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Antibiotic treatment is associated with reduced risk of a subsequent exacerbation in obstructive lung disease: A historical population-based cohort study

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Abstract

Objectives We evaluated the risk of a subsequent exacerbation after treatment of an exacerbation with oral corticosteroids without (OS) or with antibiotics (OSA), in a historical population-based cohort study comprising patients using maintenance medication for obstructive lung disease.

Methods The Pharmo database includes drug-dispensing records of more than 2 million subjects in the Netherlands. Eligible were patients ≥ 50 years who in 2003 were dispensed ≥ 2 prescriptions of daily used inhaled β_2-agonists, anticholinergics, and/or corticosteroids, and experienced at least one exacerbation before 1 January 2006. Exacerbation was defined as a prescription of OS or OSA. We compared the times to the second and third exacerbations using Kaplan-Meier survival analysis. Independent determinants of new exacerbations were identified using multivariable Cox recurrent event survival analysis.

Results Of 49,599 patients using maintenance medication, 18,928 patients had at least one exacerbation; in 52% antibiotics had been added. OS and OSA groups were comparable for potential confounding factors. The median time to the second exacerbation was 321 days in the OS group and 418 days in the OSA group ($p< 0.001$); and between the second and third exacerbation 127 vs. 240 days ($p<0.001$). The protective effect of OSA was most pronounced during the first three months following treatment (hazard ratio 0.62; 99%CI 0.60 – 0.65). In the OSA group mortality during follow-up was lower (HR 0.82; 99% CI 0.66-0.98).

Conclusion Treatment with antibiotics in addition to oral corticosteroids was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation.

Introduction

The mainstay of treatment of exacerbations of COPD consists of oral corticosteroids and antibiotics. The use of corticosteroids in this situation is well-accepted, but the role of antibiotics in exacerbations of COPD is still under debate. Patients with severe exacerbations, characterised by severe symptoms, and/ or patients with a low baseline expiratory flow rate are considered to benefit from antibiotic treatment.[1-3] A recent Cochrane review supports the use of antibiotics for short term benefits in patients with an exacerbation with increased cough and sputum purulence who are moderately or severely ill.[4] Studies conducted in general practice showed no advantage of antimicrobial treatment.[5,6,7] Given the inconclusive results from the literature, guidelines differ in their recommendations.[8-12] The main concern with antibiotic use is a rise of antimicrobial resistance, which correlates well with the overall antibiotic use in the community.[13]

The Dutch Pharmo database contains extensive data on pharmacy dispensing records from community pharmacies and hospital discharge records of more than two million residents of the Netherlands.[14] This gave us the unique opportunity to evaluate the long-term effects of treatment of exacerbations in a large patient group using maintenance medication for obstructive lung disease. In particular, we compared the risk of a subsequent exacerbation after treatment with oral corticosteroids without or with antibiotics.

Methods

Data sources

Data for this study were obtained from the PHARMO database.[14] This population-based database includes pharmacy dispensing records from community pharmacies and hospital discharge records of more than two million residents of 50 regions scattered over the Netherlands. Data are representative for the Netherlands. Both prescriptions from General Practitioners and outpatients are registered. For all residents, the drug-dispensing histories are linked to the hospital discharge records of the same patient, using a probabilistic algorithm, based on characteristics such as date of birth, gender, and a code for the GP.[15] The computerised drug-dispensing histories contain data concerning the dispensed drug and dispensing date. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[16] The hospital records include information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification).

For this study, ethical approval was not relevant because data were anonymized before entering the PHARMO database.

Patient selection

We included patients who in 2003 were dispensed at least two prescriptions of daily used respiratory drugs with ATC-code R03, i.e. inhaled beta-2-agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophylline, or a combination of these agents. We included patients aged 50 years or older, in order to exclude patients with uncomplicated asthma. Furthermore, patients using leukotriene receptor antagonists (LTRAs) (montelukast, ATC-code R03DC03) or cromoglycates (R03BC) and patients who had been hospitalised with a diagnosis of asthma (ICD-9-CM) in the previous 2 years or during follow-up were excluded. The cohort entry date was the date of first dispensing of any R03 drug in 2003. Patients were followed until 31 December 2005. If patients had died before that date, they were censored at the date of death. Apart from age, sex, and respiratory drugs, also data on co-medication for cardiovascular disease and diabetes mellitus, as well as previous hospitalisations for COPD and pneumonia were collected.

