Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis

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Abstract

Background: Observational studies and randomized controlled trials have yielded inconsistent findings about the association between the use of acid-suppressive drugs and the risk of pneumonia. We performed a systematic review and meta-analysis to summarize this association.

Methods: We searched three electronic databases (MEDLINE [PubMed], Embase and the Cochrane Library) from inception to Aug. 28, 2009. Two evaluators independently extracted data. Because of heterogeneity, we used random-effects meta-analysis to obtain pooled estimates of effect.

Results: We identified 31 studies: five case–control studies, three cohort studies and 23 randomized controlled trials. A meta-analysis of the eight observational studies showed that the overall risk of pneumonia was higher among people using proton pump inhibitors (adjusted odds ratio [OR] 1.27, 95% confidence interval [CI] 1.11–1.46, I^2 90.5%) and histamine$_2$ receptor antagonists (adjusted OR 1.22, 95% CI 1.09–1.36, I^2 0.0%). In the randomized controlled trials, use of histamine$_2$ receptor antagonists was associated with an elevated risk of hospital-acquired pneumonia (relative risk 1.22, 95% CI 1.01–1.48, I^2 30.6%).

Interpretation: Use of a proton pump inhibitor or histamine$_2$ receptor antagonist may be associated with an increased risk of both community- and hospital-acquired pneumonia. Given these potential adverse effects, clinicians should use caution in prescribing acid-suppressive drugs for patients at risk.

Recently, the medical literature has paid considerable attention to unrecognized adverse effects of commonly used medications and their potential public health impact.[1] One group of medications in widespread use is acid-suppressive drugs, which represent the second leading category of medication worldwide, with sales totalling US$26.9 billion in 2005.[2]

Over the past 40 years, the development of potent acid-suppressive drugs, including proton pump inhibitors, has led to considerable improvements in the treatment of acid-related disorders of the upper gastrointestinal tract.[3] Experts have generally viewed proton pump inhibitors as safe.[4] However, potential complications such as gastrointestinal neoplasia, malabsorption of nutrients and increased susceptibility to infection have caused concern.[5]

Of special interest is the possibility that acid-suppressive drugs could increase susceptibility to respiratory infections because these drugs increase gastric pH, thus allowing bacterial colonization.[6,7] Several previous studies have shown that treatment with acid-suppressive drugs might be associated with an increased risk of respiratory tract infections[8] and community-acquired pneumonia in adults[6,7] and children.[9] However, the association between use of acid-suppressive drugs and risk of pneumonia has been inconsistent.[10–13]

Given the widespread use of proton pump inhibitors and histamine$_2$ receptor antagonists, clarifying the potential impact of acid-suppressive therapy on the risk of pneumonia is of great importance to public health.[14] Previous meta-analyses have focused on the role of acid-suppressive drugs in preventing stress ulcer,[11,13,15] but none have examined pneumonia as the primary outcome.

The aim of this study was to summarize the association between the use of acid-suppressive drugs and the risk of pneumonia in observational studies and randomized controlled trials.

Methods

The procedures used for this meta-analysis were consistent with recent guidelines for reporting of meta-analyses. Specifically, we followed the

Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[16] for observational studies and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[17] for randomized controlled trials.

Search strategy and data sources

We searched for studies that reported an estimate of effect for a potential association between the use of acid-suppressive drugs and the risk of pneumonia. We included observational studies and randomized controlled trials that were published as original articles.

We searched MEDLINE (PubMed), Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library from inception to Aug. 28, 2009. We also searched the bibliographies of relevant articles to identify additional studies.

To identify observational studies, we used the following combinations of search terms: ("acid-suppressive therapy" OR "acid-suppressive drugs" OR "acid-suppressive medications" OR "gastric acid suppressants" OR "proton pump inhibitors" OR "proton pumps" OR omeprazole OR nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole OR "H_2 receptor antagonists" OR "histamine2 receptor antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine) AND (pneumonia OR "community-acquired pneumonia" OR "nosocomial pneumonia" OR "hospital-acquired pneumonia" OR "intensive care unit"). We restricted this search to studies involving humans that were published in English.

To identify randomized controlled trials, we used the following combinations of search terms: ("acid-suppressive therapy" OR "acid-suppressive drugs" OR "acid-suppressive medications" OR "gastric acid suppressants" OR "proton pump inhibitors" OR "proton pumps" OR omeprazole OR nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole OR "H_2 receptor antagonists" OR "histamine2 receptor antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine). We restricted this search to randomized controlled trials.

