Infections in the immunocompromised host: primary immunodeficiency disorders

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Abstract

Primary immunodeficiencies (PID), also termed inborn errors of immunity (IEI) arise usually from genetic mutations in immune-related genes, distinct from the more common secondary immunodeficiencies caused by malnutrition, HIV, or iatrogenic. This article provides an overview of PID pathophysiology and clinical presentations, emphasizing the relationship between specific immune defects and characteristic infectious susceptibilities.

The human immune system comprises interconnected innate and adaptive components that maintain tissue homeostasis through epithelial barriers, pattern recognition receptors, and adaptive lymphocyte responses. Disruption of these mechanisms by PID leads to predictable infection patterns. Antibody deficiencies, the most common PID, cause recurrent sinopulmonary infections with encapsulated bacteria due to impaired opsonization. Complement deficiencies create similar susceptibilities, with terminal complement defects uniquely predisposing to *Neisseria* infections. Whereas some PID have broader infection susceptibility, there are also sentinel infections such as *Candida* and mycobacterial infections which may also arise the suspicion of a possible underlying immunological defect. In addition to genetically-derived immune deficiencies, recent recognition of anti-cytokine autoantibodies represents a novel immunodeficiency mechanism.

Diagnostic approaches to patients with PID include functional immune assessments and genomic analysis. Treatment encompasses antimicrobial prophylaxis, immunoglobulin replacement, targeted therapies, and definitive correction through haematopoietic stem cell transplantation or gene therapy.

Keywords Herpesviruses; HPV; immune deficiency; inborn errors of immunity; infection; mycobacteria; *Neisseria*

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Key points

- Recurrent or severe infections are a common presenting feature of primary immune deficiencies (PIDs)
- PIDs typically confer susceptibility to particular spectra of infections and therefore identification of the microbes causing infection can give diagnostic clues to an underlying PID
- Antibody deficiencies, the most common form of PID, confer susceptibility to encapsulated organisms, typically resulting in recurrent chest infections
- Unusual severity and unusual organisms should prompt a clinician to consider an underlying PID

Introduction

The immune system is a complex network of tissues, cells and molecules that maintains tissue homeostasis in the face of infectious and non-infectious threats. Immunodeficiencies can arise when components of these networks are absent, dysfunctional or otherwise compromised.

Globally, malnutrition and HIV infection are the most common causes of immunodeficiency. In the developed world, iatrogenic secondary immunodeficiencies are increasingly common, arising after the use of chemotherapy or immunomodulatory drugs to treat immune-mediated inflammatory disease and cancer.

Primary immunodeficiencies, contemporarily referred to as inborn errors of immunity (IEI), are much rarer, tend to present at an early age and arise from intrinsic faults within the immune system itself. Individual immune system components are encoded by immune-related genes, and mutations in these lead to IEI.[1] Different IEI confer susceptibilities to infection ranging from near-universal fatality from a broad range of pathogens, as observed in severe combined immunodeficiency, to unique susceptibility to narrow families of pathogens such as *Neisseria,* as seen in terminal complement deficiencies (See Table 1).

Although the immune system has additional roles such as tumour surveillance, wound healing and maintenance of immunological tolerance to self-antigens, recurrent infections are the most common manifestation of IEI. Characteristic sentinel infections are pathognomonic of certain immunodeficiencies, and diagnostic delay in immunodeficiency patients contributes to end-organ damage and mortality.

This chapter provides an overview of common presentations of IEI and the relationships between underlying immune defects and infectious disease.

An overview of the human immune system

The human immune system is composed of tissues, cells and molecules that form a network supporting the maintenance of tissue homeostasis.

