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Inhaled drugs as risk factors for community-acquired pneumonia

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ABSTRACT: The effect of inhaled drugs in community-acquired pneumonia (CAP) is unclear. This case–control study was designed to determine whether inhaled drugs were risk factors for CAP.

All incident cases of confirmed CAP that occurred over 1 yr in patients with chronic bronchitis (CB), chronic obstructive pulmonary disease (COPD) or asthma were included, as well as CB, COPD and asthma controls. Risk factors for CAP and inhaled treatment were recorded during a personal interview.

An effect of inhaled drugs on the risk of CAP was observed in COPD and asthma patients after adjusting for the effect of other respiratory diseases and their concomitant treatments. In COPD patients, inhaled steroids had a risk OR of 3.26 (95% CI 1.07–9.98) and in asthma patients inhaled anticholinergics had a risk OR of 8.80 (95% CI 1.02–75.7). In CB patients, no association with CAP was observed for any inhaler. These effects were independent of adjusting variables related to severity and other respiratory and non-respiratory risk factors for CAP, including vaccines. Inhaled β_2-adrenergic agonists did not show a significant effect on the risk of CAP in any of the respiratory diseases.

Inhaled steroids may favour CAP in COPD patients, whereas anticholinergics may favour CAP in asthma patients. It is difficult to differentiate the effect of inhaled therapy from the effect of COPD or asthma severity on the risk of CAP, and these relationships may not be causal, but could call attention to inhaled therapy in COPD and asthma patients.

KEYWORDS: Community-acquired pneumonia, inhaled drug treatment, risk factors

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in industrialised countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1,000 inhabitants [1, 2], 22–51% of whom require inpatient care, with a lethality of 3–24% [3, 4]. The mortality rate varies between 0.1 and 0.7 per 1,000 persons each year [1, 5].

Strategies acting on modifiable risk factors for CAP are crucial to reduce the impact of the disease. Among them, chronic obstructive pulmonary disease (COPD) and asthma are important risk factors for CAP both in ambulatory and hospitalised patients [6–8]. Recently, it has been shown that medications delivered by metered-dose inhalers (MDIs) usually administered in the treatment of COPD and asthma may also cause pneumonia [9–12]. Inhaled drugs can be delivered through pressured MDI inhalers, with or without spacer devices, dry-powder inhalers or nebulisers [13]. Bronchodilators, including β_2-adrenergic agonists and/or anticholinergic drugs, and steroids are the most common type of active drugs administered through MDIs.

Adverse pulmonary effects recently observed with the use of some MDIs makes necessary to further study the relationship between CAP and inhaled drugs [14]. The aim of the present study was to assess the effect of drugs administered through inhalation devices on the development of CAP in patients with different chronic respiratory diseases that require inhaled therapy. The study is based on cases of clinically and radiologically confirmed CAP occurring in a large general adult population.

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PATIENTS AND METHODS

Study population

A population–based, case–control study was conducted in an extensive rural and urban area on the eastern coast of Spain, with predominantly Mediterranean climatic conditions. Details of the study have been published elsewhere [9]. Briefly, the target population included 859,033 inhabitants older than 14 yrs of age assigned to any of the 64 primary care centres, which were selected according to availability of family physicians willing to take part in the study.

Identification of cases

All patients with clinically suspected CAP presenting from November 1, 1999 to November 30, 2000 were prospectively registered. Predefined criteria for case registration were based on acute lower respiratory tract infection, for which antibiotics had been prescribed, in association with the appearance of new or previously unknown focal signs on physical examination or radiography of the chest [1]. All cases of CAP were periodically re-evaluated by chest radiography at intervals until complete recovery. Patients with suspicion of CAP in which another noninfectious respiratory disease was later confirmed were excluded from the study, as were patients with active tuberculosis, aspiration pneumonia and pneumonia acquired at nursing homes, and those having been discharged from hospital in less than 7 days before the onset of symptoms.

An active surveillance system was established to ensure the identification of all cases, based on the fact that 95% of the population belongs to the national healthcare system. This system involved all physicians working in public and private healthcare facilities in the study area and reference hospitals both inside and outside the county area. In order to maintain the system of reporting cases, a coordinator in each of the study areas established periodic contacts with the professionals of all participating centres.

