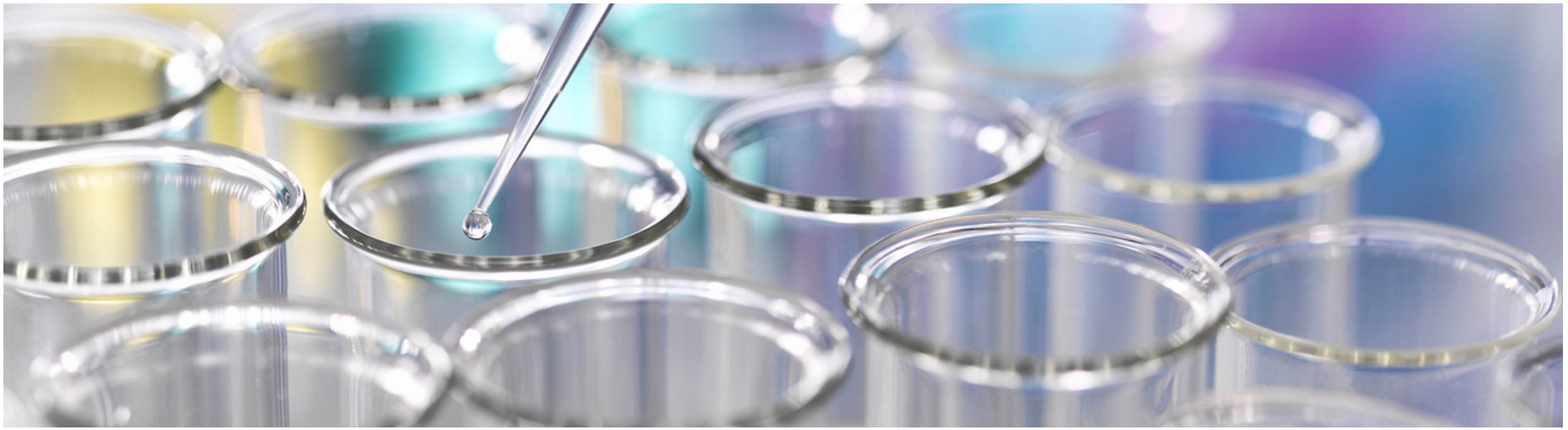
PRIMARY IMMUNODEFICIENCY (PI) – DISEASE STATE, DIAGNOSIS, AND TREATMENT OVERVIEW

RARE DISEASE HUB

C-ANPROM/UK/IG/0025 February 2022



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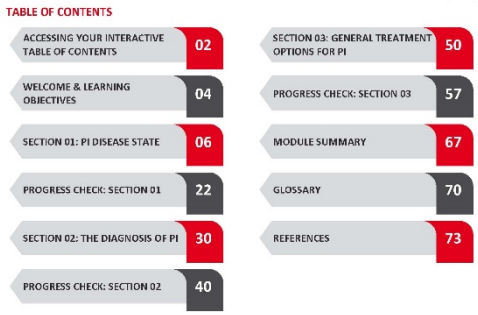

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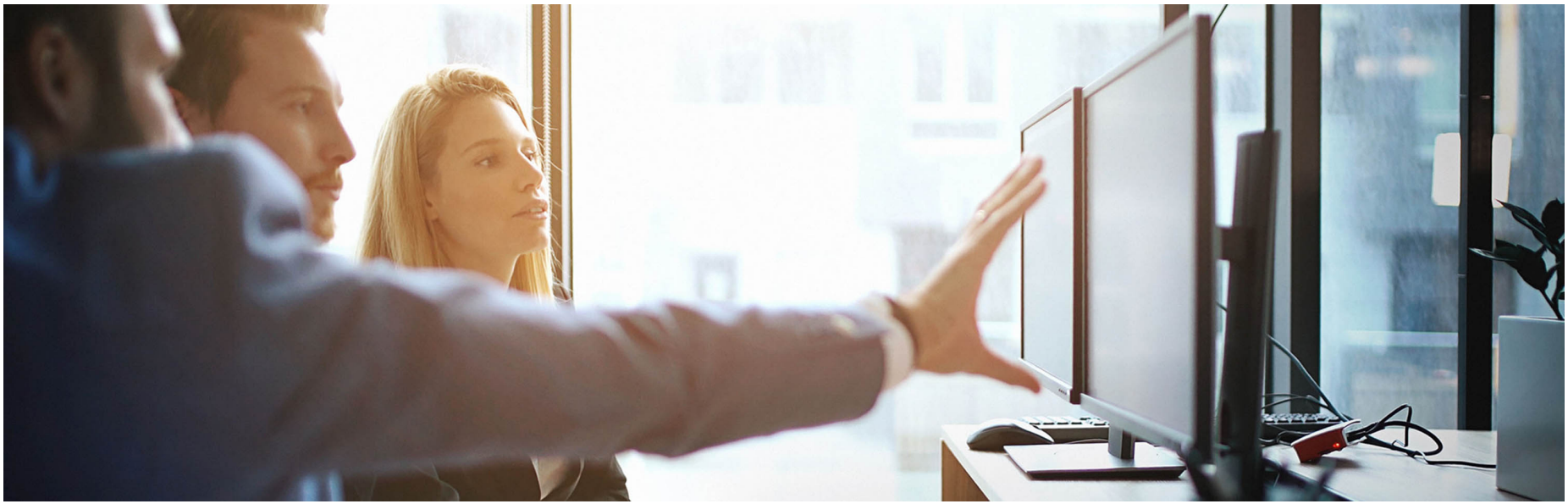


WELCOME & LEARNING OBJECTIVES

Upon completion of this module, you will be expected to demonstrate that you can…

- Discuss the epidemiology and occurrence of primary immunodeficiency (PI)
- List and describe the different categories of PI disease states
- Outline the warning signs of PI
- Discuss the diagnosis of PI
- List the general treatment options of PI

Welcome to the Primary Immunodeficiency (PI) – Disease State, Diagnosis and Treatment Overview Module!

Primary immunodeficiency (PI) is a group of more than 350 rare, chronic disorders in which part of the body's immune system is missing or functions improperly. These diseases are caused by hereditary or genetic defects, and they can affect anyone, regardless of age or gender.

So, what are the different types of PI, how are they diagnosed, and how are they treated? Answering these questions will be the focus of this module.

SECTION 01:
PI DISEASE STATE

Clinical Manifestations of PI

- Primary clinical manifestation of **primary immunodeficiency (PI)** is increased susceptibility to infection
  - Type of infection may vary depending on specific PI disease
- Some patients may also have:
  - Abnormal regulation of immune response with autoimmune disease
  - Malignancy
- No routine screening for PI
  - Detected after recurrent infections and possibly organ damage resulting in permanent impairment

Primary Immunodeficiency (PI)
The primary immunodeficiency diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and tissues of the immune system. Can be abbreviated as PI, PID and PAD.

Epidemiology of PI

- Because PI comprises many varying disease states, quantifying the condition and its patients is challenging
- No uniform population-based programs to test for all types of PI
- Incidence and prevalence estimates vary across geographies

The global prevalence of PI is estimated to be 1 per 10,000 individuals. These disorders are expected to affect at least 650,000 people worldwide*

**The precise global prevalence of PID is not clear. Data was extrapolated using a prevalence of 1:10,000 subjects and the worldwide population at the time the prevalence data was calculated.*

The United Kingdom Primary Immunodeficiency (UKPID) registry reported that the minimum PID prevalence in the UK, as of 2017, was 5.9 per 100,000.

DID YOU KNOW?

According to the Immune Deficiency Foundation (IDF), PI occurs equally in men and women (depending on the PI disease), and initial clinical presentation can occur at any age. However, certain PI diseases occur more commonly in one sex or the other, and some are more likely to manifest during childhood while others may not be detected until adulthood.

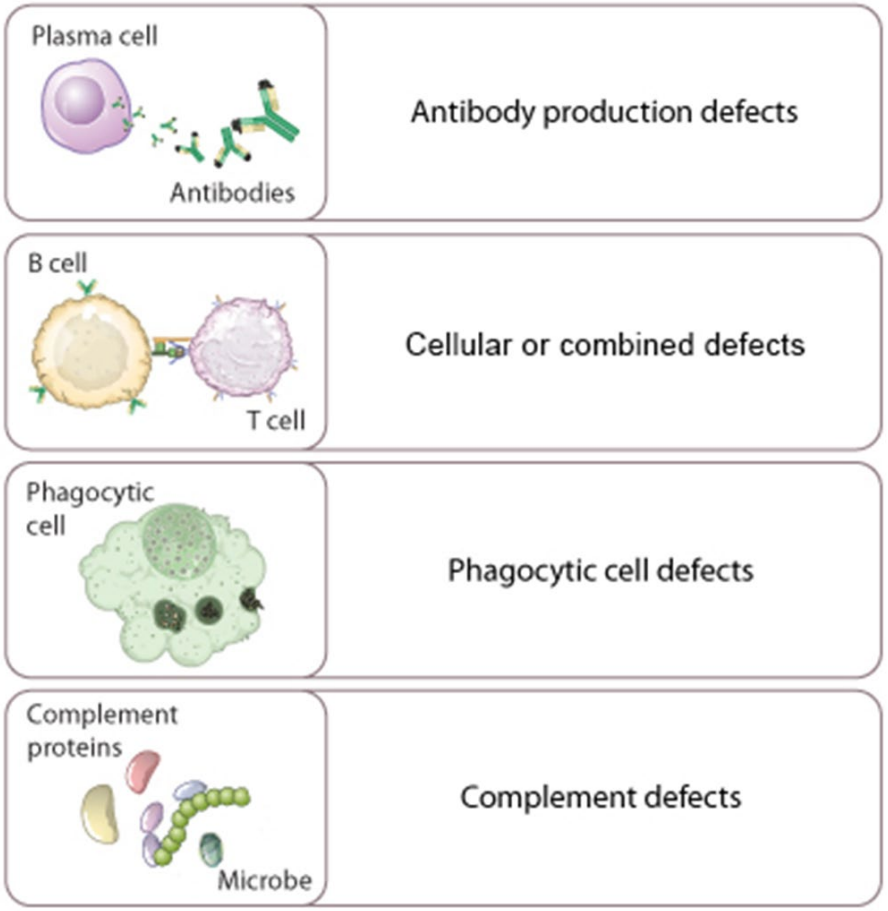
IDF statistics further show it takes an average of 12.4 years from symptom onset to a diagnosis of PI, and more than half of PI patients were not diagnosed until age 30 or older.

