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Short review

How to investigate a suspected immune deficiency in adults

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ABSTRACT

Patients with immune deficiencies can present with variable clinical phenotypes. This often translates into a significant delay in their diagnosis, and resultant patient morbidity. This review summarises the most common types of immunodeficiency disorders, primary and secondary, along with their key features. It provides a structured approach for the clinician on when to suspect an immunodeficiency, the initial investigations pathway and when a specialist referral should be considered.

1. When to suspect an immunodeficiency

1.1. In patients with infections

Infections are the most typical manifestation of immune deficiencies but it is important to exclude other risk factors as they are also common in other conditions and in healthy individuals. For example, an infection recurring at a single site usually suggests an anatomic abnormality or a local predisposing factor like COPD, smoking, asthma, α1 antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia, previous sinus operations, bone prosthesis or ventriculoperitoneal shunts. Upper respiratory infections are also less likely to be due to an immune defect; e.g., recurrent otitis is common in healthy children.

The most common presentation of immunodeficiency is recurrent sinopulmonary infections by encapsulated bacteria (*S. pneumoniae, H. influenza* etc.), which are seen in antibody deficiency (e.g. common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), hyper-IgM syndrome). Unexplained recurrent, severe, unusual, or persistent infections should raise the suspicion of an underlying immunodeficiency [1,2].

Examples of **recurrent** infections include:

- ≥4 confirmed **bacterial** infections per year (with the exception of urine infections).
- ≥2 **pneumonias** per year, or ≥2 radiologically proven pneumonias within 3 years.
- ≥2 serious **sinus** infections within a year (e.g. scoring >6 on the 10 cm Visual Analogue Scale).
- ≥4 new **ear** infections within a year.
- Use of multiple **antibiotic** courses per year is suggestive.

Examples of **severe** infections include:

- Bacterial **meningitis**: ≥2 episodes of *Neisseria* meningitis or any *Neisseria* meningitis by an unusual serotype (A/C/Y/W) should prompt investigations for a terminal complement pathway defect [3]. Other bacterial meningitis can be seen in asplenia, antibody defects, or early complement component defects and should prompt investigations if associated with recurrent infections or a family history of meningitis.
- Unexplained **deep-seated** infections: ≥2 episodes of septicaemia, deep skin or organ abscesses, endocarditis, cellulitis, meningitis or osteomyelitis. E.g. chronic granulomatous disease manifests with deep-seated abscesses, pulmonary aspergillosis and infections by catalase-positive bacteria.

Examples of **unusual** infections include:

- Confirmed infections with environmental (non-tuberculous) **mycobacteria.** E.g. ≥2 episodes of atypical mycobacterial infection with onset under the age of 30 is suggestive of Mendelian susceptibility to Mycobacterial disease.

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- Other **opportunistic** infections, e.g. *Pneumocystis, Coccidia, Cryptosporidia, Toxoplasma, CMV*.
- Infections from **live vaccines** e.g. disseminated infection after MMR, Zoster, Varicella, Yellow fever or BCG vaccination.
- **Vaccine failures**: infections or seronegativity in a previously vaccinated individual can be suggestive of an antibody deficiency.
- Common infections in an **unusual location** (e.g. pneumococcal peritonitis).

Examples of **persistent** infections include:

- Chronic unexplained **diarrhoea** with weight loss.
- Persistent oral thrush or **fungal** skin infection. E.g., persistent candidiasis of the mouth, scalp, skin, and nails are seen in 'chronic mucocutaneous candidiasis'.

Unexplained **poor response** to treatment may also be an indicator of immunodeficiency. Examples include:

- Need for **intravenous antibiotics** to clear infections.
- ≥2 months on **antibiotics** with little effect.
- Requirement for prolonged antibiotic therapy
- Multiple hospital **admissions** for infection is suggestive.
- Surgical intervention for chronic infection, such as lobectomy for bronchiectasis, recurrent insertion of grommets or recurrent incision of boils.

