

Antibiotic Choice and Duration Associate with Repeat Prescriptions in Infective Asthma Exacerbations



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What is already known about this topic? Prescription of antibiotics for asthma exacerbations occurs commonly in contrast to guidelines. There is limited knowledge of current antibiotic prescribing practice, its associations, and its consequences, such as repeat prescriptions.

What does this article add to our knowledge? Repeat antibiotic courses were common. There were fewer repeat prescriptions in younger, current smokers, with fewer previous consultations and steroid use, who initially received amoxicillin for 7 days.

How does this study impact current management guidelines? The current index prescribing preference of 7 days of amoxicillin relates to fewer repeat courses. Interventional studies building on these results are needed to demonstrate the appropriateness of this intervention and inform future guidelines.

BACKGROUND: Patients with asthma who present with lower respiratory tract infections (LRTIs) often receive antibiotics. There is uncertainty about the need for and consequences of antibiotic administration.

OBJECTIVE: To describe the demographic characteristics of and antibiotic prescriptions for adult patients with asthma with LRTI and investigate factors associated with repeat antibiotic courses.

METHODS: We analyzed prescriptions of antibiotics for LRTIs in UK primary care from 2010 to 2015 using the Optimum Care

Database. The primary outcome was a second antibiotic prescription for an LRTI code within 14 days of index prescription, as a proxy of initial treatment failure. A model for repeat prescriptions was derived using univariable and multivariable logistic regression analyses.

RESULTS: We assessed 28,289 cases with complete data sets, 6.5% of which received a second antibiotic course. Amoxicillin and clarithromycin respectively were used most commonly as index and second agents. The most frequent course length was 7 days for both index and repeat prescriptions. Multivariable analysis demonstrated that age, index antibiotic and duration, smoking status, location, and number of consultations and oral steroid courses in the previous year were significantly associated with repeat prescriptions. The derived model predicted the binary outcome adequately (Cox-Snell R^2 , 0.012; area under curve, 0.62; 95% CI, 0.61–0.63). Comorbidities, vaccinations, asthma treatment, and number of exacerbations were significant only in the univariable analysis.

CONCLUSIONS: The current index prescribing preference of 7 days of amoxicillin correlated to fewer repeat courses. Baseline asthma treatment was not associated with risk of further prescriptions. Antibiotic administration in older patients with a smoking history could be a target for future studies. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:548–53)

Key words: Asthma; Lower respiratory tract infection; Antibiotics; Primary care; Treatment failure; Exacerbations

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INTRODUCTION

More than 330 million people worldwide suffer from asthma, but Northern and Western Europe have a particularly high prevalence.¹ One in 12 adults in the United Kingdom receives treatment for asthma and an amount of £1 billion a year is spent

Abbreviations used

aOR- adjusted odds ratio
CCI- Charlson comorbidity index
COPD- Chronic obstructive pulmonary disease
ICS- Inhaled corticosteroid
LRTI- Lower respiratory tract infection
OPCRD- Optimum Patient Care Research Database
OR- Odds ratio
SABA- Short-acting β agonist

on asthma care by the National Health Service.² Exacerbations form a large part of the disease burden. The most common causes are environmental, allergic, or infectious pathogens, most of which are respiratory viruses. Current guidelines do not suggest routine antibiotic prescriptions for acute asthma exacerbations because they are not commonly caused by bacterial infections.^{3,4} However, 22% of 16.1 million asthma presentations to US hospitals over 11 years received antibiotics.⁵ In a recent trial, 45% of the screened 4582 participants with asthma exacerbations had already received antibiotics in primary care.⁶ There is currently little evidence on whether this discrepancy between guidelines and real-life prescribing translates into any differences in clinical outcomes.

Seventy-four percent of all antibiotics in the United Kingdom are prescribed in primary care, and the likelihood of antibiotic prescription for coughs and colds increased by 40% between 1999 and 2011.^{7,8} In opposition to current guidelines, antibiotic prescriptions for asthma exacerbations make a significant contribution to antibiotic prescribing in primary care. This makes primary care an ideal target for optimizing antibiotic stewardship. In line with the World Health Organization and national recommendations to reduce antimicrobial resistance and adverse drug events, the most appropriate agent should be used for the shortest effective duration,^{9,10} but evidence as to what this may be is limited. There is wide variation in antibiotic prescribing across the United Kingdom, yet the data about the full implications of these prescribing variations are scant.

In this study we characterized patterns of antibiotic prescribing for asthma exacerbations via a retrospective observational analysis of primary care data for 2 million individuals presenting with lower respiratory tract infection (LRTI) from 2010 to 2015. We explored what factors were associated with the risk of further antibiotic prescription, which may form the basis for future comparative interventional studies.