The immune system is broadly divided into the innate immune system and the adaptive immune system.[2] The innate immune system is characterized by rapid, generic responses to

Summary table of immunodeficiencies associated with infectious disease phenotypes

Sentinel infection	Phenotype	Defective immunological component	Mechanism
Bacterial disease	Recurrent sinopulmonary infections with encapsulated bacteria	BTK, NFKB1, PI3KCD, PIK3R1	B cell signalling defects resulting in antibody deficiency
		Immunoglobulins, e.g. IgG, IgA and IgM	Impaired opsonization
		Complement factors C1q, C3, properdin and factor B	Reduced opsonization and amplification of complement
	Recurrent *Neisseria* infection	Complement factors 5–9	Absent membrane attack complex formation
	Staphylococcal abscesses	NADPH oxidase complex – gp91/22/40/47/67	Impaired phagocytosis by disruption of NADPH oxidase system
		STAT3 loss of function	Impaired IL-6 signalling
		IL-6 receptor	
		IL-6 autoantibodies	
		IRAK4/MYD88/TIRAP	Impaired innate immune signalling
	Disseminated mycobacterial disease	IL-12/IL-23, IL-12, IL-12 receptor, IFN-γ, IFN-γ receptor, STAT1 loss of function, IFN-γ autoantibodies	Impaired IL-12/IL-23/IFN-γ signalling
Fungal disease	Invasive fungal disease – general	CARD9/DECTIN1 (CLEC7A)	Impaired innate immune signalling from fungal-specific PRRs
	Aspergillus abscesses	NADPH oxidase complex – gp91/22/40/47/67	Impaired phagocytosis by disruption of NADPH oxidase system
	CMC	IL-17, IL-17 receptor	Impaired IL-17 signalling
		STAT1 gain of function, STAT3 loss of function	Inhibition of CD4 + T cell differentiation to Th17 cells
		AIRE	IL-17/IL-22 autoantibodies and IFN-γ/STAT1 dysregulation
Viral disease	HSV encephalitis	TLR3, UNC93B1, TRAF3, TBK1, IRF3	Impaired IRF3 signalling after TLR stimulation
	EBV susceptibility	SAP, XIAP, CD27, CD70, CTPS1, MAGT1, PRKCD, PI3KR1	Impaired lymphocyte signalling required for control of EBV
	HPV susceptibility	CXCR4, DOCK8, EVER1/EVER2 (TMC6/TMC8)	Reduced T cell mobility to sites of HPV infection
		GATA2	Reduced dendritic cells, NK cells
	Respiratory virus susceptibility	Immunoglobulins, e.g. IgG, IgA and IgM	Impaired opsonization and neutralization
		TLR3, UNC93B1, TRAF3, TBK1, IRF3, MDA5 (IFIH1)	Impaired IRF3 signalling after TLR or RIGI-like receptor stimulation, required for IFN production

Table 1

threats, while the adaptive immune system is characterized by exquisitely specific responses against antigens and the potential to generate immunological memory. There is considerable communication and cross-dependence between the innate and adaptive immune systems, and they function together to build a coherent response to infectious threats.

Another way of considering the immune system relates to differing stages of immune responses, from pathogen recognition through to innate and adaptive immune responses and finally to resolution. These stages span the intersection of innate and adaptive immunity and allow further conceptualization.

The innate immune system employs epithelial barriers, to compartmentalize the host from external environments, alongside pattern recognition receptors (PRRs) that sense threats to tissues should those barriers be breached. PRRs detect molecular motifs, termed pathogen-associated molecular patterns (PAMPs), which are hallmarks of pathogens such as lipopolysaccharide or double-stranded RNA. If epithelial barriers are compromised and innate recognition, via PRRs, occurs, acute inflammation ensues. This is characterized by the influx of neutrophils to phagocytose pathogens, complement activation and ultimately antigen presentation to T and B cells of the adaptive immune system.

The adaptive immune system generates an enormously diverse repertoire of unique receptors on the surface of T cells and B cells that have the potential to recognize the myriad pathogens encountered during life. T cell receptors recognize short peptide sequences presented to them by antigen-presenting cells in the context of the major histocompatibility complex, while B cell receptors recognize conformational epitopes of whole molecules. Recognition of antigen by antigen-specific B cells and T cells leads to the expansion of those cells and a focused cellular (T cells) and humoral (B cells and antibody) response against the pathogen.

