LRI Children's Hospital

Investigating Suspected Primary Immunodeficiency prior to Immunology Referral

Staff relevant to:	Health Professionals managing children and young people with suspected Immunodeficiency in the Children's Hospital
Team approval date:	November 2022
Version:	2
Revision due:	November 2025
Written by: Reviewed by:	R Radcliffe, M Browning & A Price A Price, R Radcliffe
Trust Ref:	C4/2015

Contents

1. Introduction and Who Guideline applies to

Children with Primary Immunodeficiency (PID) may present in many different ways, to different specialities usually with infections, but there may be autoimmune features. This guideline outlines circumstances in which PID may present, how to investigate and referral information.

Contact information

For urgent advice for suspected severe PID;
Immunology Department X16702 - within working hours

For routine queries and advice and guidance, aim to answer within 3 working days;
Immunology Advice email: **PaedsImmunology@uhl-tr.nhs.uk**

For urgent queries when UHL staff unavailable;
Great Ormond Street Tel: 020 7405 9200, ask for immunology registrar

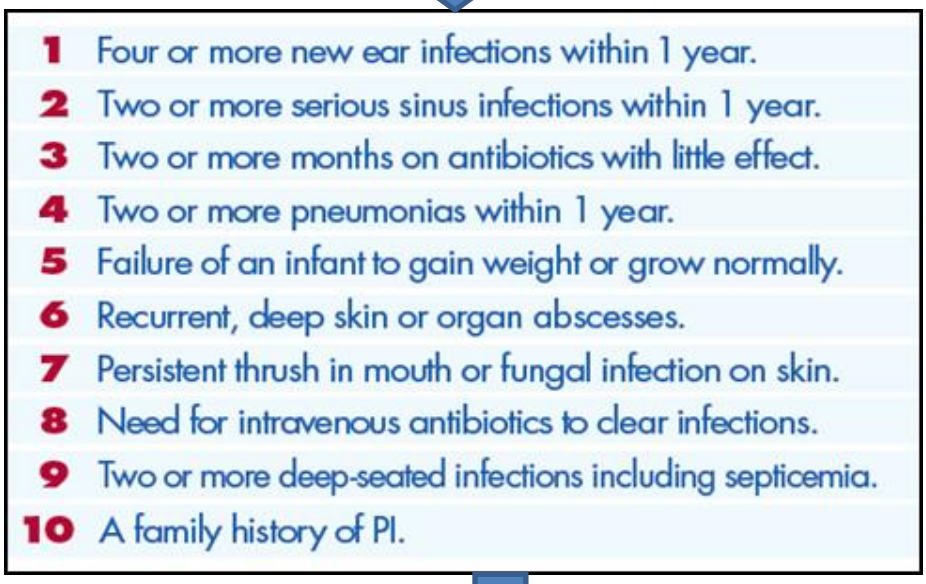
Patients with primary immunodeficiency primarily present with recurrent bacterial infection or opportunistic/atypical infection. Immunology testing is rarely indicated in children with recurrent viral URTIs, non-purulent rhinitis or recurrent dry cough. Recurrent wet cough non responsive to usual treatment or rapidly recurring after treatment may be an indication. Patients with particularly unusual organisms causing infection may be best discussed with immunology via the paeds immunology mailbox to target investigations.

Abbreviations:

CGD	Chronic Granulomatous Disease
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
PID	Primary Immunodeficiency
SCID	Severe combined immunodeficiency
URTI	Upper respiratory tract infection

2. Indications & Investigations

10 warning signs of primary immunodeficiency
Consider if Immune Deficiency screening is appropriate if 2 or more of the below
(Jeffrey Modell Foundation; https://www.info4pi.org/library/educational-materials/10-warning-signs)



Baseline immunological investigations:

- FBC
- Immunoglobulins
- Lymphocyte markers

If history suggestive, consider:

- Specific antibodies (tetanus, Hib, pneumococcus) – if strong clinical suspicion of recurrent bacterial infections and no other explanation - vaccination history necessary for interpretation of result
- Complement function (C3, C4, CH50, AP50) – e.g. recurrent invasive bacterial infections, recurrent bacterial meningitis.
- Neutrophil oxidative burst – e.g. recurrent skin & soft tissue infections/abscesses, fungal infections.
- HIV test – See Appendix 3 for associated conditions.

If concerned about severe PI, e.g. SCID, CGD please ring for immunology advice: X16702. Or contact Great Ormond Street if unavailable.
See Appendix 1 & 2 for immediate management.