METHODS

We carried out a cross-sectional database study drawing on retrospective electronic medical records from the Optimum Patient Care Research Database (OPCRD). The included subjects were on the asthma primary care register and received the first antibiotic prescription for an asthma exacerbation with an LRTI code during the study period (April 1, 2010, to April 1, 2015). LRTI codes included those for chest infection, bronchitis, and LRTI. Primary outcome was a new antibiotic prescription for an LRTI code within 14 days of index prescription. We excluded cases with a coded diagnosis of chronic obstructive pulmonary disease (COPD) and other chronic respiratory diseases, patients younger than 16 years, and patients whose index antibiotic course was longer than 28 days.

The OPCRD comprised data extracted through the Optimum Patient Care Clinical Service Evaluation (<http://optimumpatientcare.org/opcrd/>). The OPCRD is a research-quality primary care database with a focus on respiratory disease. It contained anonymized, routinely recorded electronic medical records from more than 525 UK general practices. The OPCRD was approved by Trent Multi-Centre Research Ethics Committee for clinical research use. The study protocol was approved by OPCRD's Anonymised Data Ethics Protocols and Transparency Committee.

Data were analyzed using SPSS version 22 (IBM, Armonk, NY; 2016). The primary outcome was a new antibiotic prescription with an LRTI code within 14 days of index antibiotic prescription. Only cases with a clearly documented index duration were included in the multivariable analysis. We examined multiple factors to assess the risk of repeat antibiotic prescription including demographic characteristics, smoking status, comorbidities, asthma medication and interactions with secondary care, and index antibiotic duration and class (the full list is available in this article's Online Repository at www.jaci-inpractice.org). Data on health care use in the year before all index prescriptions were also analyzed. Comorbidities were described via the Charlson comorbidity index (CCI).¹¹

Individual factors were first assessed via univariable analysis. Summary statistics, chi-square tests, and Student *t* tests were presented as appropriate for each variable on the basis of the type and distribution of data. Results were statistically significant with *P* values of .05 or less. Correlation between possible related predictors was assessed using Pearson coefficients. Variables were included in the multivariable model on the basis of clinical plausibility and statistical significance. Adjusted odds ratios (aORs) and CIs were given when appropriate. Multivariable models were created using backward logistic regression, and the derived models were tested for goodness of fit. A risk prediction score was devised from the parsimonious logistic regression output.

RESULTS

Demographic characteristics

There were 64,595 unique prescriptions for LRTI in adult patients with asthma between January 1, 2010, and December 31, 2015, in the OPCRD. The mean age was 49 years and most of the patients were women (64%; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Most variables were complete for all individuals in the study. Exceptions included smoking status and location; however, less than 8% of data were missing and so multiple imputation was not required. Smoking status was approximately equally divided between non-, current, and ex-smokers (32%, 34%, and 33%, respectively). Most patients had a CCI of 0 (61.1%) or 1 to 4 (33.5%). A significant proportion had eczema (32%) and rhinitis (33%). Forty-seven percent had received the influenza vaccination and 15% the pneumococcal vaccination. Most had 1 respiratory consultation in primary care in the previous year (mode = 1). In the previous year, 28.7% were on no active asthma treatment, 11.1% on short-acting β agonist (SABA) only, 26.4% on inhaled corticosteroid (ICS) + SABA, and the rest (33.8%) on other treatment. Overall, 59% of the individuals were on ICSs, and 32% had at least 1 documented asthma exacerbation, as defined by the American Thoracic Society criteria,¹² and received at least 1 course of oral steroids in the previous year (range, 0-13 for both). Most (85%) had eosinophil counts of 0.4×10^9 cells/L or less. A total of 242 individuals (0.4%) had attended the

TABLE I. Clinically relevant and statistically significant results from univariable analysis for repeat antibiotic prescription for LRTI within 14 d of index prescription (total number 28,289)

