

## Increased Pneumonia Risk with Gastric Acid Suppression Therapy?

Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955–60.

### Study Overview

**Objective.** To examine the association between acid-suppressive drug use and occurrence of community-acquired pneumonia (CAP).

**Design.** Population cohort study with nested case-control analysis.

**Settings and participants.** Participants were identified from Netherlands' Integrated Primary Care Information database between 1 January 1995 and 31 December 2002. Incidence rates for pneumonia were calculated for incident users and nonusers of acid suppression drugs. A case-control analysis was nested in a cohort of incident users of acid-suppressive drugs; the cases were individuals with incident pneumonia during or after stoppage of acid-suppressive drug use. Up to 10 controls per case were matched for practice, year of birth, sex, and index date. Conditional logistic regression was used to compare the risk of CAP between use of proton pump inhibitors (PPIs) and H<sub>2</sub>-receptor antagonists.

**Main outcome measures.** CAP proven by radiography, sputum culture, or clinical symptom.

**Main results.** Of the 364,683 eligible individuals, 5551 developed first occurrence of pneumonia during follow-up. The crude incidence rate of pneumonia in non-acid-suppressive drug users and acid-suppressive drug users was 0.6 per 100 person-years and 2.45 per 100 person-years, respectively. The adjusted relative risk (RR) for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% confidence interval [CI], 1.36–2.62). Compared with those who stopped, current users of H<sub>2</sub>-receptor antagonists had a 1.63-fold increased risk of pneumonia (95% CI, 1.07–2.48). A significant positive dose-response relationship was observed for current PPI users but not for H<sub>2</sub>-receptor antagonist users.

**Conclusion.** Current use of gastric acid-suppressive therapy was associated with an increased risk of CAP.

### Commentary

Dyspepsia is a common condition. The reported prevalence of dyspepsia in Western countries generally ranges from 25% to 50% [1]. A recent Canadian study investigated the effect of dyspeptic symptoms on quality of life in the general population and demonstrated that patients with dyspepsia have a significantly lower quality of life than do healthy subjects in the community [2]. Many randomized clinical trials and years of worldwide experience have confirmed the high rate of efficacy and excellent safety profile of acid-suppressive drugs, helping to spur the increased use of PPIs and H<sub>2</sub>-receptor antagonists [3]. However, until this study by Laheij et al, no large-scale population study on the risks of acid-suppressing drugs was available.

This study was made possible by the Dutch health care system's large research database, containing the electronic health records of an entire population. This database enabled appropriate assignment of study cohort (ie, those who received PPI or H<sub>2</sub>-receptor antagonist) and of the cases (ie, those with CAP diagnosis with laboratory/culture/clinical symptoms) and controls. Manual chart review was then performed to ascertain the diagnosis of CAP.

Crude RR of developing CAP for acid suppressant users was 4.5 (95% CI, 3.82–5.12). A nested case-control analysis was then performed and, although the cases included sicker participants (more diabetes, pulmonary diseases, and heart failure), the indication for acid suppressant use was not associated with the risk of pneumonia. Given the adjusted RR for PPIs and H<sub>2</sub>-receptor antagonists (1.89 and 1.63, respectively), the adjusted attributable risk percentage is 42% for PPIs and 37% for H<sub>2</sub>-receptor antagonists. Since the average duration of use in this Dutch population was 0.23 years for H<sub>2</sub>-receptor antagonists and 0.42 years for PPIs, this roughly translates to 1 case of pneumonia per 226 patients treated with PPIs and 1 case of pneumonia per 508 persons treated with H<sub>2</sub>-receptor antagonists. While variations between individual PPIs and H<sub>2</sub>-receptor antagonists exist, they were not significant.

### Applications for Clinical Practice

While this study in no way suggests that prescribing

acid-suppressing drugs should be stopped, it does highlight that there are risks associated with this group of frequently used medications generally deemed fairly benign. This study reminds us that we need to balance the risks and benefits of treatment and to treat with acid-suppressive drugs only when necessary and at the lowest possible dose. Finally, as large patient data repositories become more popular, we may see more studies identifying risks of therapies previously thought to be benign.

*—Review by Mark S. Horng, MD*

### **References**

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