

# British Society for Immunology/United Kingdom Primary Immunodeficiency Network consensus statement on managing non-infectious complications of common variable immunodeficiency disorders

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## Introduction

Common variable immunodeficiency (CVID) represents a heterogeneous group of rare disorders, with prevalence ranging from 1 in 10 000 to 1 in 50 000 in different populations [1,2]. CVID is characterized by hypogammaglobulinaemia, defective specific antibody production and increased susceptibility to recurrent bacterial infections [2–4]. In addition to the increased risk of recurrent infections, patients with

## Summary

Common variable immunodeficiency (CVID) represents a heterogeneous group of rare disorders. There is considerable morbidity and mortality as a result of non-infectious complications, and this presents clinicians with management challenges. Clinical guidelines to support the management of CVID are urgently required. The UK Primary Immunodeficiency Network and the British Society for Immunology funded a joint project to address this. A modified Delphi Survey was conducted for the assessment, diagnosis and treatment of the non-infectious blood, respiratory, gut and liver complications of CVID. A steering group of 10 consultant immunologists and one nurse specialist developed and reviewed the survey statements and agreed the final recommendations. In total, 22 recommendations and three areas for research were developed.

**Keywords:** common variable immunodeficiency, complications, antibody deficiency, hypogammaglobulinaemia

CVID are also at greater risk of autoimmune disorders and cancer [1,5,6]. Immunoglobulin replacement is the main treatment for the prevention of recurrent infections; however, there is little evidence regarding treatment options for the non-infective complications of CVID [3,7,8].

There is considerable morbidity and mortality as a result of non-infectious complications, and this presents clinicians with management challenges. Further clinical guidelines to

support the management of COVID are urgently required. The UK Primary Immunodeficiency Network and the British Society for Immunology funded a joint project, facilitated by the National Guidelines Centre (NGC), to address this. A comprehensive search of the literature undertaken by the NGC revealed little evidence or clinical guidance on the management of other non-infectious complications of COVID. The lack of evidence reflects the challenges posed in COVID and other rare diseases, where meaningful randomized controlled studies are extremely difficult to conduct.

The published evidence available to date did not support the development of a formal evidence-based guideline in this area, so a Delphi consensus process (anonymous, multi-round, consensus building technique) was adopted to address the assessment, diagnosis and treatment of the non-infectious blood, respiratory, gut and liver complications of COVID. The Delphi method was developed in the 1950s, and has been used successfully for generating, analysing and synthesizing an expert view to reach a group consensus position. The Delphi process relies upon a group of experts (in this case, all consultant immunologists and specialist immunology nurses in the United Kingdom were invited to participate) responding to and providing critical feedback on two or more consecutive surveys (in this case, a set of statements regarding the management of non-infectious complications of COVID). The initial statements were developed by a steering group of 10 consultant immunologists and a nurse specialist. Following the Delphi principles, the initial recommendations that had not met consensus after the first round of the survey were modified according to the expert feedback and recirculated to the expert group. The recommendations that achieved consensus group are described in the Results section of this paper. The group were aware of the consensus statement on granulomatous-lymphocytic interstitial lung disease (GLILD) [9] and therefore did not repeat this work.

## Methods

### Delphi methods

**Development of consensus statements.** The steering group met and identified the non-infectious complications and the areas of management to be included within the survey. The steering group agreed to focus on non-infectious blood, respiratory, gastrointestinal (GI) and liver complications as the most commonly encountered complications where there is little evidence to guide practice. The steering group formulated and validated the consensus statements at each round for the survey. The statements were revised if further clarification was required and sent back to the expert group until no further clarification was needed.

Responses were graded on a four-point Likert scale: 'strongly agree', 'agree', 'disagree' and 'strongly disagree',

with an option of 'I don't have the expertise'. A threshold of 70% to agree (strongly agree or agree) or disagree (strongly disagree or disagree) was used to evaluate the responses. This threshold is routinely used in Delphi processes as a recognized measure of consensus, and statements reaching this threshold were noted to be agreed and not included in subsequent rounds [10]. Free text boxes were included in the survey after each section to give respondents the opportunity to comment on or clarify the statements or responses. These comments were taken into account when revising the statements that did not meet consensus. There is no complete agreement about the termination of a Delphi process, and when no clear indication was given on how to amend a statement from the expert group this was removed from the survey.