Study selection

We included any study that met all of the following criteria: was a case–control study, cohort study or randomized controlled trial; investigated the association between use of acid-suppressive drugs and risk of pneumonia; quantified the outcome with adjusted odds ratios (ORs), relative risk or number of events, and corresponding 95% confidence intervals (CIs); and reported the results for proton pump inhibitors and histamine$_2$ receptor antagonists separately. For studies that provided stratum-specific estimates, we combined them by means of the inverse-variance method. We included randomized controlled trials comparing acid-suppressive drugs (intervention) with either placebo or sucralfate control, as we were interested only in the influence of acid suppression on pneumonia.

Data extraction and quality assessment

Two investigators (C.S.E., J.W.L.) independently evaluated the eligibility of all studies retrieved from the databases on the basis of the predetermined selection criteria. They resolved any disagreements by discussion or in consultation with the co-corresponding authors (S.M.P., K.S.L.).

We assessed the methodologic quality of observational studies with the Newcastle–Ottawa Scale[18] and that of randomized controlled trials with the Jadad scale[19] (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.092129/DC1). We conducted subgroup analyses according to methodologic quality (low-quality studies v. high-quality studies). For the observational studies, low quality was defined as Newcastle–Ottawa Scale score ≤ 8.0 and high quality as score > 8.0 (maximum score 9). For the randomized controlled trials, low quality was defined as Jadad scale score ≤ 3.0 and high quality as score > 3.0 (maximum score 5).

Statistical analysis

We computed a pooled OR and 95% CI from the adjusted ORs and 95% CIs reported in the observational studies. For randomized controlled trials, we computed the summary relative risk from the relative risks of the individual trials using Mantel–Haenszel weighting.

We examined heterogeneity in results across the studies using Higgins I^2 value, which measures the percentage of total variance in the summary estimate due to between-study heterogeneity.[20]

In light of the heterogeneity of study designs and population characteristics, we calculated the summary effect by means of the DerSimonian–Laird method[21] for random-effects models.

Results

We identified a total of 2377 articles in the initial search for observational studies, and we reviewed 60 abstracts and 18 full articles. We included 8 of these articles in our analysis. We identified 8513 randomized controlled trials, and we reviewed 914 abstracts and 35 full articles. We included 23 of these articles and 2 bibliographies of relevant articles in the study. In summary, we included five case–control studies,[6,7,14,22,23] three cohort studies,[2,10,24] and 23

randomized controlled trials[25–47] in the final analysis (Figure 1).

Table 1 and Table 2 summarize the general characteristics of the 31 studies that were included in the analysis.[2,6,7,10,14,22–47] The mean quality scores were 8.4 for the observational studies (maximum score 9) and 3.1 for the randomized controlled trials (maximum score 5).

Description of studies

The selected studies were published between 1985 and 2009. Five articles reported population-based studies,[2,6,7,14,23] and 26 articles, including the 23 randomized controlled trials, reported hospital-based studies.[10,22,24–47] Of the observational studies, five evaluated the association between use of acid-suppressive drugs

