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Reduced Risk of Next Exacerbation and Mortality Associated with Use of Antibiotics in COPD

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Abstract

The long-term risk of a subsequent exacerbation of COPD after treatment with oral corticosteroids without (OS) or with antibiotics (OSA) was compared in a historical general practice-based cohort.

Eligible were patients ≥ 50 years with a registered diagnosis of COPD on maintenance respiratory drugs, who experienced at least one exacerbation defined as a prescription OS or OSA. Times to second and third exacerbations were assessed using Kaplan-Meier survival analysis, the risk of a subsequent exacerbation in a Cox proportional hazards analysis, and all cause mortality.

842 patients had one or more exacerbations. The median time from first to second exacerbation was comparable for the OS group and the OSA group, but the time from second to third exacerbation differed: 189 versus 258 days. The protective effect of OSA was most pronounced during the first three months following treatment (HR 0.72; 95%CI 0.62–0.83). Exposure to antibiotics unrelated to a course of oral corticosteroids almost halved the risk of a new exacerbation. Mortality during follow-up was considerably lower in the OSA group.

Adding antibiotics to oral corticosteroids was associated with a reduced risk of a subsequent exacerbation, especially in patients with recurrent exacerbations, and a reduced risk of all cause mortality.

Introduction

Patients with an acute exacerbation of COPD are often treated with a combination of antibiotics and corticosteroids. However, in fact, only patients with severe symptoms, and/ or patients with a low baseline expiratory flow rate appear to benefit from antibiotic treatment.[1-3] A recent Cochrane review[4] supports the use of antibiotics for exacerbations of COPD with increased cough and sputum purulence in patients who are moderately or severely ill. An analysis restricted to community-based studies, however, did not demonstrate a difference between antibiotic and placebo.[4] In addition, most studies on the use of antibiotics in exacerbations of COPD focussed on the evaluation of short term recovery from exacerbation, with a follow-up period of a few weeks only.

In a previous population-based cohort study using pharmacy dispensing records,[5] we demonstrated that treatment of an exacerbation with antibiotics in addition to oral corticosteroids was associated with an increased time to a subsequent exacerbation and an improved survival. Extrapolation of our results to patients diagnosed with COPD, however, must be done with caution: we studied a heterogeneous population defined by the use of respiratory drugs used for the maintenance treatment of obstructive lung disease.[6]

Therefore, the aim of the present study was to extend our observations to a well-defined COPD population using the Second Dutch National Survey of General Practice.[7]

Methods

Data sources

The data were derived from the Second Dutch National Survey of General Practice (DNSGP-2), carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001,[7] and completed with data from the National Information Network of General Practice (LINH).[8] DNSGP-2 was performed in 104 general practices in the Netherlands, comprising 195 GPs and including 400,911 patients, and it provides a representative impression of the morbidity and prescribing habits in Dutch general practice.[7] The patients in these practices are representative for the Dutch general population with respect to age, gender and type of health care insurance. LINH, connected with NIVEL, is a computerized network of 85 general practices with almost 340,000 registered patients, providing representative information with respect to care delivered by Dutch General Practitioners (GPs), based on data from electronical medical records. In the DNSGP-2 data were collected for one year; LINH collects data continuously. General practices were selected when participating both in the DNSGP-2 as well as in the LINH registration network.

Patient selection

From the DNSGP-2 and LINH databases we selected those practices that provided complete data on morbidity and prescriptions from the cohort entry date, the date of the general practice entering the DNSGP-2 in 2001, until 31 December 2005. Patients were included who in the first year of participating in the DNSGP-2 were registered with COPD, according to International Classification of Primary Care code (ICPC) R95[9] and in addition in the first year of participating in the DNSGP-2 had at least two prescriptions of maintenance respiratory drugs, coded ATC (Anatomical Therapeutic Chemical) R03.[10] These prescriptions included inhaled beta-2-agonists, inhaled anticholinergics, inhaled

corticosteroids, oral theophylline, or a combination of these agents. In order to minimize the number of patients with asthma, only patients aged 50 years or older were included. . For the same reason, patients using leukotriene receptor antagonists (LTRAs) (montelukast, ATC-code R03DC03) or cromoglycates (R03BC) were also excluded.