The expert group for the survey was identified from the Royal College of Physicians (RCP) 2016 consultant census of immunologists. The aim was to target all the consultants practising in clinical immunology adult services in the United Kingdom. The census identified 85 consultants, in addition to the members of the steering group. The steering group did not participate in the Delphi Survey. The RCP sent out invitation e-mails and two reminders for each round of the Delphi survey. E-mails were sent to each identified consultant outlining the aim of the survey, giving instructions and a link to the survey. Nurse specialists were also invited to take part. The nurse specialists were identified from the Immunology and Allergy Nurses group, 75 of whom identify as immunology specialist nurses. The survey questionnaire was sent to all members of the expert group via SurveyGizmo software. Responses remained anonymous. The whole process was conducted online, with an 8-week cycle time between rounds. This allowed for the questionnaire invitation to be sent, for two reminders to be sent to participants for completion and for the analysis to be conducted prior to the next sequential round.

The steering committee formulated recommendations based on the consensus statements. The steering committee reviewed all free text comments from the responders and these are discussed in each section of the recommendations.

## Results

### Demographics

The steering group that developed the questionnaire consisted of a facilitator from the NGC, 10 consultant immunologists and one nurse specialist.

Thirty-nine participants from 21 immunodeficiency services (of a total of 34 adult UK immunodeficiency services) took part in the first round of the survey; 35 of 85 (41%) consultants and four of 75 (5%) nurse

specialists. The first-round survey was completed by 33 of the 39 participants, while six participants only partially completed the survey. More than 70% of the participants had worked in immunology as a speciality for more than 10 years, and each had direct involvement with more than 50 patients with CVID. Twenty-two participants, all of them consultants, from 16 immunodeficiency centres completed the second round of the survey. More than 80% of the participants had worked in immunology as a speciality for more than 10 years and 50% have direct involvement with more than 50 patients with CVID.

Of the 63 statements in the first round, 57 achieved consensus. For details of the statements that did not reach consensus see Appendix 1. Of the remaining six statements, two still did not achieve consensus in the second round. The steering group made the decision not to make recommendations based on the two statements that did not reach consensus. The statements that achieved consensus were reviewed by groups representing patients with CVID, and their comments have been incorporated into the discussions below.

### Summary of recommendations

The recommendations should be considered in the context of the individual needs of the adult with CVID.

### Baseline assessment and monitoring for non-infectious complications

Although not all people with CVID develop complications, close attention to monitoring is required to identify any complications at an early stage. It is not yet possible to confidently predict the subsets of people at high risk.

Recommendation 1. Adults with CVID should:

- be weighed at least 6-monthly
- have a clinical examination of their lymph nodes at least annually to monitor for the development of persistent lymphadenopathy
- have a clinical examination of their abdomen at least annually to monitor for the development of hepatosplenomegaly
- have a full blood count taken 6-monthly to monitor for the development of autoimmune cytopenias
- have blood tests for B12, folate and ferritin in the presence of anaemia, malabsorption or neuropathy
- have liver function tests (LFTs) assessed 6-monthly to monitor for the development of hepatitis
- have full pulmonary function tests including transfer factor at least every 3 years to monitor for the development of interstitial lung disease

- have a baseline high resolution CT (HRCT) chest to exclude bronchiectasis and lymphadenopathy/other pathology. If a HRCT chest has been performed in the last 12 months, this can be used as the baseline assessment:
  - a baseline HRCT chest should include the upper abdominal viscera to assess lymphadenopathy, spleen size and hepatobiliary architecture unless an abdominal ultrasound has been performed in the last 12 months to assess the liver and spleen.

Eighteen per cent ( $n = 7$ ) of respondents suggested that full pulmonary function testing was performed annually for all patients in their practice. Recommendation 8 increases the frequency of pulmonary function testing to annually in CVID patients who are found to have splenomegaly.