Definition of exacerbation

To address the study question, we identified those patients who experienced one or more exacerbations. Our assumption is that, in these patients who are on respiratory drugs, a short course of oral corticosteroids is almost exclusively prescribed in case of an exacerbation. Therefore, we defined an exacerbation as a documented dispensing of a short course of oral corticosteroids, with or without antibiotics. We documented the date of dispensing of oral corticosteroids (ATC code: H02AB06/ H02AB07), with or without antibiotics. We scored the antibiotics doxycyclin (ATC-code: J01AA02), amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), azithromycin (J01FA10), clarithromycin (J01FA09), ciprofloxacin (J01MA02), moxifloxacin (J01MA14), levofloxacin (J01MA12), and erythromycin (J01FA01), because, in the Netherlands, these cover almost all antibiotics dispensed for exacerbations of COPD.[17] We did not include episodes treated only with antibiotics, because information on the coinciding diagnosis was unavailable.

As symptoms, increased at the onset of exacerbation, are usually substantially improved after three weeks,[18] we presumed that a second prescription for steroids within 3 weeks suggested an exacerbation not well responding to the initial therapy. To avoid counting these prescriptions as a “next exacerbation”, we introduced a minimum interval between steroid

courses of three weeks. If the time between two dispensings exceeded three weeks, we considered the second episode as a new exacerbation. As a consequence, until three weeks after the first course was dispensed, patients were considered not to be at risk for a new exacerbation. Patients dispensed 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, because they are likely to be patients on maintenance treatment with oral corticosteroids or antibiotics, respectively.

Statistical analysis

We assessed the first exacerbation after cohort entry (first course of oral corticosteroids) and calculated the time to the second exacerbation (second course of oral corticosteroids). Similarly, we calculated the time between second and the third exacerbation. We compared these time periods between patients treated with oral corticosteroids only, and those treated with oral corticosteroids combined with antibiotics using Kaplan-Meier survival analysis. Patients were censored for exacerbation free survival. The effect of the variable of primary interest, oral corticosteroid (coded as 0) or oral corticosteroid with antibiotic (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).[19] 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.[20] The Schoenfeld residuals as obtained from the model of time to first exacerbation suggested the difference in treatment effect be highly nonproportional. Therefore, we allowed the difference in treatment effect to change at three months, six months and one year. The data were coded so that hazard ratios below unity indicated a preventive effect of adding an antibiotic to the oral corticosteroids. Potential confounding by the following factors was controlled for: sex, age, number of dispensings of respiratory drugs, including inhaled corticosteroids, co-medication for cardiovascular disease (yes/no) or for diabetes (yes/no), and previous hospitalisation for COPD and pneumonia (yes/no).[21] Dispensing of antibiotics unrelated to exacerbations were also treated as a time-dependent covariate, and assumed to be of influence for a period of three months. This means that three months after dispensing this antibiotic, the variable was again coded as no antibiotic. All-cause mortality of both treatment groups was analyzed using Kaplan-Meier survival analysis and Cox regression analysis. We calculated 99% confidence intervals. Analyses were performed using Stata software, version 9.2 (StataCorp, College Station Texas, USA), R-2.6.0 (R Development Core Team (2007). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.) and SPSS v. 14.0.2 software (SPSS Inc., Chicago, Il, USA).

Results

Patients

From the PHARMO database we identified 52 753 patients, 50 years and older, fulfilling the prespecified criteria on respiratory drug use. In total, 3114 patients who had been hospitalised with a diagnosis asthma or used LTRAs or cromoglycates were excluded, and 40 patients were excluded because of administrative errors, leaving 49 599 patients. Of these patients, 19 882 (40%) had had at least one exacerbation as previously defined. 715 patients were excluded from further analysis because they were likely to be on maintenance treatment with oral corticosteroids (n=349), or with antibiotics (n=366). 239 patients were not at risk for a next exacerbation, as they had only one exacerbation within the three weeks before the end of follow-up, leaving 18 928 patients for further analysis.

1053 patients (6%) died during the follow-up period. For 894 patients the cause of death was unknown, 159 patients died during hospitalization for COPD. This was counted as an event, and not right-censored. After the first exacerbation, 2341 hospital admissions for COPD occurred; 1636 within one month of a documented exacerbation and 546 independently from a registered exacerbation. These 546 hospital admissions were considered as an event; instead of 'time to the next exacerbation', time to hospital admission was counted. As information on in-hospital treatment was not available, they were not analyzed further.