Therefore, when assessing for PI, it is important to be aware that incidence rates, gender affected, and age of onset vary with the specific PI disease.

Types of PI

The 350+ PI diseases are classified based on the principal immunologic mechanisms that are affected.

There are various categories of PI disorders, which include:



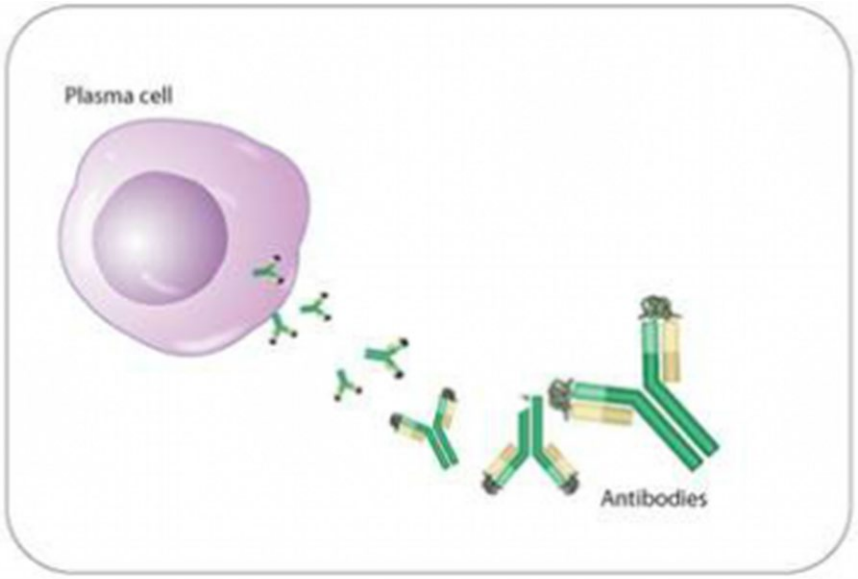
Let’s take a look at each category, starting with antibody production defects.

Antibody Production Defects

- A group of PI diseases that are characterised by the immune system's inability to produce an effective **antibody** response to a **pathogen**, such as a bacterium, virus, fungus, or parasite
- Antibody production defects can lead to low quantity and/or quality of antibody, which means antibodies are missing, not working properly, or too few in numbers to be effective

Underlying defect:

- Defects in **B cells**, which are directly responsible for antibody production
  - **T cells** help in activation and differentiation of B cells



Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combine specifically with an antigen to destroy or control it.

Pathogen
Any microorganism capable of producing disease.

B cell
Type of lymphocyte that identifies antigens and differentiates into antibody-producing plasma cells or memory cells.

T cell
Type of lymphocyte that responds to specific antigens with the assistance of antigen-presenting cells via cell-mediated immunity. May be further categorised by function as T helper cell or cytotoxic T cell.

Antibody Production Defects (Cont.)

Signs and symptoms:

- Bacterial, fungal, parasitic and viral infections
- **Sinopulmonary** infections
- **Otitis media**
- Gastrointestinal (GI) infections
- **Autoimmunity**

Sinopulmonary
Relating to the paranasal sinuses and the pulmonary airway.

Otitis media
Inflammation of the middle ear that can result in pain, fever, and hearing abnormalities.

Autoimmunity
Condition in which the body's ability to tolerate the antigens on its own cells is disrupted.

DID YOU KNOW?

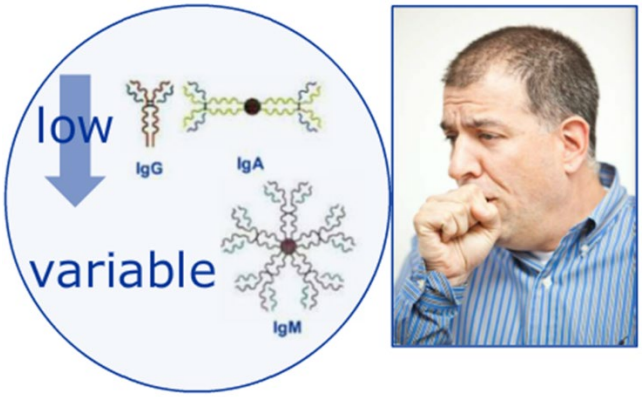
Antibody production defects are the most commonly diagnosed category of PI, accounting for about 50% of all reported cases of PI globally.

The onset of antibody production defects is typically after 6 months of age, when maternal antibodies wear off. However, antibody production defects may not present until adulthood.

Antibody Production Defects (Cont.)

Common Variable Immunodeficiency (CVID)

- CVID is the most frequently diagnosed PI requiring treatment, found in about 1 in 25,000 persons
- It is a heterogeneous group of diseases
- Features of CVID:
  - **Hypogammaglobinemia** is the predominant feature of CVID
  - Recurrent infections of the ears, sinuses, bronchi, and lungs
  - Low IgG and low IgA with variable IgM levels
  - Decreased IgG antibody responses to vaccination
  - Increased risk for developing autoimmune disorders and malignancies
  - GI complaints
  - Age of diagnosis: >2 years of age; most commonly in 20s or 30s

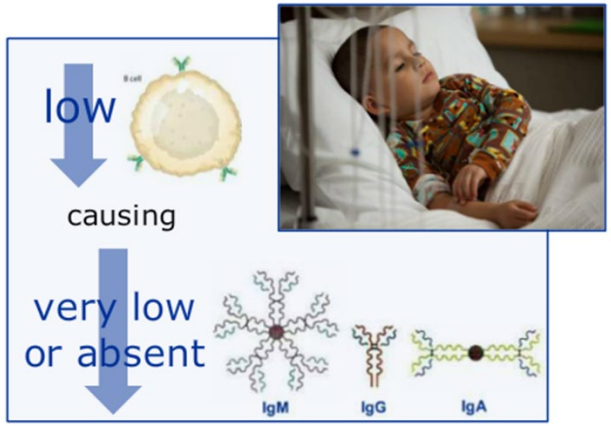


Hypogammaglobinemia
A deficiency of one or more of the five classes of immunoglobulins; caused by detective functioning of B lymphocytes (B cells).

Antibody Production Defects (Cont.)

X-Linked Agammaglobulinemia (XLA)

- XLA is a condition in which the patient has absent levels of serum immunoglobulins
- XLA results when B-cell development does not take place early in life, resulting in very low levels of circulating B cells
- Features of XLA:
  - Markedly reduced or absent IgM, IgG, and IgA
  - Reduced size and low numbers of lymphoid tissues (e.g., **adenoids, lymph nodes, tonsils**, and **spleen**)
  - Susceptibility to sinopulmonary infections and enteroviral infections (e.g., encephalitis)
  - Diagnosis is typically after 6 months of age



HERE'S THE CONNECTION

X-linked agammaglobulinemia, as its name indicates, is traceable to the X chromosome; therefore, only males are affected. There is another form of agammaglobulinemia called ARA that is inherited by females.

Adenoids
Lymphatic unencapsulated structures located on the posterior wall of the nasopharynx.

Lymph nodes
A small encapsulated lymphoid organ that filters lymph. Lymph nodes are found at junctions or branches along the lymphatic vessels. They are sites where immune responses can be generated through the interaction of antigens, macrophages, dendritic cells, and lymphocytes.

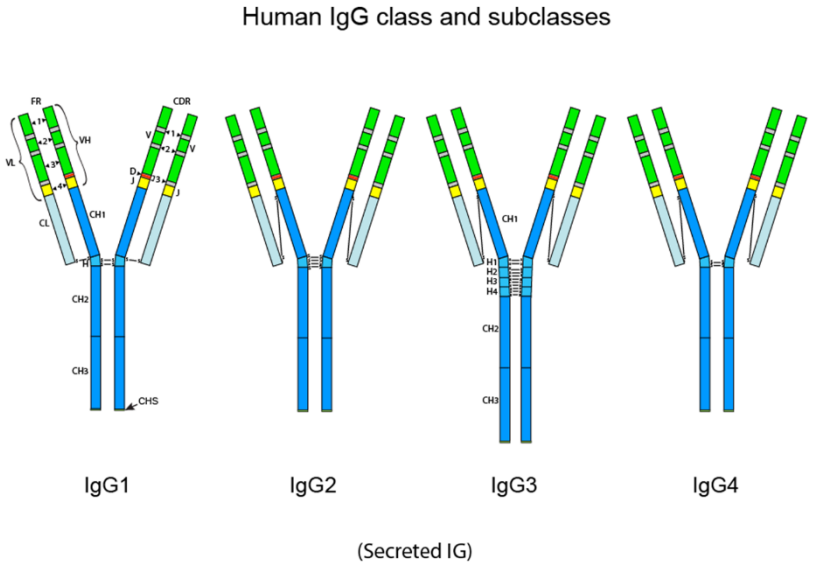
Tonsils
A mass of lymphoid tissue in the mucous membranes of the pharynx and base of the tongue.