Complications associated with infections can also be suggestive, e.g. bronchiectasis, follicular bronchiolitis, and ruptured tympanic membranes. The British Thoracic Society advises that all patients with bronchiectasis should have serum IgG, IgA, and IgM (immunoglobulins) tested [4].

1.2. In patients with a history of taking certain drugs

Look for any drugs predisposing to secondary immunodeficiency: e.g. prednisolone at a dose >20 mg for periods for >1 month (or frequent short courses), immunosuppressive drugs (cyclosporine, methotrexate etc.), biologic drugs (infliximab, rituximab, ustekinumab etc.), antiepileptic drugs (carbamazepine, phenytoin etc.) and others (antimalarials, sulfasalazine, mesalazine, captopril, penicillamine etc.).

1.3. In patients with specific features indicative of primary immunodeficiency

Specific clues for primary immunodeficiency disorders include:

- A **family history** of immunodeficiency or recurrent infections. Depending on the inheritance pattern consanguinity (in autosomal recessive disorders), infections in maternal uncles (in X-linked disorders) and unexplained childhood deaths may be present.
- **Autoimmune disorders**: these are common e.g. connective tissue disorders, autoimmune cytopenias, thyroiditis, Addison's, autoimmune enteritis [5].
- **Lymphadenopathy** and **splenomegaly**: these are not uncommon in primary immunodeficiency and should raise the suspicion of immunodeficiency if unexplained [6].
- **Granulomatous** lesions: primary immunodeficiency may be misdiagnosed as **sarcoidosis** as they can both present with granulomatous lesions. Serum immunoglobulins should be tested in all patients suspected of having sarcoidosis.

2. Types of immunodeficiency

An immunodeficiency occurs when components of the immune system become defective, rendering the patient susceptible to infections and other issues relating to a disordered immune system (e.g. autoimmunity, cancer). Immune deficiencies can be primary (not caused by another disease or environmental trigger) or secondary.

2.1. Secondary immune deficiencies

Secondary immune deficiencies are the result of another disease process or an environmental factor that affects the immune system. The signs and symptoms are the same as for primary but secondary immunodeficiency is far more common, particularly in adults [7,8]. Causes include:

2.1.1. Iatrogenic

- **Corticosteroids**, e.g. prednisolone >20 mg for >1 month or frequent use of short courses.
- Other **immunosuppressive** drugs: e.g. cyclosporine, methotrexate. These can cause bone marrow suppression with significant lymphocytopenia, neutropenia etc.
- **Biologic** drugs (monoclonal antibodies), e.g. infliximab, rituximab, ustekinumab. These have a more targeted immunosuppressive effect compared to traditional immunosuppressive drugs, but may still cause significant immunodeficiency (e.g. rituximab).
- **Antiepileptic** drugs (carbamazepine, phenytoin etc.) can result in low antibody levels.
- **Other drugs**: e.g. antimalarials, sulfasalazine, mesalazine, captopril, penicillamine.
- **Splenectomy**, asplenia or functional hyposplenism: predispose to infections by encapsulated bacteria and sepsis.
- **Others**: plasmapheresis, thymectomy (e.g. in cardiac surgery), radiation, or dialysis etc.

2.1.2. Malignancy

- **Haematological** malignancies, e.g. multiple myeloma, lymphoma, leukaemia, can predispose to various types of immune defects [9].
- **Thymoma**: this can result in **Good's** syndrome (i.e. thymoma with hypogammaglobulinemia).

2.1.3. Infections

- **HIV** is associated with lymphocytopenia, low CD4+ T cells and opportunistic infections when advanced.
- Other **viral** infections e.g. CMV, EBV, measles, and varicella-zoster can cause lymphocytopenia and decreased antibody responses.
- Any **severe** infection can cause transient hypercatabolism, resulting in hypogammaglobulinemia.