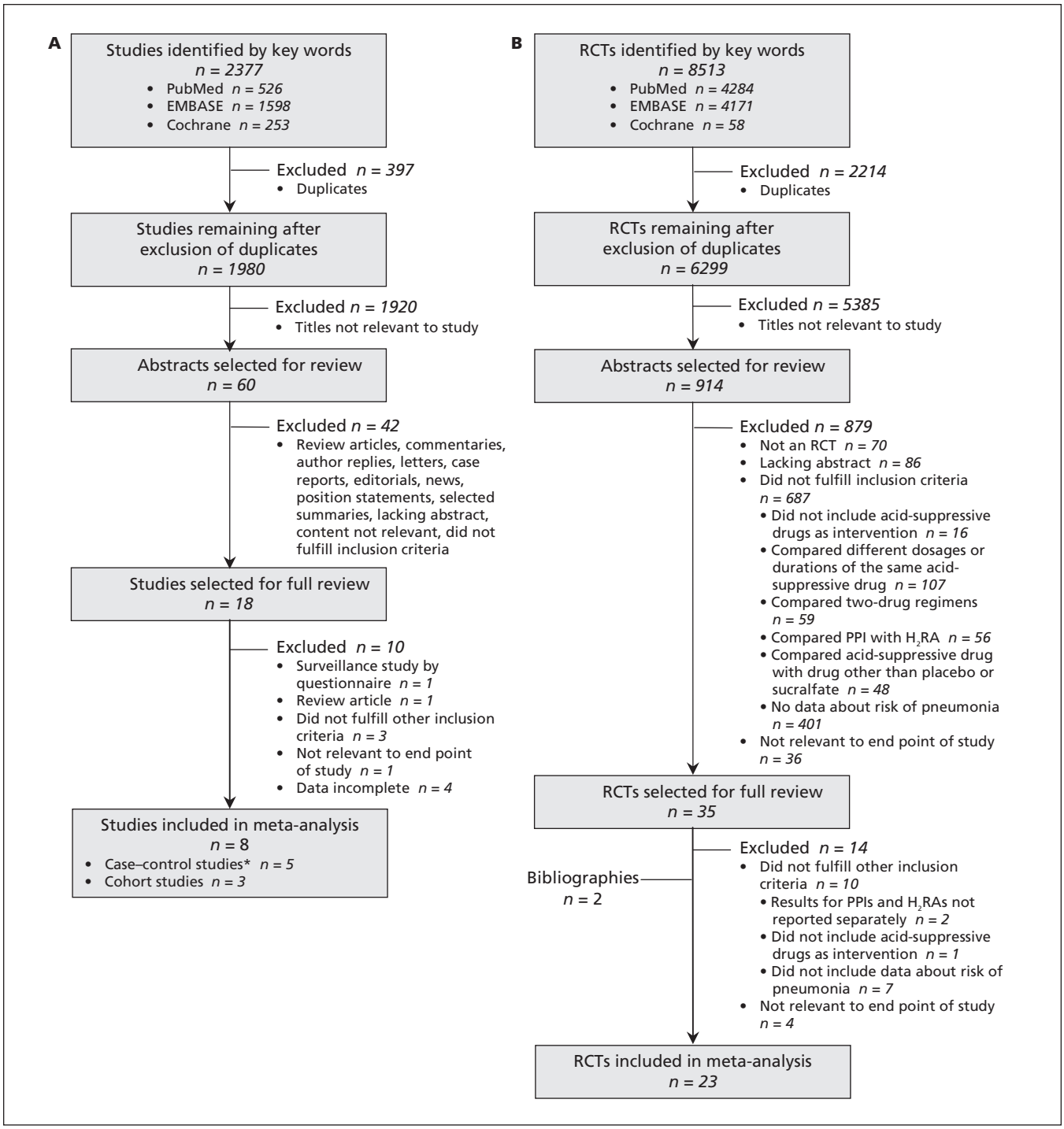

Figure 1: Selection of observational (case–control and cohort) studies (A) and randomized controlled trials (B) evaluating the risk of pneumonia in association with use of acid-suppressive drugs. *Includes nested case–control studies. H_2RA = histamine$_2$ receptor antagonist, PPI = proton pump inhibitor, RCT = randomized controlled trial.

Table 1: Characteristics of case–control and cohort studies included in the final analysis of acid-suppressive drugs* and risk of pneumonia

Study	Country	Study design	Study period	Adjustment	No. of events/ no. of patients	Quality assessment†
Community-acquired pneumonia						
Laheij et al.[6]	Netherlands	Nested case–control	1995–2002	Age, sex, calendar time, indication, diabetes mellitus, heart failure, COPD, lung cancer, stomach cancer, no. of physician visits during past year, antibiotics, systemic immunosuppressive agents	5 551/364 683	9
Gulmez et al.[7]	Denmark	Population-based case–control	2000–2004	Age, sex, previous discharge diagnosis of community-acquired pneumonia, COPD, peptic ulcer, alcohol-related diagnoses, ischemic heart disease, liver cirrhosis, renal failure, diabetes mellitus, heart failure, stroke, current use of systemic and inhaled corticosteroids, bronchodilators, NSAIDs, anticholinergic agents, antipsychotic agents	3 074/41 818	9
Sarkar et al.[14]	United Kingdom	Nested case–control	1987–2002	Age, sex, current smoking status, alcoholism, total no. of general practice visits during past year, total no. of hospital admissions during past year, community-acquired pneumonia before enrollment in General Practice Research Database, COPD, asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, any cancer other than basal-cell carcinoma, dementia	80 066/799 872	8
Myles et al.[23]	United Kingdom	Nested case–control	2001–2002	Ischemic heart disease, smoking, chronic lung disease, comorbidities, previous pneumonia, prescriptions for diuretics, calcium-channel blockers, antacids, steroids, nitrates	3 709/22 174	8
Roughead et al.[2]	Australia	Cohort	2002–2006	Sex, comorbidities, season, residential aged-care status, COPD, renin–angiotensin system medicines concurrent with furosemide, no. of prescriptions, prescribers, pharmacies, occupational therapy visits, speech pathology services	13 876/672 074	8
Hospital-acquired pneumonia						
Beaulieu et al.[10]	Canada	Cohort	2002–2004	Age, sex, inpatient status, duration of hospital stay, comorbidities, treatment received, procedures	104/787	9
Herzig et al.[24]	USA	Cohort	2004–2007	Age, sex, race, comorbidities, admitting service, admission type, season of admission, length of hospital stay, in-hospital medications	2 219/63 878	9
Marciniak et al.[22]	USA	Case–control	1999–2003	Age, sex, type of stroke, NIHSS score, side of stroke, depth of stroke	34/72	7