Selection of controls

Each case of confirmed CAP was frequency matched to a control subject by age ($\pm$5 yrs), sex and primary care centre. The selection of controls was performed every 3 months by a simple random sampling procedure from the same population-based register as cases, using the list of subjects assigned to each primary care centre. Once a control subject was identified, a maximum of three telephone calls or home visits were made, and if, after these attempts, the control subject could not be contacted, he/she was replaced following the same selection and matching criteria.

For the purposes of the present study, only cases and controls with three chronic respiratory diseases that require inhaled therapy were included: chronic bronchitis (CB) without spirometric study or without COPD (defined by its arbitrary epidemiological characterisation of cough and expectoration over 90 days per year in two consecutive years and not secondary to any specific respiratory disease [15]); COPD (presence of persistent airflow limitation diagnosed by respiratory function tests documented in the medical records or stated by the patient); or asthma (presence of episodes of validated clinical symptoms, such as attacks of cough at night or during exercise, or of occasional wheeze during a cold or whilst exercising during the last year [16]).

Data collection

A questionnaire on CAP risk factors was administered to participants at home (Appendix). It was composed of questions from the current literature and from the opinion of international experts, and its reliability has been demonstrated in previous studies [9]. When the participant could not directly answer the questions (cognitive impairment, disease or, for CAP cases, death), the questionnaire was administered to the closest family member or caregiver. The interviewers were physicians or nurses trained in interview techniques and in the administration of the study questionnaire. The questionnaire included standardised information related to the following three aspects: health habits and lifestyle; chronic respiratory diseases (COPD, CB and asthma) and other clinical conditions; and regular treatments during the last year. Treatments were confirmed by medical records, prescriptions or, when necessary, by direct observation. Information on inhaled drugs included the classes of drugs (steroids, β_2-adrenergic agonists and anticholinergic drugs), regular dose (mean puffs per day) and use of spacer devices.

All participants gave written informed consent. The study protocol was approved by the ethics committee of the Consorci Sanitari del Maresme (Barcelona, Spain).

Statistical analysis

Because COPD, CB and asthma may be present concurrently in a given patient and are associated with a higher risk for CAP, particularly COPD and CB, cases and controls were stratified into the following three groups: COPD (with or without asthma), CB (with or without asthma) and asthma alone. Estimates of the relative risk through odds ratios and 95% confidence intervals were used as a measure of association between risk factors and the occurrence of CAP. These were calculated using unconditional logistic regression for each type of respiratory disease. First, bivariate analysis was applied within each group of respiratory disease (CB, COPD and asthma) to compare the characteristics of the three classes of inhaled drugs (steroids, β_2-adrenergic agonists and anticholinergics) between cases and controls and their relationship with the risk for CAP. Secondly, multivariate analysis of the risk for CAP within each strata of respiratory disease was performed. The effect of inhaled drug treatments was adjusted for: 1) indicators of baseline disease severity, such as oxygen therapy, treatment with oral corticosteroids or use of the other classes of inhaled drugs; 2) respiratory and non-respiratory variables statistically associated with CAP in the bivariate analysis with a p value <0.10 (comorbidities, or concomitant treatments and vaccines); and 3) asthma in the CB and COPD models. Statistical significance was set at $p=0.05$.

RESULTS

From the study population of 1,336 cases of CAP and 1,326 controls [9], 473 and 235 presented with CB, COPD or asthma, respectively. Overall, in the group of patients with CAP, 284 (60.0%) were males and the mean$\pm$SD age was 59.6$\pm$20.0 yrs. In the control group 132 (56.2%) were males and the mean age was 60.9$\pm$20.7 yrs. Patient characteristics by type of respiratory disease are presented in table 1. The prevalence of male

