published in the English language. Bibliographies from index citations were reviewed for additional relevant studies. To identify relevant citations further, we also used the PubMed 'related articles' feature.

**Selection of studies:** All titles and abstracts were screened and reviewed independently and in duplicate (SM and MK) for eligibility. All observational studies evaluating the association between use of PPIs and the first episode of CAP in adults were included. We excluded studies with children (<18 years) as there are few indications for PPI use<sup>[3]</sup>, hospital acquired or ventilator associated pneumonia, immunocompromised patients, patients at increased risk of aspiration pneumonitis (i.e. perioperative patients, patients with gastric feeding tubes and patients taking PPIs for GERD).

**Data extraction and analysis:** Full texts of the relevant papers were obtained. Data was extracted. Information regarding study characteristics, demographic characteristics,

clinical details, drugs used, duration and dose of study drugs and risk of CAP was extracted. Disagreement among reviewers was resolved by discussion.

## RESULTS

Review of the abstracts reduced the number of potentially relevant manuscripts to 24. Thorough search retrieved **seven** studies<sup>[4-10]</sup> fulfilling the eligibility criteria. To minimise bias, we excluded TWO studies, one showed combined data for acid suppressive drugs<sup>[4]</sup> and the other included recurrent cases of CAP<sup>[5]</sup>. The included studies are summarized in Table 1.

A nested case-control trial was done in the Netherlands by Laheij and colleagues<sup>[6]</sup> to examine the association between acid suppressive therapy (AST) and the development of CAP. It was 4.5 times more often in patients taking AST compared to those who had never taken AST. The adjusted relative risk for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% confidence interval, 1.36-2.62), while 1.63-for H2RAs. The results of studies are depicted in Table-2.

Luis Alberto García Rodríguez and colleagues<sup>[7]</sup> performed a a nested case-control analysis using prospectively recorded data in The Health Improvement Network database in the UK. They observed a small increase in the risk of CAP associated with current PPI use ((RR -- 1.16; 95% confidence interval 1.03–1.31), particularly during the first 12 months of treatment and at higher doses, but not with H<sub>2</sub>-receptor antagonists (0.98 [0.80 –1.20])

A large population-based case control study<sup>[8]</sup> using data from the Denmark also reported moderately increased risk of CAP with recent use of PPIs. The adjusted odds ratio (OR) for current use of PPIs with CAP was 1.5 (95% CI - 1.3-1.7). A strong association of CAP (OR, 5.0; 95% 2.1-11.7) was observed with recent use of PPIs (0-7 days before index date) (Table-2)

Another nested case-control study <sup>[9]</sup> also concluded that PPIs started within the past 30 days was associated with an increased risk for CAP, whereas longer-term current use was not. For PPIs started within the previous 2 days, the adjusted OR was 6.53 [CI, 3.95 to 10.80]), for 7 days 3.79 [CI, 2.66 to 5.42]), and 14 days adjusted OR 3.21 [CI, 2.46 to 4.18]). The important limitation is to corroborate a diagnosis of CAP, no radiographic evidence was available. Jen-Tzer Gau and colleagues <sup>[10]</sup> conducted a retrospective case-control study of adults 65 years or older at a rural hospital of State of Ohio. Cases (N = 194) were those with radiographic evidence of pneumonia on admission. The crude OR and the AOR of PPI use for CAP was 1.41 [95% CI = 1.03 - 1.93] and 1.18 [95% CI = 0.80 - 1.74] after adjusting for the various confounders. No association was found between current PPI use and the risk for CAP, while inhaled corticosteroids and atypical antipsychotics use was both associated with an increased risk for CAP in hospitalized patients of a rural community.

## DISCUSSION

In our analysis of five studies with 13,04,884 patients, we found risk of CAP with PPI use, more with current use as compared to placebo or acid suppressive drugs.