- Please read and consider any comments given with results – they are there to help with interpretation.
- Seeking advice on investigation or management (email or telephone), or referral for an outpatient appointment should be a Consultant decision, after consideration of the guideline above.
- Please see Appendix 4 for patterns of infection in different types of immunodeficiency

Interpreting Antibody results

Result	Interpretation	Action
Normal immunoglobulins; with protective specific antibodies (if tested)	Antibody deficiency unlikely (consider if other PIDs likely)	No referral, unless strong suspicion of PID
Low IgG, with normal or low IgA and/or IgM (regardless of specific antibodies)	Consider antibody deficiency, if no obvious cause (e.g. protein loss / drugs)	Refer Immunology if history of infections. Email for advice if uncertain.
Low IgA with normal IgG and IgM; and protective specific antibodies	Significant immunodeficiency unlikely (partial IgAD, or maturational delay)	No referral, unless significant history of infections. Email for advice if uncertain
Low IgM, with normal IgG and IgA; protective specific antibodies (if tested)	May be viral infection (especially in young), rarely clinically significant	Monitor Igs in 3 months take advice if strong clinical suspicion of immunodeficiency
Normal immunoglobulins (or isolated low IgA or IgM), with non-protective specific antibodies	Have they had the relevant vaccines (and how long ago)? Consider specific antibody deficiency	Email for advice if uncertain (include patient's vaccination history)
Unsure of interpretation of antibody results		Email for advice (include patient's vaccination history)

Protective levels of specific antibodies:

- Tetanus 0.15 IU/ml
- Hib 1.0 mg/L
- Pneumococcus (serotype specific) 0.35 mg/L (for invasive infection)

Serotypes 1, 3, 4, 6B, 9V, 14, 18C, 19A, 23F are in Prevenar 13;
Serotypes 8,9N,12F and 15B (measured) are not in Prevenar 13 (but are in Pneumovax II)
Serotypes 6A, 7F, 19F are in Prevenar 13, but are not measured
For pneumococcus: Children should have a dynamic response (doubling from baseline and >0.35mg/L) to 50% of the tested serotypes contained in the given vaccine.
Please note that in the years following vaccination a drop in antibody levels is expected in the normal population.
If unsure whether reimmunization is appropriate, after reviewing the comment supplied with the results, please email PaedsImmunology@uhl-tr.nhs.uk for advice.
Please include a full immunisation and infection history.

If advised to re-immunise and check response:

Vaccines:

Pneumococcal -Prevenar 13
Hib and/or tetanus -Menitorix

Other branded products have less well detailed sero-activity so are not recommended.
Pneumovax II may rarely be suggested by immunology in preference to Prevenar in selected older patients, it is not recommended routinely in paediatrics.

Post-immunization blood tests:

- 4 – 6 weeks; state vaccines given and date of vaccination
- Request relevant specific antibodies (for vaccine given)
- If poor response or uncertain interpretation, email for advice.

Interpretation of other results

Result	Interpretation	Action
Persistent FBC lymphopenia (esp <2.8x10^9/L age <1yr)	Consider SCID	If severely unwell check immunoglobulins and lymphocyte subsets, otherwise repeat FBC 2-4 weeks after recovery to ensure resolution
Abnormal oxidative burst (DHR test may be low in sepsis – repeat in convalescence)	Report will say if consistent with Chronic Granulomatous Disease or repeat required	Urgent referral to Immunology if CGD is suspected
Abnormal lymphocyte markers	Various; Interpretative comment will usually be given	Refer to Immunology **if comment suggests referral, if still unsure email for advice**
Absence of T cells (with variable NK and B cells)	Consider SCID	Urgent referral to Immunology; (Lab will (try to) contact you if suggestive of SCID)
Low complement levels (C3 / C4)	Multiple possible causes. If concern about complement deficiency, do functional assay (CH50 / AP50). Mild reductions usually not indicative of complement deficiency (e.g. infections / inflammatory process; or delay in sample being received by lab).	Results suggestive of a complement deficiency will (normally) carry a comment.
Low CH50 or AP50	Complement proteins are rapidly consumed ex vivo, mild reductions in CH50/AP50 are common, delay in sample receipt may invalidate the result.	Results will usually have a comment to advise if repeat testing is needed or referral. If unsure email for advice

Strong suspicion of immunodeficiency - regardless of results	(e.g. Repeated serious infections, or infections with unusual organisms infections or associated clinical features)	Email for advice