Patient characteristics (age, gender, maintenance medication for obstructive lung disease, co-medication for cardiovascular disease and diabetes mellitus) were derived from the DNSGP-2 database.

Definition of Exacerbation

We selected COPD patients who experienced one or more exacerbations during the follow-up period. An exacerbation was defined as 'a prescription of a short course of oral corticosteroids, with or without antibiotics'. The date of prescription of oral corticosteroids (ATC code: H02AB06/ H02AB07), with or without antibiotics was recorded. The following antibiotics were selected: doxycyclin (ATC-code: J01AA02), amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), erythromycin (J01FA01), azithromycin (J01FA10), clarithromycin (J01FA09), ciprofloxacin (J01MA02), moxifloxacin (J01MA14), and levofloxacin (J01MA12). In the Netherlands, these antibiotics cover almost all antibiotics prescribed for exacerbations of COPD in primary care.[11] Episodes treated with antibiotics only were not included, as diagnoses were available in parts of the patients only and therefore these prescriptions could not automatically be considered to represent an exacerbation.

When more than one course of oral corticosteroids was prescribed within a period of three weeks, this episode was considered as a single exacerbation. If the time between two prescriptions exceeded three weeks, we considered this second episode a new exacerbation, as in the majority of patients three weeks after the onset of an exacerbation symptoms are usually considerably improved.[12]

Patients prescribed oral corticosteroids or antibiotics for more than 21 days at regular intervals, for a period of three months or longer, were excluded from the analysis, since these patients cannot be discriminated from patients on maintenance treatment.

Statistical analysis

Treatment groups were compared at time of first exacerbation with respect to age, gender, use of inhaled respiratory drugs, including inhaled corticosteroids, and co-medication for cardiovascular disease or diabetes.

We assessed the first exacerbation after cohort entry and calculated the time to the second exacerbation. The date of prescribing the exacerbation medication was considered to be the start of the second exacerbation. The time between the second and the third exacerbation was also calculated. We compared these time periods between patients treated with oral corticosteroids only (OS) and those treated with oral corticosteroids and antibiotics (OSA) using a Kaplan-Meier survival analysis. Patients were censored for exacerbation free survival.

The effect of the variable of primary interest, treatment of exacerbation, OS (coded as 0), or OSA (coded as 1), was analysed in a Cox proportional hazards model. All exacerbations from each patient were used, and time was set back to zero after each exacerbation (gap-time unrestricted model).[13] Hence, each exacerbation was treated as a separate record and time since last exacerbation as principal time scale. A correction for recurrent exacerbation events from the same individual was made by including a frailty term in the model.[14] The Schoenfeld residuals as obtained from the model of time to next exacerbation suggested the difference in treatment effect to be highly nonproportional. Therefore, the difference in treatment effect was allowed to change at three months, six months and one year. The data were coded so that hazard ratios (HRs) below unity indicated a preventive effect of adding an

antibiotic to the oral corticosteroids. Potential confounding by the following patient characteristics was controlled for: age, gender, number of prescriptions of respiratory drugs, including inhaled corticosteroids, co-medication for cardiovascular disease (yes/no) or for diabetes (yes/no).[15] Prescriptions of antibiotics without oral corticosteroids were also treated as a time-dependent covariate, and assumed to be of influence for a period of three months; three months after this antibiotic was prescribed, the variable was again coded as 'no antibiotic'.

All-cause mortality of both treatment groups during follow-up was analyzed using Kaplan-Meier and Cox proportional hazards analysis.

We calculated 95% confidence intervals. Analyses were performed using R-2.6.0[16] and SPSS v. 14.0.2 software (SPSS Inc., Chicago, Il, USA).