2.1.4. ***Protein loss*** *or* ***malnutrition***

- Nephrotic syndrome, severe burns, lymphangiectasia, and severe diarrhoea can lead to antibody **loss** through the involved organ.
- Protein **malnutrition** or vitamin defects, e.g. in anorexia nervosa or chronic infection, can result in low immunoglobulins, lymphocytes and complement levels.

2.1.5. ***Other*** *causes*

- Chronic **liver** disease (cirrhosis) can affect antibody and complement production.
- Poorly controlled **diabetes mellitus** can result in phagocytic cell dysfunction and weakened skin barrier function. Skin abscesses, candidiasis, mucormycosis and malignant otitis can be seen.
- Chronic **uraemia** affects lymphocyte proliferation, phagocytosis and chemotaxis.

- Certain **chromosomal** anomalies (chromosome 18q syndrome, monosomy 22, trisomy 8, trisomy 21) can be associated with immune defects.
- Extremes of **age** can be associated with immune defects, e.g. hypogammaglobulinemia in premature infants or weakening of the immune system in the elderly.

2.2. Primary immune deficiencies

There are >300 types of primary immunodeficiency, affecting around 1 in 500 individuals [10]. These can be classified into antibody defects, combined T and B cell defects, disorders of immune regulation, phagocytic cell defects and complement disorders - some examples of which are presented in Table 1 [11]. The most severe genetic forms are generally diagnosed in childhood but others are diagnosed in adults, either because of late onset or late diagnosis. Due to their rarity and varying clinical presentation it is estimated that the vast majority of patients with primary immunodeficiency are currently undiagnosed [12].

Commoner primary immune deficiencies include:

- **IgA deficiency**: The most common antibody deficiency but in most patients it is very mild and not associated to an increased frequency of infections.
- **Common variable immunodeficiency** (CVID): One of the most common antibody defects in adults, characterised by low IgG, IgA and sometimes IgM, with poor antibody responses to vaccines. Manifests with recurrent sinopulmonary infections by encapsulated bacteria, bronchiectasis, splenomegaly and autoimmune cytopenias.
- **X-linked agammaglobulinemia** (XLA): Characterised by very low IgG, IgA, IgM and B cells. Manifests with recurrent sinopulmonary infections, bronchiectasis, splenomegaly and autoimmune cytopenias in males.
- **Hyper IgM syndrome:** Characterised by low IgG and IgA but normal or elevated IgM. Manifests with recurrent sinopulmonary infections by encapsulated bacteria, bronchiectasis, autoimmune cytopenias and opportunistic infections (e.g. pneumocystis).
- **Chronic granulomatous disease** (CGD): Manifests in early childhood with failure to thrive, diarrhoea, granulomas, deep seated abscesses and pneumonias by catalase-positive bacteria (e.g. Staphylococci, *E. coli*, Klebsiella, Serratia, Pseudomonas).
- **Chronic mucocutaneous candidiasis** (CMC): Characterised by recurrent or persistent mucocutaneous candidiasis.
- **Mendelian susceptibility to Mycobacterial disease** (MSMD): Characterised by recurrent atypical (non-tuberculous) mycobacterial infections, e.g. *Mycobacterium avium* complex.

Table 1
Common primary immunodeficiencies grouped by the underlying immune defect. Common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), Severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome (WAS), autoimmune lymphoproliferative syndrome (ALPS), IPEX (immune deficiency polyendocrinopathy X-linked, X-linked lymphoproliferative syndrome (XLP), chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), chronic mucocutaneous candidiasis (CMC), Mendelian susceptibility to Mycobacterial disease (MSMD).

Antibody defects	T cell defects	Disorders of immune regulation	Phagocytic cell defects	Complement defects
CVID	SCID	ALPS	CGD	Classical/ alternative pathway
XLA	complete DiGeorge	IPEX	LAD	Lectin pathway
Selective IgA deficiency	WAS	CTLA4	CMC	Terminal pathway
Hyper IgM syndrome		XLP	MSMD	

3. Investigations

If an immunodeficiency is suspected some basic tests are initially required (e.g. full blood count, microbiology or radiology studies). If infections are confirmed, then Immunological investigations may be required, the type of which will depend on the clinical presentation [13–15]. With the exception of serum immunoglobulins, these are usually reserved for the specialist setting. Recurrent infections by encapsulated bacteria is the most common clinical presentation seen and a recommended investigations pathway for this scenario is given in Fig. 1.