3. Education and Training

None required

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Compliance with completing investigations prior to referral	Referrals will only be accepted in line with the guidelines	R. Radcliffe	3 yearly	Departmental audit meeting

5. Supporting References

None

6. Key Words

Immunoglobulin, Primary Immunodeficiency, SCID, CGD

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) A Price - Consultant	**Executive Lead** Chief medical officer
Details of Changes made during review: **August 2022** Updated intro to include presentations Removed specific antibodies from baseline investigations and moved to considerations Update to advice in cases of low IgM with normal IgG & IgA Interpretation of other results table updated Re-formatted AWP approved	

Appendix 1 – SCID

SEVERE COMBINED IMMUNODEFICIENCY (SCID) PROTOC OL

Severe combined immunodeficiency is mostly identified in young children who can present very unwell to inpatient paediatric services. SCID screening is being piloted in the Midlands region at the time of writing, this should pick up the majority of new babies born with SCID however children with hypomorphic variants and from non-screening regions could still present later. Normal SCID screening should not be considered to absolutely exclude SCID. Children with SCID lack a functional adaptive immune system and are at risk of life threatening infection including opportunistic infection. Early identification and treatment is key to improving outcomes. Where possible immunology advice should be available however there may be occasions such as out of hours where advice cannot immediately be accessed. The below advice is aimed to help paediatricians know when to suspect SCID and the actions needed including when to see immunology advice.

SUSPECTED SCID

When to suspect

Low lymphocyte count on FBC <2.8x10*9/L in child age under 1 years (This should never be ignored and if thought to be reactive ensure follow up repeat is arrange to confirm it normalises)

Recurrent bacterial infections

Unusual infections such as opportunistic infection or unusually severe viral infections

Persistent candidiasis

Failure to thrive

Failure to clear live vaccinations or usual childhood viruses

Actions

Arrange checking lymphocyte subsets (X1 EDTA tubes to immunology lab open Mon-Fri 0830-1800, please alert the lab before sending)

Arrange checking of total Immunoglobulins (X1 serum gel to immunology lab)

Consider other causes of immune deficiency e.g. neutropenia

Ensure consultant/registrar overseeing patient care is aware of concerns

Discuss with immunology if high clinical suspicion of immunodeficiency

CONFIRMED SCID

SCID will be confirmed initially based on the immunology results showing absence of one or many lymphocyte subsets, unusual subset patterns and low/absent immunoglobulins

In general results highly suspicious for SCID will be telephoned to the ward by immunology/lab staff

Where laboratory results indicate SCID discuss with immunology medical staff immediately

They will advise on the need to activate the “SCID management protocol”

If immunology are not available then the “SCID management protocol” can be stated in the interim until immunology staff are available and if required discuss with on call StR in Immunology at Great Ormond Street

It is vital that immunology is aware of SCID patient as soon as possible

SCID MANAGEMENT PROTOCOL

- Ensure patient is in a positive pressure isolation room discuss with ward 27
- Reverse barrier nursing
- Treat infections aggressively with high dose broad spectrum antibiotics/anti-virals/anti-fungals – discuss with microbiology/immunology
- Ensure thorough investigation of possible infection considering atypical, opportunistic and rare organisms
- Commence antibiotics, antifungal and antiviral cover as below unless contraindicated or alternatively advised by Immunology
- **Co-trimoxazole**
    - 6 weeks-6 months 120mg OD

      (if <6 weeks only start after discussion with immunology/GOSH)
    - 6 months – 5 years 240mg OD
    - 6-12 years 480mg OD
    - Over 12 years 960mg OD
- **Fluconazole**
    - <44 week gestational age 6mg/kg OD twice weekly
    - from 45 weeks gestational age 6mg/kg OD
- **Aciclovir**
    - 1-23 months 200mg 4 times daily
    - 2-17 years 400mg four times daily

- Commence intravenous immunoglobulin replacement at an initial dose of 0.4g/kg and ensure formal consent is taken and consent form completed. IVIG form (available on INSITE) must be completed and emailed to immunoglobulins.mailbox@uhl-tr.nhs.uk
- Ensure only CMV negative, irradiated blood products are used
- No live vaccinations (e.g. rotavirus, MMR, varicella, BCG)

This protocol should keep patients safe until immunology can discuss the patient and if needed attend to review them on the ward, further management can be enacted from there.

