

HOW I TREAT PRIMARY IMMUNODEFICIENCY

Primary immunodeficiency diseases (PIDs) are a group of more than 400 largely heritable genetic disorders characterised by an increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergy, and/or malignancy.¹ Due to their rarity in primary care, delays in diagnosis are common and associated with further complications and reduced survival.²

Review the following three hypothetical scenarios in which patients present with PIDs or conditions easily mistaken for PIDs. For each scenario, consider how you would best manage the patient and reflect on the questions provided.

Case study 1: Joe

Presentation

In your mid-winter busy clinic, you see Joe, a 3-year-old boy with a 3-day history of vomiting and diarrhoea. His parents are worried because he is sick 'all the time'. Joe frequently experiences upper respiratory tract infections (URTIs) and this is his second bout of gastroenteritis. He has had antibiotics on two occasions for otitis media – his ears have been checked on each occasion, with resolution of the infection each time. Joe had chicken pox last year and recovered within 10 days. He has never had thrush, and there have been no other medical problems to date. Joe has no family history of note, and his two older siblings rarely get sick.

Examination

On examination, Joe is well grown and has no dysmorphic features. He has three to four small, mobile cervical nodes palpable, and he has normal tonsillar tissue. Ear, nose and throat (ENT), chest, and abdominal examinations are normal.

Diagnosis and initial treatment

The hallmark feature of primary immune deficiencies is infection, particularly those that are severe, unusual, frequent, or recurrent.¹

? **WHAT FEATURES OF JOE'S CLINICAL HISTORY SUGGEST THAT AN UNDERLYING IMMUNE DEFICIENCY IS UNLIKELY?**

While Joe presented with several infections, the following features in his clinical history suggest that consideration of an underlying immune deficiency is unnecessary:

- ▶ Joe has no family history of immune deficiency.
- ▶ Joe has older siblings. Children with older siblings or those in day care will be exposed to more infections.
- ▶ Joe has responded well to antibiotics in the past.
- ▶ Joe has recovered completely between infections. Viral URTI symptoms last an average of 8 days, but sometimes up to 2 weeks, so it can be hard to get recovery when one infection runs in to the next. However, if symptoms are only those of a viral URTI, this is not a 'red flag'.

? **WHAT FEATURES OF JOE'S EXAMINATION ARE REASSURING?**

- ▶ Cervical nodes are palpable in up to half of normal children at any time, and the presence of normal lymph nodes and tonsils is reassuring.
- ▶ Joe has normal growth, whereas children with immune deficiency commonly have faltering growth.
- ▶ Joe has normal ENT, chest, and abdominal examination. Dysmorphic features or abnormalities of hair and skin would suggest an underlying problem.

Overall, Joe's history and physical examination don't suggest an underlying immune deficiency.



WHAT ARE THE NEXT STEPS?

- ▶ The appropriate next step for Joe involves referral, investigation, and reassurance.

Further investigations should include a full blood count and serum measurements of immunoglobulins (IgG, IgA, IgM). Blood samples for immunoglobulin (Ig) should be taken on two occasions, at least 1 hour apart with at least one sample taken when the patient does not have an infection.³ More detailed evaluation of humoral immune function can be pursued based on the results of these first-line tests.¹

Reassure the patient's family by explaining the features of Joe's examination and clinical history that are inconsistent with an immune deficiency (such as his absence of red flags), as well as the rates and characteristics of recurrent infections considered normal for his age group.

Practice points

- ▶ Viral URTIs are common in pre-schoolers: 4–8 respiratory infections per year is the average, and up to 10 or 12 infections is still 'normal'.
- ▶ Family history of immune deficiency (or sometimes of early childhood deaths) is one of the strongest risk factors for immune deficiency. Consanguinity is also important.
- ▶ Patients with immune deficiency tend to respond poorly to treatment. For example, thrush in an infant not responsive to medication, or a skin infection not responding to antibiotics, should prompt further consideration.

Case study 2: James

Presentation

James is a 9-month-old boy who has been brought into the emergency department with a 1-day history of runny nose, low-grade fever, irritability, cough, and mild tachypnoea. He has had one episode of recent gastroenteritis also affecting his older sibling and had middle ear infection 3 months prior. He is normally at day care 5 days a week.

