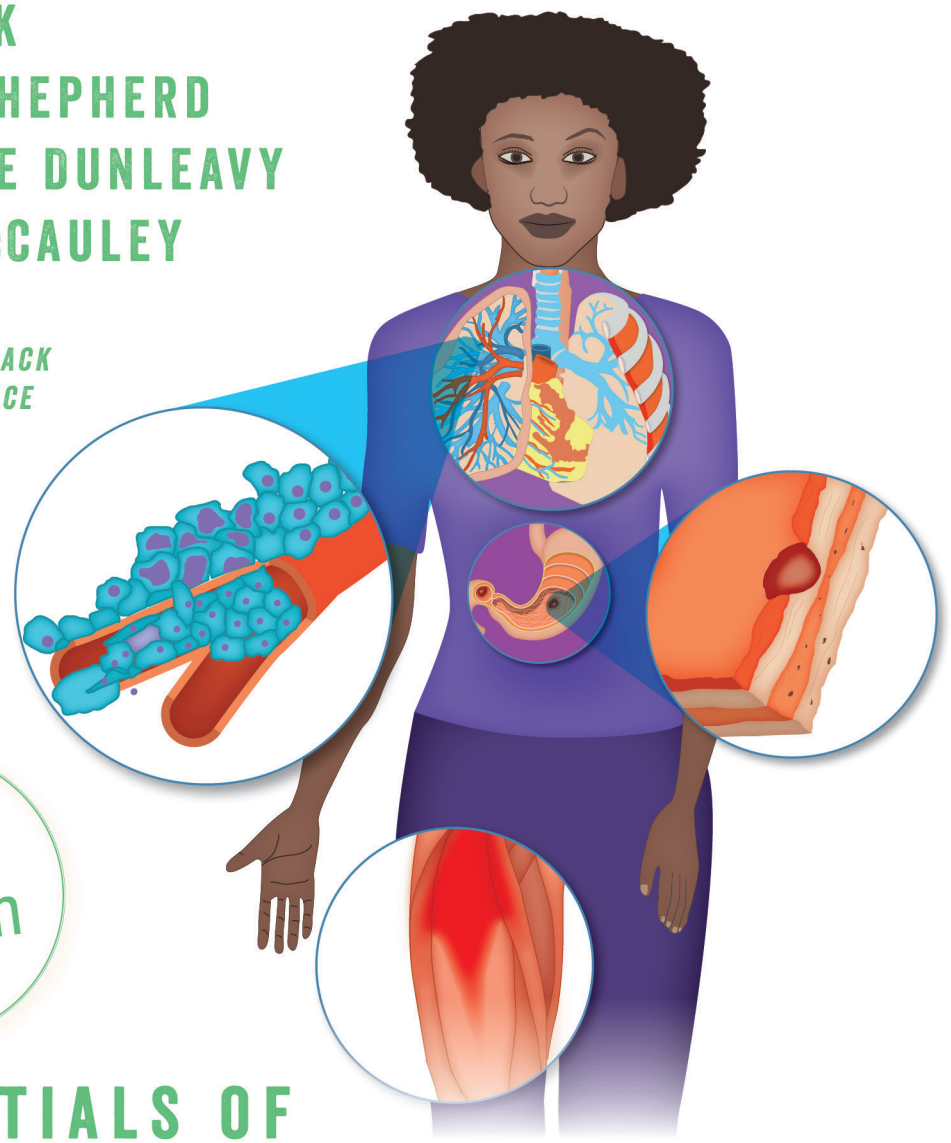
NEAL COOK
ANDREA SHEPHERD
STEPHANIE DUNLEAVY
CLAIRE McCAULEY

FOREWORD BY
BRENDAN McCORMACK
AND TANYA McCANCE



2nd Edition

ESSENTIALS OF PATHOPHYSIOLOGY FOR NURSING PRACTICE

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CONTENTS

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DISORDERS OF IMMUNITY AND DEFENCE

Understand

Chapter videos

Watch the following videos to ease you into this chapter.

The videos can be accessed by **scanning the QR code** with your smartphone camera or via **https://study.sagepub.com/essentialpatho2e**.

TYPES OF IMMUNE RESPONSES (8:06)

B LYMPHOCYTES (14:12)

Learning outcomes

When you have finished studying this chapter you will be able to:

1. Explain the mechanisms of the immune response.
2. Describe the altered immune mechanisms that lead to hypersensitivity diseases.
3. Explain the mechanisms involved in autoimmune disease.
4. Discuss primary and secondary immunodeficiency disorders.
5. Outline the factors that make a microorganism pathogenic.
6. Identify measures that contribute to the control of sexually transmitted infections.
7. Discuss the signs of sepsis and how this can lead to septic shock.
8. Identify key challenges to infection prevention, control and treatment.

INTRODUCTION

Our defence system protects us from anything it perceives as foreign to the body and therefore a potential threat to homeostasis. The immune system is a finely tuned complex system that mounts a coordinated response to harmful substances such as infectious agents, and macromolecules such as proteins or chemicals. This is referred to as the immune response and it is essential to a healthy body. In certain circumstances some of the mechanisms of the immune response can break down, causing an ineffective response (immune deficiency), or an inappropriate response such as an exaggerated response to a substance or a response against the body's own cells. This can result in disease. In this chapter we start by reviewing the normal immune response mechanisms and then go on to look at what happens when the protective mechanisms of the immune response fail.

