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Respiratory Infections and Antibiotic Usage in Common Variable Immunodeficiency

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Abstract

Background: Patients with common variable immunodeficiency (CVID) suffer frequent respiratory tract infections despite immunoglobulin replacement, and are prescribed significant quantities of antibiotics. The clinical and microbiological nature of these exacerbations, the symptomatic triggers to take antibiotics and the response to treatment have not been previously investigated.

Objective: To describe the nature, frequency, treatment and clinical course of respiratory tract exacerbations in patients with CVID, and to describe pathogens isolated during respiratory tract exacerbations.

Methods: We performed a prospective diary card exercise in 69 CVID patients recruited from a primary immunodeficiency clinic in the UK, generating 6210 days of symptom data. We collected microbiology (sputum microscopy and culture, atypical bacterial PCR, mycobacterial culture) and virology (nasopharyngeal swab multiplex PCR) samples from symptomatic CVID patients.

Results: There were 170 symptomatic exacerbations, and 76 exacerbations treated by antibiotics. The strongest symptomatic predictors for commencing antibiotics were cough, shortness of breath and purulent sputum. There was a median delay of 5 days from the onset of symptoms to commencing antibiotics. Episodes characterised by purulent sputum responded more quickly to antibiotics while sore throat and upper respiratory tract symptoms responded less quickly. A pathogenic virus was isolated in 56% of respiratory exacerbations and a potentially pathogenic bacteria in 33%.

Conclusions: Patients with CVID delay and avoid treatment of symptomatic respiratory exacerbations which could result in structural lung damage. However, viruses are commonly represented and illnesses dominated by upper respiratory tract symptoms respond poorly to antibiotics, suggesting that antibiotic usage could be better targeted.

Abstract word count: 248

Take home message for social media: CVID patients delay antibiotics for respiratory tract infections. Many Infections are associated with viruses.

Highlights box:
What is already known about this topic? Even with immunoglobulin replacement respiratory tract infections remain the commonest clinical feature in CVID and impair quality of life. Encapsulated bacteria are thought to be the most common pathogens.

What does this article add to our knowledge? This is the first detailed description of respiratory exacerbations in CVID, capturing 6210 days of data. Viruses are commonly represented. There is a delay in commencing antibiotic therapy and the response to antibiotic therapy depends on the symptomatic presentation.

How does this study impact current management guidelines? Since viral infections are common in CVID, antibiotic therapy should be considered with caution. However, self-administered antibiotic therapy should be started more promptly with symptoms of cough and purulent sputum.

Keywords: Respiratory tract exacerbations; common variable immunodeficiency; antibiotics; viral infection

Abbreviations
COPD - Chronic obstructive pulmonary disease
CT - X-ray computed tomography
CVID - Common Variable Immunodeficiency
HR - Hazard ratio
IQR - Interquartile range
IR - Odds ratio
OAT - Oral antibiotic therapy
PCR - polymerase chain reaction
SD - Standard deviation
SGRQ - St George's Respiratory Questionnaire
TE - Treated exacerbation
TSE - Treated symptomatic exacerbation
USE - Untreated symptomatic exacerbation

More detailed methodology and accompanying figures are provided in an online supplement.

Introduction

Common Variable Immunodeficiency (CVID) is a heterogeneous primary immunodeficiency, in which patients fail to produce adequate levels of immunoglobulins. With a prevalence between 1 in 10,000 and 1 in 50,000, it is the most common symptomatic primary immunodeficiency.[1-4]

Despite adequate immunoglobulin replacement, recurrent respiratory tract infections are the commonest clinical feature in CVID[2,5], and can result in progressive bronchiectasis.[6-9] Respiratory tract infections were thought to be caused largely by encapsulated bacteria.[6,10] However, recent evidence has accumulated for a significant burden of viral infection.[11,12]

Despite the high incidence of respiratory tract infections and their negative influence on quality of life in primary antibody deficiency syndromes[13], the nature of symptoms during these episodes remain unknown. Patients are often prescribed antibiotics to mitigate respiratory tract infections, both as ‘rescue’ courses to promptly self-administer for acute events and as prophylaxis to reduce infection frequency. However, the symptomatic triggers for taking breakthrough antibiotics and the clinical response to these treatments are not known.

In this prospective study, we sought to answer these questions by systematically recording daily symptoms and treatment in a cohort of CVID patients over a winter period. In a parallel analysis, we also explored bacterial and viral pathogens encountered during acute respiratory symptoms in CVID patients.