Spleen
Highly vascular ductless abdominal organ closely associated with the circulatory system that plays a role in the final destruction of red blood cells, filtration and storage of blood, and production of lymphocytes; consists largely of blood and lymphoid tissue.

Antibody Production Defects (Cont.)

IgG Subclass Deficiency and Specific Antibody Deficiency (SAD)

- IgG subclass deficiency
  - Low levels of one or more of the four IgG subclasses (IgG1, IgG2, IgG3, and IgG4), but normal or near normal total IgG and other immunoglobulin (IG) levels
  - Since IgG1 comprises 60% of the total IgG level, deficiency of IgG1 usually drops the total IgG level below the normal range, resulting in hypogammaglobulinemia
  - Susceptibility to certain kinds of infections (such as recurrent ear infections, sinusitis, bronchitis, and pneumonia) but not to others, depending on which IgG subclass is deficient
- Specific antibody deficiency (SAD)
  - Failure to produce antibody response to *Streptococcus pneumonia* infections or to vaccination against pneumonia despite normal total IgG serum levels, due to deficiency in IgG2
  - Some patients may be unable to produce specific IgG antibodies to protect against certain viral and bacterial infections



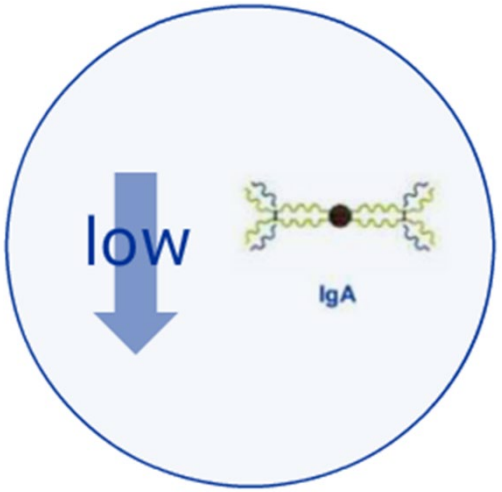
DID YOU KNOW?

Selective IgG subclass and specific antibody deficiencies occur more often in children than in adults, and the type of deficiency in children (that is, predominantly IgG2) differs from that most commonly seen in adults (IgG3). These findings suggested that at least some children may "outgrow" their deficiencies. However, it may persist in some children as well as in adults, and in some instances may evolve into common variable immunodeficiency. For these reasons, periodic re-evaluation of serum IG and IgG subclass levels, including the need for continued treatment, is necessary.

Antibody Production Defects (Cont.)

Selective IgA Deficiency

- Characterised by reduced serum IgA and normal serum levels of IgM and IgG
  - IgG subclass deficiency occurs in about 18% of IgA-deficient patients
- Features of selective IgA deficiency:
  - Since IgA is secreted onto the mucosal surfaces, symptomatic patients typically present with recurrent ear infections, sinusitis, bronchitis, and pneumonia; some patients present with GI disorders
  - Increased risk of allergies and autoimmune diseases
  - Age of diagnosis: >4 years of age



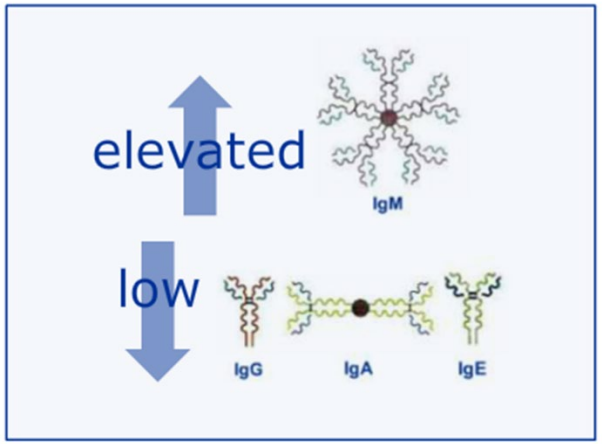
DID YOU KNOW?

IgA deficiency may have the highest prevalence of any PI (occurring in 1 in 500 patients), although many patients are asymptomatic and underdiagnosed.

Antibody Production Defects (Cont.)

Hyper IgM (HIGM)

- Characterised by severe recurrent bacterial infections, and decreased serum levels of IgG, IgA, and IgE, but normal or elevated IgM
- Underlying defect:
  - Inability of B cells to switch from production of IgM, the first IG class to be produced during the primary response of **adaptive immunity**, to the production of IgG, IgA, and IgE



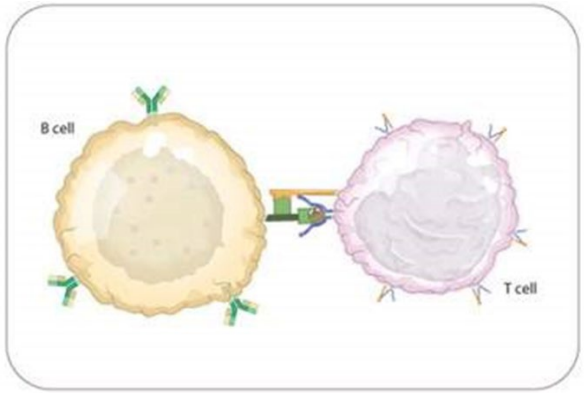
- Features of HIGM:
  - Most common problem is repeated upper and lower respiratory infections
  - Increased risk of malignant diseases (e.g., lymphoma) and liver and **biliary** tumours
  - X-linked HIGM (XHIGM) is the most common form of HIGM
    - Patients may develop opportunistic form of pneumonia or GI infection that can cause severe liver disease
    - Age of diagnosis: first few years of life

Adaptive immunity
The component of immunity that is pathogen specific and creates memory. It consists of the mechanisms of cell-mediated and antibody-mediated immunity.

Biliary
Relating to bile (fluid secreted by the liver that aids in the digestions of fats) or the biliary tract.

Cellular or Combined Defects

- Underlying defect:
  - Abnormal T-cell function
  - Combined T-cell and B-cell defects
- Signs and symptoms:
  - Affected individuals have both common and unusual infections
  - Patients susceptible to serious viral and fungal infections
  - More severe than antibody deficiencies
  - Patient presents early with failure to thrive, **disseminated** infections, skin infections, and sometimes autoimmunity
- Epidemiologic features:
  - Accounts for about 30% of all diagnosed PI cases
  - Onset is often in infancy or young childhood



Disseminated
Widely scattered throughout an organ, tissue, or the body.

Cellular or Combined Defects (Cont.)

Severe Combined Immunodeficiency (SCID)

- Potentially fatal syndrome involving T-cell and B-cell deficiencies and possibly **natural killer (NK) cell** deficiencies
- Features of SCID:
  - Characterised by severe opportunistic infections, chronic diarrhoea, and failure to thrive during infancy
  - Children with SCID may develop severe infections including pneumonia, **meningitis**, or infections of the blood stream
  - X-linked SCID is the most common form of SCID
  - Age of diagnosis: within 3 months of age

Natural killer (NK) cells
A large granular lymphocyte that can react against and destroy cancer cells and virus-infected cells without prior sensitisation to it.

Meningitis
Inflammation of the membranes of the brain and spinal cord.

DID YOU KNOW?

Newborn studies in Australia, Switzerland, and Norway showed SCID prevalence to be 0.11, 0.47, and 0.045 per 100,000 live births, respectively.

In the UK, neonatal diagnosis of SCID patients with a positive family history had improved survival rate of >90%, suggesting that neonatal screening for SCID could improve patient outcomes.

There is strong evidence to show that SCID fulfills the international criteria for a condition to be screened for at birth.

Cellular or Combined Defects (Cont.)

Wiskott-Aldrich Syndrome (WAS)

- Characterised by **thrombocytopenia** (small dysfunctional **platelets** resulting in an increased tendency to bleed), **eczematous** rash, and increased susceptibility to recurring bacterial, viral, and fungal infection
- Features of WAS:
  - Individuals with WAS have both abnormal B-cell and T-cell function
  - The initial presentation is prolonged bleeding at incision sites (such as circumcision), bloody diarrhoea, or excessive bruising; this occurs early in life
  - Common infections may include upper and lower respiratory infections, such as ear infections, sinus infections, and pneumonia
  - Risk of developing autoimmune disease and cancer
  - Occurs in males and is caused by a gene mutation located on the X chromosome
  - Age of diagnosis: toddler age and after

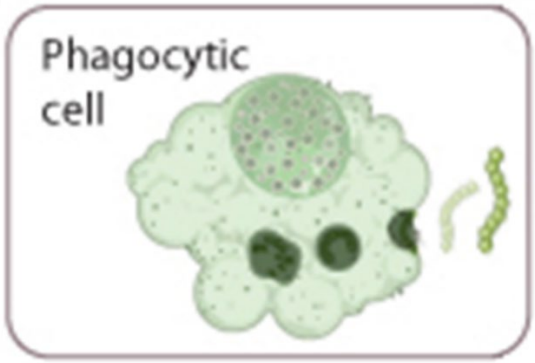
Thrombocytopenia
A condition marked by an abnormal decrease in platelet count.