The immune system has evolved to protect and defend the body against infectious agents and foreign cells. Its finely tuned but complex mechanisms are effective in achieving this but sometimes it can react inappropriately, causing disease. In this chapter we will look at what happens when the immune system overreacts, resulting in a hypersensitivity disorder, reacts inadequately, attacking the body's own tissue, resulting in autoimmune disorders, or fails to react, resulting in immunodeficiency. The subsequent effect on the body can range from mild to life-threatening illness.

Revise: A&P recap

The immune system

Before reading this chapter, you may find it useful to revise the immune system. For a full summary see Chapter 13, The Immune System: Internal Protection, in *Essentials of Anatomy and Physiology for Nursing Practice* (2nd edition) (Cook et al., 2021). Figure 13.2 (in Cook et al., 2021) clarifies the different aspects of the immune responses, and how the body responds through innate and adaptive immunity. The different lines of defence are demonstrated, including how the body removes infectious agents.

Person-centred context

The Bodie family

Every day we come into contact with substances such as microorganisms or chemical toxins that require our immune systems to work to protect us against disease. Several factors, such as our age, genetic makeup and the environment we live in, can influence how we react to these substances and our risk of developing disease. Considering the Bodie family, George and Maud are now at an increased risk of acquiring infectious diseases because of their age and both get the flu vaccine every year to help reduce the risk of developing influenza. Derek Jones has asthma and takes anti-inflammatory medication as his immune system is overreacting. Margaret Jones has hay fever, which flares up and requires the use of anti-histamines to reduce her immune response to pollen. Kwame and Michelle Zuma travel to Africa frequently, requiring vaccination against microorganisms that they would not normally be exposed to. Their baby, Danielle, is currently having routine vaccinations to help her immune system protect her from childhood infections caused by pathogens.

IMMUNE DISORDERS

Disorders of the immune system result in homeostatic imbalances and fall into three broad categories: **hypersensitivity**, where the immune system overreacts; **autoimmunity**, where the immune system attacks the body's own tissues; and **immunodeficiency**, where components of the immune system fail (Figure 6.1).

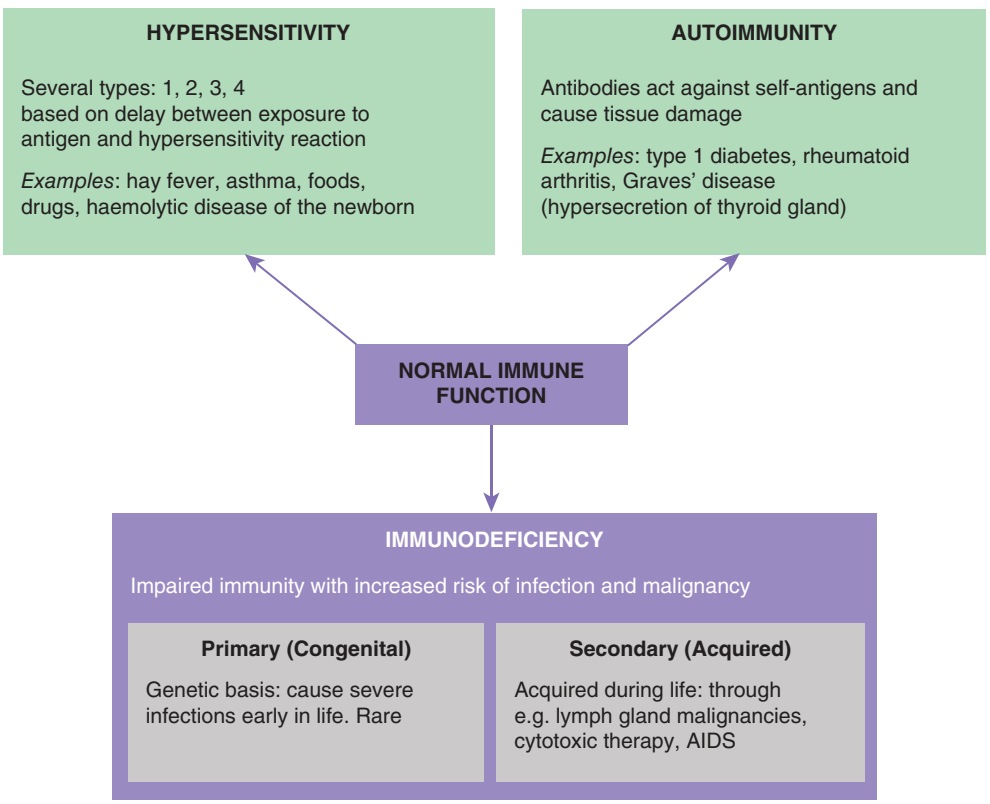

Figure 6.1 Disturbances of immune function

Source: Cook et al., 2021, Figure 13.12

HYPERSENSITIVITY

Hypersensitivity is when the immune response is altered, causing damage to cells, tissues and organs, and this is often in response to a substance that is normally harmless. Hypersensitivity diseases include allergy, autoimmunity (against **self-antigens**, failure of recognition) and **alloimmunity** (transplant tissue rejection). Hypersensitivity diseases are classified according to the type of immune response and the **antigen** responsible (Table 6.1).