### Multi-professional care

Recommendation 2. Adults with non-infectious complications of CVID should be managed as part of a multi-professional team that includes an appropriate organ-based specialist with an interest in primary immunodeficiency.

### Haematological complications

Recommendation 3. Where an autoimmune cytopenia is suspected:

- a clinical assessment for other secondary causes should be undertaken (for example, drugs, hypersplenism or lymphoproliferative disease)
- a blood film should be a first-line investigation to help identify the underlying cause
- antibody testing (for example, for anti-granulocyte, anti-platelet) should not be performed routinely

Recommendation 4. Immunology centres should agree monitoring, action or referral thresholds for adults with CVID and features of haematological complications with the local haematology team.

Recommendation 5. Adults with autoimmune haemolytic anaemia should be treated according to the British Society for Haematology Guidelines on the management of drug-induced immune and secondary autoimmune haemolytic anaemia [11].

### Respiratory complications

There is an overlap between infectious and non-infectious respiratory complications of CVID. For this reason, the Steering Group decided to include statements regarding identification and management of bronchiectasis. The management of upper respiratory tract infections is not addressed in this guideline.

Recommendation 6. Adults with CVID and ongoing frequent respiratory tract infections should have a HRCT chest at least every 5 years to monitor for the development of bronchiectasis.

Recommendation 7. Adults with CVID and bronchiectasis and ongoing frequent respiratory tract infections should have a HRCT chest at least every 5 years to monitor the progression of bronchiectasis.

Recommendation 8. Adults with CVID and splenomegaly should have annual pulmonary function tests (PFT) including transfer factor to monitor for the development of interstitial lung disease.

Recommendation 9. Centres should agree monitoring, action or referral thresholds for adults with CVID with features of respiratory complications with the local Respiratory team.

Recommendation 10. Adults with CVID and bronchiectasis should be managed jointly with a consultant chest physician and an immunologist.

In the free text section, all the respondents stressed the importance of using clinical judgement and individual patient assessment to determine the exact frequency of computerized tomography (CT) scanning and pulmonary function tests (PFT). It is acknowledged that in some cases more frequent scanning or PFT may be indicated. The radiation risk associated with CT scanning was highlighted by respondents commenting that some patients with CVID may be particularly radiosensitive, and thus potentially more susceptible to ionizing radiation. The role of PFT in place of, and as an adjunct to, HRCT was emphasized by several respondents in order to minimize radiation exposure. The committee concluded that alternatives such as low-dose HRCT and magnetic resonance imaging (MRI) may also be considered.

### GI complications

Infectious diarrhoea is the most common GI complication in CVID [12], while 9–15% of patients are reported to develop non-infectious GI complications [8,13]. Diagnosis of non-infectious GI complications requires that infection is excluded as a cause of symptoms. As a result, the steering group agreed to include statements relating to infection in the Delphi survey, even though infectious complications are not the main focus of these guidelines.

Recommendation 11. Adults with CVID and evidence of malabsorption should have the following investigations:

- haematinics
- calcium
- vitamin D
- fat soluble vitamins

Respondents highlighted that malabsorption should be considered in patients with unexplained weight loss.

### Adults with CVID and *Helicobacter pylori*

Recommendation 12. Adults with CVID and *H. pylori* should be offered eradication in line with National Institute for Health and Care Excellence (NICE) guideline CG184 (Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management) [14].

### Adults with CVID and diarrhoea

Recommendation 13. In adults with CVID and diarrhoea for more than 2 weeks the following infections should be excluded:

- *Campylobacter*
- *Clostridium difficile* toxin
- *Giardia*
- *Salmonella*
- *Shigella*
- *Cryptosporidia*
- Microsporidia
- Cytomegalovirus (CMV)
- Norovirus
- Other intestinal parasites (for example, isospora)

In the free text section, a number of respondents favoured a stepwise approach, with first-line investigations to exclude *Campylobacter*, *C. difficile* toxin, *Giardia*, *Salmonella* and *Shigella*, only proceeding to investigating for viruses, mycobacteria and other parasites if these first-line tests are negative.