The median follow-up time after the first exacerbation was 754 days [interquartile range (IQR) 437-974]. In total, 18 928 patients were followed for 36 104 person years. GPs prescribed 72% of all antibiotics, oral corticosteroids and respiratory maintenance medication, 24% came from pulmonologists and 5% from other or unknown prescribers. Antibiotics used in the treatment of first exacerbations were doxycyclin (n=4011, 41%), penicillins (amoxicillin-clavulanate and amoxicillin, n=3597, 37%), macrolides (azithromycin and clarithromycin, n=1916, 20%), and fluoroquinolones (ciprofloxacin, moxifloxacin and levofloxacin, n=260, 3%). 53 cases could not be assigned to a treatment group.

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

	Total n=18 928	Oral corticosteroids n=9 074	Oral corticosteroids and antibiotics n=9 854	p[‡]
Gender				
Male	9 395 (50)	4 536 (50)	4 859 (49)	
Female	9 533 (50)	4 538 (50)	4 995 (51)	0.35
Age (years)*	70 (61-77)	70 (61-77)	70 (61-77)	0.60
Number of respiratory dispensings in 2003*	8 (4-13)	8 (4-13)[§]	8 (4-13)[§]	<0.01
ICS[§] (maintenance medication)	16 771 (89)	7 883 (87)	8 888 (90)	<0.01
Co-medication				
Cardiovascular	12 995 (69)	6 245 (69)	6 750 (68)	0.63
Diabetes	2 682 (14)	1 264 (14)	1 418 (14)	0.36
Hospitalisation[#] for				
COPD[†]	1 925 (10)	994 (11)	931 (9)	<0.01
Pneumonia	651 (3)	325 (4)	326 (3)	0.30
Follow-up characteristics				
Follow-up time (days)*	754 (437-974)	786 (472-988)	739 (404-957)	
Number of exacerbations*	2 (1-4)	2 (1-4)	2 (1-3)	

Data are n (%), unless otherwise stated. *Median (Interquartile range). [§]ICS: Inhaled corticosteroids. [#]Once or more in previous 2 years. [†]Diagnosis: chronic bronchitis, emphysema or chronic obstructive pulmonary disease. [‡]Chi-square or Mann-Whitney test, where appropriate. [§]The oral corticosteroids and antibiotics group had a significant higher number of respiratory dispensings, but the 25th, 50th and 75th percentiles for both treatment groups were similar.

Kaplan-Meier estimates of the cumulative incidence of developing a second or third exacerbation stratified according to treatment type (oral corticosteroids with or without antibiotics)

Time to second exacerbation

Of 18 928 patients having had at least one exacerbation, the first exacerbation after cohort entry was treated with oral corticosteroids only in 48% (9074 patients) and with oral corticosteroids and antibiotics in 52% (9 854 patients). These two groups of patients were similar with respect to age, gender, use of co-medication for diabetes and cardiovascular disease, and the number of previous hospitalisations for pneumonia. However, more patients in the oral corticosteroids with antibiotics group were dispensed prescriptions of respiratory maintenance drugs and inhaled corticosteroids over time ($p<0.01$). On the other hand, this group had had fewer hospital admissions for COPD in the previous two years compared to patients in the oral corticosteroids only group ($p<0.01$) (Table 1).

The time to the second exacerbation was much shorter in the oral corticosteroids only group than in the oral corticosteroids with antibiotics group (Figure 1A). The median time between the first and the second exacerbation in the oral corticosteroids only group was 321 days (99% CI 297-345) compared to 418 (99% CI 393-443) days in the oral corticosteroids with antibiotics group. Six months after the first exacerbation, 60% in the oral corticosteroids only group had had no new exacerbation compared to 70% in the oral corticosteroids with antibiotics group. Twelve months after the first exacerbation this was 48% and 54% respectively. There were no differences between antibiotic treatment groups with respect to time to the second exacerbation. The median time to the second exacerbation was 414 (99% CI 377-451) days for doxycyclin, 415 (371-458) days for penicillins, 431 (376-486) days for macrolides and 329 (189-469) days for fluoroquinolones ($p=0.14$).