Note: COPD = chronic obstructive lung disease, NIHSS = National Institutes of Health stroke scale, NSAIDs = nonsteroidal anti-inflammatory drugs.
*All but one of the studies considered both proton pump inhibitors and histamine$_2$ receptor antagonists. The exception was the cohort study by Roughead and colleagues,[2] which studied only proton pump inhibitors.
†Assessed by the Newcastle–Ottawa scale,[18] where full score = 9.

and risk of community-acquired pneumonia,[2,6,7,14,23] and three evaluated the association between use of these drugs and risk of hospital-acquired pneumonia.[10,22,24]

Main pooled analyses and heterogeneity

Meta-analyses for observational studies with the two types of acid-suppressive drug showed significant positive associations between use of proton pump inhibitors and risk of pneumonia (adjusted OR 1.27, 95% CI 1.11–1.46, I^2 90.5%) and between use of histamine$_2$ receptor antagonists and risk of pneumonia (adjusted OR 1.22, 95% CI 1.09–1.36, I^2 0.0%) (Figure 2).

Meta-analysis of the randomized controlled trials examining risk of hospital-acquired pneu-

Table 2: Characteristics of randomized controlled trials (RCTs) included in the final analysis

Study	Country	Study design	Study agent v. comparator	No. of patients	Study setting	Quality assessment*
Cheadle et al.[25]	USA	Prospective RCT	Cimetidine v. placebo	200	Surgical unit	5
Driks et al.[26]	USA	Prospective RCT	H_2RAs, antacid v. sucralfate	130	Surgical, medical or coronary ICU	2
Laggner et al.[27]	Austria	RCT	Ranitidine v. sucralfate	32	ICU	2
Reusser et al.[28]	Switzerland	Prospective RCT	Ranitidine v. placebo	40	Neurosurgical ICU	2
Eddleston et al.[29]	United Kingdom	Prospective RCT	Ranitidine v. sucralfate	60	ICU	3
Apte et al.[30]	India	Prospective RCT	Ranitidine v. placebo	34	Medical ICU	2
Martin et al.[31]	USA	Multicentre double-blinded RCT	Cimetidine v. placebo	131†	ICU	4
Metz et al.[32]	USA	Prospective, multicentre, double-blind RCT	Ranitidine v. placebo	167†	ICU	5
Pickworth et al.[33]	USA	Prospective RCT	Ranitidine v. sucralfate	83	Trauma centre	3
Ryan et al.[34]	USA	Prospective RCT	Cimetidine v. sucralfate	114	Medicosurgical ICU	3
Ben-Menachem et al.[35]	USA	Single-blind RCT	Cimetidine v. placebo	200	Medical ICU	2
Cloud et al.[36]	USA	Multicentre parallel double-blinded RCT	Nizatidine v. placebo	126†	ICU	2
Maier et al.[37]	USA	Prospective open RCT	Ranitidine v. sucralfate	98	Trauma ICU	2
Prod'hom et al.[38]	Switzerland	RCT	Ranitidine v. sucralfate	244†	Medicosurgical ICU	3
Mustafa et al.[39]	Turkey	Prospective RCT	Ranitidine v. sucralfate	31	ICU	2
Thomason et al.[40]	USA	Prospective RCT	Ranitidine v. sucralfate	242†	Trauma, surgical or neurosurgical ICU	3
Cook et al.[41]	Canada	Multicentre, blinded, RCT	Ranitidine v. placebo	1200	ICU	5
Hanisch et al.[42]	Germany	Double-blind RCT	Ranitidine v. placebo	158†	ICU	4
Moesgaard et al.[43]	Denmark	Double-blind RCT	Ranitidine v. placebo	194†	Surgical unit	4
O'Keefe et al.[44]	USA	Prospective RCT	Ranitidine v. sucralfate	96	Severely injured patients	2
Yildizdas et al.[45]	Turkey	Prospective RCT	Ranitidine v. placebo	160†	Pediatric ICU	3
Kantorova et al.[46]	Czech Republic	RCT	Famotidine v. placebo	287†	ICU	5
Misra et al.[47]	India	RCT	Ranitidine v. placebo	141†	Patients with intracerebral hemorrhage	4