3.1. General tests

- **Microbiology** testing is very important to confirm the nature of infections, e.g. sputum/urine/stool culture, skin/throat swabs, and/or serum PCR-based assays.
- If a haematological **malignancy** is suspected, then this should be ruled out by relevant investigations (blood film, myeloma screen, imaging studies, bone marrow/lymph node biopsy etc.)**.**
- **Diabetes** (HbA1c/glucose) and **HIV** testing in the context of a relevant clinical history.
- **Full blood count** to look for neutropenia or lymphopenia. These can be transient so abnormalities should be confirmed on repeat. Autoimmune anaemia/thrombocytopenia can be seen in primary immunodeficiency.
- **Urine ACR** (albumin creatinine ratio) to check for renal protein loss if serum albumin is low.
- **CT chest** in recurrent pulmonary infections to assess for lung damage (e.g. COPD, bronchiectasis), and also lymphadenopathy or thymoma.
- **Other imaging** studies to exclude anatomical defects, e.g. ultrasound kidneys or CT sinuses if relevant infections.
- Peripheral **blood smear** to look for Howell-Jolly bodies if asplenia or hyposplenism are suspected.

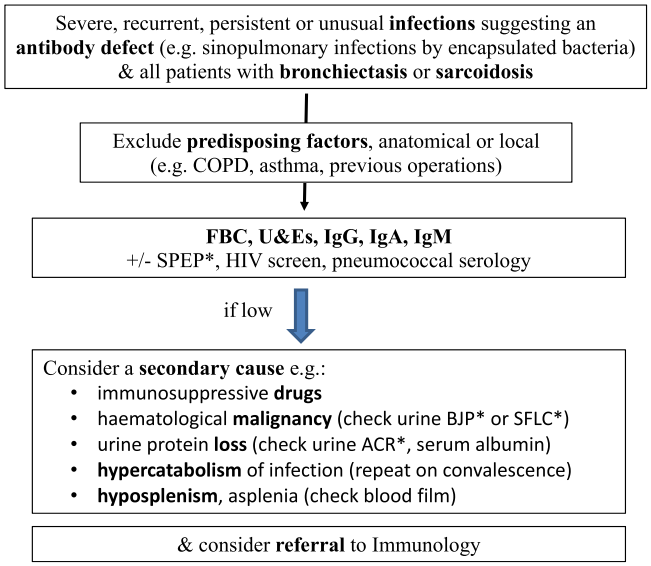

Fig. 1. Investigations pathway in patients with suspected antibody defects. * SPEP: serum protein electrophoresis, ACR: albumin creatinine ratio, BJP: Bence Jones protein, SFLC: serum free light chains.

- Investigations for **cystic fibrosis, alpha-1 antitrypsin deficiency** or **primary ciliary dyskinesia** in the context of lower respiratory infections.

3.2. Immunology tests

- Serum **immunoglobulins** (IgG, IgA, IgM). If more than one of these is low or if IgG <3 g/L then this is suggestive of immunodeficiency. Isolated low IgA is not uncommon and is not usually associated to an increased frequency of infections. Isolated low IgM can sometimes be seen in the elderly, and has also been associated (rarely) with lymphoproliferative diseases. IgG subclass measurements are usually reserved for the specialist setting.
- **Vaccine responses** (functional antibody responses) will usually be assessed by Clinical Immunology but if a referral is contemplated then baseline pneumococcal serology is helpful.
- In patients with lymphopenia, **lymphocyte subsets** can be checked to look for low T, B, or natural killer (NK) cells. This is best performed when patients are well as concurrent infections and other significant medical events can significantly affect lymphocyte subsets.
- **Complement levels and function: C3, C4** levels, **CH50** (classical pathway function) and **AH50** (alternative pathway function) activity are sometimes used, e.g. if in a history of ≥2 episodes of *Neisseria* meningitis or *Neisseria* meningitis by an unusual serotype (A/C/Y/W) [16].