Table 6.1 Classification of hypersensitivity diseases

Type of hypersensitivity	Immune mechanism	Mechanism of injury
Type I – immediate hypersensitivity	IgE antibody	Mast cells, eosinophils, mediators
Type II – antibody-mediated	IgM, IgG antibody against cell surface or extracellular matrix	Phagocytosis and opsonisation of cells
Type III – immune-complex-mediated	Immune complexes of circulating antigens and antibodies IgG or IgM	Complement-mediated activation of leucocytes
Type IV – cell-mediated	$CD4^+$ T cells (helper T cells); $CD8^+$ (cytotoxic/killer T cells)	Cytokine-mediated inflammation Direct target cell killing

Notes: IgE, immunoglobulin E; IgM, immunoglobulin M; IgG, immunoglobulin G.

Type I – immediate hypersensitivity disorders (allergy)

A person has an allergy or type I hypersensitivity when they have a hypersensitive immune response to an environmental substance. This is one of the fastest-growing conditions worldwide and is becoming a major public health problem (Tanno et al., 2016). This type of hypersensitivity is immediate and is known as an allergic reaction. The antigen, often referred to as the **allergen**, binds to immunoglobulin E (IgE) **antibodies** on the surface of mast cells and triggers a reaction specific to environmental antigens such as pollen, house dust, foods, shellfish, nuts and chemicals such as the antibiotic penicillin.

T-helper **lymphocytes**, or specifically $T_h2/CD4^{+1}$ variant, are involved in allergic reactions and the production of IgE antibodies that trigger mast cells and **leucocytes**. These IgE antibodies bind to the mast cell on exposure to the antigen. This is called **sensitisation** and is the reason why this type of reaction occurs so rapidly on subsequent exposure to the antigen as the mast cell is now already coated with the IgE antibodies (Galli and Tsai, 2012). Mast cells are present in tissue, blood vessels and nerves, which is why many of the clinical features of an immediate reaction involve these sites due to vascular and smooth muscle stimulation. Once the mast cell is stimulated, it releases mediators and **cytokines** (Figure 6.2). The most potent mediator is **histamine**, which causes bronchial smooth muscle contraction, vasodilation, increased vascular permeability and increased mucous production by nasal and bronchial glands. Histamine binds to **endothelial cells**, leading to increased vascular permeability and leakage of plasma into the tissues, resulting in **oedema**. Cytokines such as **tumour necrosis factor (TNF)** and **interleukins** are produced and are responsible for the inflammation associated with the delayed response. **Basophils** are also involved in type I hypersensitivity reactions in a similar way to mast cells.

There are two defined phases associated with many type I hypersensitivity reactions: a primary or immediate response and a late or delayed response. The immediate phase is associated with histamine release and usually occurs within minutes of exposure to the allergen. The tissues affected contain large numbers of mast cells and involve the skin, respiratory tract and gastrointestinal tract. Vasodilation of the vessels in the skin leads to oedema and urticaria, which is a skin reaction characterised by fluid-filled blisters known as wheals and surrounded by an area of redness known as flares (Figure 6.3). Bronchial smooth muscle spasm leads to bronchoconstriction and increased mucous secretion, causing difficulty in breathing. Inflammation of the mucous membranes of the nose (rhinitis) and membranes of the eyes (conjunctivitis) occurs and is a feature of allergic rhinitis (hay fever). The late phase response sustains the reaction and occurs hours later and can last for days, gradually subsiding. This phase involves eosinophils (white cells) which release **proteolytic enzymes** that damage tissue and is a feature of asthma.