TABLE 1 Patient characteristics according to the type of respiratory disease

Variable	Chronic bronchitis		COPD		Asthma alone	
	CAP	Controls	CAP	Controls	CAP	Controls
Subjects n	122	48	94	33	256	153
Females	43 (29.2)	14 (37.5)	18 (19.1)	7 (21.2)	127 (49.6)	81 (52.9)
Age	70.0±15.5	65.9±15.7	71.1±11.2	73.4±12.2	52.4±21.4	55.2±21.4
Smoking history pack yr						
0	36 (31.0)	16 (35.6)	20 (22.5)	14 (45.2)	100 (40.2)	69 (46.3)
1–150	32 (27.6)	13 (28.9)	25 (28.1)	4 (12.9)	65 (26.1)	44 (29.5)
>150	48 (41.4)	16 (35.6)	44 (49.4)	13 (41.9)*	84 (33.7)	36 (24.2)
Any hospital admission in previous 5 yrs	68 (55.7)	28 (58.3)	68 (72.3)	21 (63.6)	137 (53.5)	90 (58.8)
Upper respiratory tract infection in the past month	56 (46.3)	13 (27.1)*	44 (46.8)	9 (27.3)#	157 (61.3)	108 (70.6)#
Chronic bronchitis	122 (100)	48 (100)	94 (100)	33 (100)	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)	94 (100)	33 (100)	0 (0.0)	0 (0.0)
Asthma	71 (8.2)	22 (45.8)	47 (50.0)	14 (42.4)	256 (100)	153 (100)
Any previous CAP confirmed by chest radiography	29 (23.8)	9 (18.8)	28 (29.8)	7 (21.2)	55 (21.5)	23 (15.0)
Non-active TB	7 (5.7)	1 (2.1)	6 (6.5)	3 (9.1)	5 (2.0)	2 (1.3)
Other respiratory disease	5 (4.2)	2 (4.2)	16 (17.6)	3 (9.7)	6 (2.4)	1 (0.7)
Diabetes	27 (22.1)	12 (25.0)	28 (29.8)	11 (33.3)	33 (12.9)	22 (14.4)
Heart failure	22 (18.3)	8 (16.7)	16 (17.0)	8 (24.2)	25 (9.8)	8 (5.2)
GER	41 (33.6)	18 (37.5)	27 (28.7)	13 (39.4)	87 (34.0)	53 (34.6)
Depression	26 (21.3)	9 (19.1)	13 (13.8)	2 (6.1)	37 (14.5)	32 (20.9)#
Cancer	12 (9.8)	3 (6.4)	13 (13.8)	3 (9.1)	16 (6.3)	11 (7.2)
***N*-Acetylcysteine**	4 (3.3)	0 (0)	3 (3.2)	2 (6.1)	13 (5.1)	1 (0.7)*
Oral corticosteroids	12 (9.8)	2 (4.2)	19 (20.2)	4 (12.1)	4 (1.6)	0 (0.0)
Theophylline	6 (4.9)	2 (4.2)	12 (12.8)	2 (6.1)	3 (1.2)	0 (0.0)
Oxygen therapy	9 (8.0)	1 (2.2)	12 (13.8)	2 (6.3)	4 (3.0)	0 (0.0)*
Influenza vaccine	53 (43.4)	21 (43.8)	64 (68.1)	28 (84.8)#	74 (29.0)	62 (40.5)*
Pneumococcal vaccine at any time of life	6 (5.1)	5 (11.4)	11 (12.4)	4 (12.5)	10 (4.0)	17 (11.9)*

Data are presented n (%) or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; TB: tuberculosis; GER: gastro-oesophageal reflux. *: $p<0.05$ for differences between cases and controls within each group of patients. #: $p<0.10$ for differences between cases and controls within each group of patients.

patients, older ages and smoking were high, but more frequent in COPD patients than in CB patients and less frequent in asthmatic patients. History of hospitalisations, respiratory infections, comorbidity and influenza vaccination were common in all patients.

Upper respiratory tract infections were associated with CAP in all three groups of patients (CB, COPD and asthma); smoking and influenza vaccination were also associated with CAP in COPD patients; and depression, *N*-acetylcysteine, oxygen therapy and both influenza and pneumococcal vaccination were also associated with CAP in asthma patients.

Table 2 shows that in patients with CB there were no more cases of CAP after using inhaled therapy regularly during the last year than in controls. In patients with COPD 48.9% of cases and a 24.2% of controls used inhaled steroids regularly during the last year, which was associated to a risk OR of CAP of 2.99 (95% CI 1.23–7.31). In patients with asthma the risk for CAP was associated to inhaled anticholinergics (OR 8.13, 95% CI 1.05–62.79).

The effect on the risk for CAP of inhaled drugs, as well as of different respiratory diseases and their concomitant drug treatments, and other non-respiratory variables from table 1 potentially associated to CAP, is shown in table 3. In this multivariable analysis the adjusted effect of the inhaled treatments on the risk of CAP depended on the type of respiratory disease. In CB patients, no effect was observed for any inhaled treatment, but upper respiratory tract infections in the past month had a significant effect on the risk of CAP. In COPD patients, inhaled steroids had a risk of 3.26 (95% CI 1.07–9.98), and smoking history (pack-yrs) also had a significant effect on the risk of CAP. In asthma patients, inhaled anticholinergics had a risk of 8.80 (95% CI 1.02–75.7), whereas the pneumococcal vaccine had a 65% risk reduction on the risk of CAP.