Results

Patients

From the DNSGP-2/ LINH database, 54 practices, comprising 216,455 patients, provided complete data on morbidity and prescriptions in the selected time period. 63,721 patients were aged over 50 years, and we identified 1841 patients diagnosed with COPD (2.9%). In total 999 of these patients were excluded: 356 did not meet the prespecified criteria on the use of maintenance respiratory drugs, 532 patients did not experience a single exacerbation, as they were never prescribed oral corticosteroids, and 52 patients used LTRAs or cromoglycates, leaving 901 patients with one or more exacerbations. Of these patients, 30 were excluded because the oral corticosteroids were prescribed for other indications than COPD, 10 were on maintenance treatment with oral corticosteroids for COPD, 13 were on maintenance treatment with antibiotics, and 6 patients were not 'at risk' for a next exacerbation (only one exacerbation less than 21 days before the end of follow-up), leaving 842 patients for the final analysis (Figure 1).

Of these 842 patients, 144 (17%) died during the follow-up period. The cause of death in 23 patients was reported not to be related to COPD. 13 patients died as a result of COPD; this was counted as an event, and not right-censored. In the remaining 108 patients the cause of death could not be retrieved from the database. The median follow-up time after the first exacerbation was 1353 [interquartile range (IQR) 791-1649] days (3 years and 8.5 months). In total, 842 patients were followed for 2723 person years in total.

Of 842 patients having had at least one predefined exacerbation, 404 patients were at first exacerbation treated with oral corticosteroids (OS), and 438 with oral corticosteroids and

antibiotics (OSA). These groups were similar with respect to age, gender, respiratory medication, and use of co-medication for diabetes and cardiovascular disease (Table 1).

Table 1. Characteristics of patients according to treatment of first exacerbation.

	Oral corticosteroids n=404	**Oral corticosteroids and antibiotics** n=438	P-value[‡]
Age (years)*	70 (62-78)	71 (63-77)	0.30
Gender			
Male	217 (54)	231 (53)	0.78
Number of respiratory prescriptions[#]*	8 (4-12)	8 (4-13)	0.35
Using ICS[§]	313 (77)	360 (82)	0.88
Co-medication[#]			
Cardiovascular	301 (74)	323 (74)	0.80
Diabetes	53 (13)	50 (11)	0.45
Follow-up time (days)*	1322 (750-1627)	1375 (832-1657)	

Data are n (%), unless otherwise stated. *Median (Interquartile range). [#]In the first year of participating in the DNSGP-2. [§]ICS: Inhaled corticosteroids. [‡]Chi-square, T-test or Mann-Whitney test, where appropriate.

Of all 4038 exacerbations (median 3 (IQR 1-6) per patient), GPs prescribed OS in 54% and OSA in 46%. Antibiotics used in the treatment of first exacerbations were doxycyclin (n=218, 50%), penicillins (amoxicillin-clavulanate and amoxicillin, n=141, 32%), macrolides (azithromycin, clarithromycin, and erythromycin, n=68, 16%), and fluoroquinolones (ciprofloxacin, moxifloxacin and levofloxacin, n=11, 3%).

KM estimates of developing a second exacerbation according to treatment type (OS or OSA)

Overall, 595 patients (71%) experienced a second exacerbation. The median time to the second exacerbation was 331 (95% CI 258-404) days in the OS group compared to 312 (95% CI 265-359) days in the OSA group (p=0.31) (Figure 2A). Six months after the first exacerbation, 27% of patients treated with oral corticosteroids had experienced a second exacerbation compared to 23% of patients treated with oral corticosteroids and antibiotics; after one year this was 52% and 54% respectively.

KM estimates of developing a third exacerbation according to treatment type (OS or OSA)

Of the 595 patients having a second exacerbation, 308 (52%) were treated with oral corticosteroids only (OS) and 287 (48%) with oral corticosteroids and antibiotics (OSA). 450 patients had a third exacerbation during follow up. The time between the second and the third exacerbation was much shorter in the OS group than in the OSA group, median time 189 (95% CI 149-229) days compared to 258 (95% CI 198-318) days ($p<0.01$) (Figure 2B). Six months after the second exacerbation, 50% of patients treated with oral corticosteroids had experienced a third exacerbation compared to 41% of patients treated with oral corticosteroids and antibiotics; after one year this was 69% and 61% respectively.