Methods

Participants

Patients were recruited from the joint Immunology-Respiratory service at the Royal Free Hospital, London, UK. Patients had a diagnosis of CVID made by a clinical immunologist following the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies definitions.[14] All were receiving immunoglobulin replacement and under regular (at least 6-monthly) clinical review. The only exclusion criterion was inability to provide informed consent. All participants provided written, informed consent (REC 04/Q0501/119).

Study design

For this observational, prospective cohort study, patients completed daily checkbox symptom diaries for 90 days between December 2014 and February 2015, covering the UK winter season. Participants were asked to report new or increased respiratory symptoms from a predefined list (Table 1). Chronic or stable symptoms were not to be reported. Definitions of symptoms and instructions for diary completion were clearly explained; further details are provided in the online supplement. We have previously used such methodology in other chronic respiratory diseases.[15] Participating patients were also asked to complete the St George's Respiratory Questionnaire (SGRQ), a validated measure of respiratory health-status scored between 0 (best) and 100 (worst) quality of life.[16]

Simultaneously, but independently from the described study, we conducted a cross-sectional study in which patients experiencing acute respiratory symptoms provided samples (nasopharyngeal swabs and spontaneously expectorated sputum) for bacterial and viral testing. Sputum was considered purulent when more than 10 granulocytes per high power field were found. Samples were either collected by clinic staff or, after careful instruction on sampling, submitted directly from patients by mail.

Figure 1 summarises the two investigations undertaken on the cohorts.

Definition of exacerbations and variables

Pre-analysis, we grouped clinically related symptoms as indicated in Table 1. For calculation of total symptom count, each symptom was counted individually for each patient and each day. Cumulative total symptom count is the sum over all days of an exacerbation period.

We utilised two definitions of exacerbation, based either on symptoms or healthcare utilisation. Similar methodology has been reported and validated in COPD[17]. For the first definition, we identified a symptomatic exacerbation as an event of two or more new symptoms lasting for two or more consecutive days as recorded by the patient on their diary, whether or not they received additional treatment. The start of a symptomatic exacerbation episode was the first day of two or more new symptoms lasting for two or more consecutive days. The end of the episode was the last consecutive day with two or more symptoms (allowing symptoms to change over time). If oral antibiotic therapy (OAT) was used during a symptomatic exacerbation episode, this was termed a treated symptomatic exacerbation (TSE). If not, it was an untreated symptomatic exacerbation (USE).

We defined a healthcare utilisation exacerbation as use of OAT for worsening respiratory symptoms. We call this a treated exacerbation (TE) event, and if it coincided with diary-defined symptoms it would be a TSE. The episode was considered to last from the first day on which a symptom occurred until recovery, defined as the last day of any symptom which was present when OAT was started. Additional details regarding exacerbation and variable definitions are provided in Supplementary Methods.

Data handling and statistical analysis

Statistical analysis was performed using Stata v14.0 (StataCorp LP, College Station, TX, USA). Continuous variables are presented as median and 1st and 3rd quartiles or by mean and standard deviation (SD) as appropriate. For categorical and binary variables we present frequencies.

Missing data were not imputed. Results were considered statistically significant at p value <0.05. Data were analysed with logistic regression for trigger symptom analysis, Cox regression for antibiotic response analysis, Pearson correlation, Wilcoxon rank-sum test and t tests as indicated. Further details are provided in Supplementary Methods.

Analysis of microbial samples

A multiplex real-time PCR (RT-PCR) for Adenovirus, Coronavirus (HKU, NL63, OC43 & 229E), Enterovirus, Human metapneumovirus, Influenza virus (A&B), Parainfluenza virus (1,2,3 & 4), Parechovirus, Respiratory syncytial virus, and Rhinovirus was performed in the National Health Service Virology laboratories at the Royal Free Hospital.

Sputum samples were examined by microscopy and culture for bacteria and mycobacteria plus in-house multiplex RT-PCR for *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*. Further details are provided in Supplementary Methods.

We included multiple samples from a single patient if separated by at least two weeks and the patient was asymptomatic between episodes. Airway colonisation by pathogenic bacteria was diagnosed when the same organism had been isolated more than twice within the two years before our study.

