# Common Variable Immunodeficiency (CVID) - diagnosis and management

**Classification:** Protocol  
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**Issue number:** 5  
**Expiry Date:** May 2021

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**Document Control**
- Policy Implementation Plan
- Monitoring and Review
- Endorsement
- Equality analysis
Who should read this document?

Immunology Consultants, medical and nursing staff who are involved in the care and management of patients with immunodeficiency
As a guidance to other medical teams within the Trust who are involved in the care of patients with Common Variable Immunodeficiency (CVID)

Key Practice Points

The purpose of this protocol is to ensure that patients with CVID are diagnosed and managed as per national guidelines and current evidence.

Background/ Scope/ Definitions

This protocol describes the evaluation and management of patients with suspected Common Variable Immunodeficiency (CVID), to ensure that diagnostic tests and treatment meets the needs and requirements of such patients and conforms to accepted national guidelines.

What is new in this version?

Guideline has been re-formatted in line with trust guidelines.

Guideline/ Protocol

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency, characterised by markedly reduced serum levels of IgG and low IgA or IgM, recurrent bacterial infections, and impaired antibody responses despite the presence of B cells. The prevalence of disease is estimated to be between 1 in 25 000 to 50 000. Most patients with CVID are diagnosed between the ages of 20 and 40 years, after they have had several chest infections; however children and older adults may be affected. The majority of patients have normal numbers of B cells. Abnormalities in T cell numbers or function are common. The disease is associated with autoimmune disorders in approximately 50% of the patients and gastrointestinal diseases in 25%. Granulomatous disease and nodular lymphoid hyperplasia may affect 8-22% of cases. There is an increased risk to develop malignancies. The patho-physiologic defect(s) underlying CVID is unknown. Defects in B-cell activation, B-cell survival, numbers of circulating switched and unswitched memory B-cells, terminal B cell differentiation, T-cell signaling and cytokine expression have been identified.
**DIAGNOSTIC CRITERIA:** Diagnostic criteria have been drawn up by the Pan-American Group for Immune Deficiencies and the European Society for Immune Deficiencies (2005).

**Probable**
Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:
1) Onset of immunodeficiency at greater than 2 years of age
2) Absent isohemagglutinins and/or poor response to vaccines
3) Defined causes of hypogammaglobulinemia have been excluded

**Possible**
Male or female patient who has a marked decrease (at least 2 SD below the mean for age) in one of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria:
1) Onset of immunodeficiency at greater than 2 years of age
2) Absent isohemagglutinins and/or poor response to vaccines
3) Defined causes of hypogammaglobulinemia have been excluded

**INVESTIGATIONS:**

*First level of investigations*
- Complete blood cell count with differential,
- Total IgG, IgA, IgM and IgE levels
- Serum (and urine) electrophoresis
- Complement levels,
- Functional antibodies (Tetanus, Hib and Pneumococci).
- IgG antibodies to previous infections and/or immunisations e.g. hepatitis B, meningococcus C, measles, rubella, CMV, VZV, EBV and others if appropriate.
- If specific antibody levels are low, test immunisations (e.g. tetanus toxoid, pneumovax, Hib) should be given. Post immunisation blood samples should be taken after 4-6 weeks.
- Lymphocytes subsets including T, B and NK cell numbers.

- Switched memory B-cells (CD19*IgD*CD27*) and nonswitched (CD19*IgD*CD27*) memory B cells in the peripheral blood to identify patients with increased risk of bronchiectasis, splenomegaly or autoimmune disease.

- Liver function tests, urea & creatinine, calcium
- Urine analysis
- Other investigations (including microbiology and imaging) as required by the clinical picture

Findings of hypogammaglobulinemia or suboptimal functional antibody levels require further testing.

Absence of antigen-specific immunoglobulin in response to both polysaccharide and protein-based antigenic stimulation is consistent with a diagnosis of CVID.
Because other primary humoral immunodeficiencies can mimic CVID and in the absence of a definitive test for this disease, CVID is a diagnosis by exclusion, all other known primary or secondary causes of hypogammaglobulinemia should be excluded.

Second level of investigations

The second level of testing of patients suspected of having CVID focuses on identifying a possible genetic defect of CVID.

