

Don't Forget The Bubbles



IMMUNODEFICIENCIES

Facilitators Guide

Author **Ravi Mistry**

Expert Reviewer: **Sanjay Patel**

(Edits by the DFTB Team)

fellows@dontforgetthebubbles.com

Topic: **Immunodeficiencies**

Author: **Ravi Mistry**

Expert Reviewer: **Sanjay Patel**

Facilitator level **ST4+**

Learners level **Case 1: Foundation doctors, paediatric trainees, paediatric nurses, GPs; Cases 2+3: Paediatric trainees.**

Equipment required: **None**

OUTLINE

- Background – setting the scene and objectives for this module
- Main session – 3 x 10-15 minute cases covering 3 different cases relating to immunodeficiencies.

Ideally the cases should be reviewed sequentially as learning points from one are built upon in subsequent cases with a focus on what the general paediatrician should know about immunodeficiencies.

- Case 1 focuses on a case seen in the emergency department and explores the common parental query of a “weak immune system” in a young child who has had several recurrent upper respiratory tract infections back-to-back but is otherwise well.
- Case 2 focuses on an immunodeficiency case that will more commonly be seen in district general hospitals and their day units for ongoing care
- Case 3 focuses on a SCID presentation and outlines their initial investigations in a secondary care setting before tertiary involvement
- Quiz – 5 minutes
- Learning points – 3 minutes

PRE-READING FOR LEARNERS

https://www.youtube.com/watch?v=_jBpv9fYSU4

or https://www.youtube.com/watch?v=gR84OJ_EGxk – for those wanting a refresher of key elements of immunophysiology, watch one of these two videos provide an overview. The first video being a little more detailed. (15 mins)

Jeffrey Modell Foundation: 10 warning signs of primary Immunodeficiency in children - https://res.cloudinary.com/info4pi/image/upload/v1662306260/JMF_10_Signs_Gener-ic_Poster_photo_resize_900x1177_60a2a7ce56394_original_411895405a.jpg (1 minute)

<https://www.paediatricfoam.com/2020/09/immunodeficiency/> (10 mins) a clinically orientated overview of immunodeficiency in children

BACKGROUND

Primary immunodeficiencies (PI), or inborn errors of immunity (IEI), are a group of rare genetic conditions resulting in the abnormal function or complete inactivity of one or more parts of the immune system. Severe forms of PI can present early in life and can be life-threatening – for example, a neonate with severe combined immunodeficiency (SCID). Other PIs are more subtle and result in patients presenting with frequently recurring infections.

There are many PIs and identifying the affected gene should not be the focus for a general paediatrician. However, understanding the basic components of the immune system and how they protect against different pathogens can help the general paediatrician decide if a child with recurrent infections warrants first-line investigations for an underlying immunodeficiency.

Early detection is vital for two reasons. Firstly it minimises the scope for ongoing complications that ensue following recurrent, potentially life-threatening, infections. Secondly, detecting PIs can allow for the either prophylactic treatment to be given or potentially a curative option via a bone marrow transplant.

For the general paediatrician it is important to know several pieces of knowledge in relation to this topic. This includes:

1. Having a grasp of what is normal and what is not, so as to know when to consider primary immunodeficiency.
2. Knowing factors that increase the chances of there being an underlying primary immunodeficiency.
3. Knowing what first-line investigations to order when evaluating a child for primary immunodeficiency.

This module aims to cover the above three points with cases a general paediatrician may encounter.

CASE 1

A 3 year old boy is brought to emergency department and treated for viral induced wheeze. This is fifth episode in the last six months. His parents report he seems to “constantly” have infections and are struggling to recall a stretch of time recently where he hasn’t been unwell. She wonders if he has a “weak immune system”. In the last year, he has had multiple attendances to the emergency department and to his GP, and been prescribed two courses of oral antibiotics. He is gaining weight along the 50th centile. His birth history was unremarkable, with no input from the neonatal team after he was born. His immunisations are also all up-to-date.

What is your current impression and what would you like to ask the parents?

Based on the above information, what would say to the parents?

CASE 1 - DISCUSSION

This 3 year old boy appears to have had a number of viral upper respiratory tract infections, resulting in recurrent episodes of viral induced wheeze. Although he has been prescribed 2 courses of oral antibiotics, it is unclear whether these were indeed required. He has had no serious invasive infections requiring intravenous antibiotics or hospitalisation. It is encouraging that he is thriving. Parents should be advised that it is normal for young children to get approximately 10 upper respiratory tract infections each year. These will usually be concentrated in the winter months and may make it seem like their child is constantly unwell.