Results

Study population

134 CVID patients were given a diary. 69 (51%) patients returned a diary after completion of the study period, providing 6210 days of data (Figure 1). Demographic and clinical characteristics of included patients are presented in Table 2. Patients who completed a diary are older (median (IQR) 59.36 (46.74–68.22) vs 45.02 (36.33–53.79) years; $p<0.001$) and have a higher bronchiectasis severity index (median (IQR) 3.5 (2–6) vs 2 (1-4); $p=0.01$) than those who did not.

Patients with CVID suffer frequent respiratory exacerbations and often use antibiotics

During the study period, there were 170 symptomatic exacerbation events (mean 0.82 per patient month). 75 (mean 0.36 per patient month) of these events were treated by OAT whilst

95 (mean 0.46 per patient month) were not. Nine patients had no symptomatic exacerbations during the period. Published literature suggests that 106 courses of antibiotics were prescribed per 1,000 men and 155 per 1,000 women for respiratory tract infections by general practitioners in the UK in 2014.[18] This corresponds to 2.3 courses of antibiotics in total (0.01 per patient month) prescribed to a group similar to our cohort in the general population during three months.

Treated symptomatic exacerbation (TSE) episodes were more severe than untreated (USE) in terms of cumulative total symptom count (median (IQR) 40 (24-82) vs 12 (6-30) symptoms; $p<0.001$) and episode duration (median duration 10 v 4 days; HR 0.54; $p<0.001$).

76 treated exacerbations (TE) were covered within our study period. One TE did not meet the criteria of TSE. The median (IQR) duration of TE episodes was 14 (9-19) days; median (IQR) time from the start of symptoms until OAT was 5 (2-7) days; and median (IQR) time until recovery was 6.5 (5-14) days. Median (IQR) duration of therapy was 14 (7-14) days. A detailed description of symptom prevalence is provided in Figure 2. As treatment, patients used Co-amoxiclav for 23 (30%) exacerbations, Amoxicillin for 20 (26%), Doxycycline for 12 (16%), Ciprofloxacin for 10 (13%), Clarithromycin for 7 (9%), and Azithromycin, Erythromycin, Flucloxacillin, and Levofloxacin each for one (1%) exacerbation.

Cough, shortness of breath and purulent sputum are the strongest triggers for patients to initiate antibiotic therapy

We compared 76 days on which OAT was started with 5370 days without OAT. 764 days comprising the remainder of the antibiotic courses were ignored. In univariate analysis, all symptoms were positively and significantly associated with start of OAT. Cough (odds ratio

(OR) 48.70; 95%-CI 24.02–111.47), purulent sputum (OR 25.26; 95%-CI 15.25–42.49), increased sputum volume (OR 23.85; 95%-CI 13.85-42.70), and shortness of breath (OR 17.27; 95%-CI 10.54–28.22) showed the highest ORs (Figure 3A). In multivariate analysis, only cough (OR 13.00; 95%-CI 5.93-28.47), purulent sputum (OR 6.30; 95%-CI 1.19–33.40), and shortness of breath (OR 2.41; 95%-CI 1.31–4.46) remain significant when adjusted for other symptoms (Figure 3A).

In univariate analysis, time since start of symptoms was not positively associated with start of OAT, and instead patients started OAT at a fairly constant rate over the first 12 days of symptoms (Figure 3B). There was, however, a significant positive association between total symptom count and start of OAT (OR 2.19; 95%-CI 1.96–2.43), suggesting an approximate doubling of the odds to start OAT for each additional symptom. The mean (SD) number of symptoms on days on which OAT was started was 4.97 (1.94) versus 0.86 (1.55) symptoms on days when antibiotics were not taken ($p<0.001$).

Exacerbations characterised by purulent sputum respond rapidly to antibiotics, while those characterised by upper respiratory tract symptoms and sore throat respond more slowly

Median (IQR) time until recovery after start of OAT in all treated exacerbations was 6.5 (5-14) days (Figure 4A). In 56% of treated exacerbations time until recovery was ≤7 days; in 81% it was ≤14 days.

In univariate analysis, time until recovery was longer in the presence of upper respiratory tract symptoms (median 8 vs 5 days; hazard ratio (HR) 0.50; p=0.03; Figure 4B), sore throat (12 vs 6 days; HR 0.54; p=0.007; Figure 4C) or white sputum (12 vs 6 days; HR 0.63 p=0.03) on the day before commencing OAT. However, time until recovery was shorter in exacerbations in

which purulent sputum was present (6 vs 13 days; HR 1.98; p=0.02; Figure 4D). In multivariate analysis, upper respiratory tract symptoms, sore throat and purulent sputum were significant independent predictors for response to OAT (Figure 4E).