The generation of adaptive immune responses is slower as antigen-specific lymphocytes require time to replicate, expand and enhance their recognition capabilities. Once established, however, these have the potential to offer lifelong immunity against that pathogen. Disruption to any of the innate or adaptive processes can lead to immunodeficiency.

Encapsulated bacteria and the role of opsonization

The most common forms of IEI worldwide are antibody deficiencies.[1] Selective immunoglobulin (Ig) A deficiency is the most common antibody deficiency, affecting around 1 in 500 individuals; it is usually asymptomatic. Antibody deficiencies involving IgG (e.g. common variable immune deficiency, X-linked agammaglobulinaemia) are more likely to become symptomatic. Both are characterized by recurrent sinopulmonary infections with a relatively narrow spectrum of encapsulated bacterial pathogens (e.g. *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*).

Encapsulated bacteria have evolved a protective polysaccharide capsule that disrupts phagocytosis by macrophages and neutrophils, necessitating additional mechanisms to support the destruction of these pathogens. The word 'opsonization' refers to a process of marking microorganisms for phagocytosis and is derived from the Greek word 'opson', meaning to cater or prepare for eating.

There are two major effector mechanisms for opsonization: antibody and complement (Figure 1). Antibodies can act as a bridge between bacteria and phagocytes, overcoming the defence mechanism of the polysaccharide capsules. The Fab (antigen binding) domain of the antibody engages bacterial capsular or cell wall antigen, while the Fc tail of the antibody engages Fc receptors on the phagocyte.

The complement cascade, named as it was noted to complement the opsonophagocytic activity of antibodies, also supports opsonization of pathogens. It does this by coating them in C3b, which engages complement receptors on the surface of phagocytes, acting as a bridge between pathogen and phagocyte. The complement cascade is a series of plasma zymogens that can be initiated in three ways — the classical, alternative and mannose-binding lectin cascades — that all converge on the cleavage of whole C3 into C3a, which is chemotactic for phagocytes, and C3b, the opsonin.