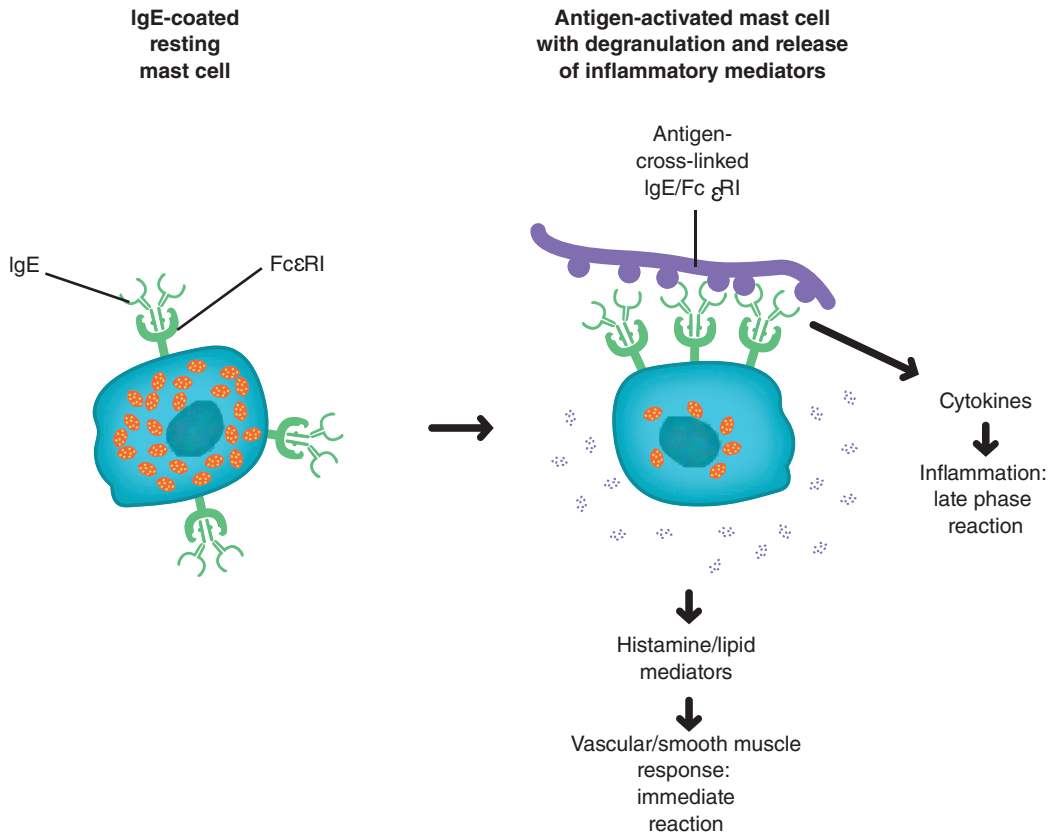

Figure 6.2 Activation of mast cells: IgE antibodies bind to receptors on the mast cell surface and stimulate degranulation and the release of histamine and cytokines

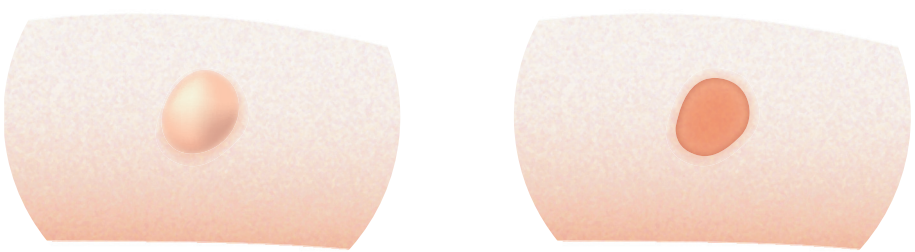

Figure 6.3 Skin reactions in allergy

Genetic susceptibility

Allergies often run in families, and certain people are genetically predisposed to develop allergies, having higher than usual quantities of IgE. Patterns of inheritance are multigenic, leading to increased susceptibility for asthma and other atopic (allergy) diseases (Kaufmann and Demenais, 2012). Environmental

factors have an impact on the development of allergy, and exposure to microbes during early childhood is thought to reduce the risk of developing allergies later in life (Bufford and Gern, 2005).

Apply

Anti-histamines and asthma

Antihistamine use in allergic reactions can inhibit urticaria but in some allergic disorders, such as asthma, they are not effective at suppressing the reaction. In asthma, bronchoconstriction is more prolonged than the effects of histamine, suggesting that other mast-cell-derived mediators are involved.

Anaphylactic reactions

Anaphylactic reactions involve a systemic response to a hypersensitivity reaction, resulting in life-threatening clinical features such as difficulty in breathing due to severe bronchoconstriction, low blood pressure as a result of vasodilation, and widespread oedema.

Anaphylactic reactions are type I hypersensitivities where the allergen is injected or absorbed across the epithelial membrane of the skin or gastrointestinal **mucosa**. This stimulates the mast cells in the area, resulting in the release of mediators which gain access to the vascular beds throughout the body (Reber et al., 2017). Systemic vasodilation and leakage cause oedema, decreased blood pressure and shock. There is constriction of the upper airways and laryngeal oedema, resulting in difficulty in breathing. This is accompanied by skin rash and itching. Gastrointestinal symptoms include vomiting and abdominal cramps. Anaphylactic reactions can be life-threatening and immediate management is to secure the airway and administer adrenaline/epinephrine to reverse the bronchoconstriction and vasodilation and improve **cardiac output**.

Apply

Anaphylaxis and EpiPen

People with a known risk of anaphylactic shock need to carry an adrenaline/epinephrine 'pen' (EpiPen) with them at all times. This is to allow quick self-administration or administration by a bystander of adrenaline in the case of exposure to the allergen. Adrenaline binds to specific receptors on smooth muscle, reversing the effects of histamine, resulting in smooth muscle relaxation and reducing life-threatening bronchoconstriction.