Patient characteristic	Description of data/test used	No further antibiotic prescription	Further antibiotic prescription	Univariable OR	95% CI	P value
Age (y)	Mean $\pm$ SD Student <i>t</i> test	49.2 $\pm$ 18.7	54.1 $\pm$ 17.8			<.001
Smoking	n (%)					<.001
Nonsmoker		13,052 (93.1)	971 (6.9)	1.00		
Current smoker		6,269 (94.9)	337 (5.1)	0.72	0.64-0.82	<.001
Ex-smoker		6,682 (92.6)	535 (7.4)	1.08	0.96-1.20	.19
Missing	443					
CCI	n (%)					<.001
0		11,048 (94.5)	649 (5.5)	1.00		
1-4		13,030 (93.0)	980 (7.0)	1.28	1.16-1.41	<.001
5-9		1,286 (91.5)	120 (8.5)	1.59	1.30-1.94	<.001
≥ 10		1,061 (90.8)	107 (9.2)	1.72	1.39-2.12	<.001
Missing	8					
Diagnosis of cardiovascular disease	n (%)					
Yes		1,324 (89.8)	151 (10.2)	1.67	1.41-2.00	<.001
No		25,108 (93.6)	1,706 (6.4)			
Diagnosis of gastroesophageal reflux disease	n (%)					
Yes		677 (91.6)	62 (8.4)	1.31	1.01-1.71	.04
No		25,755 (93.5)	1,795 (6.5)	1.00		
Number of respiratory consultations*	Mean $\pm$ SD Student <i>t</i> test	2.3 $\pm$ 2.1	2.9 $\pm$ 3.2			<.001
Number of all consultations*	Mean $\pm$ SD Student <i>t</i> test	10.8 $\pm$ 8.6	13.0 $\pm$ 10.4			<.001
Number of OCS courses*	Mean $\pm$ SD Student <i>t</i> test	0.5 $\pm$ 0.9	0.6 $\pm$ 1.0			<.001
Paracetamol prescription*	n (%)					
Yes		7,469 (92.2)	633 (7.8)	1.31	1.19-1.45	<.001
No		18,963 (93.9)	1,224 (6.1)			
Statin prescription*	n (%)					
Yes		4,781 (91.9)	424 (8.1)	1.34	1.20-1.50	<.001
No		21,651 (93.8)	1,433 (6.2)			
NSAID prescription*	n (%)					
Yes		7,581 (92.5)	614 (7.5)	1.23	1.11-1.34	<.001
No		18,851 (93.8)	1,243 (6.2)			
Influenza vaccination ever	n (%)					
Yes		14,220 (92.5)	1,148 (7.5)	1.39	1.26-1.53	<.001
No		12,212 (94.5)	709 (5.5)			
Pneumococcal vaccination ever	n (%)					
Yes		4,494 (91.6)	413 (8.4)	1.40	1.25-1.57	<.001
No		21,938 (93.8)	1,444 (6.2)			
Count of exacerbation events by ATS definition*	Mean $\pm$ SD Student <i>t</i> test	0.5 $\pm$ 0.9	0.6 $\pm$ 1.0			<.001
Number of ICS inhalers*	Mean $\pm$ SD Student <i>t</i> test	4.2 $\pm$ 5.2	4.7 $\pm$ 5.1			<.001
Count of LABA prescriptions*	Mean $\pm$ SD Student <i>t</i> test	0.2 $\pm$ 1.1	0.2 $\pm$ 1.3			.01
Count of LTRA prescriptions*	Mean $\pm$ SD Student <i>t</i> test	0.4 $\pm$ 1.9	0.5 $\pm$ 2.1			.01
Count of SAMA prescriptions*	Mean $\pm$ SD Student <i>t</i> test	0.1 $\pm$ 0.9	0.2 $\pm$ 1.1			.01
Current treatment	n (%)					<.001
SABA only		2,235 (94)	142 (6)	1.00		
ICS + SABA $\pm$ SAAC		6,995 (93.5)	486 (6.5)	1.09	0.90-1.33	.36
Other		8,875 (92.4)	732 (7.6)	1.30	1.08-1.56	.006
None		8,327 (94.4)	497 (5.6)	0.94	0.78-1.14	.53

(continued)

TABLE I. (Continued)

Patient characteristic	Description of data/test used	No further antibiotic prescription	Further antibiotic prescription	Univariable OR	95% CI	P value
Receiving ICS treatment	n (%)					
Yes		15,687 (92.9)	1,200 (7.1)			
No		10,745 (94.2)	657 (5.8)	0.80	0.73-0.88	<.001
Index drug	n (%)					
Amoxicillin		18,645 (94.5)	1,084 (5.5)			
Not amoxicillin		7,787 (91.0)	773 (9.0)	1.71	1.55-1.88	<.001
Index antibiotic duration	n (%)					<.001
<7 d		3,455 (92.9)	263 (7.1)	1.14	0.99-1.30	.07
7 d		21,432 (93.7)	1,437 (6.3)	1.00		
>7 d		1,545 (93.4)	157 (6.6)	1.52	1.28-1.80	<.001
Region in the United Kingdom	n (%)					<.001
Midlands and East		13,664 (92.7)	1,072 (7.3)	1.00		
London		245 (98.0)	5 (2)	0.26	0.11-0.63	.003
North		4,646 (93.9)	300 (6.1)	0.82	0.72-0.94	.004
South		5,791 (93.9)	376 (6.1)	0.83	0.73-0.93	.002
Missing	2,190					

Note. P value and 95% CI by chi-square test unless otherwise stated.

ATS, American Thoracic Society; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; SAAC, short-acting anticholinergic; SAMA, short-acting muscarinic antagonist.

*In year before index prescription.

emergency department for a respiratory complaint at least once in the previous year and 250 (0.4%) had been admitted for a respiratory cause. Few individuals (1.6%) had any respiratory specialist outpatient attendance in the previous year.

A total of 28,325 cases (43.9%) had a clearly documented index antibiotic duration. Most index courses were prescribed for 7 days (80.8%), followed by 5 or 6 days (12.8%). Amoxicillin, clarithromycin/erythromycin, doxycycline, and co-amoxiclav were used most commonly (69.7%, 15.7%, 6.7%, and 4.0%, respectively). The median index duration was 8 days for doxycycline and 7 days for all the other agents.

