Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis
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CRD summary
The review concluded that patients who received proton-pump inhibitors, particularly for shorter duration or at higher doses, showed an association with community-acquired pneumonia. Large differences between studies and the potential for confounding factors limit the reliability of the authors' conclusions.

Authors' objectives
To evaluate the association of proton-pump inhibitors with community-acquired pneumonia.

Searching
PubMed was searched from 1988 up to November 2011 for articles published in English. Search terms were reported. Reference lists of recent reviews and systematic reviews were handsearched.

Study selection
Cohort studies and case control studies that evaluated proton-pump inhibitors and the incidence of community-acquired pneumonia were eligible for inclusion. Studies of critically-ill patients, Helicobacter pylori treatment or paediatric patients were excluded.

The included studies considered proton-pump use alone or in combination with histamine-2 receptor antagonists. The proton-pump use in pneumonia cases ranged from 4.3% to 47%. Most studies were population-based and were conducted in the UK, the Netherlands, Canada and Denmark. Studies were conducted from 1987 to 2006.

Two reviewers independently undertook study selection and disagreements were resolved by consensus.

Assessment of study quality
Quality assessment was undertaken using the Newcastle-Ottawa Assessment Scale to give a maximum score out of 9 points.

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Data extraction
Data were extracted on the association of proton-pump inhibitors and community-acquired pneumonia infection, and used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Two reviewers independently extracted data using a standardised form and accuracy was checked by a third reviewer.

Methods of synthesis
Random-effects meta-analysis was used to calculate pooled odds ratios and 95% confidence intervals. $I^2$ was used to assess statistical heterogeneity.

Pre-specified subgroup analyses were conducted according to proton-pump inhibitor dose and duration. Tests for interaction were performed between proton-pump inhibitor dosages and durations. A priori sensitivity analyses were performed on the basis of non-population based samples and quality. Publication bias was assessed using a funnel plot.

Results of the review
Two retrospective cohort analyses and seven case-control studies were included in the review (120,615 pneumonia cases, as reported in table 1). The study sample size ranged from 36 to 80,066 pneumonia cases. Study quality scores ranged from 4 to 8 points. There was no evidence of publication bias.

Proton-pump inhibitor usage was associated with statistically significantly increased risk of community-acquired pneumonia.
pneumonia (OR 1.39, 95% CI 1.09 to 1.76; I²=98%; nine studies). The greatest association with community acquired infection was seen with higher doses of proton-pump inhibitors (OR 1.50, 95% CI 1.33 to 1.68; I²=4%; four studies) and shorter than 30 days usage (OR 1.65, 95% CI 1.25 to 2.19; I²=91%; six studies). There was no significant difference in the association of the use of proton-pump inhibitors for longer than 180 days and the development of community-acquired pneumonia (three studies). Tests for interaction was significant between the treatment duration groups, but not between treatment dose groups. Sensitivity analyses did not significantly alter results.

**Authors' conclusions**
Patients who received proton-pump inhibitors, particularly for shorter duration (under 30 days) or at higher doses, showed an association with community-acquired pneumonia.

**CRD commentary**
Inclusion criteria for the review were clearly defined. A limited search of one relevant database was undertaken. There may have been the potential for language bias as only articles in English were included. Publication bias was reportedly assessed, although the meaningfulness of an analysis with less than ten studies was limited. Attempts were made to reduce reviewer error and bias throughout the review.

Quality assessment indicated that the quality of the evidence base was variable; although only limited details were presented, which made it difficult to interpret the quality assessment. Data were combined using suitable meta-analysis techniques. Statistical heterogeneity was explored, although it remained significant most of the time. The authors noted that none of the studies controlled for gastro-oesophageal reflux disease, and many studies did not control for alcohol or tobacco use.

The high levels of statistical heterogeneity and potential for confounding factors limit the reliability of the authors' conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that practitioners need to be vigilant about adverse events of proton-pump inhibitors and consider alternative therapies when appropriate.

**Research:** The authors stated that future studies should aim to determine the number needed to treat or harm with proton-pump usage versus histamine-2 receptor antagonists. Adverse effects in the same population need to be determined along with efficacy to better quantify a risk-benefit profile of proton-pump inhibitors usable in clinical practice.

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