Is there any evidence behind this?

Two studies can help evidence this. The first is by Gruber et al (2008) where parents kept a symptom diary for 12 years tracking the number of symptomatic episodes their children had. Their data shows the upper limit of what can be a 'normal' number of annual URTIs in children aged under 5 years is approximately 11. This drops markedly as children go through primary school, falling to 4 per year.

Another useful study showing the distribution of viral infection in different ages and household setups comes from the BIG LoVE study (2015) where households had viral PCR swabs completed weekly for a year. Children under 5 years of age had virus detected 50% of the time and households with 2 children or more also tested positive over 50% of the time too. The detection rate halved for children aged over 5 years old. This is summarised in Figure 1. This study does have limitations in that swab PCR positivity doesn't necessarily indicate active infection and in some cases patients were asymptomatic. But it nonetheless can serve as a useful aid in highlighting the burden of viruses young children compared to those who are older.

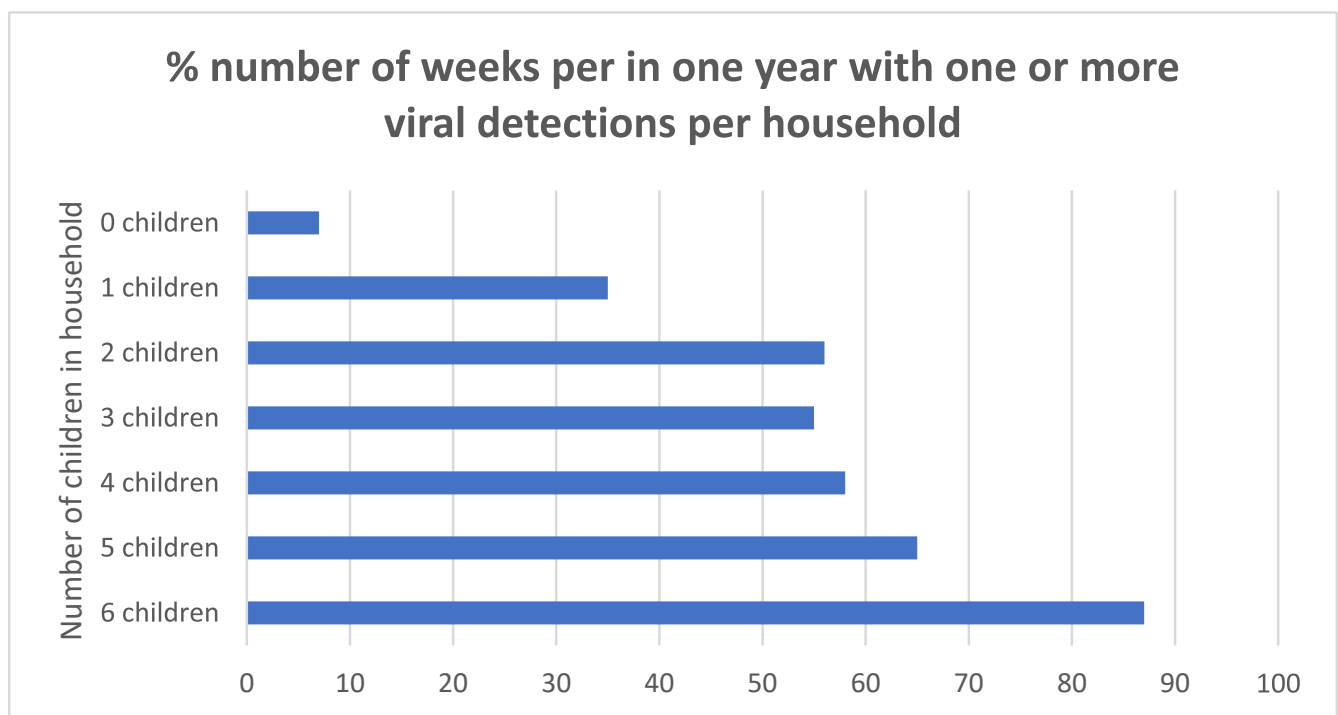
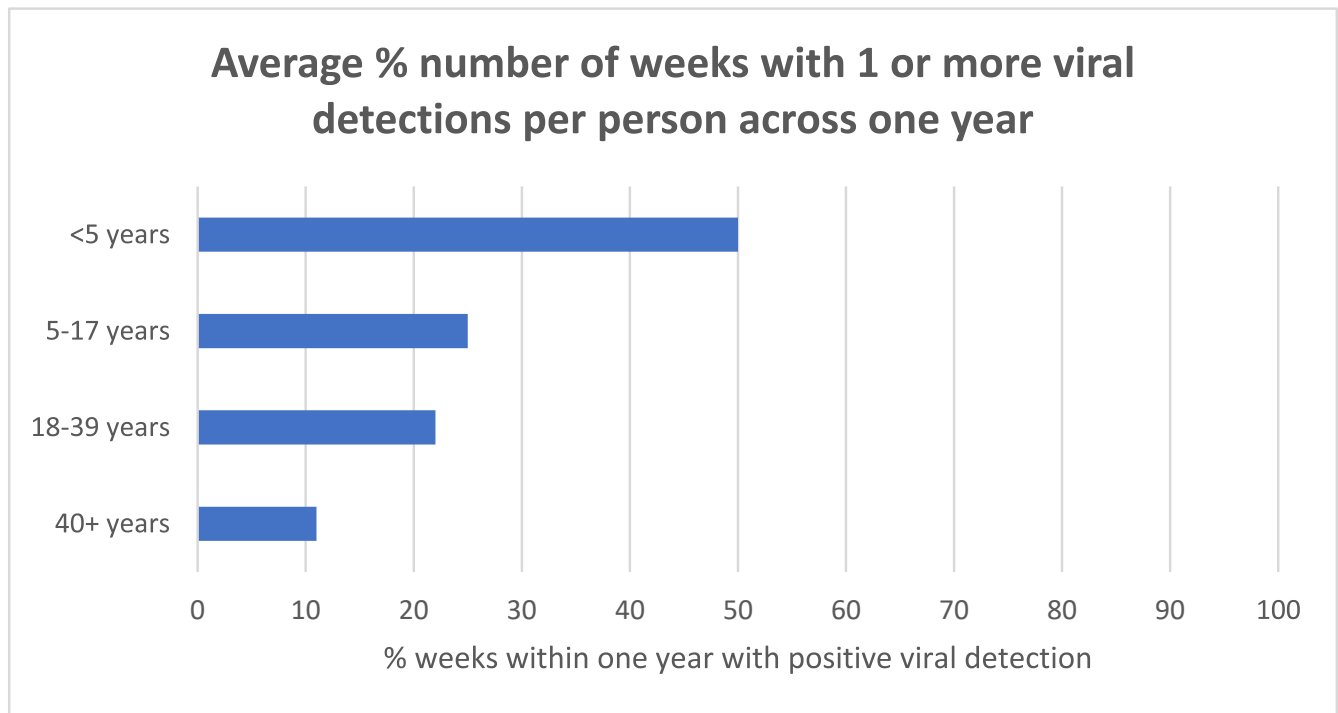