Platelets
Round or oval disk-like megakaryocyte fragments found in the blood of vertebrates that function in clotting.

Eczematous
Marked by or resembling eczema (a skin condition characterised by an itchy red rash that initially weeps or oozes serum and may become crusted, thickened, or scaly).

Phagocytic Cell Defects

- Underlying defect:
  - Lack of **phagocytes** (known as congenital **neutropenia**)
  - Defective phagocyte migration (known as **leukocyte adhesion deficiency [LAD]**)
  - Inability to process/degrade ingested organisms (known as chronic granulomatous disease [CGD])



- Signs and symptoms:
  - Bacterial, fungal, and parasitic infections
  - **Boils** and/or **cellulitis**, **lymphadenitis**, pneumonia, delayed separation of the umbilical cord, hepatic abscesses, GI disorders, **gingivitis**, and unexplained fever, malaise, and fatigue
  - Infections in CGD may involve any organ or tissue, but the skin, lungs, lymph nodes, liver, and bones are the usual sites of infections

- Epidemiologic features:
  - Phagocytic cell defects accounts for about 18% of all diagnosed PI
  - X-Linked CGD occurs more frequently in males
  - Onset is typically in childhood; however, some patients with CGD may not have infections until adulthood

Phagocytes
White blood cells (neutrophils and macrophages) that can ingest and destroy microorganisms, cell debris, and other particles in the blood or tissues.

Neutropenia
Presence of abnormally small numbers of neutrophils in the circulating blood.

Leukocyte adhesion deficiency (LAD)
A rare primary immunodeficiency disease in which white blood cells are unable to transition out of blood vessels as a response to infection.

Boil
A tender, dome-shaped lesion of the skin most frequently caused by *Staphylococcus aureus* infection around a hair follicle.

Cellulitis
A spreading bacterial infection of the skin and subcutaneous tissue usually cause by streptococcal or staphylococcal infections.

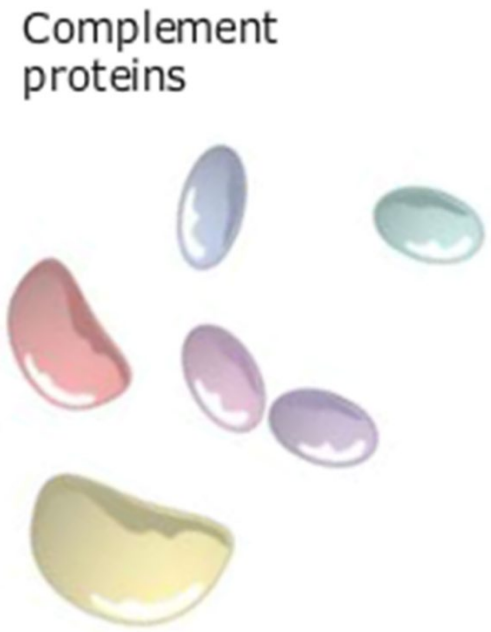
Lymphadenitis
Inflammation of the lymph nodes.

Gingivitis
Inflammation of the gums characterised by redness, swelling, and tendency to bleed.

Complement Defects

Wiskott-Aldrich Syndrome (WAS)

- Underlying defect:
  - Defective activation of the **complement** cascade; may be caused by the absence or dysfunction of the more than 25 complement proteins
- Signs and symptoms:
  - Depending on which complement protein is defective, patients may present with different symptoms of autoimmunity, episodes of **angioedema,** or recurrent bacterial infections
  - Deficiencies of early (C1 through C4) components in classical complement pathway present with symptoms of autoimmunity, episodes of angioedema, or recurrent bacterial infections (e.g., *Streptococcus pneumoniae*)
  - Deficiencies in late (C5 through C9) complement components typically present with *Neisseria* infections
  - Potential complement-related problems include renal disease, vasculitis (blood vessel **inflammation**), and age-related macular degeneration
- Epidemiologic features:
  - Account for 2% of all diagnosed PI cases
  - Can occur at any age



Complement
A group of more than 25 distinct serum proteins that play a vital role in the body's immune response though a cascade of interactions. These proteins act by directly lysing (killing) invading organisms and have a role in stimulating inflammation.

Angioedema
The development of swollen areas of the skin, mucous membranes, or internal organs that is often associated with urticaria (hives). Typically results from an allergic reaction to foods or drugs.

Inflammation
An immunological defence against injury, infection, or allergy, marked by increases in regional blood flow, immigration of white blood cells, and release of chemical toxins. Inflammation is one way the body uses to protect itself from invasion by foreign organisms and to repair wounds to tissue. Clinical hallmarks of inflammation are redness, heat, swelling, pain, and loss of function of a body part.

PROGRESS CHECK

QUESTION ONE

Think about how you would complete the following question, then select the Check Your Answer button.

Which is the primary clinical manifestation of PI?

A Deficient response to vaccination

B Allergies and autoimmunity

C Failure to thrive

D Increased susceptibility to infection

E Antigen sensitivity

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ONE

Which is the primary clinical manifestation of PI?

A Deficient response to vaccination

B Allergies and autoimmunity

C Failure to thrive

D Increased susceptibility to infection

E Antigen sensitivity

PROGRESS CHECK (CONT.)

QUESTION TWO

Think about how you would complete the following question, then select the Check Your Answer button.

Which of the following statements regarding the epidemiology of PI is TRUE?

A PI occurs more frequently in females than males

B PI is typically diagnosed in adulthood

C Antibody production defect is the most frequent type of diagnosed PI globally

D Prevalence estimates of PI are consistent in the United States and Europe

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWO

Which of the following statements regarding the epidemiology of PI is TRUE?

A PI occurs more frequently in females than males

B PI is typically diagnosed in adulthood

C Antibody production defect is the most frequent type of diagnosed PI globally

D Prevalence estimates of PI are consistent in the United States and Europe

PROGRESS CHECK (CONT.)

QUESTION THREE

Think about how you would complete the following question, then select the Check Your Answer button.

Categorise each of the following PI disease to the corresponding PI category.

	Antibody Production Defects	Cellular or Combined Defects	Phagocytic Defects	Complement Defects
Hyper IgM (HIGM)				
C2 deficiency				
Severe combined immunodeficiency (SCID)				
X-linked agammaglobulinemia (XLA)				
Chronic granulomatous disease (CGD)				
Common variable immunodeficiency (CVID)				
Selective IgA deficiency				
Wiskott-Aldrich syndrome (WAS)				
Specific antibody deficiency (SAD) & IgG Subclass Deficiency				

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION THREE

Think about how you would complete the following question, then select the Check Your Answer button.

Categorise each of the following PI disease to the corresponding PI category.

	Antibody Production Defects	Cellular or Combined Defects	Phagocytic Defects	Complement Defects
Hyper IgM (HIGM)	X			
C2 deficiency				X
Severe combined immunodeficiency (SCID)		X		
X-linked agammaglobulinemia (XLA)	X			
Chronic granulomatous disease (CGD)			X	
Common variable immunodeficiency (CVID)	X			
Selective IgA deficiency	X			
Wiskott-Aldrich syndrome (WAS)		X		
Specific antibody deficiency (SAD) & IgG Subclass Deficiency	X			

PROGRESS CHECK (CONT.)

QUESTION FOUR

Think about how you would complete the following question, then select the Check Your Answer button.

Match each key feature with the most appropriate PI disease.

Patients present with hypogammaglobulinemia along with increased risk for developing autoimmunity disorders and malignancies		WAS
Involves the block of early B-cell development, which results in very low levels of circulating B cells		Selective IgA
May be most prevalent of any PI (occurring in 1 in 500 patients), but often asymptomatic and underdiagnosed		SCID
Inability of B cells to switch type of antibody production		CVID
Potentially fatal syndrome characterised by severe opportunistic infection, chronic diarrhoea, and failure to thrive during infancy		CGD
Initial presentation is early in life and includes prolonged bleeding at incision sites, such as circumcision; bloody diarrhoea; or excessive bruising		HIGM
Most frequently diagnosed phagocytic cell immune defect		XLA

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FOUR

Match each key feature with the most appropriate PI disease.