Repeat prescriptions for LRTI

A total of 1857 patients (6.5%) received a second antibiotic course for LRTI within 14 days of index antibiotic prescription. The most commonly prescribed second-line antibiotics were clarithromycin, doxycycline, and amoxicillin (30.7%, 24.9%, and 18.8%, respectively). The most common durations were 7, 5, and 8 days (68.7%, 8.1%, and 6.8%), respectively. The median for repeat antibiotic course duration was 7 days (interquartile range, 7-7 days), identical to the median of 7 (interquartile range, 7-7) for index duration.

In the univariable analysis (see Table I), those who received further antibiotics were statistically significantly older, had a significantly higher CCI, were diagnosed with comorbid cardiovascular disease or gastroesophageal reflux disease, had more respiratory and all consultations in the previous year, more courses of oral steroids, statin, paracetamol, NSAID (nonsteroidal anti-inflammatory) prescriptions, influenza and pneumococcal vaccinations, number of exacerbations, number of ICS inhalers, and prescriptions of long-acting β agonist, leukotriene receptor antagonist, and short-acting muscarinic antagonist. Smoking status was significantly associated with repeat antibiotic prescription, as was index drug and index duration as well as ICS treatment and region. Diabetes diagnosis, eosinophil count,

emergency department attendances and admissions, and number of SABA prescriptions were not associated with repeat antibiotic prescription (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Repeat prescription for LRTI—multivariable logistic regression

Correlation was assessed for all significant factors in the univariable analysis. There was a significant correlation coefficient (Pearson $r > 0.8$) between the number of acute oral steroid courses and exacerbations; number of ICS prescriptions with total ICS and average daily ICS dose; and total ICS dose with ICS daily dose. Hence, the number of exacerbations, acute oral steroid courses, and ICS inhalers were used in further analysis. There was no correlation between individual practice and repeat antibiotic prescriptions (intraclass correlation, 0.0; 95% CI -0.01 to 0.01; κ measure of agreement, 0.0).

Multiple logistic regression analysis was carried out for all statistically significant factors ($P \leq .05$; see Table I) in the univariable analysis, because all of them could clinically be relevant to repeat antibiotic prescribing. The derived parsimonious, multivariable model included age, smoking status, number of respiratory and all consultations in primary care, index drug and duration, number of exacerbations and oral corticosteroid, and the region of London (see Table II). Older patients, those with more previous respiratory and all consultations and those receiving more steroid courses, as well as those not receiving amoxicillin and receiving a shorter index duration were at significantly increased risk of repeat prescription.

The derived model fit the dichotomous outcome moderately well (Cox-Snell R^2 , 0.012; area under curve, 0.62; 95% CI, 0.61-0.64). Introducing interaction terms between clinically logical factors did not improve the fit of the model (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

TABLE II. Final parsimonious model for repeat antibiotic prescription within 14 d of index prescription derived from backward multivariable logistic regression analysis

Predictor	aOR	95% CI	P value
Age	1.01	1.01-1.01	<.001
Location			
London	0.95	0.91-0.99	.007
Not London	1.00		
Smoking status			
Nonsmoker	1.00		
Current smoker	0.84	0.73-0.96	.01
Ex-smoker	1.01	0.90-1.13	.90
Number of respiratory consultations in primary care*	1.03	1.01-1.05	.002
Number of all consultations in primary care*	1.01	1.01-1.02	<.001
Number of exacerbations by ATS definition*	0.59	0.34-1.03	.06
Number of OCS*	1.77	1.01-3.07	.04
Index drug			
Amoxicillin	1.00		
Not amoxicillin	1.58	1.42-1.76	<.001
Index antibiotic duration			
7 d	1.00		
<7 d	1.22	1.06-1.40	.006
>7 d	1.03	0.86-1.25	.77

ATS, American Thoracic Society; OCS, oral corticosteroid.

*In year before index prescription.

DISCUSSION

Lower respiratory tract infections are globally the most common infectious cause of morbidity.¹³ Despite this prevalence, observed duration of antibiotic treatment for LRTI varies greatly, and there is disagreement between guidelines on the best duration, even in better defined conditions such as community-acquired pneumonia.¹⁴ Optimal antibiotic duration for non-pneumonic LRTI in those with asthma is an area of particular uncertainty, because exacerbations with discolored phlegm are not necessarily driven by bacterial infection.

In this large analysis of antibiotic prescribing for LRTI for asthma in primary care, we investigated more than 28,000 antibiotic prescriptions over 5 years. Most patients received 7-day index courses and amoxicillin was the most commonly used antibiotic, but there was no prescribing consensus. Of the cases, 6.5% received a second course of antibiotics for LRTI within 14 days of the index course. We used the “general practice asthma population” rather than a predefined trial population, as highlighted by the 38.9% cases that were on no or only SABA treatment.