There was no statistically significant correlation between time until starting OAT and time until recovery nor between total symptom count on the day before OAT was started and subsequent time until recovery. However, a longer time until starting OAT was associated with a longer episode duration (HR 0.92; p<0.001).

Patients taking prophylactic antibiotics have more untreated exacerbations and wait longer from the onset of symptoms to initiate breakthrough antibiotics, while patients with bronchiectasis have more treated exacerbations.

We proceeded to investigate whether the frequency and nature of exacerbations were affected by antibiotic prophylaxis or by the presence of bronchiectasis. The number of symptomatic exacerbations (total, treated and untreated) were analysed with two (prophylactic antibiotics) by two (bronchiectasis) ANOVAs.

There were more symptomatic exacerbation events in patients on prophylactic antibiotics than in patients not on prophylaxis (mean (SD) 2.87 (2.21) vs 1.71 (1.33), p=0.03). This difference was explained by more untreated symptomatic exacerbations in patients on prophylactic antibiotics (mean (SD) 1.78 (2.14) vs 0.63 (0.88), p=0.03). In contrast, patients with bronchiectasis experienced similar overall numbers of exacerbations and untreated exacerbations versus those without bronchiectasis, but more treated symptomatic exacerbations (mean (SD) 1.27 (1.15) vs 0.81 (1.08), p=0.04). Interaction effects were non-significant in all three analyses, suggesting that the effect of prophylaxis did not differ

between patients with or without bronchiectasis, and that the increased frequency of treated exacerbations in bronchiectatic patients persisted regardless of prophylaxis.

Regarding the impact of antibiotic prophylaxis on exacerbation severity, there was no significant difference in episode duration or cumulative total symptom count during symptomatic exacerbations between patients on or off prophylactic antibiotics. Patients taking prophylactic antibiotics waited longer before starting oral antibiotic treatment for breakthrough infections (median 6 vs 3 days; HR 0.55; p=0.03). However, time until recovery after commencing OAT was not significantly different between patients on or off prophylactic antibiotics.

There were no significant differences between patients with or without bronchiectasis in exacerbation severity, time until OAT, and time until recovery.

Prospective symptoms correlate modestly with cross-sectional analysis of quality of life

There was moderate correlation between the SGRQ Total Score and the number of days on which new cough (r=0.29, p=0.02), sore throat (r=0.29, p=0.02), shortness of breath (r=0.38, p=0.002) and wheeze (r=0.32, p=0.01) were present. The cumulative total symptom count or cumulative number of days of symptomatic exacerbation episodes over the study period also correlated with SGRQ Symptom Score (r=0.36, p=0.004) and SGRQ Total Score (r=0.28, p=0.03).

Respiratory exacerbations in CVID demonstrate a high frequency of viral and bacterial pathogens

54 naso-pharyngeal swabs were obtained from 41 patients with acute respiratory symptoms. Viruses were detected in 30 (56%) exacerbations (Figure 5). *Rhinovirus* was the most common virus detected (in 18 (33%) exacerbations), including two (4%) co-infections with

Respiratory Syncytial Virus, two (4%) co-infections with *Adenovirus* and one (2%) co-infection with *Human Metapneumovirus*.

43 spontaneously expectorated sputum samples were obtained from 34 patients with acute respiratory symptoms. Pathogenic bacteria were isolated in 14 (33%) exacerbations (Figure 5). The most common bacteria were *Haemophilus influenzae* in 8 (19%), *Streptococcus pneumoniae* in two (5%), and *Pseudomonas aeruginosa* in two (5%) exacerbations. Two patients accounting for four exacerbations were colonised with *Haemophilus influenzae* as defined above. All samples were negative for mycobacterial culture and PCR for atypical pneumonia organisms.

There was bacterial and viral co-infection in 25% of exacerbations; in 27.5% no pathogen was found. Microscopic evidence of purulence as measured by more than 10 granulocytes per high power field were found on microscopy in 41% of exacerbations positive for a pathogenic virus (whether or not patients produced sputum), in 69% of exacerbations positive for a pathogenic virus where contemporaneous sputum was collected and in 64% of exacerbations positive for pathogenic bacteria.