Patients should be counselled for genetic studies offered by the national NIHR BioResource- Rare Diseases- 100 000 gene study.

Further Assessment

- HRCT thorax and upper abdomen (ask to check for: thymoma, ground glass appearance in lungs and granuloma in the liver and spleen). In addition, this will provide a baseline assessment
- Lung function (dynamic and static spirometry, lung volumes and diffusion capacity)
- Bone marrow examination (if needed to exclude malignancy)
- Lung CT (if indicated) to determine pre-existing bronchiectasis

In the case of respiratory infection:
- Sputum cultures may be helpful to detect unusual organisms

In the case of intestinal symptoms
- Faeces culture
- Faeces microscopy: cysts and eggs or PCR for cryptosporidia
- Endoscopy /colonoscopy with biopsy (to identify lymphoid nodular hyperplasia, villous atrophy, granuloma or unusual pathogens)
- If Giardia is suspected, take biopsy from the duodenum
- Clostridium difficile cytotoxin
- Consider inflammatory bowel disease and coeliac disease

In the case of urinary tract symptoms:
- Urine electrophoresis
- Mycoplasma hominis/Ureaplasma urealyticum (PCR in urine)

Differential Diagnosis of Hypogammaglobulinaemia

Drug Induced

Antimalarial agents
- Captopril
- Carbamazepine
- Glucocorticoids
- Fenclofenac
- Gold salts
- Penicillamine
Phenytoin
Sulfasalazine

**Genetic Disorders**
- Ataxia Telangiectasia
- Autosomal forms of SCID
- Hyper IgM Immunodeficiency
- Transcobalamin II deficiency and hypogammaglobulinemia
- X-linked agammaglobulinemia (XLA)
- X-linked lymphoproliferative disorder (EBV associated)
- X-linked SCID
- Some metabolic disorders
- Chromosomal Anomalies
- Chromosome 18q- Syndrome
- Monosomy 22
- Trisomy 8
- Trisomy 21

**Infectious Diseases**
- HIV
- Congenital Rubella
- Congenital infection with CMV
- Congenital infection with Toxoplasma gondii
- Epstein - Barr virus

**Malignancy**
- Chronic Lymphocytic Leukaemia
- Immunodeficiency with Thymoma
- Non-Hodgkin’s lymphoma
- B cell malignancy

**Systemic Disorders**
- Immunodeficiency caused by hypercatabolism of immunoglobulin
- Immunodeficiency caused by excessive loss of immunoglobulin (nephrosis, severe burns, lymphangiectasia, severe diarrhoea)

**GENERAL MANAGEMENT:**

Early diagnosis and treatment result in better outcome as measured by lifespan, quality of life and reduced morbidity.
The mainstay of treatment is immunoglobulin replacement therapy.
Patients with chest disease need regular chest physiotherapy, antibiotics and immunoglobulin replacement therapy.
Bacterial infections need prompt antibiotics for longer periods than in immunocompetent patients
General practitioners (GP’s) and patients need to be advised about this.
Prophylactic antibiotic therapy may be indicated
Granulomatous disease usually responds to low dose steroids.
Immunisations – decisions should be made on consideration of the individual case and after referral to current Green Book on Immunisation. Live/oral polio immunisation should NOT be given. Flu vaccine can be given, although efficacy is not guaranteed.

**IMMUNOGLOBULIN REPLACEMENT THERAPY:**  
*Prior to immunoglobulin treatment*  
- HBsAg and PCR for HIV and HCV  
- Save a serum sample  
Immunoglobulin can be given intravenously every 2-3 weeks or subcutaneous weekly.

See separate protocol for consent for immunoglobulin therapy & starting immunoglobulin therapy.

**HOME THERAPY:**

Patients can be trained to give immunoglobulin infusions at home. Patients must be formally assessed for suitability before being accepted on the Home programme (see separate protocol).