In contrast to work on asthma exacerbations of all types, our regression analysis showed that the use of ICS and previous exacerbations were not associated with repeat antibiotic prescriptions.¹⁵⁻¹⁷ Age, smoking status, index duration, and antibiotic class were more influential than factors identified as risk markers for exacerbations of all types. Location was a significant predictor of repeat prescriptions. The small population of London had a very low repeat prescription rate (2%), yet location remained a significant factor even when London was combined

with the South region (odds ratio [OR], 0.84 for the South region and London vs 0.87 for the North region and 1.00 for the East region and Midlands; see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

The use of antibiotics is not included in asthma treatment guidelines.⁴ However, their use is common, and in our study 6.5% of individuals even received 2 courses. This is in keeping with previously described findings: 45% of patients had already received antibiotics in the community when they were recruited for the AZALEA trial.⁶ A significant proportion of patients presenting to hospital received antibiotics, despite the absence of infective features.^{5,18} The duration of antibiotics did not change between the first and second courses (median, 7 days for both). However, clarithromycin became the most commonly given antibiotic over amoxicillin for repeat prescriptions. Clarithromycin was also the most commonly administered second-line antibiotic for LRTI in those without chronic lung disease (unpublished data).

The lowest likelihood of repeat antibiotics was with the initial use of amoxicillin for 7 days (aOR, 1.58; 95% CI, 1.42-1.76 [for index antibiotics other than amoxicillin]; aOR, 1.22; 95% CI, 1.06-1.40 [for index duration of <7 days]; aOR, 1.03; 95% CI, 0.86-1.25 [for more than 7 days]). Yet no comparative studies exist on different index antibiotic durations in asthma exacerbations.¹⁹

More than 64,500 patients received antibiotics for an LRTI code; however, because of missing documentation we were able to analyze only 28,289 prescriptions. This reflects the true nature of documentation in primary care, even in the age of electronic medical records. Enhanced information technology may improve this in the future. Although changes have occurred in antibiotic prescribing nationally over the 5 years analyzed, the overall trends were still visible and valid because of the size and completeness of the data.

Despite analyzing a number of different clinical and disease-specific factors, our model predicted antibiotic prescribing only moderately well (area under curve, 0.62). However, the inclusion of interaction terms did not change our model significantly, indicating model stability. The moderate fit may be due to other confounding factors that were not captured in our retrospective database analysis, for example, infective symptoms or signs, presence of uncoded bronchiectasis, sinusitis or previous sputum analysis, pulmonary function, or radiological results.^{20,21} The number of current or ex-smokers suggests that patients with COPD or asthma-COPD overlap syndrome may have been present in this population. With our data we were unable to distinguish appropriate from inappropriate prescribing or physician preference. Some clinically plausible variables such as CCI or vaccinations were highly significant in the univariable analysis but did not maintain this significance in the multivariable assessment, and thus further exploration may be indicated. The true incidence of repeat prescriptions may also have been underestimated because primary care databases have limited information on secondary care contacts. We chose repeat antibiotic prescriptions as a clinically relevant (for the individual and public health) measurable outcome, but future work should also investigate whether antibiotic use had effects on hospitalization, emergency department visits, or oral corticosteroid prescriptions.

A prediction score for risk of repeat prescription incorporating significant factors derived from our logistic regression results showed differences between the groups at the extremes; however,

the means and medians were similar and the curves overlapped significantly (see Tables E5 and E6 in this article's Online Repository at www.jaci-inpractice.org). A score based on the presented data is hence potentially clinically meaningful, within the caveat of the moderately fitting model. However, interventional trials are needed to investigate this further.

This study could inform a future investigation on whether antibiotic use in asthma patients is effective and which patients may benefit from it. Interventional studies or further analyses of high versus low prescription locations could provide this information provided the baseline morbidity and demographic characteristics are considered.

CONCLUSIONS

Repeat antibiotic prescriptions for patients with asthma are common. Repeat prescriptions were associated with index antibiotic and duration, age, smoking status, location, and number of consultations and steroid courses in the previous year. Asthma treatment per se was not a risk factor for further antibiotics. The predictive score of treatment failure derived from this study could be applicable in clinical practice because it demonstrated differences between those who received further antibiotics and those who did not, but this requires validation. Interventional studies are now needed to prospectively investigate the clinical outcomes of those who appear to be at low or high risk of requiring further antibiotic treatment.