Cox analysis of developing a new exacerbation according to treatment type

In a univariate Cox regression model the Hazard Ratio (HR) of a next exacerbation after treatment with oral corticosteroids and antibiotics (OSA) compared to oral corticosteroids only (OS) was 0.73 (95% CI 0.63–0.84). In a Cox proportional hazards model, adjusting for potential confounding factors, the HR of a next exacerbation after treatment with OSA was 0.72 (95% CI 0.62-0.83) in the first three months following treatment, but the effect was not significant in subsequent time periods. In addition, the use of antibiotics prescribed without a course of oral corticosteroids, irrespective of the indication, almost halved the risk of a next exacerbation (HR 0.56; 95% CI 0.48-0.71) (Table 2).

Table 2. HR of developing a subsequent exacerbation, in a Cox proportional hazards model.

	HR of next exacerbation	95% CI for HR	
		Lower	Upper
Antibiotics and oral corticosteroids, versus steroids only			
0-3 months following treatment	0.72	0.62	0.83
3-6 months ,, ,,	0.85	0.70	1.04
6-12 months ,, ,,	1.02	0.80	1.30
> 12 months ,, ,,	1.22	0.89	1.66
Exposure to antibiotics after previous exacerbation	0.56	0.45	0.71
Female sex	0.91	0.75	1.10
Inhaled corticosteroids as maintenance medication[#]	0.87	0.68	1.12
Co-medication cardiovascular[#]	1.37	1.10	1.73
Co-medication for diabetes[#]	0.90	0.68	1.19

HR, Hazard Ratio. CI, Confidence interval. [#]In the first year of participating in the DNSGP-2. The variables 'age' and 'number of respiratory drugs prescriptions' were included in the Cox model, but were not fitted linearly, therefore HRs are not presented. The risk of a new exacerbation increased significantly with age and with a higher number of prescriptions of respiratory drugs.

Mortality of both treatment groups during follow-up

After the first exacerbation, during follow-up 62/438 (14%) patients died in the OSA group compared to 82/404 (20%) in the OS only group (p=0.02, Figure 3). The HR of all-cause mortality after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.67 (95% CI 0.48-0.93) in a univariate Cox regression model. In a Cox proportional hazards model, adjusting for the potential confounders, the HR was 0.62 (95% CI 0.45–0.87).

Discussion

In COPD patients treated by general practitioners and using maintenance respiratory medication, we compared the long-term risk of a subsequent exacerbation after treatment with oral corticosteroids with or without antibiotics. The results show that treatment of exacerbations with antibiotics in addition to oral corticosteroids, and also the use of antibiotics without oral corticosteroids is associated with a reduced risk of a subsequent exacerbation. Moreover, we show a survival benefit in the oral corticosteroid and antibiotics group. As far as we know, the demonstrated effect of antibiotic treatment on the risk of a subsequent exacerbation as well as the associated survival benefit was not reported before in an extensive population-based COPD cohort.

Strengths and limitations of this study

The DNSGP-2/ LINH database provided a selection of COPD patients according to International Classification of Primary Care code (ICPC) R95.[9] One limitation of using a registration database is that available data were not collected for the specific aim of this study, and therefore relevant information such as lung function data, may be lacking. In addition, no clinical information on the severity of the exacerbation was present, and this may have caused treatment selection bias. However, relevant baseline characteristics of the treatment groups were similar. Furthermore, patients treated with antibiotics and oral corticosteroids are likely to have more severe exacerbations compared to patients treated with oral corticosteroids only. Therefore, we suspect that bias at this point, if present, would be associated with an underestimation of the effect of treatment.