Figure 1. Prevalence of virus detection in (a) patients by age, and (b) number of children per household. Adapted from: Byington et al (2015, Clinical Infectious Disease, <https://doi.org/10.1093/cid/civ486>)

When to think about primary immunodeficiency?

In terms of thinking about whether there is an underlying immunodeficiency, it is useful to think of the SPUR acronym. Has the child had any:

- **S**evere infections
- **P**ersistent infections
- **U**nusual infections
- **R**ecurrent infections

In terms of exploring other risk factors, there's the ten signs of primary immunodeficiency from the European Society of Immunodeficiencies which includes some of the above and a few more. Having two of more should prompt clinicians to consider whether the patient has a primary immunodeficiency. These are:

1. ≥ 4 ear infections in one year
2. ≥ 2 severe sinus infections in one year
3. ≥ 2 months treatment of antibiotics with little effect
4. ≥ 2 pneumonias within one year
5. Faltering growth
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. ≥ 2 deep seated infections (meningitis, septicaemia, osteomyelitis)
10. Family history of a primary immunodeficiency

How well evidenced is this?

This list is not exhaustive and should be viewed as a screening tool. Several papers have identified the most common features from the classical warning signs are having a family history of a PI, faltering growth, and the need for intravenous antibiotics. Additionally, parental consanguinity increases the risk of a primary immunodeficiency 6-fold.

A retrospective review of patients with PI found that having one warning sign had a sensitivity of 100%; that is, every patient with a PI had at least one warning sign. However, 72% of control patients in the study also had one warning sign. With two warning signs, the sensitivity falls to 94%, with a specificity of 64% and a positive predictive value and negative predictive value of 68% and 92% respectively.

Back to our patient...