Recommendation 14. Adults with CVID and non-infectious diarrhoea or malabsorption should be referred to a consultant gastroenterologist and a dietician.

Recommendation 15. Where initial tests for infection are negative, all patients with persistent diarrhoea should be referred for lower GI endoscopy with biopsy for the assessment of:

- GLILD – including typical and atypical Crohn's disease
- inflammatory bowel disease, including typical and atypical ulcerative colitis
- lymphocytic infiltration to suggest autoimmune enteropathy
- lymphoma (T and B cell)
- infection [CMV, enteroviruses, Epstein–Barr virus (EBV)]

Recommendation 16. Where initial tests for infection are negative, all patients with persistent diarrhoea should be referred for upper GI endoscopy with biopsy for the assessment of:

- coeliac and coeliac-like enteropathy
- lymphocytic infiltration to suggest autoimmune enteropathy



- small bowel biopsy and jejunal aspirates to exclude giardia
- lymphoma (T and B cells)
- infection (CMV, enteroviruses)
- nodular lymphoid hyperplasia

Recommendation 17. Centres should agree a protocol with the local gastroenterology team to guide observations and indicate the pathological samples to be taken at endoscopy in adults with CVID.

The consensus was clear that both upper and lower GI endoscopies should be examined to exclude lymphoma, and respondents emphasized the importance of working closely with histopathologists and gastroenterologists. The respondents recognized the lack of evidence regarding the underlying reasons for the increased risk of malignancy in CVID, but there was clear consensus for the need to exclude malignancy in this clinical context. Both rounds of the survey included statements which included specific methods for identification of viruses and CD4 and CD8 T cells in gastrointestinal biopsies, and these all received high levels of agreement. However, the expert group felt that these were too restrictive, and that the intent of the recommendations was to highlight the need to exclude specific infections and lymphoma without limiting the methodologies used. The statements were condensed to reflect this.

Consensus was not reached regarding examination of stool samples for EBV and AAFB; however, it was recommended that if biopsies are taken EBV should be excluded.

### Recommendations for adults with CVID and pernicious anaemia

Recommendation 18. Adults with CVID and pernicious anaemia should have:

- an upper GI endoscopy performed within 6 months of diagnosis
- monitoring arranged according to local gastroenterology guidance

### Recommendations for adults with CVID and coeliac disease

Recommendation 19. Adults with CVID and coeliac disease should have:

- an upper GI endoscopy and biopsies performed prior to gluten avoidance
- an upper GI endoscopy and biopsies performed after 6 months on a gluten-free diet to assess response
- monitoring arranged according to local gastroenterology guidance

The steering group acknowledge the difficulty in diagnosing coeliac disease in patients with CVID in whom the serological tests are not useful. The existence of non-gluten sensitive enteropathy histologically similar to coeliac disease is also recognized [15]. Comments from the survey highlighted the possibility of using human leucocyte antigen (HLA)-DQ2/8 testing to identify patients in whom coeliac disease is unlikely.

### Hepatobiliary complications

#### Recommendations for adults with CVID and abnormal liver function tests (LFTs)

Recommendation 20. Adults with CVID and abnormal LFTs should have:

- LFTs repeated to avoid unnecessary additional investigations
- their drugs reviewed for hepatotoxicity
- advice to avoid alcohol until they have been seen by a hepatologist

Recommendation 21. Centres should agree monitoring, action or referral thresholds for people with CVID and abnormal LFTs with the local hepatology team.

Recommendation 22. Assess for granulomatous disease and autoimmune disease in other organs in adults with CVID and associated liver disease.

### Discussion

This is the first set of UK recommendations for the monitoring and management of non-infectious complications of CVID. We used the Delphi method to produce several consensus statements. This method was chosen as there is not a sufficiently large evidence base for the diagnosis and management of any of these complications on which to develop evidence-based guidelines, as is often the case with rare diseases. We started with 63 statements; 59 statements reached consensus and were condensed into 22 recommendations.