Mannose-binding lectin (MBL) measurement is rarely helpful. MBL deficiency is extremely common (in up to 5% of the general population) but insufficient to cause disease on its own.

4. Referral to Clinical Immunology

4.1. When to refer

A referral to Clinical Immunology should be considered in the following cases:

- Documented evidence of severe/persistent/unusual/recurrent **infections.**
- Laboratory investigations suggestive of immunodeficiency.
- A **primary immunodeficiency** is suspected.
- A **secondary immunodeficiency** is suspected, and this is associated with significant problems with infections while the primary cause cannot be reversed.

4.2. What information to include

- **Clinical history** focusing on infections: types, dates, hospital admissions, antibiotic use, response to treatment, complications (e.g. bronchiectasis), problems in childhood etc.
- Dates of previous **vaccinations**: pneumococcal (e.g. Pneumovax), tetanus (e.g. Revaxis), haemophilus (e.g. Menitorix) etc.
- **Drug history**, focusing on potentially immunosuppressive drugs as discussed above.
- Confirmatory evidence of **infections** (microbiological, serological, PCR based or radiological data).
- Results of **immune investigations**, if performed, IgG, IgA, IgM, HIV testing, baseline pneumococcal serology etc.

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Declaration of competing interest

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References

[1] P.D. Bright, N. Rooney, P.F. Virgo, R.J. Lock, S.L. Johnston, D.J. Unsworth, Laboratory clues to immunodeficiency; missed chances for early diagnosis? J. Clin. Pathol. 68 (2015) 1–5, https://doi.org/10.1136/jclinpath-2014-202618.
[2] P.D. Arkwright, A.R. Gennery, Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century, Ann. N. Y. Acad. Sci. 1238 (2011) 7–14, https://doi.org/10.1111/j.1749-6632.2011.06206.x.
[3] National Institute for Health and Care Excellence, Meningitis (Bacterial) and Meningococcal Septicaemia in under 16s: Recognition, Diagnosis and Management, 2015.
[4] A. T Hill, A. L Sullivan, J. D Chalmers, A. De Soyza, J. Stuart Elborn, R. Andres Floto, L. Grillo, K. Gruffydd-Jones, A. Harvey, C. S Haworth, E. Hiscocks, J. R. Hurst, C. Johnson, W. Peter Kelleher, P. Bedi, K. Payne, H. Saleh, N. J Screaton, M. Smith, M. Tunney, D. Whitters, R. Wilson, M. R Loebinger, British thoracic society guideline for bronchiectasis in adults, Thorax 74 (2019), https://doi.org/10.1136/thoraxjnl-2018-212463, 1 LP – 69.
[5] A.P. Grammatikos, G.C. Tsokos, Immunodeficiency and autoimmunity: lessons from systemic lupus erythematosus, Trends Mol. Med. 18 (2012) 101–108, https://doi.org/10.1016/j.molmed.2011.10.005.
[6] F.A. Bonilla, D.A. Khan, Z.K. Ballas, J. Chinen, M.M. Frank, J.T. Hsu, M. Keller, L. J. Kobrynski, H.D. Komarow, B. Mazer, R.P.J. Nelson, J.S. Orange, J.M. Routes, W. T. Shearer, R.U. Sorensen, J.W. Verbsky, D.I. Bernstein, J. Blessing-Moore, D. Lang, R.A. Nicklas, J. Oppenheimer, J.M. Portnoy, C.R. Randolph, D. Schuller, S. L. Spector, S. Tilles, D. Wallace, Practice parameter for the diagnosis and management of primary immunodeficiency, J. Allergy Clin. Immunol. 136 (2015) 1178–1186, https://doi.org/10.1016/j.jaci.2015.04.049.