DISCUSSION

In recent years, it has been suggested that the use of inhalers containing steroids may cause pneumonia as a severe adverse effect in patients with COPD [10–12]. This effect, together with other active medications administered with MDIs, has been further explored in the present study with chronic respiratory patients from a large population-based sample of 1,336 cases of clinically and radiologically confirmed CAP and 1,326 healthy

TABLE 2 Regular use of inhaled treatments during the last year and risk of community-acquired pneumonia (CAP)

Variable	CAP	Controls	OR (95% CI)	p-value
Chronic bronchitis				
Subjects n	122	48		
Inhaled steroids	41 (33.6)	18 (37.5)	0.84 (0.42–1.69)	0.631
0 puffs per day	57 (77.0)	23 (82.1)	1	0.746
1–4 puffs per day	16 (21.6)	5 (17.9)	1.29 (0.42–3.94)	
⩾5 puffs per day	1 (1.4)	0 (0)		
Inhaled β-agonists	52 (42.6)	23 (47.9)	0.81 (0.41–1.58)	0.531
0 puffs per day	57 (52.8)	23 (50.0)	1	0.315
1–4 puffs per day	31 (28.7)	18 (39.1)	0.70 (0.33–1.48)	
⩾5 puffs per day	20 (18.5)	5 (10.9)	1.61 (0.54–4.82)	
Inhaled anticholinergics	30 (24.6)	10 (20.8)	1.24 (0.55–2.78)	0.603
0 puffs per day	57 (65.5)	23 (69.7)	1	0.515
1–4 puffs per day	15 (17.2)	7 (21.2)	0.87 (0.31–2.40)	
⩾5 puffs per day	15 (17.2)	3 (9.1)	2.02 (0.53–7.63)	
COPD				
Subjects n	94	33		
Inhaled steroids	46 (48.9)	8 (24.2)	2.99 (1.23–7.31)	0.014
0 puffs per day	22 (44.9)	9 (64.3)	1	0.565
1–4 puffs per day	24 (49.0)	5 (35.7)	1.96 (0.57–6.76)	
⩾5 puffs per day	3 (6.1)	0 (0)		
Inhaled β-agonists	63 (67.0)	21 (63.6)	1.16 (0.51–2.66)	0.724
0 puffs per day	22 (25.9)	9 (32.1)	1	0.018
1–4 puffs per day	30 (35.3)	16 (57.1)	0.77 (0.29–2.05)	
⩾5 puffs per day	33 (38.8)	3 (10.7)	4.50 (1.09–18.5)	
Inhaled anticholinergics	41 (43.6)	10 (30.3)	1.78 (0.76–4.15)	0.180
0 puffs per day	22 (34.4)	9 (47.4)	1	0.620
1–4 puffs per day	20 (31.7)	5 (26.3)	1.64 (0.47–5.71)	
⩾5 puffs per day	21 (33.3)	5 (26.3)	1.72 (0.49–5.97)	
Asthma alone				
Subjects n	256	153		
Inhaled steroids	22 (8.6)	8 (5.2)	1.70 (0.74–3.93)	0.207
0 puffs per day	210 (96.8)	134 (99.3)	1	0.160
1–4 puffs per day	7 (3.2)	1 (0.7)	4.47 (0.54–36.7)	
⩾5 puffs per day	0 (0.0)	0 (0)		
Inhaled β-agonists	39 (15.2)	15 (9.8)	1.65 (0.88–3.11)	0.116
0 puffs per day	210 (85.4)	134 (90.5)	1	0.244
1–4 puffs per day	24 (9.8)	11 (7.4)	1.39 (0.66–2.94)	
⩾5 puffs per day	12 (4.9)	3 (2.0)	2.55 (0.71–9.21)	
Inhaled anticholinergics	13 (5.1)	1 (0.7)	8.13 (1.05–62.79)	0.017
0 puffs per day	210 (94.6)	134 (99.3)	1	0.067
1–4 puffs per day	7 (3.2)	1 (0.7)	4.47 (0.54–36.7)	
⩾5 puffs per day	5 (2.3)	0 (0.0)		

Data are presented as n (%), unless otherwise stated. Differences between the number of patients taking the inhaled treatment or by puffs per day do not coincide with the total number of patients due to missing values. COPD: chronic obstructive pulmonary disease.