An antibiotic course without steroids seemed to work even better than antibiotics combined with oral corticosteroids in preventing subsequent exacerbations. However, unfortunately, it could not be derived from the database whether the antibiotic courses were in all cases

prescribed for an exacerbation of COPD. Nevertheless, this finding is remarkable, and appears in support of the conclusion that antibiotics are beneficial in the prevention of exacerbations.

The exacerbation rate of the selected patients was 1.5 per patient per year, indicating that we selected patients with more severe COPD, as the exacerbation rate in general practice in the Netherlands is usually < 1 per patient yearly.[17] Exacerbations in patients with more severe COPD are more likely to benefit from antibiotic treatment.[2,3,4,18] The stronger treatment effect we found in time to the third exacerbation compared with the time to the second exacerbation suggests that the conclusions of this study may be especially applicable for patients with recurrent exacerbations.

Comparison with existing literature

Most studies evaluate short-term outcomes: acute resolution rates and early relapse rates. It has been noticed earlier that the use of time to the next exacerbation as primary outcome measure is especially suitable in evaluating COPD exacerbations.[19-21] As hypothesized, effective antibiotic treatment that results in bacterial eradication may prevent recurrence.[19-21] One study demonstrated for the first five months after antibiotic treatment a significant difference between two antibiotics in the recurrence rate of exacerbations, related to differences in induced bacterial eradication.[22] These effects of antibiotic treatment may become apparent in long-term evaluations, while short-term outcomes may not show these differences, as is the case in community-based studies of exacerbations comparing antibiotic and placebo.[4,23]

The present results extend, in a well-defined COPD population, the results of our previous PHARMO study, where we selected patients on the basis of prescribed medication.[6] The annual rate of exacerbations, treatment of first exacerbation (OS versus OSA), and the use of

respiratory maintenance medication were comparable in both studies. A significant difference between both studies was the effect of treatment on time between the first and second exacerbation, which was present in PHARMO but not in this study. In the PHARMO database also prescriptions by other prescribers were included, but selecting patients treated by general practitioners (74%) resulted in smaller, but still significant difference between treatment groups. An explanation for the difference might be the difference between pharmacy- and GP-based data, in that GPs' prescriptions are not always redeemed from the pharmacy. This may account for about 10% of prescriptions[24] in the DNSGP-2/ LINH study, resulting in a diminished treatment effect.

Bacteria and viruses are of influence in inducing exacerbations. Superadded bacterial infection after viral infections occurs frequently, and both bacteria and viruses may interact in a complex inflammatory process.[26-28] The beneficial effect of antibiotics that is described could be attributed to the fact that antibiotics may cause bacterial eradication. Airway inflammation is increased at the time of an exacerbation,[29-31] as is systemic inflammation.[32,33] Even more, also in clinically stable, chronically *H. influenzae*-infected COPD patients airway inflammation is more pronounced as compared to non-infected patients.[34] Systemic inflammation contributes substantially to the overall mortality in COPD patients.[35,36] It can be hypothesized that the observed survival benefit of added antibiotics is related to a stronger effect on systemic inflammation than treatment with oral corticosteroids alone. Recently bacterial colonisation was found to be related to a higher frequency of exacerbations in patients with moderate to severe COPD, suggesting the clinical relevance of the presence of bacteria in the lower airways.[37] Our finding of the beneficial role of antibiotics on the long-term recurrence rate is in line with these observations.

Conclusion

Until now, studies only showed a significant short-term effect of antibiotic treatment in more severe and in hospitalised patients[1-4], but this study now also shows (long-term) benefits for patients treated by general practitioners. However, due to the retrospective character of this study and the limitations with regard to the availability of characteristics of patients and exacerbations, the results presented here cannot be seen as a definitive proof of the long-term effects of antibiotics, but should be confirmed in randomized clinical trials.

Even one exacerbation can have a large and sustained effect on health status. Although the initial recovery can be fast, the period to full recovery may be long.[38] A number of patients even does not recover to baseline symptoms,[12,39] and a decline in FEV1 as a result of the exacerbations might contribute to this process.[40-42] Early re-exacerbation is more common in patients with a deteriorated health status after an exacerbation and in patients with severe COPD, and delays the course of recovery.[37] Patients with frequent exacerbations have a lower quality of life, an increased risk of hospital admission and greater mortality, and generate more costs than patients with less frequent exacerbations. Postponing the next exacerbation can contribute to delaying this process of deterioration.