The steering group identified a number of significant non-infectious complications of CVID to address in the Delphi statements. There is an inevitable overlap with infectious disease, particularly where exclusion of infection is critical to the diagnosis of non-infectious complications. As a result, some statements regarding infectious complications had to be included. GLILD was not addressed, as a UK consensus statement on the management of GLILD has recently been published [9].

The increased risk of malignancy in this group of patients is acknowledged; the statements recommending for regular

clinical assessment (including weight) and regular monitoring blood tests were included to take this into account. Development of further guideline/consensus on screening and monitoring for cancers such as gastric cancer and lymphomas will be required in the future.

The survey respondents were representative of medical consultants specializing in immunology working in the United Kingdom, although there was a low response rate from the nurses' group. Overall, the majority of participants (80%) had more than 10 years' experience in immunology, cared for 50 or more CVID patients (70%) and worked in 21 of the 36 immunodeficiency centres in the United Kingdom. Fifty-two per cent ( $n = 44$ ) of the current consultant immunologist workforce contributed to developing these recommendations, including the members of the steering group.

In all the areas of the survey, respondents emphasized the importance of the multi-disciplinary team approach for the management of patients, including expert histopathologists where appropriate. This is in line with the recently published guideline on GLILD, another non-infectious complication of CVID [9]. The steering group acknowledges that individual patient management should also take into account other co-morbidities and the presence of other manifestation/complications of CVID, and should be in accordance with the patient's needs.

The survey was sent to immunologists, and not the organ-based specialists who are also involved in the care of these patients. This was due to the difficulty in identifying organ-based specialists with sufficient expertise and is a limitation of this work. However, recent UK census data show that 50% of immunology services in the United Kingdom hold combined respiratory/immunodeficiency clinics and 25% combined gastroenterology/immunodeficiency clinics (data from 2017 UK Primary Immunodeficiency Network/Royal College of Physicians Quality in Primary Immunodeficiency Services census). It is therefore probable that the responses are likely to be congruent with recommended practice in these multi-disciplinary team (MDT) settings.

The steering group recognizes the flaws of the Delphi method, including the arbitrarily set level of consensus, the risk of bias when responding to feedback from participants and the difficulties when administering the Delphi electronically [16]. Despite these, the Delphi method is useful for establishing consensus in rare disease management.

We hope that this guideline will be widely adopted and will be used by centres caring for CVID patients in the United Kingdom in order to compare their current practices with these recommendations. It will also raise further research questions and encourage audit and collaboration to address the uncertainties in several areas.

## Lessons learnt

Establishing a Delphi consensus in rare diseases with few specialists can be challenging when 20% of the available medical respondents comprise the steering group.

In total, 44 consultant immunologists and four specialist nurses were involved in developing these recommendations. It is reassuring that a high level of consensus was reached in the first round, suggesting a good degree of nationwide consensus among respondents, even in the absence of high-quality evidence or previous guidelines.

Strategies to improve input organ-based specialists with relevant experience in pelvic inflammatory disease (PID) complications should be developed in future.

Responses from the nursing group were much lower: this may reflect a perceived lack of expertise in the diagnosis and medical management of the CVID complications described.

We cannot presuppose the reasons for non-responses as the reasons for not completing an online survey will vary, and it is possible that agreed single individuals may have responded on behalf of larger centres). However, it will be important to explore ways to optimize response rates with the Delphi process for future surveys. This process has emphasized the need to promote awareness of these complications and provide guidance on their identification and management.

## Areas for research

The steering group identified the following areas for future research.

1. Better description of the natural history of progression of non-infectious complications and combinations of these patient cohorts. This will help identification and early intervention where appropriate. Next-generation sequencing may help to categorize subgroups with predisposition for certain complications within the CVID cohort.
2. Improved identification of risk factors for these complications, including demographics, family history, concurrent diagnoses and genetics. This may eventually lead to pre-emptive treatment, including targeted therapies, gene therapy and stem cell transplantation.
3. Increased collection of prospective data with regard to specific complications of CVID. The study of interstitial lung disease in primary antibody deficiency [17] is an example of this. Similar initiatives are therefore urgently needed to improve treatment outcomes for other life-limiting complications of CVID. This will require co-ordinated and sustained efforts of the whole immunology community to support such prospective studies.