TABLE 3 Association between inhaled drug treatments and the risk of community-acquired pneumonia (CAP) adjusted for respiratory comorbidity and its severity, respiratory treatments and other non-respiratory risk factors, by strata of patients with specific respiratory diseases

Variable	OR (95% CI)	p-value
Chronic bronchitis		
Upper respiratory tract infection in the past month	2.56 (1.16–5.65)	0.020
Oxygen therapy	3.52 (0.38–33.0)	0.270
Inhaled steroids	0.96 (0.35–2.61)	0.930
Inhaled β-agonists	0.59 (0.22–1.57)	0.294
Inhaled anticholinergics	1.46 (0.56–3.79)	0.435
Asthma	1.73 (0.82–3.68)	0.154
Oral corticosteroids	4.05 (0.47–34.9)	0.203
COPD		
Upper respiratory tract infection in the past month	2.25 (0.84–6.01)	0.107
Oxygen therapy	1.18 (0.19–7.39)	0.863
Inhaled steroids	3.26 (1.07–9.98)	0.038
Inhaled β-agonists	0.68 (0.23–2.02)	0.483
Inhaled anticholinergics	1.19 (0.39–3.63)	0.757
Asthma	1.00 (0.38–2.62)	0.998
Oral corticosteroids	1.30 (0.31–5.47)	0.718
Smoking history pack-yrs		
0	1	0.081
1–150	4.23 (1.07–16.7)	0.039
>150	2.44 (0.83–7.21)	0.105
Influenza vaccine	0.39 (0.12–1.27)	0.118
Asthma alone		
Upper respiratory tract infection in the past month	1.46 (0.92–2.30)	0.105
Inhaled steroids	1.10 (0.40–3.00)	0.857
Inhaled β-agonists	1.24 (0.58–2.67)	0.582
Inhaled anticholinergics	8.80 (1.02–75.7)	0.048
Influenza vaccine	0.67 (0.42–1.08)	0.096
Pneumococcal vaccine at any time of life	0.35 (0.14–0.84)	0.020
N-Acetylcysteine	0.23 (0.03–1.87)	0.168
Depression	0.70 (0.40–1.21)	0.200

COPD: chronic obstructive pulmonary disease.

controls. Results indicate that inhaled steroids may increase the risk of CAP in patients with COPD, inhaled anticholinergics may increase the risk of CAP in patients with asthma, and inhaled β_2-adrenergic agonists do not appear to affect the risk of CAP.

In general, the use of inhaled drugs delivered through a MDI had an effect on the development of CAP and a dose–response relationship in terms of the mean number of daily puffs [9]. This was in agreement with the hypothesis that poor hygienic measures and contamination of inhalers, particularly of plastic pear-spacers, may represent a causal component of the mechanism of infection [11]. Indeed, the effect of inhalers on the development of CAP can be attributed to the active medication contained in the MDI.

The relation between bronchodilator therapy and some severe complications has been recognised for decades [17–19]. Nevertheless, no study has focused on the analysis of infectious complications until it was recently shown that inhaled steroids increased the risk of CAP in patients with

COPD [10, 11]. Evidence of the impact of inhaled steroids was unexpectedly documented in the TORCH (Towards a Revolution in COPD Health) study, which was designed to assess the benefit of inhaled drugs on long-term survival of COPD patients [12]. Other recent studies have also confirmed an association between inhaled steroids and the incidence, hospitalisation and death-related CAP in patients with COPD [20–22]. Nevertheless, a recent meta-analysis showed that budesonide did not increase the risk of pneumonia in patients with COPD [23]. The findings of these studies should be interpreted with caution due to the possibility of methodologic limitations and systematic errors [20, 24]. However, this association is corroborated in the current study, in which the risk of CAP for inhaled steroids was restricted to patients with COPD but not to patients with CB. A possible explanation of this finding may be that the risk of inhaled steroids would act only in patients with more severe bronchopathy, which in turn implies a diagnostic confirmation of chronic airflow obstruction, whereas inhaled steroids would not act in patients with only clinical symptoms of persistent cough and expectoration. In these patients as well, the contribution of inhaled steroids to the risk of CAP may be lower because they were administered at lower doses. The median (range) puffs per day in these patients was 2 (1–9) compared with 4 (1–9) in patients with more severe bronchopathy. This association between inhaled steroids and the risk of CAP could not be explained by the possible effect of confounding by severity because we attempted to control for this *via* with the inclusion of independent variables related to disease severity in the multivariable analysis.