During follow-up, 472/9854 (4.8%) patients died in the oral corticosteroid and antibiotic group versus 581/9074 (6.4%) in the corticosteroid only group ($p<0.01$, figure 2). In a univariate Cox regression model the Hazard Ratio (HR) of mortality after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.78 (99% CI 0.62–0.94). In a multivariable Cox model, adjusting for potential confounders (sex, age, number of dispensings of respiratory drugs, including inhaled corticosteroids, co-medication for cardiovascular disease or for diabetes, previous hospitalisation for COPD and pneumonia, and exposure to antibiotics unrelated to exacerbation), the HR was 0.82 (99% CI 0.66-0.98).

Time to third exacerbation

Of the 18 928 patients with a first exacerbation, 10 588 had had a second exacerbation. Of these exacerbations, 5420 (51%) were treated with oral corticosteroids and 5168 (49%) with oral corticosteroids and antibiotics. After the second exacerbation the difference between the two treatment groups with respect to the time to the next (third) exacerbation was even more pronounced than after the first exacerbation (Figure 1B). The median time between the second and the third exacerbation was 127 (99% CI 117-137) days in the oral corticosteroids only group and 240 (99% CI 222-258) days in the oral corticosteroids with antibiotics group. Six months after the second exacerbation, 42% of patients treated with oral corticosteroids had not had a third exacerbation compared to 57% of patients treated with oral corticosteroids

and antibiotics; after one year this was 30% and 39% respectively.

Cox recurrent event survival analysis of developing new exacerbations: effect of treatment type

In a univariate Cox regression model the Hazard Ratio (HR) of a new exacerbation after treatment with oral corticosteroids and antibiotics compared to corticosteroids only was 0.63 (99% CI 0.61–0.66)) in the first three months following treatment. In a multivariable Cox model adjusting for potential confounders, the HR of a new exacerbation after treatment with corticosteroids with antibiotics was 0.62 (99% CI 0.60-0.65) in the first three months following treatment, but the effect difference decreased in subsequent time periods. Exposure to antibiotics unrelated to exacerbations decreased the risk of a new exacerbation [HR 0.82 (99% CI 0.78-0.87)]. Hospitalisation for COPD in the previous two years increased the risk [HR 1.45 (99% CI 1.35-1.57)]. The variables 'age' and 'number of respiratory drugs dispensings in 2003' were included in the Cox model, but were not fitted linearly, therefore HR are not presented. The risk of a new exacerbation increased with age until 80 years and with a higher number of respiratory drugs dispensings in 2003 up to a number of 50 dispensings, but decreased after these values.

Table 2. Hazard Ratio's of determinants of developing a next exacerbation after oral corticosteroids with antibiotics - compared to oral corticosteroids only -treatment in a multivariable Cox model

	Hazard ratio of new exacerbation	99% CI for hazard ratio	
		Lower	Upper
Antibiotics added to treatment with oral corticosteroids			
0-3 months following treatment	0.62	0.60	0.65
3-6 months ,, ,,	0.68	0.65	0.73
6-12 months ,, ,,	1.03	0.96	1.12
> 12 months ,, ,,	1.31	1.18	1.45
Exposure to antibiotics after previous exacerbation	0.82	0.78	0.87
Female sex	0.95	0.91	1.00
Inhaled corticosteroids as maintenance medication	0.91	0.84	0.98
Co-medication cardiovascular	1.16	1.10	1.23
Co-medication for diabetes	1.05	0.98	1.12
Hospitalisation* for COPD†	1.45	1.35	1.57
Hospitalisation for pneumonia	1.19	1.05	1.34

CI, Confidence interval. *Once or more in previous 2 years. †Diagnosis: chronic bronchitis, emphysema or chronic obstructive pulmonary disease. The variables 'age' and 'number of respiratory drugs dispensings in 2003' were included in the Cox model, but were not fitted linearly, therefore HR are not presented.

Checking the assumption that a short course of oral corticosteroids in patients who are on respiratory drugs, is dispensed in case of an exacerbation of COPD.

We defined an exacerbation as a course of oral corticosteroids (with or without antibiotics), assuming that (in the Netherlands) a course of oral corticosteroids in this population of patients on maintenance respiratory drugs is almost exclusively prescribed because of an exacerbation of COPD. We checked this assumption by investigating data based on the Second Dutch National Survey of General Practice (DNSGP-2), carried out by The Netherlands Institute for Health Services Research (NIVEL). This registration database gives a representative impression of morbidity and prescribing habits in Dutch general practice.[22] From 01 January 2002 to 31 December 2002, from 1037 patients with COPD defined according to the international classification of primary care (ICPC) code R95,[23] we analysed

1355 prescriptions of oral corticosteroids. Twelve hundred and fifty-four prescriptions (92%) were COPD-related. Forty prescriptions (3%; upper limit of the 95% CI: 4.0) were prescribed for 'other musculoskeletal/connective disorders' (ICPC-code L99). In addition, sixty-one prescriptions (4%; upper limit of the 95% CI: 5.7) were prescribed for other indications. Extrapolating these findings to the present study, we think our definition of exacerbation was appropriate, and this small percentage of misclassified patients would cause bias towards the null.