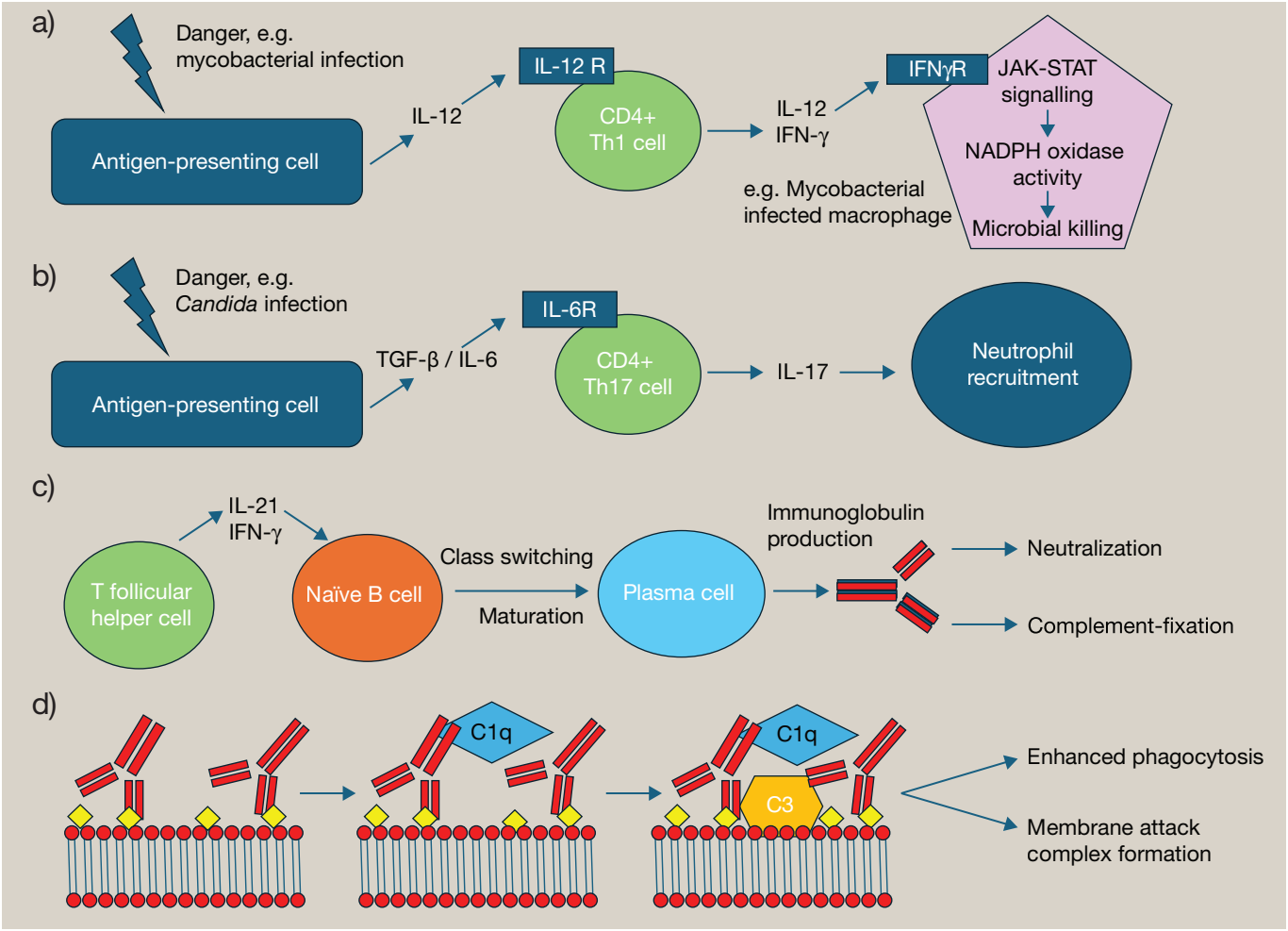

Figure 1 Outline of select immune responses. (**a**) The IL-12/Th1/IFN-γ axis, important for killing intracellular bacteria and fungi. (**b**) Pathways required for neutrophil recruitment in response to extracellular pathogens such as *Candida*. (**c**) Follicular T helper cells aiding the differentiation of naive B cells into immunoglobulin-secreting plasma cells. (**d**) Classical pathway of complement activation by immunoglobulin binding to antigen. TGF-β, transforming growth factor-β. For other abbreviations, see text.

The classical pathway involves binding of antigen by complement-fixing antibody types such as IgG3, IgG1 and IgM. The alternative pathway is initiated by spontaneous hydrolysis of C3 with immediate regulation occurring on host tissues; the absence of this regulation on pathogens leads to continued activity and amplification of the cascade. The mannose-binding lectin (MBL) pathway is initiated by the direct binding of MBL to mannose on microbial cell surfaces. These pathways converge by leading to the deposition of C3b on the target surface.

C3b not only acts as an opsonin itself, but also initiates the formation of the membrane attack complex (MAC; complement components C5b–C9), which can form pores in the membranes of the target cell.

Individuals lacking complement components belonging to the classical pathway are susceptible to encapsulated organisms because a key effector mechanism of antibody – initiation of the classical complement cascade – is reduced.[3] Patients with MAC genetic defects (C5b–C9) are uniquely susceptible to infection with *Neisseria* species because their cell walls are particularly thin and susceptible to MAC lysis; other organisms with thicker cell walls are less susceptible to direct lysis by MAC. Individuals lacking complement components in the amplifying alternative pathway are susceptible to a wide variety of bacterial pathogens since the amplification provided by the alternative pathway is important for both opsonization and MAC formation.

Failure of phagocyte killing: chronic granulomatous disease (CGD)

After successful recognition and phagocytosis, pathogens must be destroyed. The phagosome, into which the pathogen is internalized, is fused with a lysosome, which contains enzymes and molecules to kill the pathogen. Reactive oxygen species are one important mechanism of bacterial killing and are generated by the multi-subunit reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex.