Conversely, inhaled steroids were not found to be a risk factor for CAP in patients with asthma. In the only two studies in which this relationship has been analysed, an association between inhaled steroids and CAP was not observed [25, 26]. These results suggest that, although bronchial asthma is *per se* a risk factor for CAP [8, 9, 27, 28], the effect on inhaled steroids would only occur in the presence of local and systemic pathophysiological conditions of COPD. For this reason, in asthmatic patients the crude effect of inhaled steroids of 1.70 (95% CI 0.74–3.93) was diluted to 1.10 (95% CI 0.40–3.00) after adjusting for underlying respiratory diseases and other counfounding factors.

Inhaled drug treatment with anticholinergics was found to be associated with CAP in asthma patients. Only the effect of the short-acting antimuscarinic ipratropium bromide was assessed in our study because the new generation long-acting tiotropium bromide was not commercialised at the time of the study. The effect of inhaled anticholinergics was of considerable magnitude and independent of underlying respiratory illnesses, related treatments and the remaining risk factors of CAP. However, the uncertainty associated with this effect estimate was considerable because asthma patients who are anticholinergic users are uncommon. The CAP risk of inhaled anticholinergics did not reach statistical significance in CB and COPD patients.

Anticholinergic drugs cause bronchodilation by inhibition or parasympathetic activity of the airways by blocking muscarinic receptors [29, 30]. In patients with stable COPD, the use of tiotropium with or without β_2-adrenergic agonists depends on the drug availability and the individual response, but the role of this agent as a first-line or second-line option in the treatment of stable COPD is a matter of discussion pending data from further long-term studies [15, 31–35]. In patients with asthma, a meta-analysis of randomised clinical trials, conducted to determine whether the addition of inhaled ipratropium to inhaled β-agonist therapy was effective in the emergency treatment of adults with acute asthma exacerbation, concluded that the use of combination ipratropium and β-agonist therapy was reasonable since the addition of ipratropium seemed to provide physiological evidence of benefit without risk of adverse effects [36]. In our study, 5.1% of cases and 0.7% of controls with asthma used inhaled anticholinergics. We believe that they were on treatment with ipratropium because they might be patients with difficult to control disease, either because they had moderate or serious exacerbations in the context of a severe asthma, or they were also treated with other types of inhalers and experienced poor response to them, or because they had other respiratory comorbidities.

In relation to safety, the anticholinergics appear to have a wide therapeutic margin and to be well tolerated by patients, the only significant side-effect being dryness of the mouth. Occasional prostatic symptoms, and an unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide have also been reported [37, 38]. The risk of CAP for inhaled anticholinergics has not been previously reported, but in no study has this effect been analysed as a primary outcome [33, 35, 39, 40]. In the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study, based on COPD patients of at least 40 yrs of age, anticholinergics were associated with a reduction in the risk of exacerbations, but not specifically with a reduction in the risk of CAP [40]. In fact, no association between the use of inhaled anticholinergics and CAP was found in comparison with placebo or other inhaled drugs. There are some biological explanations that can make this effect plausible: an inhibition of the ciliary activity, and a reduction in the clearance mechanism of the mouth and mucous secretion related to the anticholinergic effect of dry mouth [41] may favour the growth of pathogens and increase the probability of colonisation. The muscarinic antagonism may also contribute the reduction of neutrophil infiltration of the airways [42]. This potentially beneficial effect could nevertheless impair the defenses of the respiratory tract, particularly cell-mediated immunological host response, and favour the propagation of pathogens and subsequent pulmonary infection.

In the present study, the use of inhaled β_2-adrenergic agonists did not show an effect on the risk of CAP after adjusting for underlying respiratory diseases and their corresponding oral drug treatments. In consequence, the use of inhaled β_2-adrenergic agonists would have no effect on the occurrence of CAP.

Our findings should be interpreted taking into account some limitations of the study, especially the small number of patients in some of the subsets analysed. This circumstance also prevented a rigorous adjustment for the variables of disease and severity that may be correlated with inhaled drug treatments. In addition, more stringent variables related to disease severity could be used, especially for asthma patients.