Bronchial asthma

Bronchial asthma is an inflammatory disease of the airways caused by repeated immediate hypersensitivity and late phase allergic reactions (Abbas et al., 2015). The person with bronchial asthma will often have other allergic disorders, such as hay fever and **eczema**. The early phase response leads to reversible airway obstruction and difficulty in breathing due to bronchoconstriction and the production of thick mucus. There is also increased vascular permeability, causing mucosal oedema. The late phase

response leads to inflammation and increased airway responsiveness. Epithelial injury and changes in mucociliary function can result from chronic inflammation of the lung tissue. Mast cells, basophils and eosinophils produce mediators that cause constriction in airway smooth muscle. About 70% of asthma cases are associated with IgE-mediated reactions and 30% may be stimulated by non-immune stimuli such as cold air, exercise, **respiratory tract infections** or emotional upset (Abbas et al., 2015). See Chapter 13 for further information on bronchial asthma.

Allergic rhinitis (hay fever)

This is perhaps the most common allergic disease and is characterised by sneezing, itching and watery discharge from the nose and eyes. It is an immediate hypersensitive response to common allergens, such as pollen, dust mites, fungal spores or animal hair, and can occur all year round or seasonally when levels of the allergen are high, such as pollens in the summer months. There is mucosal oedema with leucocyte and eosinophil **infiltration**, and increased mucus secretion, resulting in coughing, sneezing and difficulty in breathing. This type of exposure is associated with intense symptoms. Management involves treating the symptoms and the use of antihistamines.

Food allergies

Food allergies are immediate hypersensitive responses to allergens in food. Common food allergens are contained in milk, eggs, nuts, particularly peanuts, fish and shellfish. Ingested food leads to the release of IgE-mediated factors from the gut mucosa, resulting in oedema, skin rash, itching, increased **peristalsis**, vomiting and diarrhoea (Sicherer and Sampson, 2018). A systemic response occurs more commonly with peanut and shellfish allergens and a person may be highly sensitive to these, so much so that they may not need to ingest them to develop a systemic response.

Apply

Immunotherapy treatment for allergies

Immunotherapy treatment for allergies is aimed at altering the response of the immune system to the allergen where the person is gently exposed to a miniscule amount of the allergen through subcutaneous injections in repeated doses over a period of time. This is known as desensitisation and it appears to help reduce the response to the allergen, thus resulting in less severe symptoms (Larsen et al., 2016).

Watch this video clip to get a summary of type II hypersensitivity reactions.

The video can be accessed by **scanning the QR code** with your smartphone camera or via **https://study.sagepub.com/essentialpatho2e**.

TYPE II HYPERSENSITIVITY (9:04)

Type II – antibody-mediated disorders

Antibodies IgG and IgM or immune complexes cause this type of immune response. The antibody binds to tissue-specific antigens on the cell surface, resulting in either cell dysfunction or destruction. This is often referred to as cytotoxic hypersensitivity. There are several processes by which type II reactions happen:

- Antibodies attach to antigens on the cell surface, causing the cell to be more vulnerable to **phagocytosis** by **macrophages**. **Complement proteins** are activated which facilitate phagocytosis, a process known as **opsonisation** (Cook et al., 2021). This leads to destruction of the cell. This mechanism is seen in autoimmune **haemolytic anaemia**, ABO blood group or Rhesus (Rh) incompatibility and mismatched blood transfusion reactions.
- Where antibodies bind to normal cell receptors they can cause the cell to malfunction, but they do not destroy the cell. The cell receptor (but not necessarily the cell) is inappropriately stimulated or destroyed. For example, antibodies bind to and activate receptors for thyroid-stimulating hormone (TSH) on thyroid cells, leading to hyperthyroidism associated with **Graves' disease** (Justiz Vaillant and Zito, 2018).
- Complement- and antibody-mediated inflammation is another mechanism where antibodies stimulate **neutrophils** and macrophages to release toxins, including **lysosomal enzymes**, leading to inflammation and tissue injury. This mechanism is responsible for some forms of **glomerulonephritis**.

Type III – immune complex-mediated disorders

Antigen–antibody complexes are formed when antibodies bind to either self-antigens or foreign antigens in the circulation and are then deposited in the vessel wall or tissues. Complement is activated, and neutrophils are attracted to the antigen–antibody complex and attempt to ingest it but often cannot as the complex is attached to a large area of tissue (Rote, 2017). This results in the release of large amounts of enzymes, leading to tissue damage. Features of the disorder depend on the tissue involved, rather than the cell, as in other hypersensitivity reactions, and are often systemic, involving multiple tissues.

The tissues of the blood vessels, joints and glomerulus of the kidney are particularly vulnerable where antigen–antibody complexes are deposited and bind to the basement membrane of the vessels. Leucocytes and mast cells are activated to produce cytokines and vasoactive mediators, which increase vascular permeability and blood flow, causing **vasculitis**. Characteristics of type III reactions include fever, enlarged lymph nodes, rash and pain at sites of inflammation. These features were originally described following injection for immunisation using animal serum and the term '**serum sickness**' was used to describe this type of reaction. Serum sickness is a systemic reaction and is usually short-lived unless there is repeated administration of the antigen. A localised reaction is known as an Arthus reaction, where there is repeated exposure to an antigen that reacts with a preformed antibody and forms an immune complex in the walls of the blood vessels (Abbas et al., 2015). This causes local vasculitis and **thrombosis** of the affected vessel and tissue necrosis. This can be observed following injection, ingestion or inhalation of allergens.