Individuals with CGD have mutations in one of the genes encoding the subunits of this complex and typically present in infancy with infections with abscesses of catalase-producing organisms (e.g. *Staphylococcus aureus*, *Aspergillus fumigatus*) in deep tissues such as the liver. Prophylaxis with antibacterial and antifungal agents is required to compensate for the failure of neutrophils to adequately control these pathogens. However, the emergent standard of care is to correct the immune defect through haematopoietic stem cell transplantation (HSCT), with gene therapy approaches also likely to become mainstream.

Failure of phagocytosis in macrophages: mendelian susceptibility to mycobacterial disease (MSMD)

Whereas phagocytic failure in neutrophils leads to susceptibility to certain extracellular pathogens such as *Staphylococcus aureus* and *Aspergillus fumigatus*, intracellular pathogens such as mycobacteria are dealt with largely by macrophages, aided by CD4+ helper T cells.

After phagocytosis by macrophages, efficient killing of intracellular pathogens depends on the Th1 subset of CD4+ helper T cells. These cells produce interferon-γ (IFN-γ) and interleukin (IL)-12, which augments NADPH oxidase formation in phagocytes and sustains IFN-γ signalling, respectively (see Figure 1).

Loss-of-function genetic defects in this pathway include genes encoding the cytokines themselves (e.g. *IFNG*, *IL12B*), the cytokine receptors (e.g. *IFNGR1/2*, *IL12RB1/2*) or the intracellular transduction of the cytokine pathway, including JAK1 (Janus kinase 1) and STAT1 (signal transducer and activator of transcription protein 1). Loss-of-function mutations can lead to a failure to clear intracellular bacteria such as mycobacteria, non-typhoidal *Salmonella* spp., *Listeria monocytogenes* and dimorphic fungi such as *Histoplasma* and *Blastomycetes*.[4]

Beyond genetic defects, autoantibodies to cytokines such as IFN-γ have also been shown to confer susceptibility to mycobacteria, underpinning the key role of this pathway in managing intracellular pathogens.

The most common presentation of MSMD in developed countries is ulceration, lymphadenopathy and sometimes disseminated BCG-osis after BCG (bacillus Calmette–Guérin) vaccination in infancy.

Chronic mucocutaneous candidiasis (CMC): the importance of Th17 cells

Candida infections are common and usually result from extrinsic factors that temporarily increase permissibility for the growth of this ubiquitous yeast (e.g. use of broad-spectrum antibiotics). CMC, on the other hand, can be caused by an underlying monogenic IEI that impairs the function of a subset of CD4+ helper T cells that produce interleukin (IL)-17, termed Th17 cells.

The differentiation of CD4+ helper T cells into subsets is determined by the cytokine milieu that naive CD4+ T helper cells encounter during their early development. During an acute infection, multiple PAMPs engage multiple PRRs; subtle differences in the patterns of cytokines produced and their downstream signalling skew the development of CD4+ T cells towards Th1, Th2 or Th17 cells that best support adaptive immune responses against the original pathogen.

Th17 cells require IL-6 and transforming growth factor-β (TGF-β), along with downstream STAT3 signalling, to differentiate. Upon activation, Th17 cells produce IL-17 and IL-22, which facilitate the recruitment of neutrophils and the release of antimicrobial peptides that help control *Candida* at mucosal surfaces. Genetic disruption of this pathway, through absence of IL-17, STAT1 gain of function or STAT3 loss of function influencing the cellular responses to cytokines and impairing Th17 development, can result in CMC and the attendant risk of malignancy through chronic *Candida*-induced inflammation.

Failure to control herpesvirus infections

Another major class of intracellular pathogens are viruses. Presentations of herpes viral infections that are suggestive of an IEI include herpes simplex encephalitis (HSE) and florid disease after Epstein–Barr virus (EBV) infection.

