ARTICLE SUMMARY

Investigation of adult immunodeficiency and indications for immunoglobulin replacement therapy

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Underlying immunodeficiency needs to be excluded in adults presenting with recurrent infections. These patients fall into one of three groups: (*i*) with recurrent localised infections, it is mandatory to exclude an underlying predisposing, anatomical defect, e.g. base of skull fractures presenting with recurrent pneumococcal meningitis, urinary tract obstruction presenting with recurrent urinary infections, and recurrent sinusitis after previous extensive surgery that results in bacterial colonisation on abnormal mucosal surfaces; (*ii*) secondary immune deficiency, which can be due to underlying diseases or a complication of immune suppression, e.g. HIV, diabetes, liver cirrhosis and nephrotic syndrome, haematological diseases, autoimmunity and malignancy; (*iii*) primary immune disorders, which can present for the first time in adulthood, involving defects in antibody production, T-cell function, complement deficiencies, or phagocytic function. Defects in humoral immunity are most commonly encountered in clinical practice, involving the following conditions:

Selective immunoglobulin (Ig) A deficiency. Patients may be asymptomatic or present with recurrent sinopulmonary and gastrointestinal infections, e.g. recurrent giardiasis.

Abnormalities in serum IgM levels. Patients with selective IgM deficiency may present with septicaemia or recurrent respiratory infections. Those with hyper-IgM syndrome usually present in childhood with elevated serum IgM but reduced IgG and IgA levels owing to mutations in the CD40-mediated signalling pathway. Milder mutations may result in a less severe clinical course later in life.

Common variable immunodeficiency (CVID) is the most common primary intrinsic disorder of antibody production in both children and adults.

IgG subclass deficiency and specific antibody deficiency (SAD). Diagnosis of clinically significant IgG subclass deficiency requires a significant reduction in one or more IgG subclass concentrations, together with evidence of antibody dysfunction evidenced by recurrent infections, and an inadequate antibody response to vaccine challenge. SAD can cause recurrent infections despite normal total serum immunoglobulin as well as IgG subclass levels owing to defective specific antibody production against protein or polysaccharide organisms.

Selective IgG deficiency. Patients with borderline serum IgG are commonly referred for immune evaluation. They may have allergic rhinitis and recurrent sinusitis, and are also often asthmatic, with significant steroid use. Chronic infections are usually poorly defined and accompanied by fatigue and a modest reduction in serum IgG of 5 - 7 g/L (normal range 7 - 16 g/L).

Defective cellular immunity often accompanies hypogammaglobulinaemia in CVID, while patients with acquired antibodies to inteferon (IFN)-γ are increasingly being described and can present with disseminated *Mycobacterium avium* or Salmonella infections. Defects in phagocytocis are usually diagnosed in childhood with recurrent pyogenic infections, deep-seated abscesses and sepsis, but these can also present in adults.

Immune investigations

- Quantification of IgA, IgM, IgG and IgE.
- Myeloma often needs exclusion with serum protein electrophoresis and free serum light-chain assay, and urine light chains.
- IgG subclasses and a baseline vaccination status are obtained by requesting serum IgG 'memory'-specific antibody levels against capsular polysaccharide organisms and tetanus toxoid and diphtheria.
- Defective phagocytic function can be diagnosed by flow cytometry to measure phagocytic index and respiratory burst of polymorph neutrophils and monocytes.
- Measurement of peripheral blood subsets provides percentage and absolute numbers of circulating T cell, B cell and natural killer cells. A reduction in 'switched' memory B cells in CVID correlates with recurrent respiratory infections and bronchiectasis more than actual serum immunoglobulin concentration.
- T-cell function can be assessed by measuring proliferative responses to stimulation by mitogens (phytohaemagglutinin/Con-A), antigens (purified protein derivative) and *Candida*.

Patients with recurrent infections despite optimal management of predisposing conditions, such as allergic rhinitis and asthma, and a trial of prophylactic antibiotics, can be considered for immunoglobulin replacement therapy. Documented suboptimal responses to vaccination with polysaccharide and/or protein antigens are generally a prerequisite for funding by medical aids, as treatment is costly, can be associated with side-effects, and is usually lifelong.

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