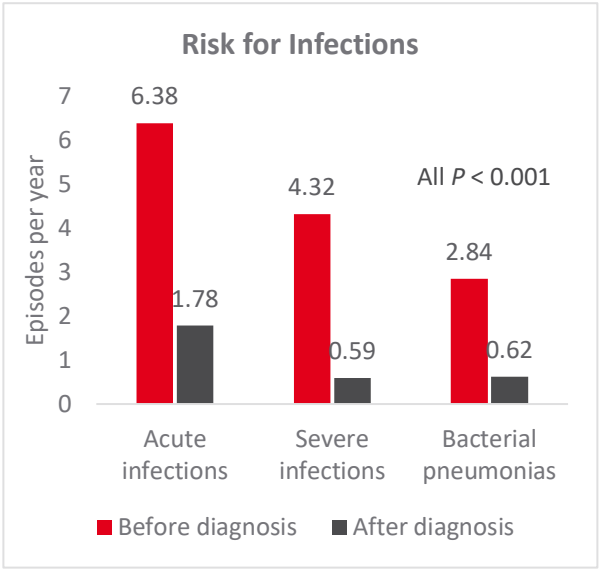
Patients present with hypogammaglobulinemia along with increased risk for developing autoimmunity disorders and malignancies	CVID
Involves the block of early B-cell development, which results in very low levels of circulating B cells	XLA
May be most prevalent of any PI (occurring in 1 in 500 patients), but often asymptomatic and underdiagnosed	Selective IgA
Inability of B cells to switch type of antibody production	HIGM
Potentially fatal syndrome characterised by severe opportunistic infection, chronic diarrhoea, and failure to thrive during infancy	SCID
Initial presentation is early in life and includes prolonged bleeding at incision sites, such as circumcision; bloody diarrhoea; or excessive bruising	WAS
Most frequently diagnosed phagocytic cell immune defect	CGD

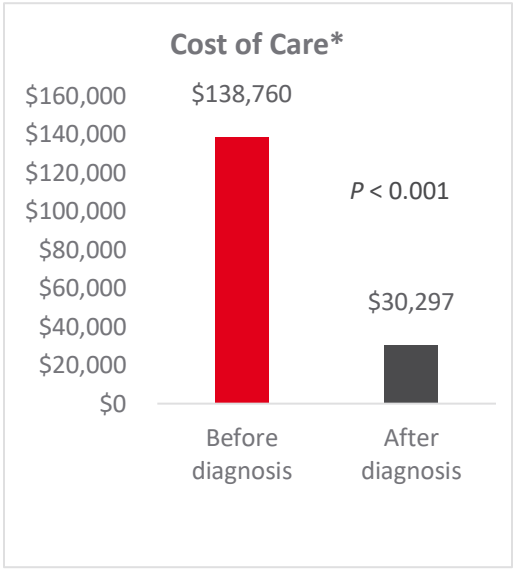
SECTION 02:
THE DIAGNOSIS OF PI

Challenges and Benefits of Diagnosis

- A large, global study demonstrated impact of identifying patients with underlying PI
  - Decreased risk of acute and serious infections, hospitalisations, and missed school and workdays
  - Substantial cost of care savings
- Despite the importance of early detection, awareness and appropriate and timely management of PIs are low among physicians and the general public, and many patients are undiagnosed

Diagnosis decreases acute and serious infections and cost of care for Primary Immunodeficiency Diseases





**This does not include the cost of immunoglobulin, estimated to be $30,000 per year*

(A 2011 study of 60,364 patients in 64 countries worldwide)

HERE'S THE CONNECTION

There are no sensitive or economical screening methods to identify all types of PI in the general population. As a result, PI diseases are typically diagnosed after the patient has experienced numerous recurrent infections and possible organ damage resulting in permanent impairment.

Warning Signs of PI

10 Warning Signs of PI for Children

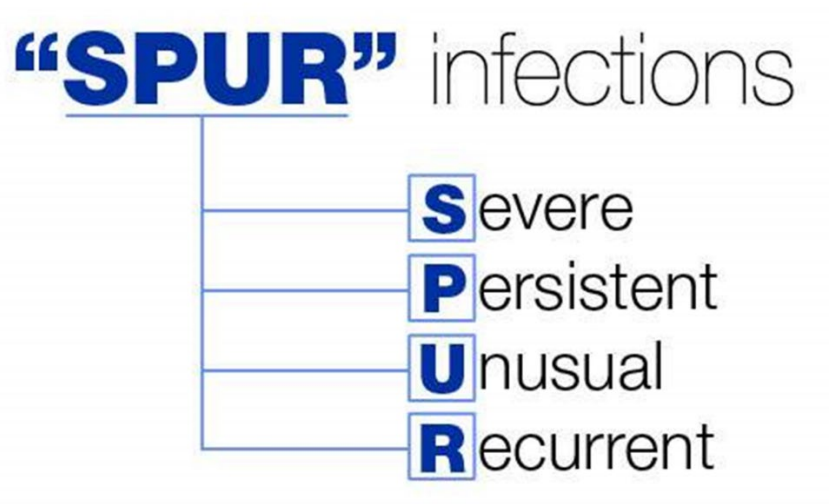
1	Four or more new ear infections within 1 year
2	Two or more serious sinus infections within 1 year
3	Two or more months on antibiotics with little effect
4	Two or more pneumonias within 1 year
5	Failure of an infant to gain weight or grow normally
6	Recurrent, deep skin or organ abscesses
7	Persistent thrush in mouth or fungal infection on skin
8	Need for intravenous antibiotics to clear infections
9	Two or more deep-seated infections including septicaemia
10	A family history of PI

10 Warning Signs of PI for Adults

1	Two or more new ear infections within 1 year
2	Two or more new sinus infections within 1 year, in the absence of allergy
3	One pneumonia per year for more than 1 year
4	Chronic diarrhoea with weight loss
5	Recurrent viral infections (colds, herpes, warts, condyloma)
6	Recurrent need for intravenous antibiotics to clear infections
7	Recurrent, deep abscesses of the skin or internal organs
8	Persistent thrush or fungal infection on skin or elsewhere
9	Infection with normally harmless tuberculosis-like bacteria
10	A family history of PI

Warning Signs of PI (Cont.)

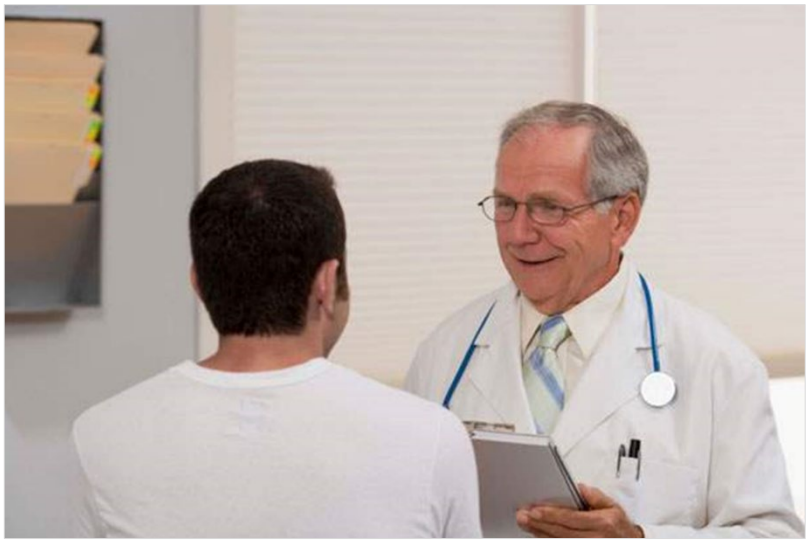
The Immune Deficiency Foundation (IDF) has come up with an acronym to help remember the warning signs of PI:



Let's now review the overall diagnostic approach for suspected PI.

Medical History and Physical Exam

Suspicion of PI may begin with the evaluation of a patient by a primary care physician, paediatrician, or other type of healthcare professional who may or may not have specific expertise in immunology. If PI is suspected, the physician should collect a thorough patient and family medical history. In addition, a physical exam should be performed with a focus on findings that might suggest PI. Let's take a closer look at both of these.



Medical History of Patient and Family

This includes questions regarding:

- Type, length, severity, and frequency of infection
- Response to therapy
- Family members with similar symptoms, which may include severe and recurrent infections, early deaths, only boys affected, and medical history of PI

Medical History and Physical Exam (Cont.)

Physical Examination Findings That May Suggest PI

Area	Finding	Possible PI
HEENT (head, eyes, ears, nose, throat)	Scarred **tympanic membranes**	Antibody production defects
	Absent or small tonsils	Antibody production defects (XLA)
Lungs	Abnormal breath sounds—**rhonchi** or **rales** (suggesting bronchial damage)	Antibody production defects Phagocytic cell defects (CGD)
Abdomen	**Splenomegaly**	Antibody production defects (CVID)
Lymph nodes	Absent or small lymph nodes	Antibody production defects (XLA) Cellular or combined defects (SCID)
	Disseminated **lymphadenopathy**	Cellular or combined defects (SCID) Antibody production defects (HIGM)
Skin	Eczema	Cellular or combined defects (WAS)
	Boils/Soft tissue abscesses	Phagocytic cell defects (CGD)

Tympanic membrane
The three-layered membrane at the inner (medial) end of the external auditory canal, forming the lateral boundary of the middle ear cavity. Also known as the ear drum.

Rhonchi
Low-pitched wheezing, snoring, or squeaking sounds heard on auscultation (listening with a stethoscope) of the chest and caused by air passing through bronchi that are narrowed by tumours, spasm of smooth muscle, or presence of mucus or other secretions in the airway.

Rales
Adventitious lung sounds heard on auscultation (listening for diagnostic purposes) of the chest, which may be heard on inspiration or expiration. Also known as crackles.

Splenomegaly
Enlargement of the spleen.

Lymphadenopathy
Appearance of enlarged lymph nodes, typically greater than 1.5 cm in size, caused by activation or propagation of white blood cells within lymph nodes or by tumour.

Laboratory Tests

In cases of suspected PI, laboratory screening should include several routine tests that assess immune function. The exact testing regimen will depend on the PI category.

Laboratory Tests (Cont.)