Examination

On examination, James appears well and active, with no dysmorphic features. He has a low-grade temperature at 37.7°C and rhinorrhoea with mild wheeze.



WHAT FEATURES OF JAMES' CLINICAL HISTORY SUGGEST THAT AN UNDERLYING IMMUNE DEFICIENCY IS UNLIKELY?

- ▶ James does not have any 'red flags' that would increase suspicion for an immune deficiency.
- ▶ James' presentation meets the normal rates for infections for children his age.

Diagnosis and initial treatment

James' history and physical examination do not suggest an underlying immune deficiency. A clinical diagnosis of viral respiratory infection is made.



WHAT ARE THE NEXT STEPS IN JAMES' TREATMENT?

- ▶ James may be treated for his respiratory infection. No further investigations are warranted.

Practice points

- ▶ Infections are common in children and tend to be more frequent in those attending communal day care or those with older siblings at school.
- ▶ Several 'red flags' increase suspicion for an immune deficiency:
 - Failure to thrive.
 - Opportunistic infections.
 - Invasive infections.
 - Infections responding poorly to treatment.
 - Family history of immune deficiency.
- ▶ The rate of annual infections considered normal includes:
 - 6–8 respiratory infections per year for the first 10 years of life.
 - Up to six episodes of otitis media per year for the first 2–3 years of life.
 - More than two episodes of gastroenteritis a year should be assessed.

Case study 3: Anna

Presentation

Anna is seven years old and the middle child of three children. Her siblings and parents are all well. Her growth has been satisfactory, but Anna has always been a small child, with growth along the 15th percentile since early childhood. There is no known family history of recurrent infection or immune problems. She has no history of thrush and had uncomplicated chicken pox at 6 years of age. Anna has had frequent chest and ear infections, including multiple hospitalisations for chest infections, including one admission to the paediatric intensive care unit.

Examination

Anna presents for review of a productive persistent cough and work-up for immunodeficiency given her frequent infections. On examination, Anna is a small child. She appears miserable, with a frequent, productive cough. A physical examination reveals:

- pulse rate: 90 bpm
- respiratory rate: 18 breaths per minute
- temperature: 38.8°C.

She has some small palpable lymph nodes. Her left ear is normal, with some mucopurulent discharge on the right. Her nose is normal, and her throat injected with no exudate. She has good air entry bilaterally with scattered coarse crepitations plus some bronchial breath sounds in the left base. Examination is otherwise normal.

A left-sided pneumonia is confirmed on chest x-ray and Anna is referred to hospital for treatment.

Diagnosis

? GIVEN HER PRESENTATION, WHAT TYPE OF IMMUNE DEFICIENCY WOULD YOU BE MOST CONCERNED ABOUT?

- ▶ Anna's presentation is suggestive of PID with antibody deficiency.

? WHAT INITIAL INVESTIGATIONS ARE REQUIRED?

- ▶ Initial investigations should include a full blood count, differential, lymphocyte subsets, and blood samples for Ig (IgG, IgA, IgM), C-reactive protein, blood, and sputum culture. Blood samples for Ig should be taken on two occasions, at least 1 hour apart with at least one sample taken when the patient does not have an infection.³

Anna's Ig tests reveal:

- IgG 1.5 g/L (reference range: 6–15 g/L)
- IgA < 0.07 g/L (reference range: 0.7–2.3 g/L)
- IgM 0.2 g/L (reference range: 0.5–2.2 g/L).

Treatment

Based on her presentation and the above test results, Anna is likely to need lifelong Ig replacement therapy (IRT). Specifically, Anna meets the following qualifying criteria for Ig therapy:

- > 4 years of age.
- Marked decrease in IgG and IgA.
- Serum IgG < 2 g/L and at risk from delays in IRT due to the presence of invasive bacterial infections (pneumonia).
- Increased susceptibility to infection (chest and ear).

The complete set of qualifying criteria for Ig therapy across all eligible conditions can be reviewed on the National Blood Authority's site: [*Criteria for the clinical use of immunoglobulin in Australia*](#).

To access Ig under the Criteria, a diagnosis must be made by an immunologist.