Type IV– cell-mediated hypersensitivity disorders

This type of response is cell-mediated rather than antibody-mediated. T-cell lymphocytes induce inflammation and/or directly kill target cells in type IV hypersensitivity disorders (Abbas et al., 2015). There are two types of Type IV reactions: direct cell-mediated cytotoxicity and delayed-type hypersensitivity (Figure 6.4).

1. **Direct cell-mediated response** involves CD8⁺ cytotoxic T lymphocytes that directly kill target cells expressing foreign antigens. This can happen where persistent microbes, primarily viruses, have infected a cell and resist phagocytosis and antibody eradication. Cytotoxic T lymphocytes kill the infected cell, causing tissue damage, regardless of whether the virus is harmful to the host. T cells can also react with self-antigens, leading to cytokine release, promoting inflammation and tissue injury. This is seen in many autoimmune disorders, such as **multiple sclerosis**, type 1 diabetes and **rheumatoid arthritis**.
2. **Delayed-type mediated hypersensitivity (DTH)** involves the activation of CD4⁺ T-helper cells and the secretion of cytokines that promote an inflammatory reaction. This reaction occurs in people who have had previous exposure to the antigen and are therefore sensitised. The reaction is delayed as it develops 24–72 hours after exposure to the antigen and involves the activation of **T-helper cells** (T_h1 cells) that are ultimately responsible for the reaction. Cytokines, macrophages, **fibroblasts** and leucocytes are also involved in the process.

