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Recurrent Infections

Definition / Supporting Information

Healthy children experience 6–8 upper respiratory tract infections per year in the first few years of life. Most children who present with signs and symptoms suspicious of an underlying immune dysfunction will in fact have a normal immune system. However, consideration of possible primary immunodeficiency is the key to diagnosis and reduction of morbidity and mortality.

Keywords / also known as: autoimmune, immunodeficiency

Essential History

Ask about:

- Characteristics of previous infections
  - Chronic infections (eg, sinusitis, osteomyelitis)
  - Infections in unusual sites (liver, brain abscess)
  - Types of pathogens and infections, particularly infections caused by atypical organisms
  - Need for hospital admission
  - Increased frequency of common infections
  - Repeated serious bacterial infections
    - More than one serious bacterial infection warrants investigation.
  - Any infections with prolonged duration or that fail to respond as expected to appropriate anti-microbial treatment
  - Extensive or persistent candidiasis
- Operations
  - Grommets
  - Drainage of deep seated abscesses
  - Lobectomies
- Structural damage (eg, bronchiectasis)
- Poor wound healing
- Delayed separation of umbilical cord
- Detailed family history, including deaths in infancy
- Faltering growth
- Intractable diarrhoea and malabsorption
- Autoimmune conditions
- Eczema
- Immunisation history

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- History of maternal HIV or risk factors for HIV
- Housing conditions including house mould and fuel poverty

'Red Flag' Symptoms and Signs

Ask about:

- Faltering growth
- Intractable diarrhoea and malabsorption
- Family history of immunodeficiency
- Delayed separation of umbilical cord
  - Leucocyte adhesion deficiency

Look for:

- Dysmorphic features
  - DiGeorge's syndrome
- Neurodevelopmental problems
  - Purine nucleoside phosphorylase (PNP) deficiency
- Ataxia
  - Ataxia telangiectasia
  - PNP deficiency
- Evidence of autoimmune conditions (eg, fever, rash, joint pains / swelling)
  - Common variable immunodeficiency (CVID)
  - IgA deficiency
  - X-linked agammaglobulinaemia (XLA)
- Mouth ulceration
  - Neutropenia
- Finger clubbing
  - Bronchiectasis (eg, CVID)
- Hepatomegaly / splenomegaly / lymphadenopathy
  - Hyper-IgM syndrome
  - CVID
  - HIV
- Eczema
  - Wiskott–Aldrich syndrome
  - Severe combined immunodeficiency syndrome (SCID)
  - Hyper-IgE syndrome (Job's syndrome)
  - Omenn's syndrome
- Oculocutaneous albinism
  - Chédiak–Higashi syndrome
  - Griscelli's syndrome

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- Absence of thymic shadow on chest X-ray (normally seen up to three years of age)
  - DiGeorge's syndrome

Differential Diagnosis / Conditions

Secondary immunodeficiency

- Infection
  - HIV
  - Congenital rubella
- Cancer
  - Leukaemia
  - Lymphoma
- Medication
  - Cytotoxic
  - Immunosuppressive
  - Corticosteroids
  - Following organ transplantation
    - Stem cell transplant, bone marrow
    - Solid organ
  - Anti-cytokine therapies
- Protein-losing states
  - Nephrotic syndrome
  - Burns
  - Protein-losing enteropathies
- Malnutrition
- Splenic dysfunction
  - Splenectomy
  - Sickle cell disease
  - Congenital asplenia
- Metabolic disorders
  - Uraemia
  - Malnutrition
  - Diabetes
  - Galactosaemia
- Implants
  - Heart valves
  - Catheters
- Chromosomal disorders
  - Down's syndrome
  - Bloom's syndrome

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- Prematurity
- Chronic kidney disease

