This document is intended as a concise guide to aid the appropriate investigation and diagnosis of suspected paediatric primary immune deficiency (PID) by general paediatricians within the SPAIIN network.

Please note that there are now over 100 separate PIDs recognised and that this document is only intended to help in the commoner diagnoses. The timely identification of a PID relies on a high index of suspicion amongst clinicians and families combined with prompt investigation and referral where necessary. A PID should be considered in a child with a severe, unusual, recurrent or recalcitrant infection requiring iv antibiotics to clear (not urinary tract infections). Unfortunately children with PID still experience long diagnostic delays, multiple reviews and referrals and are being diagnosed with established end organ damage. Earlier diagnosis offers better prognosis. Recognising when a child’s experience of infection is abnormal is the first step in diagnosing PID and thereafter prompt investigation with an initial limited set of investigations aimed at excluding a PID with rapidly fatal complications. Early liaison with a paediatric immunologist (or regional immunology laboratory) is advised in those children with a suggestive history, abnormal results or those in whom clinical problems persist.

Primary antibody deficiency makes up more than 50% of reports to the ESID (European Society of Immunedeficiency) database and the measurement of immunoglobulins (IgG, IgA and IgM) should be carried out in any child suspected of having a PID. An abnormal measurement of any of these in the context of a child with severe, unusual, recurrent or recalcitrant infection should be discussed with an immunologist. Unfortunately normal immunoglobulin levels do not exclude a diagnosis of primary antibody deficiency and may need to be discussed with an immunologist in the context of the clinical presentation.

This guidance is laid out according to the 4 types of infectious presentations covering the majority of PIDs. It is not comprehensive however and with some patients it may be unclear which presentation type they fall into. The more complex immunological investigations should be discussed with a paediatric immunologist (or regional immunology laboratory) prior to ordering.

When to discuss with/refer to an immunologist

- A convincing history of severe, unusual, recurrent or recalcitrant infections
- Abnormal investigation results in the context of severe, unusual, recurrent or recalcitrant infections
- Persistent clinical concerns despite normal investigations

Further information and advice is available on the UKPIN website (www.ukpin.org.uk)
History of recurrent/chronic/opportunistic infections

Take history of – numbers of infections, confirmed pathogens, numbers of invasive infections e.g. pneumonias, bacteraemias, and abscesses needing drainage, chronic candidiasis, chronic diarrhoea, number of courses of oral and use of iv antibiotics for sepsis, hospitalisations, immunisation history, growth and family history of immune deficiency* or unexplained infant deaths

Types of infection

Sinopulmonary
- pyogenic bact
Enteric
- enteroviruses
- giardia

Pneumonias
- pyogenic
Severe viral inf
Fungal infections
Pneumocystis
Chronic diarrhoea
Failure to thrive

Skin
Reticuloendothelial
Bone, liver
Abscesses
- pyogenic, fungal
or enteric bact

Sepsis - recurrent or severe
- pyogenic bact
- Neisseria spec

? B cell disorder

? T cell or combined T & B cell

? Phagocytic

? complement

FBC/diff
Alb
Igs
LSS
Func.abs
HIV

FBC/diff
Alb
Igs
LSS
Func.abs
HIV

FBC/diff
Igs
CD18
NBT/DHR
IgE
HIV

FBC/diff
Igs
CH/APCH50
Spenic US
HIV

Discuss abnormal results with immunologist

* In a cohort of children in the north of England the combination of failure to thrive, iv antibiotics for sepsis and family history predicted 89% of children with either a T lymphocyte, neutrophil or complement disorder (Pediatrics 2011;127;810)
? B cell disorder

Low Igs / poor ab response

? Brutons / ARA (no B cells)

? CVID (+ B cells)

? T cell or combined T & B cell disorder

-↑IgM, ↓IgG/A


Low Ca, abnormal facies, heart defect – consider genetic test for DiGeorge syndrome. Other less common variants of CID e.g. HIGM, WAS, CMC, AT diagnosed by combination of clinical features, genetic testing and specific immune tests.

? Phagocytic disorder

↓neutrophils - neutropenia
↓CD18 – LAD type I
↓NBT/DHR – CGD
↑IgE - ?HIES

? complement deficiency

- if low functional assay of either classical or alternative complement activation pathway consider individual factor assay

LSS – lymphocyte subsets, NBT – nitrobluetetrazolium, DHR – dihydrorhodamine, Igs - immunoglobulins, Func abs – functional antibody responses to tetanus, haemophilus influenza type B and pneumococcus, CD18 – expression measured by flow cytometry, CH50 or APCH50 are functional assays of classical and alternative complement pathways. ↑↓normal, high or low.

Children and adolescents with a primary immune deficiency diseases can also present with non-infectious complications e.g.

- angioedema (without features of increased susceptibility to infection)
- autoimmunity and/or lymphoproliferation (with or without features of increased susceptibility to infection)
- chronic or recurrent inflammation (with or without features of increased susceptibility to infection)
- specific syndromal phenotypes

1. Angioedema without urticaria
   Consider hereditary angioedema which is an autosomal dominant trait (only 20% of presentations are new mutations). Check C4 level - if deceased then discuss with immunologist

2. Autoimmunity and/or lymphoproliferation
   Autoimmunity can occur in antibody deficiency (IgA defn, CVID), complement deficiency, WAS and Di George syndrome. Autoimmunity and lymphoproliferation can occur together in autoimmune lymphoproliferative disorder. Autoimmune polyendocrinopathy can occur with chronic candidiasis (APECED syndrome) or with enteropathy (IPEX syndrome)

3. Chronic inflammation can be a manifestation of immunodysregulation and can occur in CGD, as a result of autoimmunity (see above) or manifest as haemophagocytosis (haemophagocytic lymphohistiocytosis syndromes). Recurrent inflammation (usually without increased susceptibility to infection) is a feature of the autoinflammatory disorders (e.g. Familial Mediterranean Fever).

4. Specific syndromal phenotypes. There are numerous syndromes where recognition of a specific phenotype leads to a recognition of associated immunodeficiency e.g. DNA repair defects, Di George syndrome, Hyer IgE syndrome etc.