Discussion

In this historical follow-up study among 18 928 patients with an exacerbation of obstructive lung disease, and focussing on relapse and not on short-term recovery, we showed that treatment with oral corticosteroids and antibiotics compared to treatment with oral corticosteroids alone was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation. Exposure to antibiotics between exacerbations was also associated with a lower risk of a subsequent exacerbation. In addition, in the group also treated with antibiotics mortality during follow-up was significantly lower. As in the majority of cases the cause of death was unknown, we are cautious to claim a survival benefit, but this finding is important and certainly warrants confirmation in a prospective study.

Deriving the data from a pharmacy database enabled us to measure actually dispensed medication in a very large number of patients treated with maintenance treatment for obstructive lung disease. Prescriptions both from general practitioners and pulmonologists were documented.

A limitation of observational studies might be the presence of treatment selection bias, due to unknown, potentially prognostic important differences among patients.[24] In our study, clinical information on patients was not available. However, patients treated with antibiotics and oral steroids are likely to have more severe exacerbations compared to patients treated with oral steroids only. Therefore, we suspect that any treatment selection bias, if present, would cause bias towards the null, thus underestimating the effect of adding antibiotics.

We found the effect of treatment was strongest in the first three months following treatment and then gradually decreased, and even reversed after one year. Apparently the protective effect of antibiotics wanes over time, which is to be expected.

Patients could not be selected based on a diagnosis of COPD or chronic bronchitis. Therefore, we selected patients who used maintenance respiratory drugs used in the treatment of obstructive lung disease. We included patients aged 50 years or older, in order to exclude patients with uncomplicated asthma. Furthermore, we excluded patients who had been hospitalised with a diagnosis of asthma and those using LTRAs or cromoglycates. Nevertheless, a small proportion of patients with asthma may still have been included in this study.

Recent studies stress the benefits from antibiotic treatment in exacerbations of COPD,[25] and a recent Cochrane review reports reduction of mortality and treatment failure, although in community-based studies no differences were found between antibiotic and placebo.[4] Most studies so far have been conducted in clinical settings, frequently in hospitalised patients, with merely severe exacerbations. For patients treated in general practice, studies showed no advantage of antimicrobial treatment on short-term outcome.[5,6,7] In the population we studied, GPs were responsible for 72% of all dispensings. In general, these COPD patients can be classified as GOLD 2 (moderate COPD).[26] So, also in patients with less severe exacerbations, antibiotic treatment added to treatment with oral corticosteroids seems advantageous. The differences we found with respect to time from the first to the second exacerbation and from the second to the third exacerbation, suggest that in patients with frequent exacerbations the benefits of antibiotic treatment added to treatment with oral corticosteroids may be greater. Most randomised trials have follow-up durations of not more than six weeks.[27] Benefits from antibiotic treatment may become more apparent in the long-term follow-up compared to short-term evaluations, possibly due to antibiotic treatment decreasing bacterial load. The finding that exposure to antibiotics for any indication also decreased the risk of a next

exacerbation may suggest that some COPD patients carrying bacteria in a stable state could benefit from antibiotics.

There is sufficient evidence for the contributory role of bacteria in exacerbations. During bacterial exacerbations bacteria are present in the lower airways, associated with airway inflammation, and in sufficient concentrations (>1 000 cfu/mL) to cause invasive infections.[28] Inflammatory changes are also related to recurrent exacerbations.[29] Immune responses to bacteria play an important role, and especially nontypeable *H influenzae* is known for its role in the process of colonisation and infection.[30-33] Isolation of new strains of bacterial pathogens increases the risk of an exacerbation.[34] Increased sputum purulence is the main sign of a new or increased significant bacterial stimulus.[25,28,35,36] In addition, patients with severe exacerbations are known to benefit most from antibiotic treatment.[1-4]

We showed that treatment with oral corticosteroids and antibiotics compared to treatment with oral corticosteroids alone was associated with a longer time to the next exacerbation, and a decreased risk of developing a new exacerbation. On the other hand, treating all exacerbations with antibiotics will significantly increase overall antibiotic consumption, which might fuel the increasing rates of resistance among respiratory pathogens.[37-41] Therefore, future prospective studies should explore for which exacerbations with respect to patient profiles and clinical symptoms in particular antibiotics are indicated.

