UK PRIMARY IMMUNODEFICIENCY NETWORK
STANDARDS of CARE
This document represents the consensus of the PIN Standard of Care Group. These Standards of care are for the diagnosis and management of the condition stated, for use by Immunologists and Immunology Specialist Nurses.
Clinical judgement supersedes the Standards of care wherever necessary.

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A list of current Standards of care is available at www.ukpin.org.uk

KEY STANDARDS ARE LISTED AT THE END OF THE DOCUMENT

Introduction
Common Variable Immunodeficiency Disorders (CVID) are a collection of poorly understood conditions with primary hypogammaglobulinaemia leading to an increased risk of infections, with autoimmune and granulomatous complications in some patients.

Diagnostic Criteria
As stated by ESID (European Society for Immune Deficiencies)
http://www.esid.org/workingparty.php?party=3&sub=2&id=73#Q2

Main Clinical Features
- Patients usually present with recurrent bacterial infection secondary to encapsulated organisms.
- Gastro-intestinal infection and bacterial conjunctivitis are also common.
- Approximately 20% of patients have an autoimmune disorder, the commonest being thrombocytopenic purpura, autoimmune haemolytic anaemia and thyroid disease.
- A proportion (10-20%) of patients have granulomatous disease which may involve the lungs, liver, spleen and skin, and are probably a distinct subgroup.

Key Diagnostic Tests

To establish the diagnosis:
- Serum Immunoglobulin concentrations (IgG, IgA, IgM)
- Antibody responses to specific vaccines (ideally change in level pre-post vaccine)
- Lymphocyte subsets including class-switched memory B cells
- Electrophoresis of serum and urine (adults)

For baseline assessment of patient:
- Chest x-ray to look for consolidation/lung disease (and also exclude thymoma)
- All adult patients should have a baseline High Resolution CT thorax performed to assess lung disease. Need for scanning in children should be made on a case by case basis.
- Lung function tests
- Urea, electrolytes and liver function tests
- Lymphoproliferative disease should be excluded in all patients. Extent of investigations depends on the age and presentation of the patients
- In patients with clinical evidence of granulomatous disease: ultrasound abdomen to assess presence of hepatosplenomegaly and lymphadenopathy
- The molecular basis of CVID is currently being elucidated (e.g. mutations in TACI) and molecular tests may be considered in specific patients (These are available in a number of UK and European centres).

Diagnostic Considerations
- Secondary causes include
  - Haematological malignancies especially in adults, CLL, NHL, myeloma,
  - Thymoma
  - Protein losing enteropathy / nephrotic syndrome
  - Drugs eg anti-convulsants, disease modifying anti-rheumatic drugs.
- Advice on and testing for diagnosis of other primary immunodeficiencies is available from UK centres including UCL Centre for Immunodeficiency (Great Ormond Street Hospital and Royal Free Hospital)
  - Examples include
    - X-linked agammaglobulinaemia,
    - CD40 ligand deficiency,
    - X-linked lymphoproliferative disease

Treatment

Initial

- Patients must be managed by a Clinical Immunology Team including a Consultant Immunologist and Nurse Specialist with appropriate experience in treating primary immune-deficiencies.
- Paediatric patients must be treated in a child-appropriate environment.
- Ideally paediatric patients should be treated by a Paediatric Immunologist but if not available (which is usually the case) treatment should be shared between an adult Consultant Immunologist and a Paediatric Consultant with experience in immune-deficiencies.
- The mainstay of treatment is immunoglobulin replacement therapy (see separate standard of care on administration of IVIG and SCIG).
- Home immunoglobulin therapy must be managed by an accredited Home Therapy centre (See UK-PIN website for further information).

Ongoing management

- Patients must be reviewed in an Immunology Consultant-led clinic at least 12 monthly (6 monthly if on immunoglobulin replacement therapy)
- Many patients may need to be seen more frequently if clinically necessary
- Prophylactic antibiotics should be used if infections continue despite adequate Immunoglobulin replacement therapy
- Patients with bronchiectasis should be managed by or in conjunction with a physician with appropriate respiratory skills
- The treatment plan for patients with bronchiectasis must include assessment of need for (and teaching of) chest physiotherapy.
- Patients with chronic sinus disease should be managed in conjunction with a specialist with appropriate ENT skills.
- Autoimmune manifestations should be looked for and treated by an appropriate specialist with experience in autoimmune conditions
- Enteropathy is a recognised complication and should be investigated by an appropriate specialist
- Live vaccines should be avoided (specifics should be discussed with an Immunologist)
- Annual influenza vaccination is advised
- In the event of pandemic flu, DH guidelines for immunocompromised individuals must be followed.
- Household contacts are recommended to receive the yearly influenza vaccination

Specific acute problems

- Bacterial infections need prompt, full-dose, antibiotics for longer periods than in immunocompetent patients
- Symptomatic granulomatous disease may require treatment. Options include steroids.
- In patients with bronchiectasis, or frequent infections despite adequate replacement immunoglobulin therapy, consideration should be given to patient-held antibiotics for rapid administration at first respiratory symptoms.