Principle Laboratory Tests for Suspected PI

Test	Description	Category of PI Screened
CBC with differential	Establishes whether **lymphocyte**, **neutrophil**, and platelet counts are normal.	Antibody production defects Cellular/combined defects Phagocytic cell defects
Quantitative serum IG measurements	Measures levels of IgG, IgA, IgM, and IgE in the blood, and compares the results to normal values for the patient's age. Checks for humoral (B cell) immunodeficiency.	Antibody production defects
Antibody response to vaccine testing	Evaluates the body's ability to mount an antibody response (as measured by antibody titre) to the **antigens** contained in certain routinely administered vaccines.	Antibody production defects (including SAD)
Delayed-type hypersensitivity skin tests	Measures the presence of selective T cell deficiencies.	Cellular/combined defects
Total haemolytic complement assay	Assesses deficiencies in complement proteins.	Complement defects

Complete blood count (CBC) with differential

Blood count that includes separate counts for red and white blood cells as well as separate counts for each kind of white blood cell.

Lymphocytes

White blood cells formed in the bone marrow and distributed throughout the body in lymphatic tissue, including T cells, B cells and natural killer cells; responsible for much of the body's immune protection.

Neutrophils

Most common white blood cell responsible for much of the body's protection against infection. Has a primary role in inflammation functioning as a phagocyte. Releases microbe-destroying enzymes when killed during inflammation.

Antigen

Any substance that is capable of activating an immune response or binding with an antibody.

Laboratory Tests (Cont.)

Typical Laboratory Test Results for Antibody Production Defects

The combined results of the different laboratory tests aid in the diagnosis of a specific PI disease, as shown in this table.

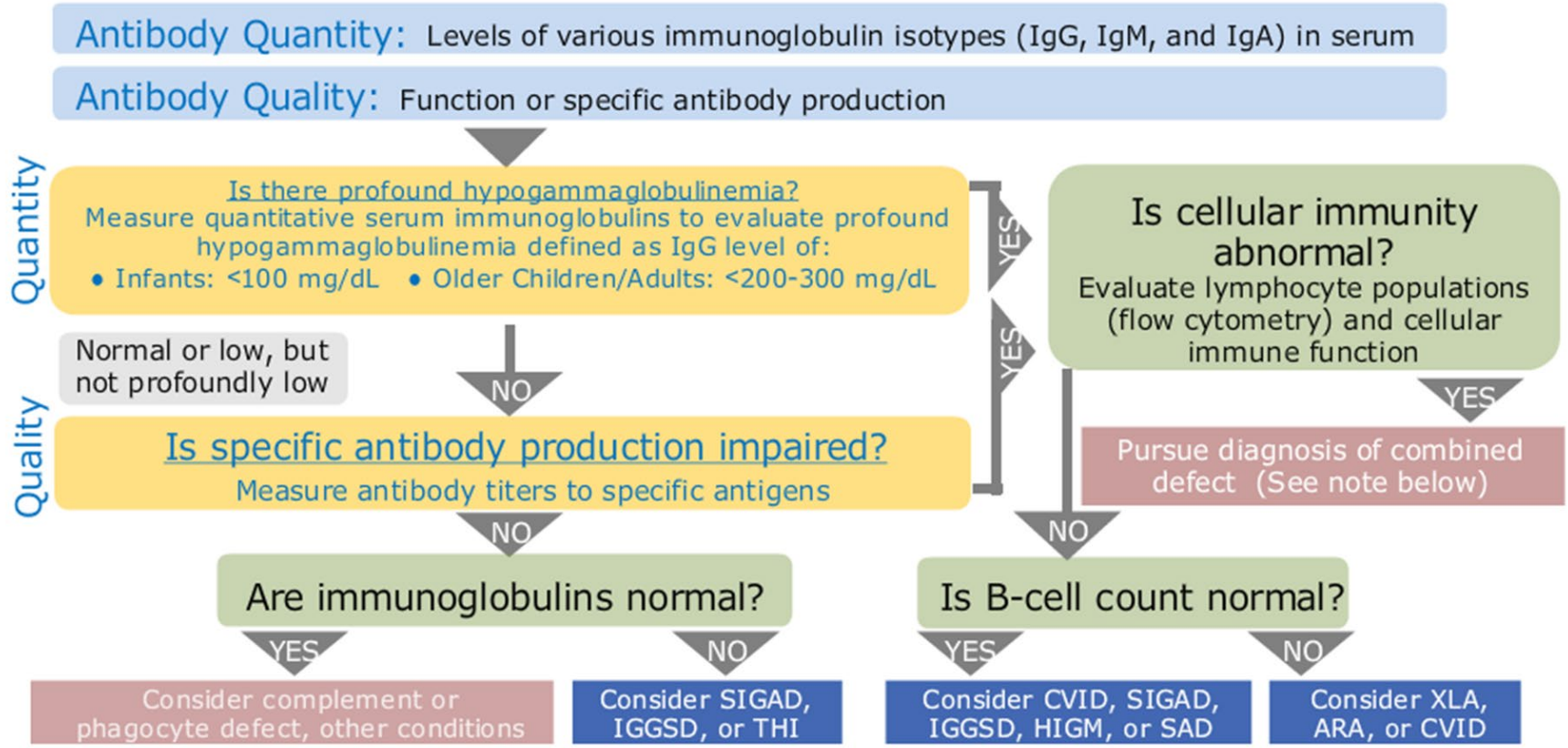
Disorder	Quantitative Serum IG Levels	Specific Antibody Response to Vaccination	CBC with Differential
CVID (common variable immunodeficiency)	Low IgG and low IgA with variable IgM levels	Decreased IgG response	Normal or low B-cell counts
Selective IgA deficiency	Low IgA Other types normal, except occasional IgG2 and/or IgG4 subclass deficiency	Normal IgG response	B-cell deficiency
XLA (X-linked agammaglobulinemia)	Low or absent IG levels	Decreased or absent IgG response	Decreased or absent B-cell counts
HIGM (Hyper IgM syndrome)*	Low IgG and IgA Normal or high IgM	Decreased or absent IgG response	Neutropenia in 50% of patients
SAD (specific antibody deficiency or IgG subclass deficiency)	Normal total IgG	Decreased IgG response to pneumonia infection or vaccine	Normal B-cell counts

**Definitive diagnosis of HIGM requires identification of a mutation affecting the CD40 gene.*

Diagnosing Antibody Production Defects

Patients with antibody production defects typically present with sinopulmonary bacterial infections.

The following algorithm was adapted from the Bonilla article to demonstrate the steps of immunological testing in these patients.



Abbreviations: ARA=Autosomal recessive agammaglobulinemia; CVID=common variable immunodeficiency; HIGM=hyper-IgM syndrome; IGGSD=IgG subclass deficiency; SAD=specific antibody deficiency; SIGAD=selective IgA deficiency; SIGAD=selective IgA deficiency; THI=transient hypogammaglobulinemia of infancy; XLA=X-linked agammaglobulinemia.
NOTE: This algorithm is intended to be applied to evaluate patients suspected of an antibody production defect only and is not intended to be applied in the evaluation of other categories of PI.

PROGRESS CHECK

QUESTION FIVE

Think about how you would complete the following question, then select the Check Your Answer button.

Fill in the blanks about PI diagnosis.

Patients can be diagnosed at any age. The average time from symptom onset to PI diagnosis is _____.

More than half of PI patients were not diagnosed until _____.

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FIVE

Fill in the blanks about PI diagnosis.

Patients can be diagnosed at any age. The average time from symptom onset to PI diagnosis is **12.4 years**.

More than half of PI patients were not diagnosed until **age 30 or older**.

PROGRESS CHECK (CONT.)

QUESTION SIX

Think about how you would complete the following question, then select the Check Your Answer button.

A physician mentions the acronym SPUR while discussing PI. What does this mean?

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SIX

A physician mentions the acronym SPUR while discussing PI. What does this mean?

- **S: Severe**
- **P: Persistent**
- **U: Unusual**
- **R: Recurrent**

PROGRESS CHECK (CONT.)

QUESTION SEVEN

Think about how you would complete the following question, then select the Check Your Answer button.

Why is early diagnosis and treatment of PI important?

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SEVEN

Why is early diagnosis and treatment of PI important?

The impact of identifying patients with underlying PI is a decreased risk of acute and serious infections, and substantial cost of care savings. Diseases diagnosed after numerous recurrent infections and possible organ damage may result in permanent impairment.

PROGRESS CHECK (CONT.)

QUESTION EIGHT

Think about how you would complete the following question, then select the Check Your Answer button.

Which of the following best represents the standard diagnostic approach to suspected PI?

A Patient and family medical history, physical examination, and de/re-challenge of antibiotic therapy to treat recurrent infection

B Physical examination, patient and family medical history, and consultation with infectious disease specialist

C Physical examination, patient and family medical history, and annual testing of antibody titres to pneumococcal vaccine

D Patient and family medical history, physical examination, and laboratory testing of CBC with differential and IG blood levels

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION EIGHT

Which of the following best represents the standard diagnostic approach to suspected PI?

A Patient and family medical history, physical examination, and de/re-challenge of antibiotic therapy to treat recurrent infection

B Physical examination, patient and family medical history, and consultation with infectious disease specialist

C Physical examination, patient and family medical history, and annual testing of antibody titres to pneumococcal vaccine

D Patient and family medical history, physical examination, and laboratory testing of CBC with differential and IG blood levels

PROGRESS CHECK (CONT.)