From the history we have so far on the patient, there's no red flags to consider a primary immunodeficiency. Parents of young children will regularly pose the question of whether their children have a "weak immune system" in view of lots of repeated upper respiratory tract infections in particular. In this case, it would be sensible to try to reassure the parent that if they don't have any worrying signs; that as frustrating and difficult as it may seem, these recurrent 'simple' infections are within normal limits of childhood; and that as the child grows up, we'd expect him to have fewer infections.

CASE 2

A 2 year old boy is referred to the paediatric clinic. His parents and GP are concerned about him having recurrent infections. He was born at term with an unremarkable antenatal and postnatal course. His growth and development have been satisfactory and he has received his routine immunisations to-date. Of concern is the recurrent number of ENT and respiratory tract infections he had which have required antibiotics. He has been treated four times for pneumonia, two of which were confirmed radiologically and required hospitalisation, and he has also experienced recurrent bouts of otitis media. His parents are non-consanguineous and there's nobody else in his wider family with recurrent infections.

On examination you hear right sided inspiratory crackles and his parents inform you he has just finished a course of oral antibiotics for a chest infection. He is afebrile.

What investigations would you like to request and why?

His investigations show the following:

Haemoglobin: 128 g/L	[110 – 140 g/L]
Platelets: 260 x 10 ⁹ /L	[150 – 450 x10 ⁹ /L]
WCC: 6.6 x 10 ⁹ /L	[5.0 – 12.0 x10 ⁹ /L]
Neuts: 2.2 x 10 ⁹ /L	[2.0 – 6.0 x10 ⁹ /L]
Lymph: 3.8 x 10 ⁹ /L	[1.5 – 7.0 x10 ⁹ /L]
Mono: 0.4 x 10 ⁹ /L	[0.3 – 2.1 x10 ⁹ /L]
Eos: 0.2 x 10 ⁹ /L	[0.1 – 0.8 x10 ⁹ /L]

LFTs: normal liver enzymes, normal albumin and total protein

U&Es: normal	
CRP: 22 mg/L	[<5 mg/L]
IgG: 0.8 g/L	[5 – 12 g/L]
IgA: 0.04 g/L	[0.4 – 1.3 g/L]
IgM: 0.06 g/L	[0.27 – 1.4 g/L]

Tetanus vaccine response: reported markedly low by laboratory

HIV: Not detected

Blood film: no abnormalities reported

What is the most likely diagnosis, how is it managed and what is its prognosis?

CASE 2 DISCUSSION

Investigations:

This child should be investigated for a primary immunodeficiency given his history. A useful starting point would be the following investigations which could help localise which compartment(s) of the immune system may be properly functioning. More advanced investigations can take place subsequently which can be more targeted, and also include various genetic analyses to confirm a molecular diagnosis. First-line investigations can include:

- **FBC and blood film** – allows for gross inspection of total white cell counts and key lineages. Platelet count and mean platelet volume can help identify microthrombocytopaenia (for Wiskott Aldrich Syndrome). A blood film can help provide evidence of hyposplenism if Howell-Jolly bodies are present. It is also useful for consider whether there could also be a malignancy present which could also present similarly.

- **Immunoglobulin profile (IgG, IgA, IgM)** – these are helpful in evaluating B-cell function

- **Vaccine responses** – these are helpful in evaluating B-cell function. Before performing this test, it is important to ensure the patient has in fact had the vaccine being tested for.

- **Lymphocyte subsets** – this allows for evaluation of different types and stages of lymphocytes using flow cytometry. The test gives absolute counts and relative (percentage) counts of different lymphocyte populations differentiated by expression of particular transmembrane proteins. B-cells of all stages of maturity express CD19. T-helper cells express CD4, cytotoxic T-cells express CD8. T-regulatory cells can be identified by their expression of FoxP3. Natural killer cells express CD56/16.

- **HIV test** - while HIV is an acquired (secondary) immunodeficiency, it is important not to miss this in cases of suspected immunodeficiency. Similar to PIs, early detection allows for minimisation of complications from infections and for early treatment.

- Complement function – patients with abnormal complement function or complement deficiencies are at higher risk of infections with encapsulated organisms such as *Neisseria*, *Streptococcus* and *Haemophilus*. However, tests such as complement function and neutrophil oxidative burst are more complex and you may consider discussing the case with a paediatric immunologist or referring the patient to them.

It is important to remember that a lot of the above laboratory tests' normal ranges will vary with in accordance with the child's age. If in doubt with reference ranges, it is best to speak to the laboratory the test gets sent to as a starting point.