## Conclusions

We present the first set of UK recommendations for the monitoring and management of non-infectious complication of COVID. This will help to standardize practices and facilitate future audit, quality improvement work and research for this cohort of patients.

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## APPENDIX 1

## Statements that did not achieve consensus in the first round.

## Free text comments from the survey regarding statements that did not reach consensus

*Annual ultrasound monitoring for hepatosplenomegaly*

In the first round the comments supported an annual clinical examination, agreeing that this was important for monitoring for hepatosplenomegaly and lymphadenopathy, but noted that an annual ultrasound was unnecessary if there was no clinical suspicion of organomegaly. This added another appointment for the patient and is not useful in directing clinical management. The respondents commented that the frequency of an ultrasound should be guided by clinical findings and not for monitoring. One respondent highlighted that clinical examination for hepatosplenomegaly is not sufficiently sensitive except for major organ enlargement. This steering group agreed that a revised statement about clinical examination was more appropriate and was included in the subsequent Delphi round.

*Annual screening for H. pylori*

In the first round the comments strongly agreed that the routine screening of *H. pylori* was unnecessary, and the value of doing this was unclear. The steering group agreed to amend the focus of the recommendation to adults with CVID and *H. pylori* and to direct clinicians to the NICE guideline for details on *H. pylori* eradication. This recommendation was moved from the monitoring section to the gastrointestinal (GI) complications section.

*Blood tests for GI complications*

In the first round, the comments noted that blood tests used in monitoring could be performed as markers for

other conditions, such as malabsorption and neuropathy, and not simply anaemia. The steering group re-phrased the statement to 'Adults should have blood tests for B12, folate and ferritin in the presence of anaemia, malabsorption or neuropathy'. In the second Delphi survey round this statement reached 90% consensus strongly agree/agree. This recommendation was moved from the monitoring section to the GI complications section.

*Excluding HIV, EBV, AAFB in patients with persistent diarrhoea*

No consensus was achieved on screening for HIV, EBV or AAFB in patients with diarrhoea. The steering group rephrased this statement to 'if diarrhoea is prolonged and no other cause has been identified consider testing for HIV, EBV and AAFB'. Consensus was only achieved for HIV screening (85%) in the second round and was included in the recommendation for assessment on biopsy when a patient has persistent diarrhoea. Consensus was not reached for EBV and AAFB assessment (63 and 68.5%) in the second Delphi round and the steering group agreed to exclude these assessments from the recommendations. The comments from respondents for these two pathogens predominantly referred to their likelihood of being unusual causes of diarrhoea in the setting of CVID, and therefore should not be part of first line investigations.

*Additional statement added in the second round*

This statement, 'adults with CVID and malabsorption should be tested for the following: haematinics, calcium, vitamin D and fat soluble vitamins' was added to the second round survey in response to comments made in the first Delphi round about checking for micronutrient deficiencies. This statement achieved consensus in the second round and was added to the recommendations.

**Table A1.** Delphi statements where consensus was not reached in the first round on the monitoring of non-infectious complications

	Results %	
	Strongly disagree/ disagree	Strongly agree/agree
Adults with CVID should have an ultrasound of upper abdomen performed at least annually to monitor for the development of hepatosplenomegaly	64	36
Adults with CVID should have annual screening for <i>Helicobacter pylori</i>	53	47
Adults with CVID should not have blood tests for B12, folate and ferritin unless anaemia is present	35	65
In adults with CVID and diarrhoea for more than two weeks the following opportunistic infections should be excluded:		
Human immunodeficiency virus (HIV)	40	60
Epstein-Barr virus (EBV)	39	61
Alcohol and acid-fast bacilli (AAFB)	43	57

CVID = common variable immunodeficiency.