Studies looking at the possible association between community acquired pneumonia and PPIs have shown conflicting results. A meta analysis of six studies by Jhonstone et al <sup>[11]</sup> found newly prescribed PPIs had double risk of acquiring CAP as compared to non users while no difference was observed for chronic users. They included a study (Eurich) with recurrent CAP cases. They observed significant heterogeneity which limits the interpretation of the summary odds ratio. To avoid heterogeneity, we have not included that study.

Despite various studies have been done over past few years, to date the exact mechanism of PPIs

causing CAP is not well established. One reason could be overgrowth of bacteria in stomach due to loss of protective gastric acid and subsequent micro aspiration of bacteria in lower airways leading to pneumonia, especially in patients with compromised oropharyngeal protective reflexes (eg, patients on mechanical ventilation). <sup>[12]</sup> However, these do not explain association of CAP with duration of PPIs use and need further evaluation.

There are several limitations of the present study. Our study search was limited to English language that may serve a source of bias. Though only studies meeting inclusion criteria were selected, we could not neglect possibility of bias and heterogeneity. Difference in demographic characteristics like age, sex, comorbidity factors; difference in type, dose and duration of PPIs used, difference in methods of conducting studies and adjustment of confounding variables could be important factors leading to heterogeneity in studies. Moreover, the observational studies are mainly limited by inability to account for unmeasured confounders, a problem virtually eliminated by randomization strategies in prospective studies. However, Su Golder <sup>[13]</sup> from his methodological overview concluded that difference on average in the risk estimate of adverse effects of an intervention derived from meta-analyses of RCTs and meta-analyses of observational studies is not significant.

## CONCLUSION

In a review of 13,04,884 patients, we found possible risk of CAP with current use of PPIs. Further randomised controlled trials are needed to explore the risk of CAP with PPI use. Our review can serve as a signal for future randomised controlled trials. A rational approach to prevent is: PPIs, like any other drugs, should be prescribed only if indicated and continued till required. Vigilant clinicians and robust pharmacovigilance system can only solve the question.

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**Table-1 Studies evaluating risk of CAP with use of PPIs**

Sl No.	Study	Sample size (Cases+ control)	Methods	Population	Intervention	Outcome Measured
1	Robert J. F. Laheij	3,64,683 (5551+)	Nested case control	Netherlands database (1995-2002)	Acid suppressive drugs	CAP
2	García Rodríguez 2009	17,290 (7297+9993)	Nested case control	UK (2000-2005)	PPIs- Dose and duration	Hospitalized/ outpatient
3	Gulmez 2007	41,818 (7642+34,176)	Case control	Denmark (2000-2004)	PPIs- Dose and duration	First Hospitalization with CAP in that year
4	Monika Sarkar 2008	8,79,947 (80,066+7,99,881)	Nested case control	UK (1989-2002)	PPIs- Dose and duration	Hospitalized/ outpatient
5	Jen-Tzer Gau 2010	1146 (194+952)	Retrospective case control	Athens Medical records of 2004 and 2008	PPIs	First Hospitalization with CAP in that year

**Table-2 Results of included studies**

Sr.No	Study	Results	Conclusion
1	Robert J. F. Laheij, 2004	Adjusted OR current use 1.89 (95%CI, 1.36-2.62)	Current use is associated with CAP. Positive response with dose seen.
2	García Rodríguez, 2009	Relative Risk Current use - 1.16 (95%CI, 1.03–1.31)	Small risk ,increases after 60years , smoking, high dose.
3	Gulmez ,2007	Adjusted OR Current use -1.5 (1.3-1.7, p<0.001)	Moderate increase in risk , more with new users. No dose response seen.
4	Monika Sarkar, 2008	Adjusted OR Current use -2.5 (95%CI, 1.96-2.15)	Association seen with current and high dose of PPI. Not with 1.5DDD.
5	Jen-Tzer Gau, 2010	Adjusted OR Current use -1.18(95%CI, 0.80-1.74) Crude OR-1.41 (95%CI, 1.03-1.93)	No/ weak association with current use after adjusting for various confounders.

OR- Odds Ratio, DDD- Defined daily dose

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