[7] S.Y. Patel, J. Carbone, S. Jolles, The expanding field of secondary antibody deficiency: causes, diagnosis, and management, Front. Immunol. 10 (2019) 33. https://www.frontiersin.org/article/10.3389/fimmu.2019.00033.
[8] S. Ress, Immunodeficiency diseases presenting in adults - diagnosis and management, Curr. Allergy Clin. Immunol. 21 (2008).
[9] S. Sánchez-Ramón, A. Bermúdez, L.I. González-Granado, C. Rodríguez-Gallego, A. Sastre, P. Soler-Palacín, L. Allende, L. Alsina, A.M. Bielsa, S. Calleja-Antolín, C. Cámara, J. Carbone, C. Carreras, A.D.A. Martín, A. Deyá, C. Díaz de Heredia, R. Dieli-Crimi, J. Luis Díez, N. Domínguez-Pinilla, L. Fernández-Pereira, J. M. García, J. Gil-Herrera, A. Gutiérrez, I. Jarque, M. Juan, F. Lendínez, P. Llobet, M. López, A.L. de la Guía, M. López-Hoyos, A. Martín-Nalda, M. Martínez, J. Melero, A. Méndez-Echevarría, P. Moral, O. Neth, M. Núñez, G. Ocejo-Vinyals, J. Ochoa-Grullón, P. Olbrich, R. Oña, M. Pérez-Encinas, J. Pons, C. Rodríguez, B. Sánchez, J.L. Santos-Pérez, M. Elena Seoane, A. Vlagea, Primary and secondary immunodeficiency diseases in oncohaematology: warning signs, diagnosis, and management, Front. Immunol. 10 (2019) 586. https://www.frontiersin.org/article/10.3389/fimmu.2019.00586.
[10] A.A. Bousfiha, L. Jeddane, F. Ailal, W. Al Herz, M.E. Conley, C. Cunningham-Rundles, A. Etzioni, A. Fischer, J.L. Franco, R.S. Geha, L. Hammarström, S. Nonoyama, H.D. Ochs, C.M. Roifman, R. Seger, M.L.K. Tang, J.M. Puck, H. Chapel, L.D. Notarangelo, J.-L. Casanova, A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside, J. Clin. Immunol. 33 (2013) 1078–1087, https://doi.org/10.1007/s10875-013-9901-6.
[11] C. McCusker, R. Warrington, Primary immunodeficiency., allergy asthma, Clin. Immunol. 7 (Suppl 1) (2011), https://doi.org/10.1186/1710-1492-7-S1-S11.
[12] C. Picard, H. Bobby Gaspar, W. Al-Herz, A. Bousfiha, J.-L. Casanova, T. Chatila, Y. J. Crow, C. Cunningham-Rundles, A. Etzioni, J.L. Franco, S.M. Holland, C. Klein, T. Morio, H.D. Ochs, E. Oksenhendler, J. Puck, M.L.K. Tang, S.G. Tangye, T. R. Torgerson, K.E. Sullivan, International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity, J. Clin. Immunol. 38 (2018) 96–128, https://doi.org/10.1007/s10875-017-0464-9.
[13] E. de Vries, Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update, Clin. Exp. Immunol. 167 (2012) 108–119, https://doi.org/10.1111/j.1365-2249.2011.04461.x.
[14] J.D. Folds, J.L. Schmitz, 24. Clinical and laboratory assessment of immunity, J. Allergy Clin. Immunol. 111 (2003) S702–S711, https://doi.org/10.1067/mai.2003.122.
[15] J.B. Oliveira, T.A. Fleisher, Laboratory evaluation of primary immunodeficiencies, J. Allergy Clin. Immunol. 125 (2010) S297–S305, https://doi.org/10.1016/j.jaci.2009.08.043.
[16] National Institute for Health and Care Excellence, Meningitis (Bacterial) and Meningococcal Septicaemia in under 16s: Recognition, Diagnosis and Management, 2015. https://www.nice.org.uk/guidance/CG102.