For these reasons, there is still the possibility of a residual confounding in our results. However, the adjustment by different variables that are inter-correlated may increase the inaccuracies in the estimations of the risk of CAP, introducing bias and reducing their statistical significance. Finally, missing values for the doses of some treatments, particularly of inhaled steroids, limit assessment of a dose–response relationship. Therefore, and given that this is the first study that describes the effects of inhaled anticholinergics on the risk of CAP, it is necessary to perform further studies specifically designed to confirm the present findings.

This study intended to separate the effect of inhaled drugs from the effect of the underlying respiratory disease and its severity on the risk of CAP using different strategies of analysis. The present results suggest that inhaled steroids and anticholinergics (but not β-agonists) may be risk factors for CAP according to the type of underlying respiratory disease. Inhaled steroids may increase the risk for CAP in patients with COPD, while inhaled anticholinergics may favour CAP in patients with asthma. These findings may not be causal but further confirmation of these relationships might be of clinical importance in the therapeutic management of inhalers in COPD and asthma patients.

APPENDIX: ITEMS INCLUDED IN THE QUESTIONNAIRE

Identification and sociodemographic data

Identification number.

Birth date.

Sex.

City.

Date of the interview.

Not responding reason.

Person who answers the questionnaire.

Medical history

Hospital admission in the previous 5 yrs, number of admissions, date of the last admission.

Diagnostic studies in the previous year: nose, pharynx, bronchoscopy, gastroscopy, nasogastric tube, general anaesthesia.

Upper respiratory tract infection in the previous year, number of episodes, purulent tonsillitis.

Upper respiratory tract infection in the previous month, number of episodes, purulent tonsillitis.

Any previously radiographically confirmed pneumonia.

Pathologic conditions

Diabetes, any diagnosis and treatment.

Heart failure, any diagnosis.

Valve heart disease, any diagnosis.

Coronary heart disease, any diagnosis.

Chronic bronchitis, any diagnosis. Type of COPD according to spirometry.

Asthma. Any diagnosis.

Other chronic respiratory diseases (enphysema, bronchiectasis, *etc.*).

Non-active pulmonary tuberculosis, any diagnosis.

Epilepsy, any diagnosis.

Parkinson, any diagnosis.

Debilitating neuromuscular disorder (amyotrophic lateral sclerosis, multiple sclerosis, *etc.*), any diagnosis.

Conditions involving the cranial nerves, any diagnosis.

Dementia or Arzheimer disease, any diagnosis.

Stroke, any diagnosis.

Gastroesophageal reflux, any diagnosis, hiatal hernia, peptic ulcer.

Chronic liver disease, any diagnosis.

Hepatitis B virus infection or hepatitis C virus infection, any diagnosis.

Chronic renal failure, any diagnosis.

Mental disorder or depression, any diagnosis.

Tonsillectomy or adenoidectomy, any surgical removal.

Cancer, type, any diagnosis, treatments in the previous year.

HIV infection.

Drug treatment

Regular treatments in the previous year: *N*-acetylcysteine, digoxin, amiodarone,

diuretics, aminophylline, benzodiazepines, oxygen, inhalers with holding chamber

(type and active drug), inhalers without holding chamber (type and active drug),

antimicrobials (active compound).

Anthropometric and present conditions

Height and weight.

Visit to the dentist in the previous month.

Abscess.

Edentulous.

Caries.

Dental prosthesis.

Vaccinations

Influenzae in the previous year.

Antipneumoccocal, year of administration.

Toxic habits

History of tobacco use to calculate pack-yr smoking history.

Passive smoking at work or home.

Frequency of consumption of alcoholic beverages.

Registration of consumption of alcoholic beverages to calculate daily ingestion of pure alcohol (in grammes).

Lifestyle and working conditions

Civil status.

Living with more than 10 persons at home.

Living or working with children <15 yrs of age.

Pets, number and classes.

Education level.

Occupation.

Work-life contact with smoke, vapours, petrol or hydrocarbons, dust, organic fibres, inorganic fibres, ionising radiation, non-ionising radiation, animals, excrements, or visceras.

Sudden changes of temperature in the workplace in the previous 3 months.

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STATEMENT OF INTEREST

A statement of interest for A. Torres can be found at www.erj.ersjournals.com/misc/statements.xhtml

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