Discussion

This is the first prospective cohort study describing symptoms and treatment of respiratory tract infection in CVID. We discovered a clinically important delay in commencing antibiotic therapy and that many symptoms are untreated, especially in patients taking prophylactic

antibiotics. Episodes characterised by purulent sputum respond more quickly to antibiotics while sore throat and upper respiratory tract symptoms respond less quickly: perhaps correspondingly, in many respiratory exacerbations we detected a pathogenic virus.

CVID patients are frequently prescribed antibiotics and educated to promptly take them if they suffer 'break-through' infections. However, their actual behaviours in relation to this therapy have not previously been documented. Here, across 6,210 days of data, we discovered that individual 'warning' symptoms (cough, shortness of breath, and purulent sputum) are the most important triggers for patients to start OAT. Time since start of symptoms is a less important trigger, and the proportion of patients starting therapy each day is fairly constant across the first 12 days of symptoms. Consequently, and despite the fact that all patients should have antibiotics available for immediate usage, there is a median delay of five days in starting OAT. We are investigating whether delays to commencing treatment are explained more by patient choice or by access to healthcare.

A longer time to commencing therapy did not adversely impact subsequent response to antibiotics (measured by time until recovery), but inevitably increases the total length of an infectious episode. Since infections in CVID can lead to structural lung damage[2,13], this delay may be clinically significant. Similarly, many exacerbations (95 across the study period) were untreated and may not have been reported without prospective data collection. Indeed, it is well documented that untreated symptomatic exacerbations often go unreported in COPD[19], with up to three times more exacerbations collected by symptom diaries than by interview; COPD patients also treat only half of all exacerbations recorded in diaries.[20]

Response to OAT, judged by time until recovery, did not correlate with delay to commencing therapy or total symptom count, but depended on individual symptoms. There was a slower response in patients with upper respiratory tract symptoms and sore throat, which we hypothesise may be explained by a purely viral aetiology for some of these episodes. Conversely, exacerbations with purulent sputum resolved more quickly on antibiotics, perhaps indicating a dominant bacterial component.

The number of untreated symptomatic exacerbations, and delay to commencing OAT, were higher in patients on prophylactic antibiotics. This could imply a reluctance to start OAT in this group due to over-reliance on prophylaxis or as an increased tolerance of symptoms (generally prophylaxis is only instituted in patients with a high background incidence of exacerbations). We found no difference in severity or duration of individual symptomatic exacerbations with or without prophylaxis: this could indicate effectiveness of prophylaxis, but conversely there is no evidence that prophylaxis attenuates the severity of breakthrough exacerbations.

There was a modest correlation between some acute symptoms reported in diaries and the SGRQ, which measures the impact of symptoms on health-related quality of life.[16] Cumulative total symptom count and cumulative number of days of symptomatic exacerbation over the study period also correlated with SGRQ scores, confirming that symptomatic exacerbations have a significant impact on patients. However, our study design only included new or worsening symptoms rather than chronic symptoms, which presumably explains only moderate correlation between diary-derived parameters and SGRQ scores.

In our analysis of pathogens isolated during symptomatic exacerbations, we detected a virus in 56% of patients' samples. This is similar to other reports: for example, Kainulainen *et al* reported positive viral PCR in 54% of 65 exacerbations within 12 patients[11]. Bacterial pathogens, most commonly encapsulated organisms, were found in 33% of symptomatic exacerbations.

Interestingly, in exacerbations positive for a pathogenic virus but where the patient also expectorated sputum, there was evidence of purulence as measured by high microscopic granulocyte count in 69% of samples. Although this may be partly explained by underlying bronchiectasis in some patients, we frequently observed co-infection with bacteria. While this may represent simply colonising bacteria in the presence of an acute viral exacerbation, there is evidence from COPD that rhinovirus infections adversely affect microbiome and the prevalence of pathogenic bacteria[21,22]. Our earlier results suggest that new or worsening purulent sputum predicts rapid response to antibiotic therapy, regardless of the organism isolated. Further research is required to investigate how the pathogens identified here influence the balance of other organisms in the respiratory tract and thereby the response to antibiotic therapy. However, our current recommendation would be to promptly treat exacerbations characterised by purulent sputum irrespective of virology results, not least because neutrophil elastase is significantly implicated in bronchiectasis pathogenesis.[22]

Our study has some limitations. It was performed at a single tertiary care centre during the winter, when respiratory tract infections are more frequent[24,25]. The true incidence of symptomatic exacerbations and antibiotic use throughout the year thus cannot not be extrapolated. We cannot exclude that factors particular to our geographic location and

particular to the brief study period have influenced our results.

