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EDITORIALS

# Proton pump inhibitors and community acquired pneumonia

## The observed link is probably due to protopathic bias and confounding by indication

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Concerns about proton pump inhibitors (PPIs) and the risk of community acquired pneumonia initially arose in 2004 after the publication of a nested case-control study,[1] in which the risk of community acquired pneumonia was significantly higher among current users of PPIs than among those who had discontinued use. This finding was supported by a strong biological rationale: acid suppression may result in bacterial overgrowth and an increased risk of bacterial aspiration. Several observational studies and corresponding meta-analyses have subsequently been conducted.[2 3] The most recent meta-analysis found that PPIs were associated with an increased risk of community acquired pneumonia (pooled estimate 1.49, 95% confidence interval 1.16 to 1.92; $I^2$=99.2%).[3] Although formal meta-analysis of these data is probably inappropriate given the presence of substantial heterogeneity, a qualitative review of the same data also suggests that PPI users are at an increased risk of community acquired pneumonia.

In *The BMJ* (doi:10.1136/bmj.i5813), Othman and colleagues report the results of a retrospective cohort study examining the association between PPIs and the risk of community acquired pneumonia.[4] The authors did three complimentary analyses: a traditional cohort analysis; a self controlled case series analysis, a within subject approach that compared the rate of pneumonia before and after the start of PPI treatment; and a prior event rate ratio analysis, a before-after analysis that adjusted for differences in the underlying event rate between exposure groups to minimise time fixed confounding.

Although the cohort analysis found that PPIs were associated with an increased risk of community acquired pneumonia (incidence rate ratio 1.67, 1.55 to 1.79), the other analyses did not. The self controlled case series analysis found a higher risk in the 30 days before starting PPIs (incidence rate ratio 1.92, 1.84 to 2.00) than in the 30 days after starting (1.19, 1.14 to 1.25), and the prior event rate ratio analysis found that PPIs were associated with a reduced risk (hazard ratio 0.91, 0.83 to 0.99). The authors concluded that any apparent increase in risk was probably due to confounding.

The evidence certainly supports an association between these agents and pneumonia, but careful scrutiny shows that the link is unlikely to be causal. Many of the previous studies reported large increases in risk after relatively short periods of exposure, with one study finding a nearly sixfold increased risk within two days of starting PPIs.[5] It is not biologically plausible for PPIs to increase the risk of community acquired pneumonia within such a short timeframe, suggesting the presence of protopathic bias or reverse causality (that is, PPIs were prescribed to treat the early symptoms of pneumonia such as chest pain, mistakenly attributed to reflux).

It now seems likely that confounding is a strong contributor to the observed increase in risk of pneumonia among adults taking PPIs. To determine the effect of PPIs independent of the effect of underlying gastro-oesophageal reflux disease, the Canadian Network for Observational Drug Effect Studies (CNODES) analysed restricted cohorts of new users of non-steroidal anti-inflammatory drugs in seven jurisdictions from three countries.[6] With exposure defined by a new PPI prescription on the same day as the non-steroidal anti-inflammatory drug prescription, the restricted cohort allowed for the examination of prophylactic PPI use among patients who were less likely to have reflux, removing the confounding by indication present in previous studies. When data were pooled across all sites, PPIs were not associated with an increased risk of hospital admission for community acquired pneumonia (odds ratio 1.05, 0.89 to 1.25; $I^2$=0%). An increased risk was observed in Nova Scotia (odds ratio 3.73, 1.12 to 12.36), where formulary restrictions limited PPI use to patients with evidence of gastric erosion, further supporting the hypothesis that gastro-oesophageal reflux disease, rather than PPIs, is responsible for the increased risk of pneumonia. This hypothesis is consistent with the findings of Othman and colleagues, who report a higher risk in the 30 days before starting PPIs than in the 30 days after it.[4] In another study, PPIs were associated with an increased risk of pneumonia as well as increased risks of osteoarthritis, chest pain, and urinary tract infections.[7] With PPIs unlikely to be causally related to these three outcomes, this study adds further credence

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to confounding as a likely source of the association between PPIs and community acquired pneumonia.

Although strong evidence of an increased risk of community acquired pneumonia among PPI users exists, this association is unlikely to be causal. Othman and colleagues have added to the growing evidence that any increase in risk results from a combination of protopathic bias and confounding by indication due to underlying reflux rather than a true adverse effect of PPIs.[4]

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