## Original Article

# Respiratory Infections and Antibiotic Usage in Common Variable Immunodeficiency

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*What is already known about this topic?* Even with immunoglobulin replacement, respiratory tract infections remain the commonest clinical feature in common variable immunodeficiency (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?* Because 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.

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.

OBJECTIVES: 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 patients with CVID recruited from a primary immunodeficiency clinic in the United Kingdom, generating 6210 days of symptom data. We collected microbiology (sputum microscopy and culture, atypical bacterial PCR, and mycobacterial culture) and virology (nasopharyngeal swab multiplex PCR) samples from symptomatic patients with CVID.
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 characterized by purulent sputum responded more quickly to antibiotics, whereas 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.    © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Respiratory tract exacerbations; Common variable immunodeficiency; Antibiotics; Viral infection

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Common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency in which patients fail to produce adequate levels of immunoglobulins. With a prevalence

*Abbreviations used*
*COPD-* Chronic obstructive pulmonary disease
*CVID-* Common variable immunodeficiency
*HR-* Hazard ratio
*IQR-* Interquartile range
*OAT-* Oral antibiotic therapy
*OR-* Odds ratio
*SGRQ-* St George's Respiratory Questionnaire
*TE-* Treated exacerbation
*TSE-* Treated symptomatic exacerbation
*USE-* Untreated symptomatic exacerbation

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 shows that there may be a significant contribution from viral infections.[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 remains 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 patients with CVID over a winter period. In a parallel analysis, we also explored bacterial and viral pathogens encountered during acute respiratory symptoms in patients with CVID.

## METHODS
### Participants
Patients were recruited from the joint Immunology-Respiratory service at the Royal Free Hospital, London. Patients had a diagnosis of CVID made by a clinical immunologist following the definitions of the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies.[14] All were receiving immunoglobulin replacement and were 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 I). 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 this article's Online Repository at www.jaci-inpractice.org. 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

**TABLE I.** 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 color | White, yellow, green, not present | White sputum Purulent sputum |
| Sputum volume | Equivalent to teaspoon, egg cup, cup, not present | Increased sputum volume |

*Note.* "Upper respiratory tract symptoms" are generated by a combination (inclusive disjunction) of blocked nose, nasal discharge, and sinus pain. Sputum color with 4 possible values was separated into 2 binary variables. Sputum volume with 4 possible values was reduced to a binary variable.

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 hpf were found. Samples were either collected by clinic staff or, after careful instruction on sampling, submitted directly from patients by mail. Figure 1 shows the 2 investigations undertaken on the cohorts.

### Definition of exacerbations and variables
For preanalysis, we grouped clinically related symptoms as presented in Table I. 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 used 2 definitions of exacerbation, based either on symptoms or health care utilization. Similar methodology has been reported and validated in chronic obstructive pulmonary disease (COPD).[17] For the first definition, we identified a symptomatic exacerbation as an event of 2 or more new symptoms lasting for 2 or more consecutive days as recorded by the patient in their diary, whether or not they received additional treatment. The start of a symptomatic exacerbation episode was the first day of 2 or more new symptoms lasting for 2 or more consecutive days. The end of the episode was the last consecutive day with 2 or more symptoms (allowing symptoms to change over time). If oral antibiotic therapy (OAT) was used during a symptomatic exacerbation episode, this was considered a treated symptomatic exacerbation (TSE). If not, it was an untreated symptomatic exacerbation (USE).

We defined a health care utilization 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 that was present when OAT was started. Additional details regarding exacerbation and variable