**FOLLOW-UP:**

Patients with CVID need follow up to:

Assess the efficacy of treatment. 
IgG trough levels are monitored regularly, number of infection and number of required antibiotic courses are documented, immunoglobulin dose is adjusted accordingly. 
Monitor for complications of treatment 
Adverse reactions to treatment 
Transmissible agents 
Monitor for complications of disease 
- Infections e.g. Bronchiectasis, sinusitis, conjunctivitis etc 
- Auto-immune e.g. cytopenias, thyroid, diabetes etc 
- Granulomatous disease 
- Enteropathy 
- Malignancy 
Assess overall health 
Family / educational / psychological issues etc 
Given the changing nature of CVID, regular review of the diagnosis is recommended.
ROUTINE FOLLOW-UP INVESTIGATIONS / ASSESSMENT

1. Blood should be taken prior to intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) infusion 6-12 monthly (or more frequently if clinically indicated):
   a) Liver function tests
   b) Trough IgG level
   c) CRP
   d) Full blood count (and haematinics as required)
   e) Save serum annually

-Save serum sample on changing to a different immunoglobulin product.
2. Assessment of frequency of infections and general well-being using diary charts and infusion logs where appropriate. Appropriate samples for microbiology should be sought where possible.
3. Pulmonary function tests (spirometry, lung volumes and transfer factor) every year.
4. Mycoplasma infection should be suspected in patients with routine culture negative arthritis or negative culture chronic/recurrent respiratory infections failing to respond to usual antibiotics.
   Reference lab: The Respiratory and Systemic Infection Laboratory/HPA Centre for Infections, Colindale, London (020 8327 6906/73310)
5. Imaging (e.g. CXR, Chest CT scan, abdominal USS) as indicated clinically.
6. Additional investigations as indicated by clinical status. These may include biochemistry (renal function, thyroid function, tests of malabsorption including vitamin E and D), β2 microglobulin, lymphocyte subsets, chest CT.
7. Neurological complications: refer to a neurologist, alerting them to the possibility of JC virus progressive multifocal encephalopathy (PML), Enteroviral meningoencephalitis and vitamin E deficiency induced central neurological manifestations.
8. Refer to Joint Respiratory Immunology clinic if patient has bronchiectasis and recurrent chest infections
9. Refer to a haematologist if the patient has autoimmune cytopenia (haemolytic anaemia, thrombocytopenia...)
10. Refer to Gastroenterologist if the patient has symptoms suggestive of inflammatory enterocolitis

Standards (section number should follow on from the preceding section)

United Kingdom Primary Immunodeficiency Network (UKPIN) standards for accreditation. www.pinguidelines.org.uk
Explanation of terms

IgA – immunoglobulin A deficiency (antibodies)
IgM – Immunoglobulin M (antibodies)
IgG – Immunoglobulin G (antibodies)
PCR – polymerase chain reaction
CMV – Cytomegalovirus
HIV - human immunodeficiency virus
VZV – Varicella zoster virus
EBV - Varicella zoster virus

References and Supporting Documents

Adapted from UKPIN standards of care – www.ukpin.org.uk


Roles and responsibilities

Consultant Immunologist/ Specialist Registrar:

- Initial clinic assessment of patient with possible primary antibody deficiency-Common Variable Immunodeficiency (CVID)
- Investigations and diagnosis
- Discuss different treatment options with patient/ family/ specialist nurse
Initiate treatment, obtain consent if applicable
Follow up patient in clinic

Specialist Immunology Nurse:
- Initiate immunoglobulin therapy
- Immunoglobulin infusion training and competency assessment
- Home visit
- Assess patient pre clinic
- Initiate blood sampling investigations
- Give immunisations if applicable/ follow up samples
- Keep DoH immunoglobulin record up to date
- Enrol patients in UKPIN registry
- Identify patients for genetic studies
- Discuss treatment options with patient and medical staff
**Common Variable Immunodeficiency (CVID) - diagnosis and management**

**Lead Author:** Dr Hana Alachkar  
**Additional authors:** Dr Archana Herwadkar  
**Document owner:** Dr Hana Alachkar  
**Contact details:** 0161 206 0522

**Classification:** Protocol  
**Scope:** Immunology Department and for guidance for other medical teams  
**Applies to:** Immunology medical and nursing staff  
**Document for public display:** Yes

**Keyword:** antibody deficiency, immunoglobulin, immunodeficiency, CVID, management of,

**Associated Documents:**  
Administration of immunoglobulin for Adults with Immunodeficiency.  
Consent for immunoglobulin replacement therapy.  
Home therapy with Intravenous immunoglobulin.  
Home therapy with Subcutaneous immunoglobulin.