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Author Contributions: Roede had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: J Prins, Bresser and Bindels.
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Analysis and interpretation of data: J Prins, Bresser, Bindels, and Roede.
Drafting of the manuscript: Roede.
Critical revision of the manuscript for important intellectual content: all authors.
Statistical analysis: M Prins, ter Riet, Kok, Geskus and Roede.
Study supervision: J Prins, Bresser and Bindels.

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Competing interests
None declared.

Figure legends
Figure 1. Kaplan-Meier estimates of the cumulative incidence of developing a second (Fig 1A) or third exacerbation (Fig 1B) stratified according to treatment type
Figure 2. Kaplan-Meier estimates of the cumulative survival stratified according to treatment type

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Figure 1. Kaplan-Meier estimates of the cumulative incidence of developing a second (Fig 1A) or third exacerbation (Fig 1B) stratified according to treatment type

Figure 1A

n = 18 928

Figure 1B

n = 10 588

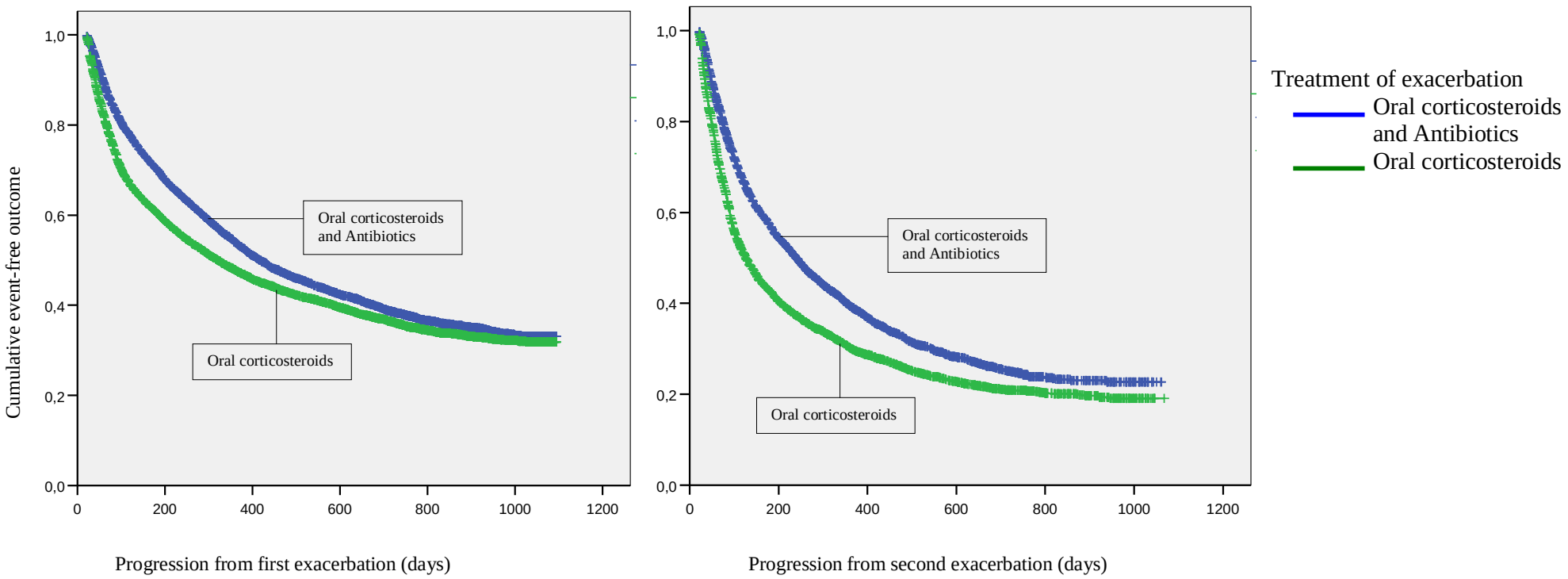

Figure 2. Kaplan-Meier estimates of the cumulative survival stratified according to treatment type