Primary immunodeficiency

- Evaluation of the child for a primary immunodeficiency should be considered after non-immunological and secondary immunodeficiency syndromes have been ruled out.
- Most children are symptomatic within the first few years of life, except in common variable immunodeficiency.
- Primary immunodeficiency is classified by the component of the immune system that is affected.
- Humoral immunodeficiencies
  - Comprise 50–70% of symptomatic primary immunodeficiencies
  - Children are susceptible to recurrent sinopulmonary infections with encapsulated bacteria such as *Streptococcus pneumonia* or *Haemophilus influenzae*.
    - X-linked agammaglobulinaemia
      - Sinopulmonary and gastrointestinal infections
      - Sepsis
      - Meningitis
      - Asymmetric arthritis
      - Dermatomyositis
      - Malabsorption
      - Absence of tonsils, adenoids, and lymph nodes
    - Transient hypogammaglobulinaemia of infancy
      - Recurrent sinopulmonary infections
    - X-linked hyper-IgM syndrome
      - Recurrent bacterial infections
      - Infections associated with T-cell defects (eg, *Pneumocystis [carinii] jiroveci*)
    - Common variable immunodeficiency
      - Bronchiectasis
      - Sinopulmonary infections
      - Malabsorption
      - Autoimmune disease
    - IgA deficiency
      - Very common (1 in 400 individuals) but usually asymptomatic
      - Recurrent pulmonary infections
    - Specific antibody deficiency with normal immunoglobulins
      - Recurrent bacterial infections of the respiratory tract
    - IgG-subclass deficiency

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        - Impaired antibody responses to polysaccharide antigens
        - Clinical significance not well delineated
- Combined defects in cellular and humoral immunity
    - Affected children are characteristically more susceptible to bacterial, fungal, mycobacterial, and viral infections.
    - Common viral infections of childhood such as varicella may cause severe or recurrent disease in affected children.
        - DiGeorge syndrome
            - Hypocalcaemia
            - Hypoparathyroidism
            - Congenital heart disease
            - Abnormal facies
        - Severe combined immunodeficiency (SCID)
            - Faltering growth, diarrhoea
            - Most common (50%) form is X-linked thymic hypoplasia
            - Both B-cell and T-cell deficiencies present
            - Cartilage–hair hypoplasia with certain forms
        - Ataxia telangiectasia
            - Recurrent sinopulmonary infections
            - Truncal ataxia
            - Mental retardation
            - Thymic hypoplasia
            - Telangiectasiae of skin and conjunctivae
            - Glucose intolerance
            - Increased risk for malignancy
        - Wiskott–Aldrich syndrome
            - Recurrent sinopulmonary infections
            - Eczema
            - Thrombocytopenia
            - Increased risk for malignancy
- Complement deficiencies
    - Least common among the primary immunodeficiencies
    - Occurs in older children and in adolescents
        - May experience recurrent meningococcal infection (meningitis or meningococcaemia)
- Phagocytic defects
    - Children typically experience recurrent skin infections, abscesses, sinopulmonary infections, poor wound healing, delayed umbilical cord separation, gingivitis, and eczema.
        - Absence of a particular cell type

        - Congenital neutropenia
        - Cyclical neutropenia
    - Defects in chemotaxis
        - Leucocyte adhesion disorder
    - Defects in effector function
        - Chronic granulomatous disease
- Ectodermal dysplasia (NEMO)
- Endocrinopathy
    - Chronic mucocutaneous candidiasis
    - IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)
    - APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy)

Investigations

To be undertaken by non-specialist practitioners (eg, General Practitioner (GP) Team):

- Laboratory evaluation should be guided by the type of infections the child is experiencing in liaison with specialist practitioners (eg, General Paediatric / Paediatric Infectious Disease Team(s)):

To be undertaken by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Infectious Disease Team(s)):

- Full blood count and differential (neutrophil, lymphocyte, and eosinophil counts and platelet volume)
- Serum immunoglobulin concentration (IgG, IgA, and IgM) with IgE if hyper-IgE syndrome is suspected
- With advice from specialists in infectious disease and/or immunology:
    - Vaccine responses (tetanus, Hib, and pneumococcus)
        - This should be interpreted with respect to vaccines received and may be performed before and after vaccination.
    - HIV and TORCH screen if indicated
    - Lymphocyte subpopulations (B-cell, T-cell, and NK-cell counts)
    - Nitroblue tetrazolium test or flow cytometric assays of neutrophil function
    - Complement
        - C3, C4, CH50, and AP50
        - Haemolytic assay of classical and alternative complement pathways
    - Bacterial sepsis and meningococcal septicaemia
        - See Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management [NICE clinical guideline 102, recommendations 1.5.8–1.5.15]
    - T-cell proliferation to mitogens

