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Guidance for Investigation of Low Immunoglobulins

The purpose of this protocol is to provide guidance on the further investigation of patients with immunoglobulin results below the relevant reference intervals. It is not meant to be exclusive or fully comprehensive. There will be occasional patients that fall outside the guidance or where clinical opinion/suspicion requires specific actions outside those specified.

Current immunoglobulin reference intervals are age and sex dependent. The relevant reference range is included in all reports.

Differential Diagnosis of Patients with Low Immunoglobulins

Low immunoglobulins may be due to a:

- **Primary cause** may be hereditary or acquired e.g. *de novo* mutation which affects immune system function.

- **Secondary cause** (acquired and much more common) such as:
  - lymphoproliferative disease
  - medication (many immunosuppressive drugs used in oncology and rheumatology including long-term steroids, but also others such as sodium valproate)
  - increased loss, typically through the gut or kidneys
  - increased consumption, including myotonic dystrophy
  - immunological senescence associated with old age

Patients with a primary antibody deficiency commonly suffer from recurrent infections for many years before an immune defect is considered. During this time, patients' typically have recurrent respiratory tract, sinus, ear and gastrointestinal infections. These can cause irreversible end organ damage (e.g. bronchiectasis). Early diagnosis and treatment limits this significantly.

Similarly, patients with a lymphoproliferative disorder may present with secondary antibody deficiency and early diagnosis improves prognosis.

Further Assessment(s) and Investigation(s) to Consider

Assess clinically for indications of lymphoproliferative disease (e.g. lymphadenopathy, hepatosplenomegaly, bone pain).

Request FBC to investigate potential cytopenias

Request LDH if concerned about lymphoproliferative disorders, or serum protein electrophoresis if myeloma is a differential. If you wish to add these tests to a current sample then please see: https://tinyurl.com/labtestadd

Guidance on When to Refer Patients with Low Immunoglobulins to Immunology

Results	When to refer
Isolated IgA deficiency	IgA deficiency is common and generally asymptomatic. Suggest discuss with Immunology only if there are recurrent or unusual infections (via eRS Advice and Guidance).
IgG below reference range, regardless of IgA/M	Low immunoglobulins could be secondary to medications, lymphoproliferative disease or increased loss. Suggest discuss with Immunology if IgG is below 4 g/L **OR** there are recurrent or unusual infections (via eRS Advice and Guidance).
Isolated IgM deficiency	Isolated reduction in IgM level is common but could be secondary to medications, lymphoproliferative disease or old age. Suggest discuss with Immunology only if there are recurrent or unusual infections (via eRS Advice and Guidance).

Further Advice
Immunology clinical advice for York and Scarborough NHS Teaching Hospital NHS Foundation Trust is provided by Hull University Teaching Hospitals. Advice is available via the eRS Immunology Advice and Guidance in Hull or by phone/e-mail:

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