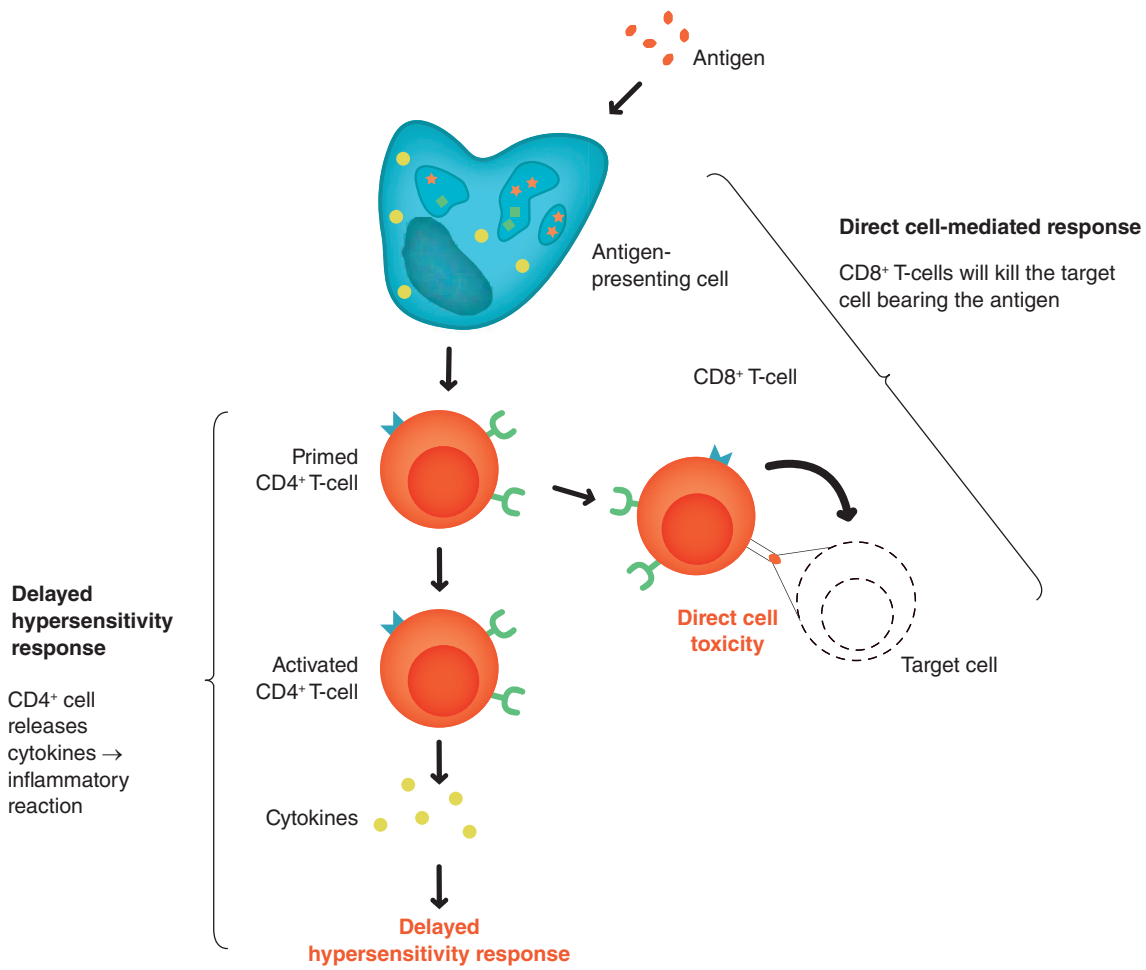

Figure 6.4 Reactions in type IV cell-mediated hypersensitivity

The reaction can be illustrated in the tuberculin skin test (Mantoux), which uses this mechanism to identify if the person has been previously exposed to the tuberculin antigen. A small amount of the tuberculin antigen is injected under the skin and within 4 hours neutrophils accumulate around the injection site. Within 12 hours T cells infiltrate the area and blood vessels become permeable. **Fibrinogen** leaks from the plasma into the surrounding tissue and is converted into **fibrin**. The surrounding tissue becomes oedematous and appears firm (due to the fibrin) and inflamed. This indicates previous exposure to the **tuberculosis mycobacterium**. This sequence of events leads to the formation of T_h1 cells, **memory cells** responsible for the reaction on subsequent exposure to the antigen. This is an example of the protective role of this mechanism, but it can also cause disease, for example contact hypersensitivity and **granulomatous hypersensitivity**.

Contact hypersensitivity is a type IV response to a wide range of substances, such as metal, plants, chemicals or cosmetics, and this response is confined to the skin. An incomplete lipid-soluble antigen, called a **hapten**, penetrates the epidermis where it combines with a protein carrier and is recognised as an antigen by sensitised $CD4^+$ cells (Schrijvers et al., 2015). These cells release cytokines and stimulate the inflammatory response, resulting in oedema, pruritis and skin blisters. If no further exposure takes place, the reactions decrease after about 72 hours as the antigen is degraded (Young-Peterson, 2013). Contact dermatitis is a common example of delayed-type hypersensitivity (DTH) reaction.

Activity 6.1: Apply

Mantoux test

Watch the following short video about the Mantoux skin test for TB delayed hypersensitivity.

The video can be accessed by **scanning the QR code** with your smartphone camera or via **https://study.sagepub.com/essentialpatho2e**.

MANTOUX TEST (8:35)

Apply

Latex allergy

Natural rubber latex is used widely in health care environments and single-use disposable gloves are the most significant way health care workers are exposed to latex. Allergy to latex can be a type IV or type I reaction and therefore many health care employers have policies on or about the use of latex gloves (NHS/RCP, 2008).

If you are interested in finding out more on latex allergy, the British Association of Dermatologists (BAD) has produced a useful leaflet. You can find this by searching online using the terms BAD and latex allergy.

Granulomatous hypersensitivity

Granulomatous hypersensitivity reactions represent a chronic type IV reaction where macrophages are activated in response to microbial antigens. Microbes are localised in an area of tissue and are not destroyed by macrophages. T cells and macrophages produce cytokines and growth factors to increase the reaction, thus maintaining a prolonged inflammatory response which leads to the formation of **granulomas**. These are a collection of inflammatory cells and **connective tissue** that eventually become fibrotic nodules and progressively change the local tissue environment. Granulomatous inflammation causes tissue damage and functional impairment. It is characteristic of persistent microbes, such as *Mycobacterium tuberculosis*, which causes tuberculosis. T-cell-mediated (Type IV) hypersensitivity presents in autoimmune diseases of rheumatoid arthritis, multiple sclerosis and type 1 diabetes, which we will look at in the next section.

AUTOIMMUNE DISORDERS

Autoimmune disease is the result of the immune system reacting to the body's own antigens and its failure to recognise these as self-antigens. The immune system needs to be able to differentiate between self and foreign antigens so that it is unresponsive to the body's own tissue antigens. This is known as **self-tolerance**. In autoimmune diseases the mechanism of self-tolerance is lost.

Autoimmune disease can affect almost any cell or tissue in the body. The exact cause is unknown, but it is thought to be related to a combination of genetic susceptibility and environmental triggers, such as infections or tissue injury (Farh et al., 2015). Genetic susceptibility can lead to autoimmune disease through the disruption of B-cell tolerance and T-cell tolerance pathways. Infections or tissue injury can expose self-antigens and activate **antigen-presenting cells** (APCs) and lymphocytes in tissues, leading to the creation of autoantibodies (Kumar et al., 2018).

Autoimmune diseases can be debilitating and progressive and have a huge impact on the person and their family. Some of the more common autoimmune diseases include **systemic lupus erythematosus (SLE)** and rheumatoid arthritis (RA) (Chapter 9).

Systemic lupus erythematosus

SLE, also referred to as 'lupus', is an antibody-mediated autoimmune disease characterised by chronic inflammation of the tissues of the skin, kidney, blood vessels and other tissues. A large number of autoantibodies are found in the circulation, particularly **antinuclear antibodies (ANA)**, which react against nucleic acid antigens, e.g. single-stranded and double-stranded DNA. In total, 180 autoantibodies have been isolated in people with SLE and it is thought their production could be antigen-driven (Gal et al., 2015). Approximately 95% of people with lupus are positive for ANA (Gordon et al., 2018). The autoantibody reacts with the circulating antigen and forms immune complexes which are deposited in the connective tissue anywhere in the body. This activates complement and the inflammatory process, which can lead to tissue necrosis. Common sites of inflammation are the blood vessels, kidneys, lungs, heart, brain, skin and digestive tract. Some of the symptoms result from a type II hypersensitive reaction, such as the destruction of erythrocytes, leading to anaemia, and some occur as a result of

type III hypersensitivity reaction. Signs and symptoms can be mild to severe and can mimic other diseases (Frieri and Stampfl, 2016).