Abnormal results, especially with lymphocyte subsets, may need repeating several weeks after a child recovers from their acute episode; many viral illnesses can result in a suppressed leucocyte count. It is also important to review whether any medicines the child may have taken could have resulted in a suppressed cell count. However it is always important to notice a lymphopaenia and follow it up as it could indicate a low T-cell count, which can point towards more severe immunodeficiencies if persistently low.

Diagnosis

The patient's results show low levels of all types of antibody (hypogammaglobulinaemia). The most likely diagnosis here is X-linked agammaglobulinaemia.

X-linked agammaglobulinaemia (XLA) is a genetic disorder which primarily affects males due to being a defect on the X chromosome. Depending on the population studied, the literature indicates that around half the cases of XLA occur from a de novo mutations. Mutations affect the BTK gene that producing the BTK protein which has a role in B-cell development. It ultimately results in diminished levels of antibodies as a result of early B-cells not maturing and subsequently not entering the systemic circulation.

Patients usually present with recurring bacterial infections, notably in the respiratory tract and ears. These can be severe and challenging to treat, leading to chronic lung complications if not managed effectively.

Management entails lifelong replacement therapy with intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) infusions. These infusions confer passive immunity by providing a supply of the absent antibodies, thus diminishing the frequency and severity of infections. You may encounter these

patients on paediatric day units, although the majority self-administer their subcutaneous immunoglobulin at home.

It is important to highlight the immunoglobulin infusions are a lifesaving intervention as it prevents severe infections from taking hold, as well as a life-improving intervention due to the reduction in number of illness episodes and hospital admissions. Their prognosis is typically good provided they regularly have their immunoglobulin infusions regularly.

CASE 3

A 4 month old boy is admitted to the ward with pneumonia. On a wider review, his parents report him having persistent diarrhoea for two months. Examination additionally reveals oral thrush. His growth chart demonstrates faltering growth, having originally being born on the 50th centile for weight and now is below the 2nd centile. His parents are consanguineous and he is their first child.

There was one previous pregnancy with miscarriage. Pregnancy with him was uncomplicated, with normal scans, an elective C-section delivery and no neonatal input following birth. Both his parents were born in the UK and was not indicated to receive the BCG vaccine. He has had his two and three month immunisations as per the UK schedule. His parents are both fit and well and there is no family history of any medical conditions.

His bloods show the following:

Hb 105	g/L	[110 - 140 g/L]
WCC	$14.1 \times 10^9/\text{L}$	$[6.0 - 15.0 \times 10^9/\text{L}]$
Lymph	$1.1 \times 10^9/\text{L}$	$[4.0 - 10.0 \times 10^9/\text{L}]$
Neuts	$11.3 \times 10^9/\text{L}$	$[1.5 - 8.0 \times 10^9/\text{L}]$
Mono	$1.3 \times 10^9/\text{L}$	$[0.3 - 1.1 \times 10^9/\text{L}]$
Eos	$0.4 \times 10^9/\text{L}$	$[0.1 - 1.0 \times 10^9/\text{L}]$
CRP	16 mg/L	$<5 \text{ mg/L}$

What diagnosis needs to be ruled out?

What further investigations would be helpful?

From his investigations, the following results are seen:

CD3+	$309 \times 10^6/\text{L}$	$[2284 - 4776 \times 10^6/\text{L}]$
CD4+	$173 \times 10^6/\text{L}$	$[1523 - 3472 \times 10^6/\text{L}]$
CD8+	$136 \times 10^6/\text{L}$	$[524 - 1583 \times 10^6/\text{L}]$
CD19+	$331 \times 10^6/\text{L}$	$[776 - 2238 \times 10^6/\text{L}]$
CD56/16+	$468 \times 10^6/\text{L}$	$[230 - 801 \times 10^6/\text{L}]$

HIV Test: Negative

Which team should this patient be referred to and what might they offer?

What possibilities exist for potentially detecting this earlier?

DISCUSSION

Diagnosis and investigations

Severe combined immunodeficiency (SCID) needs to be ruled out. He is presenting with recurrent and severe infections, as well as faltering growth, alongside a low absolute lymphocyte count. A reasonable starting point would be to perform a HIV test and check his lymphocyte subsets and immunoglobulin levels (IgGAM).

Linking this case back to the discussion from the first case, warning signs for PID here include a persistent infection and faltering growth on a background of consanguinity. Another useful piece in the history is that of a miscarriage, which could potentially have been due to a non-viable foetus, the chances of which are increased due to consanguinity.