Despite near-universal infection with herpes simplex virus 1 (HSV-1), relatively few individuals develop HSE. Most cases of HSE have no obvious monogenic cause, but several genes are involved in the induction of a type 1 IFN response after the recognition of viral nucleic acid, particularly via TLR3 (Toll-like receptor 3) signalling, that confer susceptibility to HSE; these

include *TLR3, UNC93B1, TBK1, TICAM1, TRAF3* and *IRF3*. These genes also confer susceptibility to severe presentations of acute respiratory viruses such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Monogenic susceptibility to EBV can lead to a variety of clinical pictures including fulminant EBV infection with a severe infectious mononucleosis-type picture, haemophagocytic lymphohistiocytosis (HLH), chronic active EBV and EBV-driven lymphomas or smooth muscle tumours. HLH reactions induced by EBV may be caused by defects in SLAM-associated protein (SAP), which disrupts CD8+ T cell responses and can result in EBV-driven lymphomas. In contrast, XIAP (X-linked inhibitor of apoptosis) and perforin deficiencies lead to susceptibility to severe acute EBV infection and HLH but without the same susceptibility to lymphomas.

Mutations in *MAGT1* lead to disrupted magnesium signalling, important for activation of cytotoxic T cells and natural killer cells. The syndrome caused by dysfunctional MAGT1 (magnesium transporter 1) is termed XMEN syndrome (X-linked immunodeficiency, Magnesium defect, EBV infection, Neoplasia) and is characterized by chronic EBV replication. Several other genetic defects are associated with failure to control EBV, highlighting the comprehensive immunological coordination required to prevent EBV-related disease.

Failure to control human papillomavirus (HPV) infection

Severe chronic HPV infection, manifesting as intractable warts, or HPV-induced intraepithelial neoplasias, can be a sentinel infection raising suspicion of an IEI. Combined immunodeficiencies result from a combination of impaired humoral immunity and cellular immunity, so HPV infection can be seen in a variety of combined immunodeficiencies. Some monogenic IEI such as heterozygous GATA2 (GATA-binding protein 2) deficiency result in recalcitrant HPV because of impaired antigen presentation through reduced dendritic cells, monocytes and reduced antiviral activity through natural killer cells.

Other IEI resulting in chronic HPV infection can arise from defective T cell receptor signalling, as is seen in DOCK8 (dedicator of cytokinesis 8) deficiency; this leads to disordered cytoskeletal remodelling in lymphocytes after their activation, or mutations in the chemokine receptor CXCR4 causing WHIM syndrome (Warts, Hypogammaglobulinaemia, Infections, Myelokathexis), impairing the ability of cytotoxic T cells to migrate to sites of infection.

Adult patients with JAK3 mutations who have undergone HSCT for severe combined immunodeficiency have corrected lymphocyte function. However, florid HPV infection can persist as JAK3 plays an important role in cytokine signal transduction in non-haemopoietic cells, including keratinocytes.

Anti-cytokine autoantibodies: a novel type of immunodeficiency

The dependence upon cytokines for communication between immune cells opens a potential avenue for immunocompromise. Microbes themselves often employ mechanisms to interfere with cytokine signalling to evade the immune system; however, it has been recently appreciated that autoantibodies against cytokines can also play a role in human disease.[5]

Autoantibodies against type 1 IFN, disrupting innate responses to viral infection, were shown to be present in as many as 10% of patients admitted to hospital with severe coronavirus disease 2019 (COVID-19) infection and other viral infections. IFN-γ autoantibodies, disrupting Th1 CD4 + responses, can result in acquired cases of susceptibility to mycobacterial disease, particularly among individuals from South-East Asia.

Other cytokine autoantibodies have also been implicated in the development of infectious diseases, for example anti-granulocyte-macrophage colony-stimulating factor and anti-IL-6 autoantibodies conferring susceptibility to cryptococcal and staphylococcal disease, respectively.