**Unique Identifier:** D1  
**Issue number:** 5  
**Replaces:** 4  
**Authorised by:** Immunology Team  
**Authorisation date:** 23/03/2018  
**Next review:** May 2021

**Policy Implementation Plan**

This policy will be cascaded via immunology team meetings and all policies and protocols discussed at the regional immunology meetings.

**Monitoring and Review**

The policy will be reviewed by the immunology team and every 3 years.
# Endorsement

<table>
<thead>
<tr>
<th>Name of Lead Clinician/Manager or Committee Chair</th>
<th>Position of Endorser or Name of Endorsing Committee</th>
<th>Date</th>
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<tbody>
<tr>
<td>Dr Alachkar</td>
<td>Immunology Consultant</td>
<td>13/05/2014</td>
</tr>
<tr>
<td>Immunology team Dr Archana Herwadkar/Dr Hana Alachkar</td>
<td>Immunology team</td>
<td>13/05/2014</td>
</tr>
<tr>
<td>Dr Hana Alachkar</td>
<td>Immunology Consultant</td>
<td>23/03/2018</td>
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### Screening Equality Analysis Outcomes

The Trust is required to ensure that all our policies/procedures meet the requirements of its service users, that it is accessible to all relevant groups and furthers the aims of the Equality Duty for all protected groups by age, religion/belief, race, disability, sex, sexual orientation, marital status/civil partnership, pregnancy/maternity, gender re-assignment. Due consideration may also be given to carers & socioeconomic factors.

<table>
<thead>
<tr>
<th>Have you been trained to carryout this assessment?</th>
<th>yes</th>
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<tr>
<td>If 'no' contact Equality Team 62598 for details.</td>
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**Name of policy or document**: Common Variable Immunodeficiency (CVID) - diagnosis and management  
**Key aims/objectives of policy/document**: To provide a guideline/recommendation for diagnosis and management of CVID (impact on both staff & service users)

1) a) Who is this document or policy aimed at?  
   - Immunology specialist nurses and immunology Consultants. Other medical teams within the Trust caring for patients with CVID

2) a) Is there any evidence to suggest that your ‘end users’ have different needs in relation to this policy or document; (e.g. health/employment inequality outcomes) (NB If you do not have any evidence you should put in section 8 how you will start to review this data)  
   - No

3) a) Does the document require any decision to be made which could result in some individuals receiving different treatment, care, outcomes to other groups/individuals?  
   - No  
   b) If yes, on what basis would this decision be made? (It must be justified objectively)  
   -  

4) a) Have you included where you may need to make reasonable adjustments for disabled users or staff to ensure they receive the same outcomes to other groups?  
   - Yes.

5) a) Have you undertaken any consultation/involvement with service users or other groups in relation to this document?  
   - No
b) If yes, what format did this take? 
Face/face or questionnaire? (please provide details of this)

c) Have any amendments been made as a result?

6) a) Are you aware of any complaints from service users in relation to this policy? No

b) If yes, how was the issue resolved? Has this policy been amended as a result?

7) a) To summarise; is there any evidence to indicate that any groups listed below receive different outcomes in relation to this document?

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<tr>
<th>Category</th>
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<td>Age</td>
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<td>Religion &amp; Belief</td>
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<td>Gender Reassignment</td>
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<td>Carers *1</td>
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<tr>
<td>Socio/economic**2</td>
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1: That these two categories are not classed as protected groups under the Equality Act.
2: Care must be taken when giving due consideration to socio/economic group that we do not inadvertently discriminate against groups with protected characteristics

**Negative Impacts**

*If any negative impacts have been identified you must either a) state below how you have eliminated these within the policy or b) conduct a full impact assessment:

7) How will the future outcomes of this policy be monitored?

Regular review by medical staff

9) If any negative impact has been highlighted by this assessment, you will need to undertake a full equality impact assessment:

Will this policy require a full impact assessment? No
(if yes please contact Equality Team, 62598/67204, for further guidance)

High/Medium/Low Type/sign: Victoria Blakeley 23/03/2018