In addition to evaluating for a pneumonia and its complications, a chest radiograph can also be used in very young children to see if the thymus is absent which could indicate various forms of SCID or a condition like DiGeorge Syndrome.

Who should he be referred to and what treatment might they offer?

His results show a lymphopaenia that is characterised by profoundly low numbers of T and B cells. This is in keeping with SCID. By definition, SCIDs are T-cell negative (T-). They can then be classified by the presence/absence of B-cells (B-cell positive, B+; B-cell negative, B-), followed by the presence of natural killer cells (NK+/NK-). This patient has a T-/B-/NK+ SCID. He will require genetic analyses to determine if there is a known mutation that underpins his phenotype. One potential cause for this could be a RAG1/RAG2 mutation, which is a commoner cause for this phenotype but still rare overall. He will need to be referred to a paediatric immunology team who can lead these investigations and begin the work-up for a bone marrow transplant.

Bone marrow transplantation reconstitutes the patient's immune system and can be curative for patients with SCID. It is long and physiologically challenging, for which patients need to be medically optimised prior to commencing treatment. Following the transplant, engraftment takes approximately four weeks, during which patients are very closely monitored. Life threatening complications from bone marrow transplant include infections during their immunosuppressed state, graft versus host disease, and veno-occlusive disease. Patients are initially on a

prophylactic combination of antibiotics, antivirals and antifungals as well as replacement immunoglobulin, which may rapidly need to be escalated if there is suspicion of an infection especially in the earliest stages post-transplant.

Detecting SCIDs

Depending on whether this patient had presented to services previously, it might have been possible with careful history taking and a high degree of vigilance to have detected this earlier.

However there also could be a possibility of detecting SCID cases and several other primary immunodeficiencies earlier through screening. SCID is identifiable from birth, is life-threatening and also treatable. This makes it a good candidate for screening. Furthermore, detection of a biomarker, T-cell receptor excision circles (TRECs) suitable for analysis from a dried bloodspot, means there is potential for this to take place. TRECs are a by-product of T-cell receptor (TCR) recombination process which results in diversifying the host's TCRs. A low number of TRECs indicates there could be a low number of T-cells, which in turn could heavily point towards SCID.

Using TRECs to screen for SCID has been used in the USA since 2018 and UK is currently undertaking a pilot of whether to include it as part of the day 5 newborn bloodspot screen. Patients with a low number of TRECs would then get invited for further testing, which would include checking lymphocyte subsets.

Not only would early detection minimise complications of infections and facilitate early transplantation, it would also ensure that babies with SCID are not given live vaccines such as the rotavirus or BCG vaccines, avoiding an iatrogenic life-threatening infection.

QUIZ QUESTIONS: (10 MINUTES)

Question 1.

In otherwise healthy children, how many simple upper respiratory tract infections are considered to be normal within one year?

- 1. One
- 2. Four
- 3. Ten
- 4. Fifteen

Answer: (3)

Question 2.

Which of the following features should prompt a consideration for whether a child has an underlying primary immunodeficiency

- 1. Five episodes of bronchiolitis in 2 years
- 2. Six episodes of upper respiratory tract infections 6 months
- 3. Two episodes of pneumonia in 3 months
- 4. One episode of bacterial meningitis across their life

Answer: (3)

Question 3.

Which of the following results would be expected in a patient with X-linked Agammaglobulinemia?

1. Reduced WCC
2. Reduced vaccine responses
3. Small platelet volume
4. Elevated CD19 (B-cell) count
5. Elevated CD3 (T-cell) count

Answer: (2)

Question 4.

What marker could be used to screen for SCID as part of the newborn blood spot test?

1. CD3
2. CD19
3. CD4:CD8 ratio
4. TREC
5. HLA typing

Answer (4)

Take home tips (learning points)

1 URTI ARE COMMON

It is normal for young children to get around 10 simple upper respiratory tract infections per year

2 REMEMBER THE WARNING SIGNS

Be familiar with the 10 warning signs of immunodeficiency, in particular paying attention to faltering growth, the need for IV antibiotics to clear infections, family history of immunodeficiency, and multiple deep-seated infections.

3 SPUR

Another useful framework to prompt you to think about primary immune deficiencies in relation to infections is the acronym SPUR (severe / persistent / unusual / recurrent).

4 TREC AND SCID

T-cell receptor excision circles (TRECs) are biomarker to screen for SCID in newborns

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 fellows@dontforgetthebubbles.com