Due to its design, this study lacks a healthy control group. We therefore cannot discuss differences in quality or quantity of exacerbations between CVID and non-immunocompromised patients, but available data from other sources[18] suggest that the usage of antibiotics in our cohort is many times higher than in the general population.

We only have data from patients who agreed to complete a diary (69 patients) and not the entire CVID cohort (134 patients). This may result in a selection bias, especially since these patients are older and have more clinically severe bronchiectasis. Although our symptomatic exacerbations did not differ in number nor severity in patients with or without bronchiectasis, generalizability to other CVID patients is limited, as the prevalence of bronchiectasis varies throughout centers[2].

The symptomatic definition of a respiratory exacerbation in CVID is not standardised and we therefore operated with a simplified definition, which has been validated in COPD[17].

Although patients were carefully instructed to record only new or worse symptoms, we cannot exclude the possibility that some reported chronic morbidity. We note that the mean number of 'new' symptoms even on days without antibiotic therapy was 0.86; however, this includes the period before and after antibiotic therapy in exacerbations, and may also reflect a genuinely high frequency of acute symptoms.

As many patients reside a significant distance from the hospital, we were unable to perform microbiology and virology tests on diary-defined exacerbations and thus performed two parallel studies (Figure 1).

In summary, we have demonstrated that respiratory exacerbations are extremely common in CVID, but that patients delay starting antibiotics and ignore symptoms. Although viruses

were identified commonly, patients should nevertheless be educated to take antibiotics promptly if they develop purulent sputum.

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Tables

Table 1: List of symptoms collected in diaries and variables used for analysis.

Variable	Values	Analysis Group (all dichotomous)
Blocked nose	Present, not present	Upper respiratory tract symptoms
Nasal discharge	Present, not present	
Sinus Pain	Present, not present	
Sore Throat	Present, not present	Sore Throat
Cough	Present, not present	Cough
Shortness of breath	Present, not present	Shortness of breath
Wheeze	Present, not present	Wheeze
Sputum colour	White, yellow, green, not present	White Sputum
		Purulent Sputum
Sputum volume	Equivalent to tea spoon, egg cup, cup, not present	Increased sputum volume

'Upper respiratory tract symptoms' is generated by combination (inclusive disjunction) of 'blocked nose', 'nasal discharge', and 'sinus pain'. Sputum colour with four possible values was separated into two binary variables. Sputum volume with four possible values was reduced to a binary variable.

Table 2: Patient characteristics at study enrolment

	69 patients who completed symptom diaries	65 patients who did not completed symptom diaries	p-value
Age (years), median (IQR)	59.36 (46.74 – 68.22)	45.02 (36.33 – 53.79)	<0.001
Female patients, n (%)	41 (59)	36 (55)	0.73
IgG trough level (g/l)*, median (IQR)	9.0 (8.0 – 10.0)	9.0 (7.8 – 10.6)	0.99
Prophylactic antibiotic, n (%)	45 (65)		
Amoxicillin, n (%)	7 (10)		
Azithromycin, n(%)	22 (32)		
Ciprofloxacin, n (%)	3 (4)		
Clarithromycin, n (%)	3 (4)		
Co-amoxiclav, n(%)	2 (3)		
Cotrimoxazole, n (%)	2 (3)		
Doxycycline, n (%)	4 (6)		
Lymecycline, n (%)	1 (1)		
Penicillin, n (%)	1 (1)		
Current smoker, n (%)	6 (9)	4 (6)	0.92
Past smoker, n (%)	15 (22)	15 (23)	
Never smoker, n (%)	48 (70)	46 (71)	
Bronchiectasis on CT, n (%)	37 (57.81)	29 (49.15)	0.22
BSI score†, median (IQR)	3.5 (2 - 6)	2 (1-4)	0.01
FEV1 (l)‡, median (IQR)	2.24 (1.80 – 3.23)	2.63 (2.12 - 3.36)	0.11
FEV1 predicted (%)§, median (IQR)	93.2 (73.3 - 102.9)	93.5 (74.6 - 105.4)	0.95
SGRQ** Total scores, median (IQR)	24.47 (8.41 - 45.54)		
SGRQ Symptoms score, median (IQR)	39.28 (23.76 - 58.56)		
SGRQ Activity score, median (IQR)	29.31 (5.96 - 59.46)		
SGRQ Impact score, median (IQR)	14.90 (1.98- 29.90)		