In this study in primary care COPD patients, who used respiratory maintenance treatment, addition of antibiotics to oral corticosteroids in the treatment of an exacerbation was associated with a reduced risk of a subsequent exacerbation; in particular, this goes for patients with recurrent exacerbations. Moreover, during follow-up we demonstrated a survival benefit in the patients treated with antibiotics next to corticosteroids. If confirmed in future prospective studies, these observations may have a major impact on exacerbation management in COPD patients. Before general implementation, however, the pros and cons

of antibiotic use, in particular the risk of increasing rates of resistance among respiratory pathogens, should be weighed against each other.

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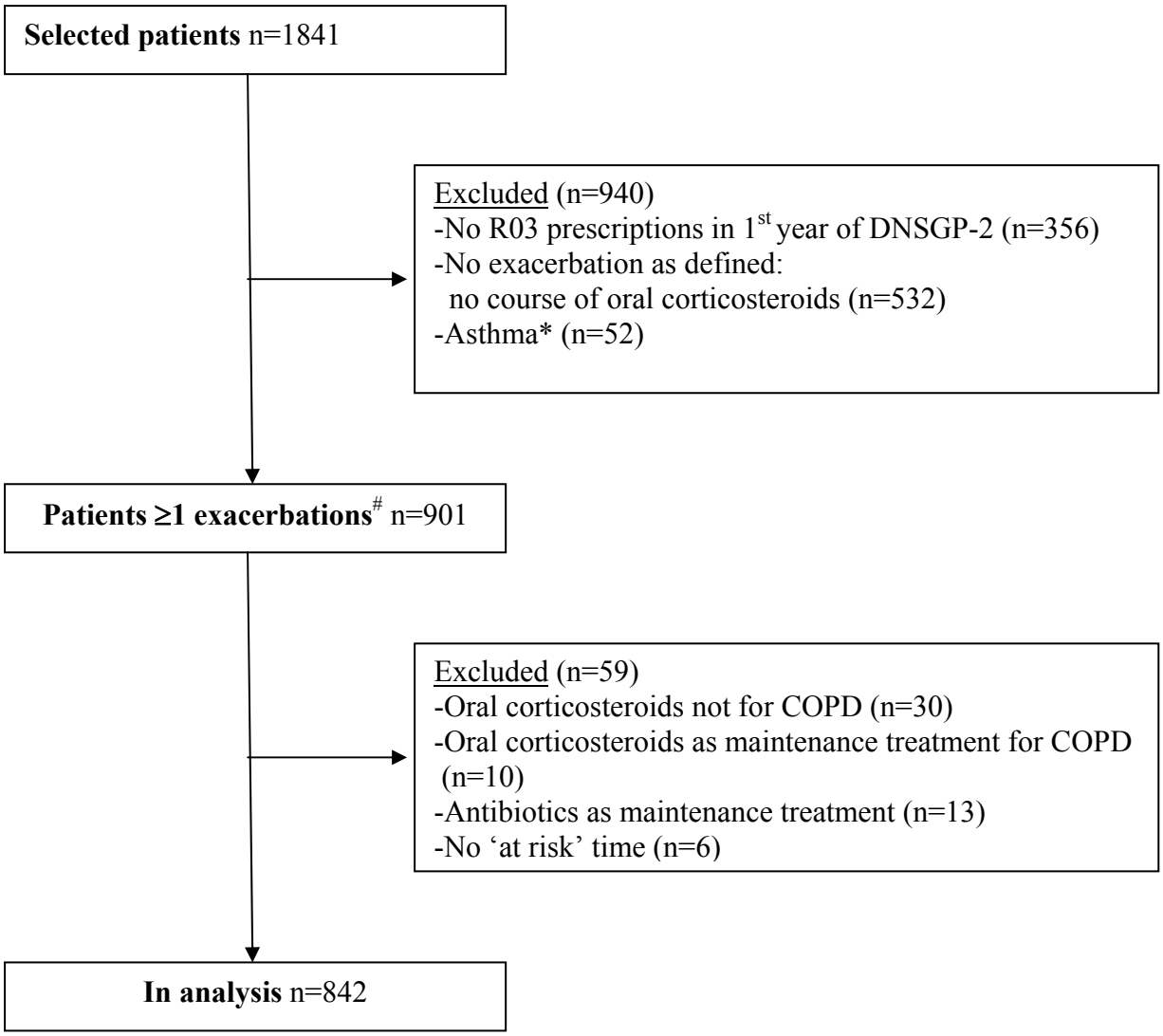
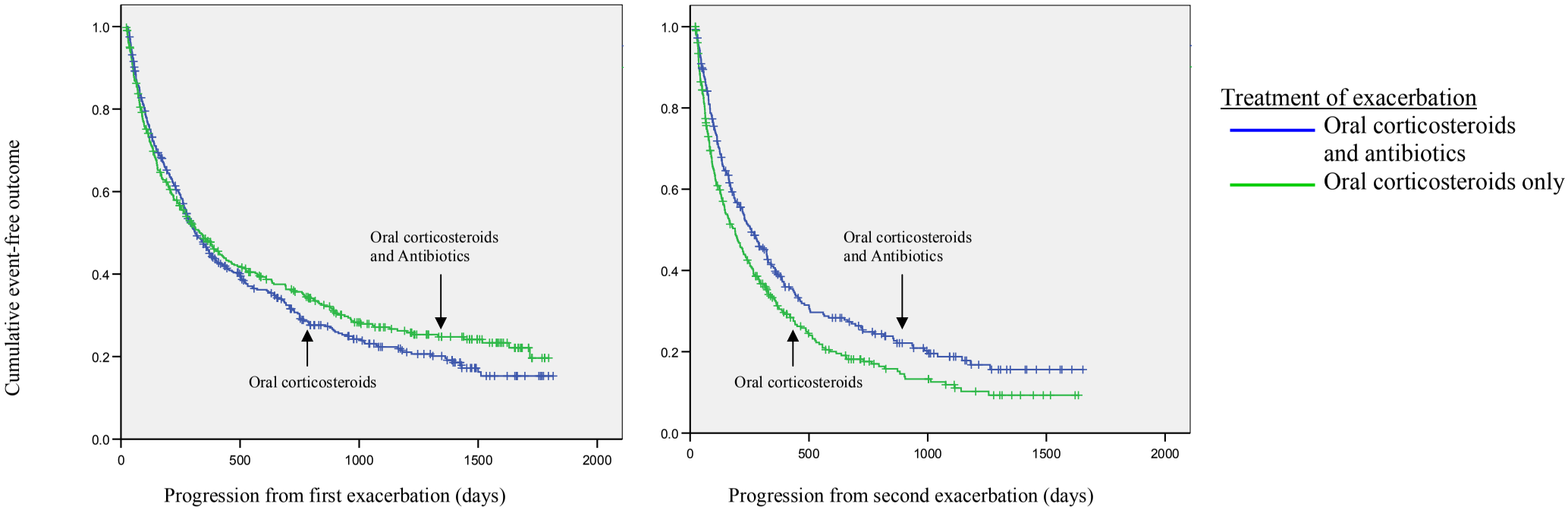
Figure 1. Flow diagram of patients in the analysis



*asthma medication: LTRAs or cromones
Prescription oral corticosteroids with or without antibiotics