Note: H_2RAs = histamine$_2$-receptor antagonists, ICU = intensive care unit.
*Assessed by Jadad scale,[19] where full score = 5.
†Some patients or comparison arms in these studies were excluded from the current meta-analysis (see Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.092129/DC1).

monia in association with use of histamine$_2$ receptor antagonists confirmed the findings of the observational studies (relative risk 1.22, 95% CI 1.01–1.48, I^2 30.6%) (Figure 3).

Subgroup meta-analyses

In subgroup analyses by type of pneumonia, we observed a significant positive association between use of proton pump inhibitors and community-acquired pneumonia (adjusted OR 1.34, 95% CI 1.14–1.57, I^2 93.6%) and between use of histamine$_2$ receptor antagonists and hospital-acquired pneumonia (adjusted OR 1.24, 95% CI 1.05–1.47, I^2 0.0%) (Table 3).

Subgroup analyses by dose indicated a dose–response relationship. A higher dose of proton pump inhibitors was more strongly associated with pneumonia (adjusted OR 1.52, 95% CI 1.31–1.76, I^2 27.5%) than the usual dose (adjusted OR 1.37, 95% CI 1.08–1.74, I^2 86.5).

Subgroup analyses by duration of exposure showed that the strength of the association between use of proton pump inhibitors and risk of pneumonia decreased with longer duration of therapy before the index date (date of diagnosis of pneumonia). There were significant positive associations between risk of pneumonia and use of proton pump inhibitors within 7 days before the index date (adjusted OR 3.95, 95% CI 2.86–5.45, I^2 0.0%), within 30 days before the index date (adjusted OR 1.61, 95% CI 1.46–1.78, I^2 30.6%) and from 30 to 180 days before the index date (adjusted OR 1.36, 95% CI 1.05–1.78, I^2 84.3%). The risk of pneumonia was greater with the use of histamine$_2$ receptor antagonists within 7 days before the index date (adjusted OR 5.21, 95% CI 4.00–6.80, I^2 not available). The risk also appeared greater with the use of these drugs within 30 days before the index date (adjusted OR 1.49, 95% CI 0.82–2.72, I^2 80.4%) and from 30 to 180 days (adjusted OR 1.21, 95% CI 0.94–1.56, I^2

Study	Exposed *n/N*	Unexposed *n/N*	OR (95% CI)
Proton pump inhibitors			
Laheij et al.[6]	131/12 337	5 366/345 224	1.73 (1.33–2.25)
Gulmez et al.[7]	817/7 642	1 584/34 176	1.50 (1.30–1.70)
Beaulieu et al.[10]	NR/292	NR/495	0.63 (0.39–1.01)
Sarkar et al.[14]	3 455/10 031	73 187/770 626	1.02 (0.97–1.08)
Herzig et al.[24]	1 340/25 374	610/30 956	1.30 (1.10–1.40)
Marciniak et al.[22]	17/30	19/42	1.80 (0.50–6.80)
Myles et al.[23]	387/1 644	2 638/18 161	1.55 (1.36–1.77)
Roughead et al.[2]	4 225/138 228	9 651/533 846	1.16 (1.11–1.22)
Overall (I^2 = 90.5%)			1.27 (1.11–1.46)
Histamine$_2$ receptor antagonists			
Laheij et al.[6]	54/10 177	5 366/345 244	1.59 (1.14–2.23)
Gulmez et al.[7]	161/7 642	512/34 176	1.10 (0.80–1.30)
Beaulieu et al.[10]	NR/432	NR/355	1.52 (0.88–2.63)
Herzig et al.[24]	176/5 686	610/30 956	1.20 (0.98–1.40)
Marciniak et al.[22]	17/28	19/44	2.00 (0.70–6.50)
Myles et al.[23]	122/640	2 736/18 000	1.14 (0.92–1.40)
Overall (I^2 = 0.0%)			1.22 (1.09–1.36)