Investigation of inborn errors of immunity

Suspicion of underlying IEI requires prompt investigation, with support from clinical immunology teams. Antibody function can be assessed by measuring total quantities of immunoglobulin (typically IgG, IgA and IgM) as well as measuring specific antibodies directed against bacterial or viral pathogens to which the individual has been exposed through either infection or vaccination. Assessing vaccine responses by measuring specific antibodies before and after vaccination is the cornerstone of investigating antibody deficiency.

Functional complement assays are also available and can be used to localize defects in the complement cascade. Neutrophil function tests assessing the respiratory burst are also available and can help diagnose CGD.

Relatively few tests are available to assess other aspects of immunity and they are usually only available in tertiary referral laboratories. These include cytokine production assays and flow-cytometric assays to determine particular proteins involved in IEI.

Increasingly, a key investigation in the assessment of suspected immunodeficiency is genomic investigation with bioinformatic analysis of key immune-related genes and subsequent functional validation.

Treatment of immunodeficiencies

A variety of treatments can be offered to tackle the infectious complications of immunodeficiency. Prophylactic administration of antibiotic, antiviral or antifungal agents provides some antimicrobial defence and can be appropriate based on a risk—benefit analysis, accounting for the risk of developing resistance.

Immunoglobulin replacement treatment is the mainstay of therapy for patients with antibody deficiency and can be administered either subcutaneously or intravenously, with equivalent efficacy. Immunoglobulin replacement from pooled donor serum provides a broad repertoire of antibody, although only IgG is replaced, such that some residual infection burden can persist.

Several drug treatments, often repurposed from other conditions, are available to treat monogenic IEIs. These include JAK inhibitors for IEI with mutations causing gain of function in JAK/STAT signalling pathways. These represent a small but growing option for rare IEI.

Definitive management of many forms of IEI comes from allogeneic HSCT, or in certain cases gene therapy, effectively correcting the underlying intrinsic immune defect. First developed for severe combined immune deficiency, such treatments have been transformative, curing an increasing number of patients with a broad range of IEI. However, existing end-organ damage and extra-immune features of IEI may not be corrected

by HSCT and the conditioning regimens required for transplantation are themselves immunosuppressive, increasing infection risk during and after transplantation. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 3-year-old boy presented with fever.

Investigations

- Ultrasonography of the abdomen showed a large abscess within the liver
- Neutrophil function test was abnormal

What is the most likely immunodeficiency associated with this presentation?

A. Chronic granulomatous disease
B. STAT1 gain of function
C. DOCK8 deficiency
D. Severe combined immunodeficiency
E. X-linked agammaglobulinaemia

Question 2

A 30-year-old woman presented with a fever and productive cough. It was her fifth presentation in 2 years for infections of the upper and lower respiratory tract.
On clinical examination, there were crackles at the left lung base.

Investigations

- Chest X-ray showed left lower lobe consolidation
- White cell count 19.8 $\times$ 10^9/litre (4.0–11.0)
- Neutrophils 16.1 $\times$ 10^9/litre (1.5–7.0)
- Lymphocytes 3.0 $\times$ 10^9/litre (1.5–4.0)
- HIV negative
- Immunoglobulin (Ig)A undetectable
- IgG 2.1 g/litre (6–16)
- Sputum culture showed *Moraxella catarrhalis*

What is the most likely diagnosis?

A. Common variable immunodeficiency
B. HIV infection
C. Interferon-α (IFN-α) autoantibody production
D. Severe combined immunodeficiency
E. X-linked agammaglobulinaemia

Question 3

A 19-year-old woman developed sudden-onset headaches, neck stiffness and photophobia, and required intensive therapy unit admission for refractory hypotension. She had previously been well.

Investigations

- Blood cultures grew *Neisseria meningitidis* serogroup B

What of the following investigations is most likely to determine the underlying immunodeficiency?

A. Flow cytometry to determine CD40L expression
B. Flow cytometry to enumerate lymphocyte subsets
C. Functional complement assays
D. Measurement of C3/C4 to assess for complement deficiency
E. MRI examination to assess for cerebrospinal fluid leakage