*IgG trough level, serum immunoglobulin G level measured immediately before the following immunoglobulin replacement is administered. †Bronchiectasis severity Index (BSI), ranging from 0 (best) to 25 (worst), a validated multi-component score in bronchiectasis which predicts future risk of exacerbations, hospitalisations and mortality. ‡FEV1, forced expiratory volume in one second. §FEV1 predicted, proportion of actual FEV1 versus predicted forced expiratory volume in one second in accordance with ERS guidelines of 1993. **St George's Respiratory Questionnaire (SGRQ), a validated measure of respiratory health-status scored between 0 (best) and 100 (worst) quality of life. P-values were calculated using to a Wilcoxon Ranksum test for continuous variables and Fisher's exact test for categorical variables.

Legends

Figure 1. Study design and analysis flow chart. Out of 134 CVID patients, 69 completed a symptom diary for investigation 1 and 41 provided microbiological samples for investigation 2. Details of further analyses and the numbers of participants included for each are provided. CVID, Common Variable Immunodeficiency; SGRQ, St George's Respiratory Questionnaire.

Figure 2. Characterisation of respiratory exacerbations treated with antibiotics. Symptom prevalence (%) and total symptom count (TSC) are displayed over time (days) for 76 antibiotic-treated respiratory exacerbations in CVID patients. Bar diagram reflects mean (SD) total symptom count. Day 1 is defined as start of oral antibiotic therapy (OAT). URTS, upper respiratory tract symptoms.

Figure 3. Trigger Symptom Analysis for CVID patients to commence antibiotic therapy. A. Prospective diary data of respiratory symptoms and oral antibiotic therapy (OAT) usage was collected from 69 CVID patients. The forest plot displays odds ratios and 95%-CI as a measure of effect size for individual symptoms to trigger the start of OAT (higher odds ratios imply a strong association between the symptom and starting OAT). Results are derived from univariate and multivariate logistic regression based on 5446 observations (days). URTS, upper respiratory tract symptoms; SoB, shortness of breath; ISV, increased sputum volume.

B. Bar graph shows the proportion of patients initiating OAT on each of the first 14 days of consecutive symptoms. The time since start of symptoms is defined as the number of days for which two or more symptoms were present. The OAT initiation proportion is the proportion of OAT which was started after a specific time since start of symptoms.

Figure 4. Antibiotic Response Analysis of predictor symptoms. Kaplan-Meier plots display time until recovery based on 76 antibiotic-treated respiratory exacerbations in CVID patients: (A) for all exacerbations, (B) according to presence or absence of upper respiratory tract symptoms (URTS), (C) according to presence or absence of sore throat (ST), and (D) according to presence or absence of purulent sputum (PS) .

E. Forest plot displays hazard ratios for time until recovery after start of oral antibiotic therapy (OAT) depending on the presence of specific symptoms. A multivariate Cox model was calculated for all symptoms which proved to be significant in univariate analysis (multivariate data are only shown for these variables). Hazard ratio reflects the 'risk' for earlier complete symptomatic remission over time.

SoB, shortness of breath, ISV, increased sputum volume; CI, confidence interval.

Figure 5. Pathogenic Viruses and Bacteria Analysis. Viral and bacterial pathogens are frequently isolated in CVID-related respiratory exacerbations. A. Viral PCR was performed on nasopharyngeal swabs in 54 symptomatic respiratory exacerbations in CVID patients. No pathogen (grey) was found in 24 (44%) exacerbations. A pathogenic virus was found in 30 (56%) exacerbations. Rhinovirus was found in 18 (33%) exacerbations; among those where two co-infections with Adenovirus (Adeno), two with Respiratory Syncytial Virus (RSV), and one with Human metapneumovirus (hMPV).

B. Bacterial culture was performed on spontaneously expectorated sputum in 43 symptomatic respiratory exacerbations in CVID patients. No pathogen (grey) was found in 29 (67%) exacerbations. A pathogenic bacterium was found in 14 (33%) exacerbations. *Pseudomonas aeruginosa* was isolated in three (7%) exacerbations; among those was one co-infection with *Streptococcus pneumoniae*. Two patients (accounting for four exacerbations) were probably