Monitoring

Clinical

- Patients must be reviewed regularly to assess infection rate and progression/development of bronchiectasis/sinus disease
- Patients must undergo regular pulmonary function tests depending on baseline results e.g. spirometry, lung volumes and transfer factor usually every year if known lung disease; less often may be adequate if no respiratory disease or symptoms
- Respiratory monitoring must be undertaken in children, but will be limited in young children by their ability to perform standard lung function. Infant lung function tests may be available and conducted in some centres after discussion with the appropriate paediatric team

Laboratory

- Patients on immunoglobulin replacement therapymust have trough IgG levels and liver function tests performed regularly (at least quarterly)
- Patients must have a full blood count regularly (6 monthly or more frequently if autoimmune cytopenias)
- Patients on immunoglobulin therapy must have their hepatitis (B and C) status tested and a serum sample saved annually or at change of product
- Samples should be sent for Microbiology analysis whenever possible

Radiology

- Repeat High Resolution CT scanning of the thorax should be considered every 3-5 years or more frequently if recurrent clinical infections or change in pulmonary tests suggesting deterioration in pulmonary function

Referral and Governance issues

- Paediatric patients may need review at regional Paediatric Centre if the clinical course is complex
- Shared care may be appropriate with adequate input from the regional centre
- For children, transition to adult care must be an active, planned process

Care of the family

- It is important to be aware that the diagnosis of primary immune deficiency and the prospect of life-long therapy can have a profound impact on the patient and their family.
- Psychological support should be an integral part of patient care
- Patients should be offered contact details of patient support groups such as the Primary Immunodeficiency Association (PIA)

Nursing and other health professionals

- Patients with bronchiectasis should receive training from a chest physiotherapist

References

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Common Variable Immune Deficency: clinical and Immunological features of 248 patients. Clin Immunol 92:34-48, 1999

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J Clin Immunol. 2007 May;27(3):308-16.

Glocker E, Ehl S, Grimbacher B.Common variable immunodeficiency in children. Curr Opin Pediatr. 2007 Dec;19(6):685-92.

CVID Key Standards of Care

1. **If CVID is suspected after history and examination a minimum of the following tests must be undertaken**
    a. Immunoglobulins (IgG, IgA, IgM)
    b. Specific antibodies to vaccines
    c. Lymphocyte subsets
    d. Electrophoresis of serum and urine (adults)

2. **Secondary causes of hypogammaglobulinaemia must be considered and excluded, including consideration of:**
    a. Protein loss via gut and kidney
    b. Lymphoproliferative disease
    c. Drugs

3. **If Diagnosis likely the following baseline assessment must be undertaken**
    a. Chest x-ray to look for consolidation/lung disease (and also exclude thymoma)
    b. High Resolution CT thorax performed (all adults, assess need in children on individual basis)
    c. Lung Function (all adults, assess need in children on individual basis)
    d. Urea, electrolytes and liver function tests

4. **Treatment**
    a. Patients must be managed by a Clinical Immunology Team including a trained Consultant Immunologist and Nurse Specialist with appropriate experience in treating Primary Immune deficiencies, including paediatric experience for children
    b. Immunoglobulin therapy must be considered in all patients and, if required, started promptly
    c. During the wait for PCT approval the patients ned to be treated with prophylactic antibiotics
    d. Patients on immunoglobulin must have trough IgG levels and liver function tests performed regularly (at least quarterly)
    e. Regular samples and details of infusions must be stored to ensure a “look-back” programme could be undertaken
    f. Home therapy of Immunoglobulin treatment must be managed by an accredited Home Therapy centre
    g. Patients must be reviewed in an Immunology Consultant-led clinic at least 12 monthly (6 monthly if on Immunoglobulin replacement therapy)
    h. Complications must be managed in conjunction with an appropriate specialist (eg respiratory, gastroenterology)