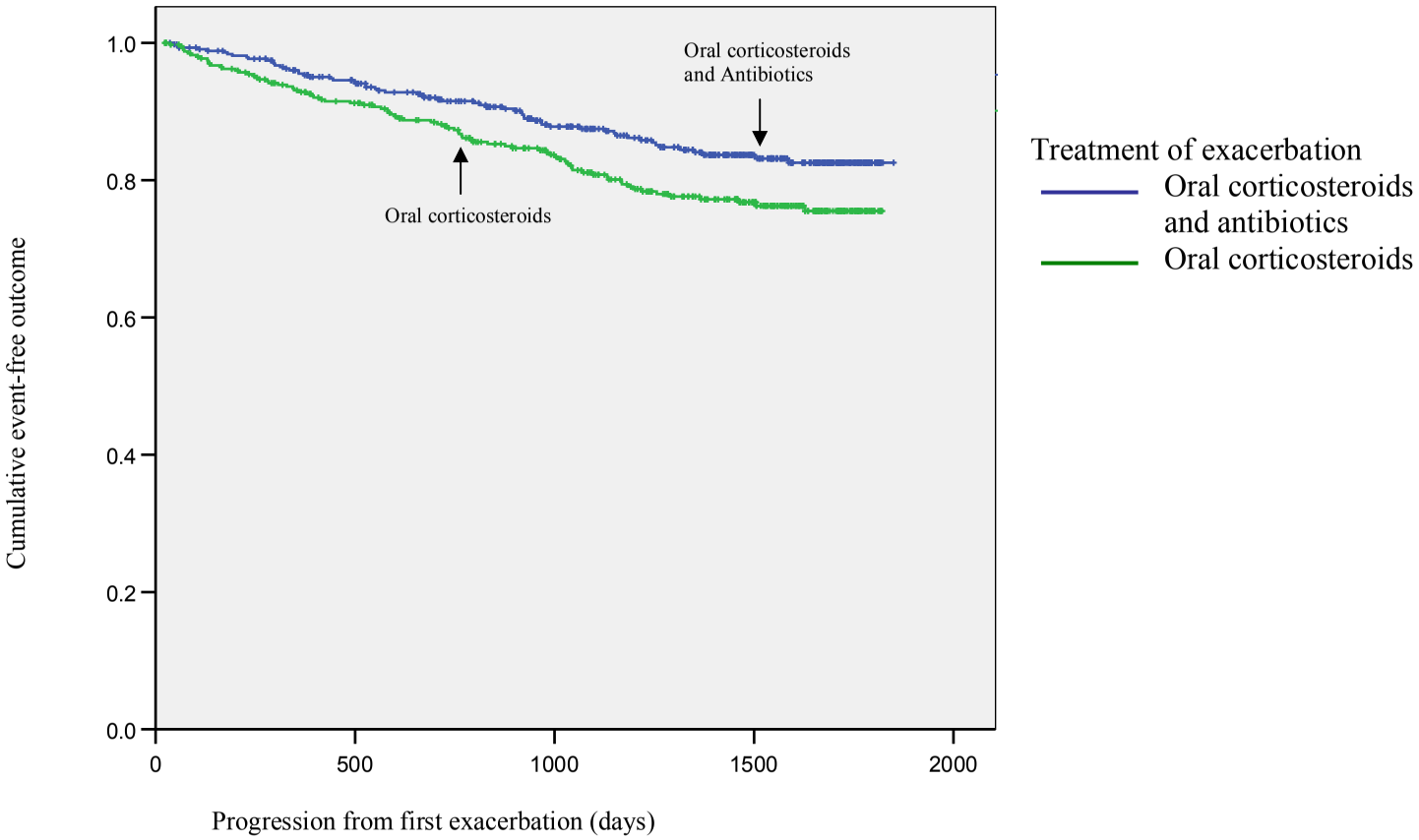
Figure 2. Kaplan-Meier estimates of the fraction of patients that is free of a second (Fig 2A) or third exacerbation (Fig 2B) stratified according to treatment type



The calculated median differences between both treatment groups (19 days); p = 0.31 (Fig. 2A) and 69 days, p<0.01 (Fig. 2B) respectively, by log-rank.

Figure 3. Kaplan-Meier estimates of the cumulative survival stratified according to treatment type

n=842



Difference between both treatment groups, p = 0.02, by log-rank.