IRT for PIDs is administered via intravenous (IVIg) infusion or subcutaneous (SCIg) injection. IVIg is typically administered in the hospital or clinic setting, whereas SCIg is typically self-administered in the home setting. Because Anna's serum IgG levels are < 4 g/L, one loading dose of 0.4 g/kg should be administered in the first month of therapy. Maintenance doses should be delivered at least every 4 weeks for IVIg and at least every week for SCIg, with the goal of achieving IgG trough levels of at least the lower limit of her age-specific IgG reference range. Therapy should continue at the lowest safe and effective dose for each patient.³

Further immunologic investigation is needed to confirm Anna's diagnosis, along with evaluation for possible bronchiectasis.⁴

Review

All patients receiving IRT should be routinely reviewed by an immunologist. While the frequency of visits should be determined by clinical status, an initial review at 6 months and reviews annually (at minimum) thereafter are required.³

The primary review criteria for PIDs with an antibody deficiency are adequate replacement of antibodies and demonstration of clinical benefit from treatment.³ Clinical effectiveness may be assessed by:

- ▶ monitoring serum Ig levels and any history of infection
- ▶ a confirmed diagnosis of PID with antibody deficiency.

Practice points

- ▶ The most appropriate route of administration for a given patient requires an assessment of the risks and benefits of each approach, alongside patient preferences, and individual pharmacokinetics.
- ▶ The BloodSTAR **dose calculator** can be used to determine the appropriate dose of Ig based on the patient's indication and body weight.

Note: In addition to meeting the clinical and diagnostic criteria for access (as defined in the Criteria), patients must access SCIg treatment through an approved SCIg facility. This ensures that SCIg is appropriately managed, including making sure that patients are appropriately supported to use the product at home. There may be a waiting list to receive training, and SCIg clinics may not be available in all geographic locations.⁵

Access to Ig in Australia

In Australia, the National Blood Authority's (NBA) Immunoglobulin Governance Program provides the framework for access to Ig products currently funded under the National Blood Agreement (the Agreement). The NBA manages contracts with suppliers to ensure a safe, secure, adequate, and affordable supply of blood and blood-related products such as Ig sourced from domestic and imported plasma. The NBA has contracted the Australian Red Cross LifeBlood to assess, authorise and provide clinical advice on established or emerging therapeutic medical conditions identified in the Criteria for the clinical use of immunoglobulin in Australia (the Criteria).³ The Criteria also define the conditions for which Ig can be used in exceptional circumstances.

Ig products are funded by governments and are provided to eligible patients at no direct cost. To access Ig under the Agreement, approved health providers (medical officers) are required to request product through the National online system BloodSTAR. The system manages the authorisation request and review process and ensures that access to Ig products is consistent with eligibility, as defined by the Criteria. Patients who are ineligible to access Ig under the Criteria may be able to access Ig through a Jurisdictional Direct Order, at a cost to the approved health provider or can be self-funded by the patient.

Additional resources

- ▶ NPS MedicineWise [Immunoglobulin replacement therapy for primary immunodeficiencies: Clinical Guidance Article](#)
- ▶ A full list of the conditions eligible for government-funded Ig: [Criteria for the clinical use of immunoglobulin in Australia](#)
- ▶ NPS MedicineWise: [Immunoglobulin dose adjustment, weaning and cessation: a conversation guide for health professionals](#)
- ▶ NPS MedicineWise: [Immunoglobulin replacement therapy for PID: consumer factsheet](#)
- ▶ NPS MedicineWise: [Immunoglobulin management and wellbeing plan](#)

REFERENCES

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5. National Blood Authority. Access to subcutaneous immunoglobulin (SCIg). Canberra: Commonwealth of Australia. <https://www.blood.gov.au/SCIg> (accessed 24 March 2022).

VALUE IN PRESCRIBING PROGRAM – IMMUNOGLOBULIN PRODUCTS

Increasing the awareness and understanding amongst health professionals of access to immunoglobulin products in Australia, and improving health outcomes for patients through access to better health information to manage their health conditions. Funded by the Australian Government Department of Health through the Value in Prescribing Program: Immunoglobulins Products Grant.