Appendix 2 – CGD

CHRONIC GRANULOMATOUS DISEASE (CGD)

CGD is an inherited defect of the neutrophil respiratory burst mechanism leading to an inability of neutrophils and macrophages to lyse the phagocytosed bacterial/fungi. It classically presents in early childhood and early treatment can significantly improve morbidity and mortality. Approximately 2/3 of cases are X linked, the remainder are autosomal recessive. Where possible immunology advice should be available however there may be occasions such as out of hours where advice cannot immediately be accessed. The below advice is aimed to help paediatricians know when to suspect CGD and the actions needed including when to see immunology advice.

SUSPECTED CGD

<u>When to suspect CGD</u>

Recurrent abscesses especially in multiple different or unusual sites

Very early onset IBD

Recurrent Infections with catalase positive organisms (e.g. staphylococcus, nocardia, serratia)

Fungal chest infections

Liver abscesses – CGD must be excluded in children

Osteomyelitis

BCG-itis

<u>Actions</u>

Arrange to check a DHR test of neutrophil respiratory burst (X1 EDTA to Immunology lab open Mon-Fri 0830-1800, please alert the laboratory in advance)

Exclude other causes of immunodeficiency e.g. neutropenia

Ensure consultant/registrar overseeing patient care is aware of concerns

Discuss with immunology if high clinical suspicion of immunodeficiency

CONFIRMED CGD

This will be based on DHR testing, please note the DHR can be reduced in sepsis and MPO deficiency and repeat testing may be needed

Abnormal DHR tests will usually be telephoned to the ward

If DHR test suggests CGD discuss urgently with Immunology medical staff

In cases of confirmed CGD if immunology are not available then the “CGD management protocol” can be started in the interim until immunology staff are available and if required discuss with on call StR in Immunology at Great Ormond Street

It is vital that immunology is aware of CGD patient as soon as possible

CGD Management Protocol

- Treat infections aggressively with high dose broad spectrum antibiotics /anti-fungals, empiric antifungals may be needed if not responding to antibiotics
- Ensure thorough investigation of possible infection considering atypical, opportunistic and rare organisms – discuss with microbiology/immunology
- If collection/abscess consider early drainage
- Commence prophylactic Antibiotic & antifungal as below, unless contraindicated:

Co-trimoxazole

- 6 weeks-6 months 120mg OD
- 6 months – 5 years 240mg OD
- 6-12 years 480mg OD
- Over 12 years 960mg OD

Itraconazole (liquid preparation for absorption)