QUESTION NINE

Think about how you would complete the following question, then select the Check Your Answer button.

A patient's lab results revealed low total IgG levels, absent IgG response to vaccination, and absent B-cell count. This suggests that the patient has:

A XLA

B HIGM

C Selective IgA deficiency

D CVID

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION NINE

A patient's lab results revealed low total IgG levels, absent IgG response to vaccination, and absent B-cell count. This suggests that the patient has:

A XLA

B HIGM

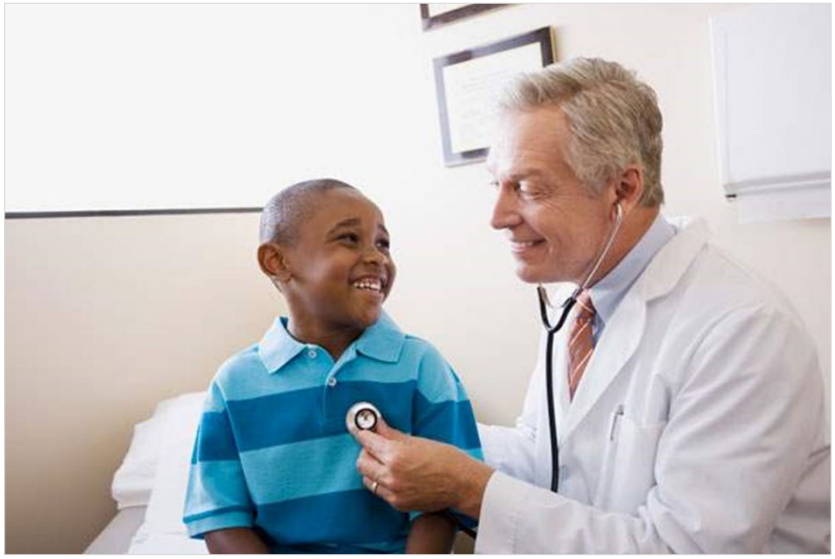
C Selective IgA deficiency

D CVID

SECTION 03:
GENERAL TREATMENT OPTIONS FOR PI

Goals of Treatment

- Prevent or reduce infections
- Aggressively treat any active infections
- Reduce risk of long-term organ damage



Types of Treatment

There are four possible types of treatment for PI:

- **IG replacement therapy**
- Antibiotic/antifungal/antiviral therapy
- **Haematopoietic stem cell (HSC)** transplantation
- Gene therapy

Immunoglobulin (IG) replacement therapy
Replacement of antibodies that are missing or not working properly; also known as antibody replacement therapy.

Haematopoietic stem cell (HSC)
A progenitor cell in the bone marrow that can replicate itself and produce precursor cells of the various blood cell lineages.

Types of Treatment (Cont.)

IG Replacement Therapy

- Administered **intravenously** or **subcutaneously**
- Replaces antibodies that are missing or not working properly
- Patients receive IG antibodies to a wide variety of bacterial and viral agents, enabling the body to fight off infections
- IG replacement therapy does not correct the body's inability to produce IgG antibodies on its own
  - As a result, SID patients may require repeated IG infusions throughout their lifetime (e.g. daily to once a month) to protect against recurrent and/or severe infections

Subcutaneous
Beneath the skin.

Intravenous
Within or into a vein.

DID YOU KNOW?

A survey of 21 countries revealed that the current regular treatment for PI patients is via IG replacement therapy, either alone or in combination with other therapies. 53% of IG therapy patients received IG product intravenously (IVIG), 45% received it subcutaneously (SCIG), and 2% received it by other routes.

Types of Treatment (Cont.)

Antibiotic/Antifungal/Antiviral Therapy

Antibiotics are used to treat active infections and can be used prophylactically to try to prevent recurrence.

This type of treatment may be used across the different categories of PI disorders:

Types of PI	Treatments
Antibody production defects	Antibiotics
Cellular or combined defects	Antibiotics
Phagocytic cell defects*	Antibiotics and antifungals
Complement defects	Antibiotics

Phagocytic cell defects (e.g., CGD) may also be treated with **gamma-interferon.*

Gamma-interferon
Antiviral protein (type II interferon) produced by T cells, natural killer cells and helper T cells; involved in the activation antigen-presenting cells, especially macrophages.

Types of Treatment (Cont.)

HSC transplantation

HSC transplantation replaces stem cells in patients with selected PIs. Examples of HSC include:

- Bone marrow
- Cord blood
- Peripheral blood

HSC donors provide a stem cell graft that is transplanted into the patient. HSC transplantation can be used for:

- Antibody production defects: XHIGM
- Cellular or combined defects: SCID, WAS
- Phagocytic cell defects: CGD

HERE'S THE CONNECTION

A stem cell is a type of cell that can differentiate into different types of immune cells, such as B cells and T cells. Matched siblings are the preferred donor source to minimise the risk of graft rejection. Without a successful HSC transplant, SCID patients are at constant risk for severe or fatal infection.

Types of Treatment (Cont.)

Gene therapy

Gene therapy is a new technology aimed at correcting the patient's defective gene with a normal gene.

- Involves risks (i.e., high rate of leukaemia in patients with SCID); research is underway to reduce risks
- Considered an experimental treatment

Has been used for:

- Cellular or combined defects: SCID, WAS
- Phagocytic cell defects: CGD

PROGRESS CHECK

QUESTION TEN

Think about how you would complete the following question, then select the Check Your Answer button.

Which of the following are types of treatment for antibody production defects? Select all that apply.

A IG replacement therapy

B Anti-inflammatories

C Blood transfusions

D HSC transplantation

E Antibiotic/antifungal/antiviral therapy

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TEN

Which of the following are types of treatment for antibody production defects?

A IG replacement therapy

B Anti-inflammatories

C Blood transfusions

D HSC transplantation

E Antibiotic/antifungal/antiviral therapy

PROGRESS CHECK (CONT.)

QUESTION ELEVEN

Think about how you would complete the following question, then select the Check Your Answer button.

List the three goals of PI treatment.

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ELEVEN

List the three goals of PI treatment.

- **Prevent or reduce infections**
- **Treat active infections**
- **Reduce risk of long-term organ damage**

PROGRESS CHECK (CONT.)

QUESTION TWELVE

Think about how you would complete the following question, then select the Check Your Answer button.

For each PI treatment, which of the categories of PI can it be used for?

	Antibiotic/antifungal/ antiviral therapy	IG replacement therapy	HSC transplantation
Antibody production defects			
Cellular or combined defects			
Phagocytic cell defects			
Complement defects			

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWELVE

For each PI treatment, which of the categories of PI can it be used for?

	Antibiotic/antifungal/ antiviral therapy	IG replacement therapy	HSC transplantation
Antibody production defects	X	X	X
Cellular or combined defects	X	X	X
Phagocytic cell defects	X		X
Complement defects	X		

PROGRESS CHECK (CONT.)

QUESTION THIRTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

A parent is told his child's HIGM might be treated with both antibody replacement therapy and an HSC transplant. What direct benefit does the HSC transplant provide?

A Primes the body to fight recurrence of bacterial infection

B Infuses donor plasma-derived IgG antibodies

C Graft donor stem cells that can differentiate into healthy immune cells which help to restore normal immune function

D Repairs defective genes in the patient's own stem cells

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION THIRTEEN

A patient's lab results revealed low total IgG levels, absent IgG response to vaccination, and absent B-cell count. This suggests that the patient has:

A Primes the body to fight recurrence of bacterial infection

B Infuses donor plasma-derived IgG antibodies

C Graft donor stem cells that can differentiate into healthy immune cells which help to restore normal immune function

D Repairs defective genes in the patient's own stem cells

PROGRESS CHECK (CONT.)

QUESTION FOURTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

Which of the following PI diseases are treated with IG replacement therapy? Select all that apply.

- **A** XLA
- **B** CVID
- **C** CGD
- **D** C2 deficiency
- **E** HIGM
- **F** IgA deficiency without IgG subclass deficiency

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FOURTEEN

Which of the following PI diseases are treated with IG replacement therapy? Select all that apply.

A XLA

B CVID

C CGD

D C2 deficiency

E HIGM

F IgA deficiency without IgG subclass deficiency

Module Summary

Description of PI

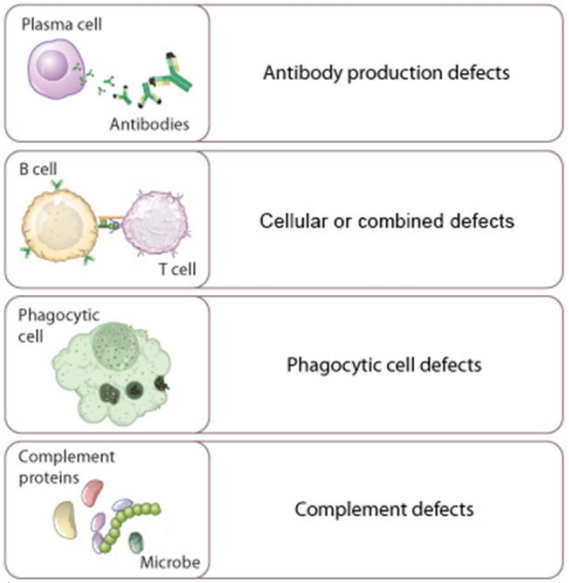
- PI encompasses more than 350 diverse diseases
- PIs usually result from defects in T cells, B cells, NK cells, phagocytic cells, or the complement system
- The primary clinical manifestation of PI is increased susceptibility to infection

Epidemiology of PI

- Incidence and prevalence estimates of PI vary across geographies – no uniform population-based programs to test for all types of PI
- Overall, PI occurs equally in men and women (depending on PI disease) and can present at any age

PI Categories

- PI diseases are classified into subgroups based on the components of the immune system affected. Some PI subgroups include antibody production defects, T-cell or combined B-cell/T-cell defects, phagocytic cell defects, and complement defects



Module Summary (Cont.)