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TABLE E1. Baseline demographic and clinical characteristics of overall OPCR population

Variable	All patients (n = 64,595) n (%) [unless otherwise indicated]
Sex: female	40,514 (63.7)
Age (y), mean $\pm$ SD	49.4 $\pm$ 18.9
BMI, mean $\pm$ SD	29.2 $\pm$ 7.0
Smoking status	
Nonsmoker	16,943 (32.2)
Current smoker	18,101 (34.4)
Ex-smoker	17,571 (33.4)
Missing	11,980 (18.5)
Location	
London	303 (0.5)
Midlands and East	40,471 (66.3)
North	11,236 (18.4)
South	9,066 (14.8)
Missing	3,519 (5.4)
Recorded comorbidity	
CCI score	
0	39,467 (61.1)
1-4	21,652 (33.5)
5-9	1,884 (2.9)
≥ 10	1,580 (2.4)
Eczema diagnosis	20,813 (32.2)
Rhinitis diagnosis	21,029 (32.6)
Diabetes diagnosis	5,859 (9.1)
Anxiety/depression diagnosis	7,126 (11.0)
Cardiovascular disease diagnosis	2,401 (3.7)
Gastroesophageal reflux disease diagnosis	1,531 (2.4)
Nasal polyps diagnosis	226 (0.3)
Anaphylaxis diagnosis	43 (0.1)
β -blocker prescription*	3,357 (5.2)
Paracetamol prescription*	19,589 (30.3)
Statin prescription*	12,320 (19.1)
NSAID prescription*	19,536 (30.2)
Influenza vaccination ever	30,494 (47.2)
Pneumococcal vaccination ever	9,681 (15.0)
Blood eosinophil count closest to index antibiotic prescription ($\times 10^9$ cells/L)	
≤ 0.4	40,708 (84.9)
> 0.4	7,251 (15.1)
Number of respiratory consultations in primary care*	
1	39.1%
2	31.0%
3	14.6%
≥ 4	15.3%
Number of all consultations in primary care,* mode	4
Number of OCS,* mode	0
Number who had at least 1 OCS course*	20,574 (31.9)

(continued)

TABLE E1. (Continued)

Variable	All patients (n = 64,595) n (%) [unless otherwise indicated]
Number of inpatient admissions for asthma or LRTI code,* mode (range)	0 (0-3)
Number who had at least 1 inpatient admission for asthma or LRTI code*	250 (0.4)
Number of inpatient admissions for any complaint,* mode (range)	0 (0-12)
Number who had at least 1 inpatient admission for any complaint*	4,299 (6.7)
Number of outpatient attendances with respiratory code*	
0	98.4%
1	1.2%
≥ 2	0.4%
Number of exacerbations by ATS definition,* mode (range)	0 (0-13)
Number who had at least 1 ATS-defined exacerbation*	20,797 (32.2)
PEF% predicted, mean $\pm$ SD	119 $\pm$ 32.9
$< 50\%$ predicted	2,670 (10.5)
50%-79% predicted	394 (1.6)
$\geq 80\%$ predicted	22,269 (87.9)
Asthma treatment	
Number of SABA inhalers,* median (IQR)	1 (1-4)
Number of ICS inhalers,* mode (range)	2 (2-6)
Number of LAMA prescriptions, mode (range)	0 (0-19)
Number of LABA prescriptions,* mode (range)	0 (0-30)
Number of theophylline prescriptions,* mode (range)	0 (0-52)
Number of LTRA prescriptions,* mode (range)	0 (0-53)
Current asthma treatment	
Number using ICS	38,105 (59.0)
Number using SABA only	7,198 (11.1)
Number using ICS + SABA $\pm$ SAAC	17,068 (26.4)
Number using other treatment	21,814 (33.8)
No treatment	18,515 (28.7)

ATS, American Thoracic Society; BMI, body mass index; IQR, interquartile range; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; OCS, oral corticosteroid; PEF, peak expiratory flow; SAAC, short-acting anticholinergic; SABA, short-acting muscarinic antagonist.

*In year before index prescription.

TABLE E2. Results of univariable analysis of all factors for repeat antibiotic prescription for LRTI code