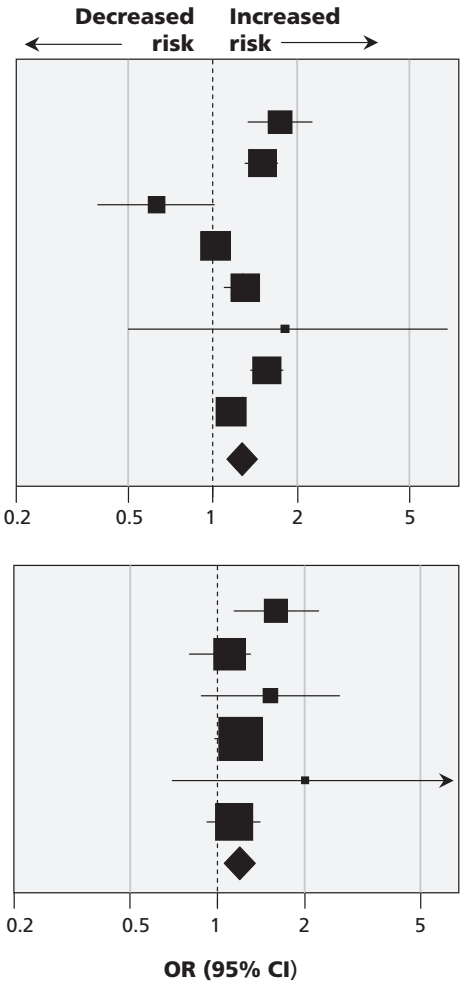

Figure 2: Meta-analyses of observational studies evaluating the risk of pneumonia among patients receiving acid-suppressive drugs, based on random-effects model. Adjusted odds ratios (ORs) greater than 1 indicate increased risk of pneumonia. CI = confidence interval, I^2 = heterogeneity, *n* = number of events, *N* = number of patients, NR = not reported.

27.6%), but these associations were not statistically significant.

Subgroup analyses of the 23 randomized controlled trials by comparators showed a significant positive association between use of histamine$_2$ receptor antagonists and risk of pneumonia in studies that employed sucralfate as a control (relative risk 1.33, 95% CI 1.04–1.69, I^2 24.7%). Placebo-controlled studies also indicated an overall increase in the risk of pneumonia with these drugs, but the result was not statistically significant (relative risk 1.09, 95% CI 0.80–1.48, I^2 37.9%).

We conducted subgroup meta-analyses of the observational studies and randomized controlled trials by methodologic quality. Among the observational studies, we observed a significant positive association for both high-quality studies (adjusted OR 1.29, 95% CI 1.17–1.42, I^2 0.0%) and low-quality studies (adjusted OR 1.15, 95% CI 1.00–1.32, I^2 82.1%). Among the randomized controlled trials, the risk of pneumonia appeared greater in low-quality studies (relative risk 1.35, 95% CI 1.10–1.67, I^2 12.5%), whereas there was no effect among the high-quality studies (relative risk 0.96, 95% CI 0.65–1.43, I^2 47.0%).

Interpretation

Main findings

Our results suggest that the use of acid-suppressive drugs is associated with an increased risk of pneumonia. Given the widespread use of acid-suppressive drugs, the implications of this increased risk are serious. If we assume that 19.7 cases of pneumonia occur for every 1000 individuals not receiving acid-suppressive drugs who are admitted to hospital,[24] and if we also assume a 1.22- to 1.27-fold increase in the risk of pneumonia due to acid-suppressive drugs, as determined in this study, 24 or 25 cases of pneumonia can be expected for every 1000 recipients of these drugs. This translates to about one case of pneumonia for every 200 inpatients treated with acid-suppressive drugs. Given that 40%–70% of patients admitted to hospital receive acid-suppressive drugs,[48] a considerable burden of morbidity and mortality of hospital-acquired pneumonia may be attributable to this type of therapy. In the context of community-acquired pneumonia, the impact of these drugs could be even more serious.