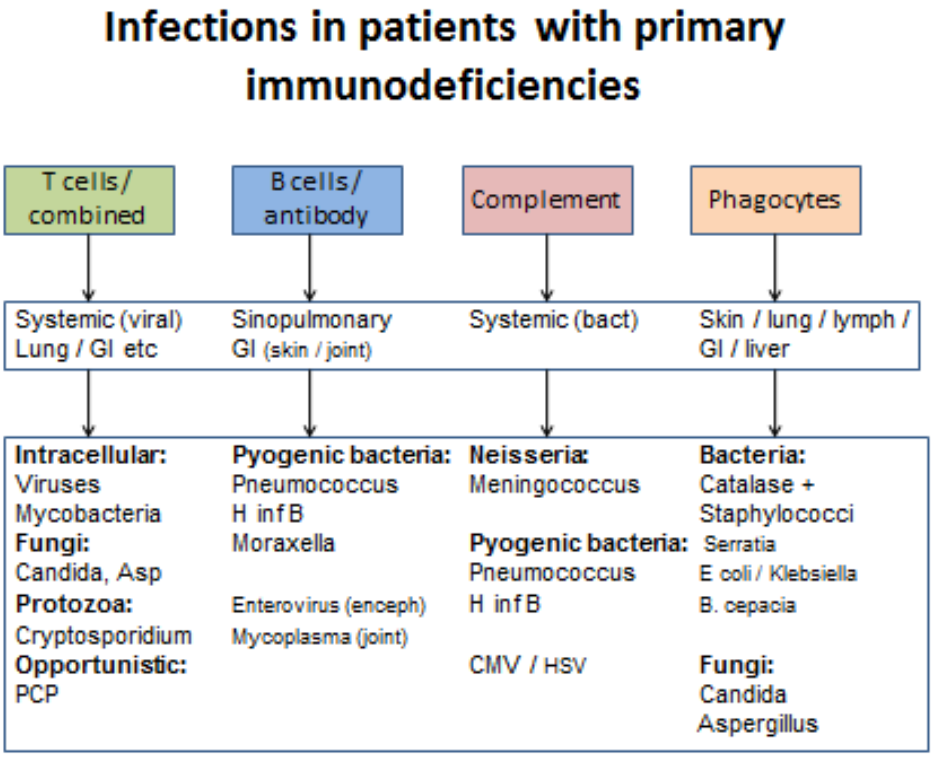
- All ages 5mg/kg/day

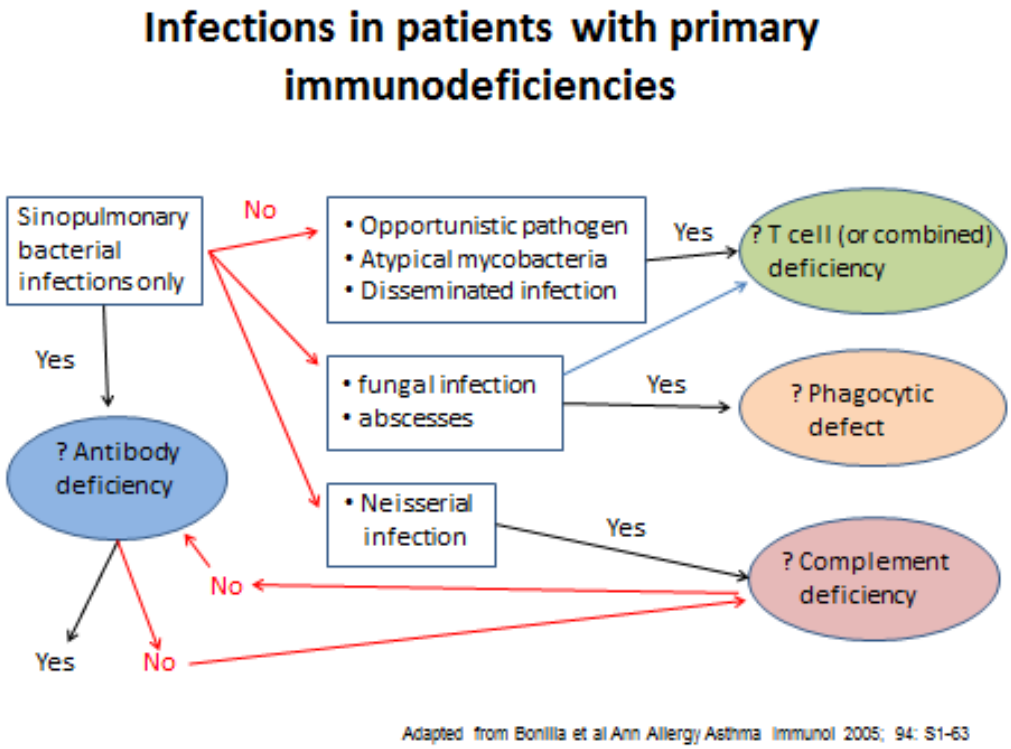
- Avoid BCG vaccination
- Patient must avoid areas with high fungal burden e.g. compost/leaf mulch
- If for blood transfusion discuss with transfusion lab to check Kell antigen status, if Kell negative must have Kell negative blood

Appendix 3 HIV - Clinical Indicator Diseases

ENT	Chronic parotitis Recurrent or troublesome ear infections
ORAL	Recurrent oral candidiasis Poor dental hygiene
RESPIRATORY	Pneumocystis pneumonia CMV pneumonitis Tuberculosis Recurrent bacterial pneumonia Lymphoid interstitial pneumonia Bronchiectasis
NEUROLOGY	Encephalopathy Meningitis/encephalitis Developmental delay Childhood stroke
DERMATOLOGY	Kaposi's sarcoma Severe or recalcitrant dermatitis Recurrent fungal infections Multidermatomal or recurrent herpes zoster Extensive warts or molluscum
GASTROENTEROLOGY	Wasting syndrome Persistent cryptosporidiosis Unexplained persistent hepatosplenomegaly Hepatitis B infection Hepatitis C infection
HAEMATOLOGY	Any unexplained blood dyscrasia including –Thrombocytopenia –Neutropenia –Lymphopenia
ONCOLOGY	Lymphoma Kaposi's sarcoma
OPTHALMOLOGY	Cytomegalovirus retinitis Any unexplained retinitis
OTHER	Pyrexia of unknown origin Recurrent bacterial infections e.g. meningitis, sepsis, osteomyelitis, Pneumonia

Appendix 4: Infections in patients with primary immunodeficiencies





Adapted from Bonilla et al Ann Allergy Asthma Immunol 2005; 94: S1-63

Appendix 5: Paediatric Immunology referral and triage pathway