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  - Neutrophil markers (CD11 / CD18)
  - Oxidative metabolism
    - Nitroblue tetrazolium reduction test
    - Oxidative burst determined by flow cytometric analysis
  - Naive and memory T-cells
  - Other investigations to consider depending on the clinical scenario
    - Autoimmune profile
    - Imaging studies
    - Exclusion of secondary causes
    - Lung function
    - Stool cultures
      - See Diarrhoea and vomiting caused by gastroenteritis in under 5s [NICE clinical guideline 84, recommendation 1.1.2.2]

Treatment Approach

To be undertaken by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Infectious Disease Team(s)):

- Intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin
  - Patients with humoral and combined immunodeficiencies
- Prophylactic antibiotics
- Enzyme replacement
  - Certain forms of SCID (adenosine deaminase deficiency)
- Cytokine therapy
  - Interleukin-2 deficiency
- Interferon-γ treatment
  - Decreases the number of infections in patients with chronic granulomatous disease
- Gene therapy
- Blood transfusion
  - When needed, should be with cytomegalovirus-negative, irradiated cells to prevent graft-versus-host disease
- Physiotherapy
- Bone marrow transplantation
  - SCID
  - Wiskott–Aldrich syndrome
  - DiGeorge’s syndrome
- Immunosuppression is often required for associated autoimmunity.

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When to Refer

Refer to specialist practitioners (eg, General Paediatric / Paediatric Infectious Disease Team(s)) if:

- Recurrent serious bacterial infections (more than one)
  - Sepsis
  - Pneumonia
  - Meningitis
- Serious bacterial infection in the context of failure to thrive
- Infection with an opportunistic pathogen
  - *Pneumocystis*
  - *Cryptococcus*
- Vaccine-preventable infections
- Unusual age for infection
  - Zoster
  - Thrush
- Unusual severity or chronicity for a given infection
- Persistent thrush
- Family history of immunodeficiency

‘Safety Netting’ Advice

- Advise parents and carers to seek medical advice if any red flag symptoms develop or if poor response to treatment
- Pending a complete immunological evaluation, children who are thought to have immunodeficiency syndromes should not receive live attenuated vaccines, such as BCG, varicella, rotavirus, measles / mumps / rubella and nasal flu vaccine to avoid the possibility of vaccine-associated infection.
  - See Contraindications and special considerations in ’The Green Book’.

Patient / Carer Information

Please note: whilst these resources have been developed to a high standard they may not be specific to children.

- Primary Antibody Deficiency (Web page), Patient

Resources

National Clinical Guidance

Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (Web page), NICE clinical guideline CG102, National Institute for Health and Care Excellence

Diarrhoea and vomiting caused by gastroenteritis in under 5s: diagnosis and management (Web page), NICE clinical guideline CG84, National Institute for Health and Care Excellence

Medical Decision Support

Contraindications and special considerations (Web page), Public Health England's Green Book

Suggested Resources

Please note: these resources include links to external websites. These resources do not have national accreditation and therefore PCO UK cannot guarantee the accuracy of the content.

De Vries, Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists.
Clin Exp Immunol 2005;145(2):204-214 [PubMed]

Hackett S, Lissauer S, Welch S, Hackett S. Immune deficiencies in children: an overview. Arch Dis Child Educ Pract Ed. 2013;98(5):186-196 [PubMed]

Recurrent Infections May Signal Immunodeficiencies (Factsheet), American Academy of Allergy, Asthma & Immunology

Immune Deficiency Foundation (Web page), The Immune Deficiency Foundation

The health impacts of cold homes and fuel poverty 2011 (PDF), Marmot review team

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Content Editor: Dr Srini Bandi

Clinical Expert Reviewers: Dr Jolanta Bernatoniene and Dr Christine Jones

GP Reviewer: Dr Janice Allister

AAP Reviewer: Deepak Kamat, MD, PhD, FAAP

Paediatric Trainee Reviewer: Dr Ahtzaz Hassan

Update reviewer: Dr Pemantah Sandheeah Ramdeny (trainee paediatrician)

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Key Practice Points
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