Several lines of evidence point to the bio-

Study	Intervention *n/N*	Control *n/N*	RR (95% CI)
Cheadle et al.[25]	13/100	3/100	4.33 (1.25–14.97)
Driks et al.[26]	16/69	7/61	2.02 (0.89–4.58)
Laggner et al.[27]	2/16	0/16	5.00 (0.26–96.59)
Reusser et al.[28]	7/19	8/21	0.97 (0.43–2.16)
Eddleston et al.[29]	10/30	3/30	3.33 (1.02–10.92)
Apte et al.[30]	13/16	9/18	1.63 (0.97–2.73)
Martin et al.[31]	0/56	4/61	0.12 (0.01–2.20)
Metz et al.[32]	12/84	15/79	0.75 (0.38–1.51)
Pickworth et al.[33]	5/44	6/39	0.74 (0.24–2.23)
Ryan et al.[34]	7/56	8/58	0.91 (0.35–2.33)
Ben-Menachem et al.[35]	13/100	6/100	2.17 (0.86–5.47)
Cloud et al.[36]	7/81	4/38	0.82 (0.26–2.64)
Maier et al.[37]	14/51	10/47	1.29 (0.64–2.62)
Prod'hom et al.[38]	21/80	10/83	2.18 (1.10–4.33)
Mustafa et al.[39]	9/16	3/15	2.81 (0.94–8.45)
Thomason et al.[40]	27/80	30/80	0.90 (0.59–1.37)
Cook et al.[41]	114/596	98/604	1.18 (0.92–1.51)
Hanisch et al.[42]	10/57	12/57	0.83 (0.39–1.77)
Moesgaard et al.[43]	11/77	19/87	0.65 (0.33–1.29)
O'Keefe et al.[44]	14/49	10/47	1.34 (0.66–2.72)
Yildizdas et al.[45]	20/42	17/42	1.18 (0.72–1.91)
Kantorova et al.[46]	7/71	5/75	1.48 (0.49–4.45)
Misra et al.[47]	2/45	5/47	0.42 (0.09–2.05)
Overall (I^2 = 30.6%)	354/1835	292/1805	1.22 (1.01–1.48)

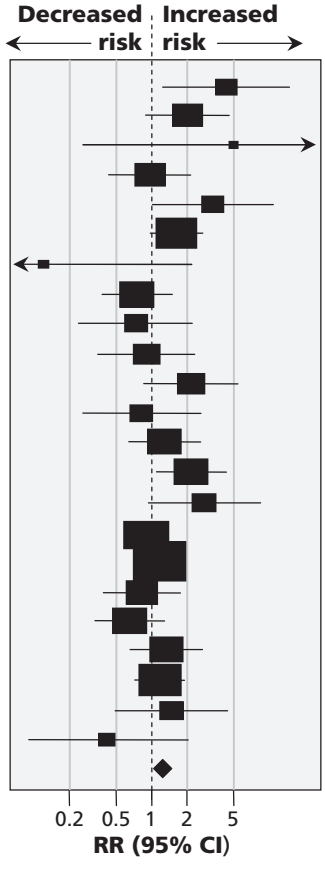

Figure 3: Meta-analysis of randomized controlled trials evaluating the risk of hospital-acquired pneumonia among patients using histamine$_2$ receptor antagonists, based on random-effects model. Relative risk (RR) values greater than 1 indicate increased risk of pneumonia. CI = confidence interval, I^2 = heterogeneity, *n* = number of events, *N* = number of patients.

logical plausibility of these observations. First, acid-suppressive drugs may increase the risk of pneumonia by inhibiting the secretion of gastric acid, thus allowing bacterial overgrowth and colonization in the upper alimentary tract and subsequent translocation to the lungs by aspiration.[6,7,49] Second, hydrogen potassium adenosine triphosphatase is present not only in the parietal cells of the stomach, but also in the respiratory tract.[50,51] It is conceivable that use of a proton pump inhibitor could alter the pH of the seromucinous secretions by inhibiting this enzyme, thereby encouraging bacterial growth in the respiratory tract, which could in turn lead to increased risk of pneumonia.[52] Third, in vitro studies have shown that acid-suppressive drugs may impair the function of neutrophils and the activity of natural killer cells.[53–59]

Interestingly, the most striking increase in the risk of pneumonia in association with proton pump inhibitors was observed in the first week of use. The risk of pneumonia in association with use of proton pump inhibitors was attenuated, but still significant, between 30 and 180 days. Recipients of histamine$_2$ receptor antagonists between 30 and 180 days before the index date appeared to have an increased risk of pneumonia, but the association was not statistically significant. These findings might reflect tolerance.[52] Tolerance to histamine$_2$ receptor antagonists generally develops within two weeks with repeated administration, resulting in a decline in acid suppression.[60] Another reason may be that those who are more susceptible to pneumonia become ill with this disease early after starting acid-suppressive drugs, leaving fewer such individuals among those using these drugs for longer periods. That is, patients who remain on the drug are those who can tolerate it, whereas those who are susceptible select themselves out of the population at risk. This depletion of susceptible effect has been considered in other pharmacoepidemiologic studies of adverse events.[61]