Patient characteristic (N = 28,289) (January 1, 2010, to December 31, 2015)	No LRTI antibiotic prescription within 14 d of index prescription	LRTI antibiotic prescription within 14 d of index prescription	P value by χ^2 test unless otherwise stated
Sex, n (%)			.07
Female	16,200 (93.2)	1,178 (6.8)	
Male	10,232 (93.8)	679 (6.2)	
Age (y), mean $\pm$ SD	49.2 $\pm$ 18.7	54.1 $\pm$ 17.8	<.001 Student <i>t</i> test
BMI, mean $\pm$ SD	29.19 $\pm$ 6.87	29.50 $\pm$ 6.80	.12 Student <i>t</i> test
Smoking, n (%)			<.001
Nonsmoker	13,052 (93.1)	971 (6.9)	
Current smoker	6,269 (94.9)	337 (5.1)	
Ex-smoker	6,682 (92.6)	535 (7.4)	
Missing	443		
Location in UK, n (%)			<.001
Midlands and East	13,664 (92.7)	1,072 (7.3)	
London	245 (98.0)	5 (2)	
North	4,646 (93.9)	300 (6.1)	
South	5,791 (93.9)	376 (6.1)	
CCI, n (%)			<.001
0	11,048 (94.5)	649 (5.5)	
1-4	13,030 (93.0)	980 (7.0)	
5-9	1,286 (91.5)	120 (8.5)	
≥ 10	1,061 (90.8)	107 (9.2)	
Missing	8		
Number of respiratory consultations in primary care,* mean $\pm$ SD	2.33 $\pm$ 2.13	2.85 $\pm$ 3.20	<.001 Student <i>t</i> test
Number of all consultations in primary care,* mean $\pm$ SD (Ind T)	10.76 $\pm$ 8.60	12.98 $\pm$ 10.36	<.001 Student <i>t</i> test
Number of acute oral steroid courses,* mean $\pm$ SD (Ind T)	0.45 $\pm$ 0.88	0.56 $\pm$ 0.98	<.001 Student <i>t</i> test
β -Blocker prescription,* n (%)			.43
Yes	1,314 (92.9)	100 (7.1)	
No	25,118 (93.5)	1,757 (6.5)	
Paracetamol prescription,* n (%)			<.001
Yes	7,469 (92.2)	633 (7.8)	
No	18,963 (93.9)	1,224 (6.1)	
Statin prescription,* n (%)			<.001
Yes	4,781 (91.9)	424 (8.1)	
No	21,651 (93.8)	1,433 (6.2)	
NSAID prescription,* n (%)			<.001
Yes	7,581 (92.5)	614 (7.5)	
No	18,851 (93.8)	1,243 (6.2)	
Influenza vaccination ever, n (%)			<.001
Yes	14,220 (92.5)	1,148 (7.5)	
No	12,212 (94.5)	709 (5.5)	
Pneumococcal vaccination ever, n (%)			<.001
Yes	4,494 (91.6)	413 (8.4)	
No	21,938 (93.8)	1,444 (6.2)	
Blood eosinophil count closest to index antibiotic prescription, n (%)			.056
≤ 0.4	15,866 (92.8)	1,227 (7.2)	
> 0.4	3,132 (93.7)	209 (6.3)	
Missing	7,855		
Attendances to ED for respiratory complaint,* mean $\pm$ SD	0.01 $\pm$ 0.10	0.01 $\pm$ 0.08	.52 Student <i>t</i> test

(continued)

TABLE E2. (Continued)

Patient characteristic (N = 28,289) (January 1, 2010, to December 31, 2015)	No LRTI antibiotic prescription within 14 d of index prescription	LRTI antibiotic prescription within 14 d of index prescription	P value by χ^2 test unless otherwise stated
Number of ED attendances,* mean $\pm$ SD	0.13 $\pm$ 0.46	0.11 $\pm$ 0.40	.10 Student <i>t</i> test
Number of inpatient admissions for asthma or lower respiratory code,* mean $\pm$ SD	0.01 $\pm$ 0.09	0.00 $\pm$ 0.07	.25 Student <i>t</i> test
Number of all inpatient admissions,* mean $\pm$ SD	0.17 $\pm$ 0.56	0.17 $\pm$ 0.55	.67 Student <i>t</i> test
Number of outpatient visits for asthma or lower respiratory code,* mean $\pm$ SD	0.02 $\pm$ 0.24	0.02 $\pm$ 0.18	.39 Student <i>t</i> test
Number of all outpatient visits,* mean $\pm$ SD	0.08 $\pm$ 0.40	0.10 $\pm$ 0.49	.059 Student <i>t</i> test
Count of exacerbation events by ATS definition,* mean $\pm$ SD	0.46 $\pm$ 0.89	0.57 $\pm$ 0.98	<.001 Student <i>t</i> test
PEF% predicted, mean $\pm$ SD	119.63 $\pm$ 33.0	119.05 $\pm$ 32.2	.51 Student <i>t</i> test
Number of SABA prescriptions,* mean $\pm$ SD	2.37 $\pm$ 3.74	2.46 $\pm$ 3.74	.33 Student <i>t</i> test
Number of ICS inhalers,* mean $\pm$ SD	4.17 $\pm$ 5.19	4.68 $\pm$ 5.12	<.001 Student <i>t</i> test
Count of LAMA prescriptions,* mean $\pm$ SD	0.10 $\pm$ 0.94	0.11 $\pm$ 0.94	.44 Student <i>t</i> test
Count of LABA prescriptions,* mean $\pm$ SD	0.15 $\pm$ 1.09	0.22 $\pm$ 1.32	.01 Student <i>t</i> test
Count of theophylline prescriptions,* mean $\pm$ SD	0.12 $\pm$ 1.30	0.11 $\pm$ 1.06	.66 Student <i>t</i> test
Count of LTRA prescriptions,* mean $\pm$ SD	0.37 $\pm$ 1.94	0.49 $\pm$ 2.14	.01 Student <i>t</i> test
Count of SAMA prescriptions,* mean $\pm$ SD	0.09 $\pm$ 0.90	0.15 $\pm$ 1.14	.01 Student <i>t</i> test
Current asthma treatment, n (%)			<.001
SABA only	2,236 (94)	142 (6)	
ICS + SABA $\pm$ SAAC	6,995 (93.5)	486 (6.5)	
Other	8,875 (92.4)	732 (7.6)	
None	8,327 (94.4)	497 (5.6)	
Receiving ICS treatment, n (%)			<.001
Yes	15,687 (92.9)	1,200 (7.1)	
No	10,745 (94.2)	657 (5.8)	
Index drug, n (%)			<.001
Amoxicillin	18,645 (94.5)	1,084 (5.5)	
Not amoxicillin	7,787 (91.0)	773 (9.0)	
Index antibiotic duration, n (%)			<.001
<7 d	3,455 (92.9)	263 (7.1)	
7 d	21,432 (93.7)	1,437 (6.3)	
>7 d	1,545 (93.4)	157 (6.6)	