PI Category	Underlying defect	Epidemiologic features	Signs and symptoms	Key diseases
Antibody production defects	• B cell defects (primarily) • B cells are activated by T cells	• Most common category of PI, accounting for 50% of all cases of PI globally • Onset is typically after 6 months of age, but may not present until adulthood	• Sinopulmonary infections, otitis media, GI infections, autoimmunity	• CVID, XLA, selective IgA deficiency, HIGM, SAD, IgG subclass deficiency
Cellular or combined defects	• Abnormal T-cell function • Combined T-cell and B-call defects	• Accounts for about 30% of all PIs • Onset is often in infancy or young childhood	• Patients susceptible to serious viral and fungal infections • Patient presents early with failure to thrive, disseminated infections, skin changes, and sometimes autoimmunity	• SCID, WAS
Phagocytic cell defects	• Lack of phagocytes (congenital neutropenia) • Defective phagocyte migration (leukocyte adhesion deficiency) • Inability to process/ degrade ingested organisms (chronic granulomatous disease)	• Accounts for about 18% of all PIs • Onset is typically in childhood; however, some patients with CGD may not have infections until adulthood	• Boils and/or cellulitis, lymphadenitis, pneumonia, delayed separation of the umbilical cord, hepatic abscesses, GI disorders, gingivitis, and unexplained fever, malaise, and fatigue • CGD infections may involve any organ or tissue, but skin, lungs, lymph nodes, liver, and bones are usual infection sites	• CGD
Complement defects	• Defective activation of the complement cascade	• Accounts for 2% of all PIs • Can occur at any age	• Autoimmunity, angioedema, bacterial infections, renal disease, vasculitis, age-related macular degeneration	• Complement component deficiencies

Module Summary (Cont.)

Diagnosis of PI

- PI diseases are typically diagnosed after the patient has experienced numerous recurrent infections and possible organ damage resulting in permanent impairment
- Identification of PI has been shown to decrease risk of infections and provide substantial cost savings
- The presence of PI should be suspected if the patient has:
  - Two or more of the 10 warning signs of PI (Jeffrey Modell Foundation)
  - Severe, persistent, unusual, and/or recurrent (SPUR) infections (Immune Deficiency Foundation)
- The diagnostic approach to suspected PI includes:
  - Patient and family medical history
  - Physical exam with a focus on findings that might suggest PI
  - Laboratory tests

Treatment of PI

- Goals of PI treatment are:
  - Prevent or reduce infections
  - Treat active infections
  - Reduce risk of long-term organ damage
- PI is routinely treated with one or more of the following four therapies, depending on the type of PI:
  - IG replacement therapy: replaces antibodies that are missing or not working properly
  - Antibiotics, antifungals, or antiviral therapy: used to treat current infections and try to prevent recurrent infections
  - HSC transplant: provides donated stem cells that will differentiate into healthy cells of the immune system
  - Gene therapy: experimental treatment aimed at replacing the patient's defective gene

GLOSSARY

Adaptive immunity
The component of immunity that is pathogen specific and creates memory. It consists of the mechanisms of cell-mediated and antibody-mediated immunity.

Adenoids
Lymphatic unencapsulated structures located on the posterior wall of the nasopharynx.

Angioedema
The development of swollen areas of the skin, mucous membranes, or internal organs that is often associated with urticaria (hives). Typically results from an allergic reaction to foods or drugs.

Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combine specifically with an antigen to destroy or control it.

Antigen
Any substance that is capable of activating an immune response or binding with an antibody.

Autoimmunity
Condition in which the body's ability to tolerate the antigens on its own cells is disrupted.

B cell
Type of lymphocyte that identifies antigens and differentiates into antibody-producing plasma cells or memory cells.

Biliary
Relating to bile (fluid secreted by the liver that aids in the digestions of fats) or the biliary tract.

Boil
A tender, dome-shaped lesion of the skin most frequently caused by *Staphylococcus aureus* infection around a hair follicle.

Complete blood count (CBC) with differential
Blood count that includes separate counts for red and white blood cells as well as separate counts for each kind of white blood cell.

Cellulitis
A spreading bacterial infection of the skin and subcutaneous tissue usually cause by streptococcal or staphylococcal infections.

Complement
A group of more than 25 distinct serum proteins that play a vital role in the body's immune response though a cascade of interactions. These proteins act by directly lysing (killing) invading organisms and have a role in stimulating inflammation.

Disseminated
Widely scattered throughout an organ, tissue, or the body.

GLOSSARY (CONT.)

Eczematous
Marked by or resembling eczema (a skin condition characterised by an itchy red rash that initially weeps or oozes serum and may become crusted, thickened, or scaly).

Gamma-interferon
Antiviral protein (type II interferon) produced by T cells, natural killer cells and helper T cells; involved in the activation antigen-presenting cells, especially macrophages.

Gingivitis
Inflammation of the gums characterised by redness, swelling, and tendency to bleed.

Haematopoietic stem cell (HSC)
A progenitor cell in the bone marrow that can replicate itself and produce precursor cells of the various blood cell lineages.

Hypogammaglobinemia
A deficiency of one or more of the five classes of immunoglobulins; caused by detective functioning of B lymphocytes (B cells).

Immunoglobulin (IG) replacement therapy
Replacement of antibodies that are missing or not working properly; also known as antibody replacement therapy.

Inflammation
An immunological defence against injury, infection, or allergy, marked by increases in regional blood flow, immigration of white blood cells, and release of chemical toxins. Inflammation is one way the body uses to protect itself from invasion by foreign organisms and to repair wounds to tissue. Clinical hallmarks of inflammation are redness, heat, swelling, pain, and loss of function of a body part.

Intravenous
Within or into a vein.

Leukocyte adhesion deficiency (LAD)
A rare primary immunodeficiency disease in which white blood cells are unable to transition out of blood vessels as a response to infection.

Lymph nodes
A small encapsulated lymphoid organ that filters lymph. Lymph nodes are found at junctions or branches along the lymphatic vessels. They are sites where immune responses can be generated through the interaction of antigens, macrophages, dendritic cells, and lymphocytes.

Lymphadenitis
Inflammation of the lymph nodes.

Lymphadenopathy
Appearance of enlarged lymph nodes, typically greater than 1.5 cm in size, caused by activation or propagation of white blood cells within lymph nodes or by tumour.

Lymphocytes
White blood cells formed in the bone marrow and distributed throughout the body in lymphatic tissue, including T cells, B cells and natural killer cells; responsible for much of the body's immune protection.

Meningitis
Inflammation of the membranes of the brain and spinal cord.

Natural killer (NK) cells
A large granular lymphocyte that can react against and destroy cancer cells and virus-infected cells without prior sensitisation to it.

Neutropenia
Presence of abnormally small numbers of neutrophils in the circulating blood.

Neutrophils
Most common white blood cell responsible for much of the body's protection against infection. Has a primary role in inflammation functioning as a phagocyte. Releases microbe-destroying enzymes when killed during inflammation.

GLOSSARY (CONT.)

Otitis media
Inflammation of the middle ear that can result in pain, fever, and hearing abnormalities.

Pathogen
Any microorganism capable of producing disease.

Phagocytes
White blood cells (neutrophils and macrophages) that can ingest and destroy microorganisms, cell debris, and other particles in the blood or tissues.

Platelets
Round or oval disk-like megakaryocyte fragments found in the blood of vertebrates that function in clotting.

Primary immunodeficiency (PI)
The primary immunodeficiency diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and tissues of the immune system. Can be abbreviated as PI, PID and PAD.

Rales
Adventitious lung sounds heard on auscultation (listening for diagnostic purposes) of the chest, which may be heard on inspiration or expiration. Also known as crackles.

Rhonchi
Low-pitched wheezing, snoring, or squeaking sounds heard on auscultation (listening with a stethoscope) of the chest and caused by air passing through bronchi that are narrowed by tumours, spasm of smooth muscle, or presence of mucus or other secretions in the airway.

Sinopulmonary
Relating to the paranasal sinuses and the pulmonary airway.

Spleen
Highly vascular ductless abdominal organ closely associated with the circulatory system that plays a role in the final destruction of red blood cells, filtration and storage of blood, and production of lymphocytes; consists largely of blood and lymphoid tissue.

Splenomegaly
Enlargement of the spleen.

Subcutaneous
Beneath the skin.

T cell
Type of lymphocyte that responds to specific antigens with the assistance of antigen-presenting cells via cell-mediated immunity. May be further categorised by function as T helper cell or cytotoxic T cell.

Thrombocytopenia
A condition marked by an abnormal decrease in platelet count.

Tonsils
A mass of lymphoid tissue in the mucous membranes of the pharynx and base of the tongue.

Tympanic membrane
The three-layered membrane at the inner (medial) end of the external auditory canal, forming the lateral boundary of the middle ear cavity. Also known as the ear drum.

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