Comparisons with other studies

Previous meta-analyses[11,13,15] examined the effect of acid-suppressive drugs on pneumonia as a secondary outcome in randomized controlled trials. Cook and associates[11] showed that the rate of pneumonia was higher among patients taking histamine$_2$ receptor antagonists than among controls, but the difference was not statistically significant (OR 1.25, 95% CI 0.78–2.00). Conversely, Messori and colleagues[13] found no difference in the risk of pneumonia between those who were given ranitidine and those who were given placebo (OR 0.98, 95% CI 0.56–1.72). However, they found an increased risk of nosocomial pneumonia in studies comparing ranitidine and sucralfate (OR 2.21, 95% CI 0.86–5.65). Finally, Pongprasobchai and coworkers[15] reported that the incidence of nosocomial pneumonia did not differ between patients receiving proton pump inhibitors and those receiving histamine$_2$ receptor antagonists. Compared with the previous meta-analyses, our review included more studies, which led to greater power to detect an effect. We also included observational studies, which enrolled a greater diversity of individuals, especially those taking high doses of acid-suppressive drugs.

Table 3: Subgroup analyses for use of acid-suppressive agents and risk of pneumonia using random-effects model for observational studies

Factor	No. of studies	Summary adjusted OR (95% CI)	I^2, %
Proton pump inhibitors			
Study design			
Case–control and nested case–control	5	1.44 (1.09–1.91)	93.7
Cohort	3	1.14 (0.96–1.36)	79.1
Study population			
General	5	1.34 (1.14–1.57)	93.6
Hospital	3	1.04 (0.58–1.88)	76.9
Type of pneumonia			
Community-acquired	5	1.34 (1.14–1.57)	93.6
Hospital-acquired	3	1.04 (0.58–1.88)	76.9
Dose			
Usual	3	1.37 (1.08–1.74)	86.5
High	3	1.52 (1.31–1.76)	27.5
Duration of exposure, d			
< 7	2	3.95 (2.86–5.45)	0.0
< 30	4	1.61 (1.46–1.78)	30.6
30–180	4	1.36 (1.05–1.78)	84.3
Histamine$_2$ receptor antagonists			
Study design			
Case–control and nested case–control	4	1.20 (1.01–1.43)	15.5
Cohort study	2	1.23 (1.04–1.45)	0.0
Study population			
General	3	1.19 (0.99–1.42)	25.7
Hospital	3	1.24 (1.05–1.47)	0.0
Type of pneumonia			
Community-acquired	3	1.19 (0.99–1.42)	25.7
Hospital-acquired	3	1.24 (1.05–1.47)	0.0
Duration of exposure, d			
< 7	1	5.21 (4.00–6.80)	NR
< 30	2	1.49 (0.82–2.72)	80.4
30–180	2	1.21 (0.94–1.56)	27.6

Note: CI = confidence interval, I^2 = homogeneity, NR = not reported, OR = odds ratio.

Strengths and limitations

Our analysis incorporated all relevant studies that we could identify to August 2009, including both observational and randomized controlled trials. We were also able to identify sources of heterogeneity by stratifying analyses on key variables.

Despite these strengths, our study had some limitations. First, we included only English-language publications for the selection of observational studies. We performed a subsequent search for all relevant observational studies without any language restrictions and found about 18% more citations. However, none of these articles met the inclusion criteria. It is unlikely that the language of the studies would have altered the validity or magnitude of the associations between acid-suppressive drugs and pneumonia. Second, the presence of gastroesophageal reflux disease might be a confounder,[49] as those who receive acid-suppressive drugs often experience this condition, which in itself could be a risk factor for pneumonia. However, given that the included studies adjusted for factors such as comorbidities and other medications, any resulting bias was unlikely to have been great enough to explain the observed effect. Third, although the high-quality observational studies showed a significant effect, the high-quality double-blinded randomized controlled trials did not show a significant effect. This discrepancy might be attributable to methodologic rigour, but differences in study characteristics may also have contributed to the heterogeneous results.

Conclusion

Clinicians should carefully consider any decision to prescribe acid-suppressive drugs, especially for patients who are already at risk for pneumonia.[62] Since it is unnecessary to achieve an achlorhydric state in order to resolve symptoms, we recommend using the optimal effective dose of the drug necessary to achieve desired therapeutic goals.

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