ATS, American Thoracic Society; BMI, body mass index; ED, emergency department; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PEF, peak expiratory flow; SAAC, short-acting anticholinergic; SAMA, short-acting muscarinic antagonist.

*In year before index antibiotic prescription.

TABLE E3. Comparison of effects of clinically plausible interaction terms on final multiple logistic regression model for repeat antibiotic prescription for LRTI

Model	AUC	95% CI	Cox-Snell R^2
Original model	0.624	0.611-0.637	0.012
Original model with interaction term			
Index antibiotic and index duration	0.624	0.611-0.637	0.012
Smoking status and antibiotic duration	0.625	0.612-0.638	0.012
Age with CCI	0.624	0.611-0.637	0.012
Age and smoking status	0.625	0.612-0.638	0.012
Age and antibiotic duration	0.625	0.612-0.638	0.012
Number of exacerbations* and number of primary care consultations for asthma/LRTI code*	0.624	0.611-0.637	0.012
Number of exacerbations* and number of ICS inhalers*	0.624	0.611-0.637	0.012
CCI and all primary care consultations*	0.624	0.611-0.637	0.012

AUC, Area under curve.

*In year before index prescription.

TABLE E4. Final parsimonious model for repeat antibiotic prescription within 14 d of index prescription derived from backward multi-variable logistic regression analysis when combining London and South regions

Predictor	aOR	95% CI	P value
Age	1.01	1.01-1.01	<.001
Location			
Midlands and East	1.00		
North	0.87	0.76-0.99	.04
South and London	0.84	0.74-0.95	.005
Smoking status			
Nonsmoker	1.00		
Current smoker	0.84	0.73-0.96	.01
Ex-smoker	1.01	0.90-1.13	.90
Number of respiratory consultations in primary care*	1.03	1.01-1.05	.002
Number of all consultations in primary care*	1.01	1.01-1.02	<.001
Number of exacerbations by ATS definition*	0.59	0.34-1.03	.06
Number of OCS*	1.77	1.01-3.07	.04
Index drug			
Amoxicillin	1.00		
Not amoxicillin	1.58	1.42-1.76	<.001
Index antibiotic duration			
7 d	1.00		
<7 d	1.22	1.06-1.40	.006
>7 d	1.04	0.86-1.25	.72

Note. AUC for this model is 0.62 and 95% CI is 0.61-0.64.

ATS, American Thoracic Society; AUC, Area under the curve; OCS, oral corticosteroid.

*In year before index prescription.

TABLE E5. Comparison of risk of repeat antibiotic prescription prediction score, derived from results of parsimonious backward logistic regression between groups

	Repeat antibiotics for LRTI	No repeat antibiotics for LRTI
Mean $\pm$ SD	2.29 $\pm$ 0.44	2.11 $\pm$ 0.43
Median	2.26	2.07
Range	0.35 to 5.95	−0.14 to 4.88

TABLE E6. Prediction score results for different fictional “patients,” as examples

Predictor	Regression coefficient	Example 1	Example 2	Example 3	Example 4	Example 5
Age	0.01	85	18	85	85	35
Smoking status						
Nonsmoker						
Current smoker	−0.18		Yes	Yes		Yes
Ex-smoker	0.01	Yes			Yes	
Number of respiratory consultations in primary care*	0.03	4	0	0	4	0
Number of all consultations in primary care*	0.01	12	0	0	12	0
Number of exacerbations*	−0.52	0	2	2	0	2
Index antibiotic						
Amoxicillin			Yes	Yes	Yes	Yes
Not amoxicillin	0.46	Yes				
Number of OCS courses*	0.57	6	2	2	6	2
Index antibiotic duration						
7 d			Yes	Yes		
<7 d	0.20	Yes			Yes	Yes
>7 d	0.28					
Location						
London	−0.05	Yes	Yes	Yes		
Not London					Yes	Yes
Prediction score		5.13	0.05	0.72	4.72	0.47
Probability of repeat prescription†		0.57	0.01	0.02	0.47	0.01

OCS, Oral corticosteroid.

*In year before index prescription.

†The probability of repeat prescription was derived from the logistic regression model results.