Common Variable Immunodeficiency (CVID) - diagnosis and management

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Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who should read this document</td>
<td>2</td>
</tr>
<tr>
<td>Key practice points</td>
<td>2</td>
</tr>
<tr>
<td>Background /scope/definitions</td>
<td>2</td>
</tr>
<tr>
<td>What’s new in this version</td>
<td>2</td>
</tr>
<tr>
<td>Guideline</td>
<td>2-8</td>
</tr>
<tr>
<td>Standard</td>
<td>8</td>
</tr>
<tr>
<td>Explanation of terms</td>
<td>8</td>
</tr>
<tr>
<td>References and supporting documents</td>
<td>9</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>10</td>
</tr>
</tbody>
</table>

Appendix

Document control information (Published as separate document)
- Document Control
- Policy Implementation Plan
- Monitoring and Review
- Endorsement
- Equality analysis

Current Version is held on the Intranet
Check with Intranet that this printed copy is the latest issue
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 1 in 10,000. Most patients with CVID are recognized to have immunodeficiency in the second, third or fourth decade of life, 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; however, some have low or absent 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%. A smaller proportion has granulomatous disease and nodular lymphoid hyperplasia. There is an elevated risk to develop malignancies. The pathophysiologic defect(s) underlying CVID is unknown. Defects in B-cell activation, B-cell survival, numbers of circulating switched and un-switched 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 (at least 2 SD below the mean for age) in two out of three 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

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, IgG subclasses
- 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.
- Anti-IgA antibodies if IgA below local limit of detection
- 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 subtypes of CVID.
Flow cytometric analysis of switched (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. Since 2003, different genes have been shown to be linked with primary antibody failure. These include ICOS, TNFRSF13B (encoding TACI), TNFRSF13C (encoding BAFF-R) and CD19. Identification of the molecular genetic causes of CVID will facilitate optimal treatment of patients and has implications for genetic counselling.

BAFF-R and CD19 are done at Salford Royal NHS Foundation Trust (cellular/flow cytometry) and TACI genetic study is done at Royal Free Hospital/London.

**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
- Specific genetic tests to exclude other primary immune defects if appropriate

_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 BNF and “Immunisation of the Immunocompromised Child”. See RCPCH website. 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.
Trough levels are monitored regularly, number of infection and number of required antibiotic courses are documented, immunoglobulin dose is adjusted accordingly.

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.
Monitor for complications of treatment
Adverse reactions to treatment
Transmissible agents
Monitor for complications of disease
- Infectious e.g. bronchiectasis, sinusitis, conjunctivitis etc
- Autoimmune 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

-Hepatitis C PCR only before starting treatment and 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 2 years.

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.  
Samples [CSF, blood, joint aspirates and respiratory samples (sputum, BAL, NPA) ≥ 0.2mL]  
Reference lab: The Respiratory and Systemic Infection Laboratory/HPA Centre for Infections, Colindale, London (020 8327 6906/73310)

5. Imaging (e.g. CXR, CT) 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](http://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 - Epstein–Barr 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:
- Assess patient pre clinic
- Initiate blood sampling investigations
- Give immunisations if applicable/ follow up samples
- Discuss treatment options patient and medical staff
- Initiate immunoglobulin therapy