Epidemiology

Lupus can present at any age but most commonly affects women aged 17–55 years old. It affects almost 1 in 1000 of the population in the UK and is most frequently seen in women of Black Caribbean and Asian origin (Rees et al., 2016). In North America, the incidence is 23.2/100,000 person-years and the prevalence is 241/100,000 (Rees et al., 2017). The pathogenesis of SLE is multifactorial and includes genetic, environmental and hormonal factors. Genetic factors include the inheritance of particular **human leucocyte antigen (HLA) alleles** HLA-DR2 or HLA-DR3, increasing the risk of developing SLE. Family members of a person with SLE have an increased risk for development of the disease. Environmental factors such as exposure to UV radiation lead to apoptosis and an increased number of nucleic antigens, which result in autoantibody formation.

Clinical signs and symptoms

The clinical presentation of SLE varies greatly because it is a multisystem disease. Often the person presents with a rash on the face, referred to as a butterfly rash. Joint inflammation (arthritis) may cause joint pain (**arthralgia**) and there may be pleuritic chest pain and **photosensitivity**. Abnormal urinary findings, such as **haematuria** or **proteinuria**, may be present, and anaemia and **thrombocytopenia** may be prominent. Coronary artery disease may develop. The person may go through periods of **remission** and exacerbation. Diagnosis is based on clinical features and diagnostic tests confirming the presence of antinuclear antibodies (ANAs) in the serum (Gordon et al., 2018). The common effects of SLE are shown in Table 6.2.

Table 6.2 Common clinical findings in SLE

Facial rash confined to cheeks
Discoid rash (raised patches, scaling)
Photosensitivity (development of a skin rash following exposure to sunlight)
Oral or nasopharyngeal **ulcers**
Non-erosive arthritis of at least two peripheral joints
Serositis (inflammation of the membranes of lung or heart)
Renal disorder
Neurological disorders
Haematological disorders
Immunological disorders
Presence of antinuclear antibody (ANA)

The treatment and management of SLE aim to control symptoms and prevent further damage to vital organs. Minimising exacerbations by avoiding triggers, such as exposure to UV light and excessive

fatigue, can help. Non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen reduce inflammation and relieve pain. **Corticosteroids** are used to reduce the immune response and inflammation. Cytotoxic immunosuppressive drugs should be considered in active lupus to reduce disease activity and treat severe symptoms where vital organs are involved (NICE, 2016a). Advances in the understanding of SLE are improving and new approaches are focusing on antibody therapy (Abbas et al., 2015).

Rheumatoid arthritis

Rheumatoid arthritis (RA), which is also discussed in Chapter 9, is an autoimmune disease characterised by inflammation of the joints and destruction of the joint cartilage and bone. Both cell-mediated and humoral immune responses may contribute to inflammation. T-helper cells ($CD4^+$), activated B lymphocytes, macrophages and proinflammatory cytokines are present in the inflamed joint (Abbas et al., 2015). Cytokines, particularly tumour necrosis factor, interleukin (IL)-1β, IL-6, IL-7 and IL-21, recruit leucocytes and cause the **synovial cells** to produce proteolytic enzymes such as **collagenase** that destroy the cartilage, ligaments and tendons of the joints. The synovial tissue becomes thickened and this is known as '**pannus**' (Figure 6.5). The pannus invades the bone and, along with increased osteoclast activity, leads to bone destruction with resultant pain, joint deformity and loss of function. The joints most commonly affected are the fingers, wrists, elbows, toes, ankles and knees.

Activated B cells, IgG or IgM antibodies react with their own molecules to become autoantibodies and are known as **rheumatoid factors (RF)**. The autoantibodies perpetuate inflammation and the continuous formation of immune complexes can be used in diagnostic testing. During inflammation, the amino acid arginine is modified to citrulline, changing the structure of the protein (**citrullination**), and stimulates the autoimmune response through the production of specific antibodies by the immune system.

Like other autoimmune diseases, RA is a complex disorder in genetically susceptible people, triggered by an unknown environmental influence. There is breakdown of self-tolerance and activation of inflammatory processes. Genetic susceptibility is linked to human leucocyte antigen (HLA) areas of the **major histocompatibility complex (MHC)**. **Polymorphisms** in a gene called *PTPN22*, which encodes for the protein tyrosine phosphate, are associated with the development of RA. It is thought that this causes the protein to be defective, leading to excessive lymphocyte activation (McInnes and Schett, 2017).

Clinical features

RA can initially have general signs of fever and inflammation and generalised aching. Joints become tender and stiff, swollen and enlarged, leading to pain and loss of function. Limited mobility of the joints eventually leads to deformity. Rheumatoid nodules can form outside the joint in the subcutaneous tissue but may also invade the cardiac valves, pericardium, lung tissue and spleen. Systemic complications of RA include vasculitis and lung injury.

Treatment is aimed at slowing progression of the disease and reducing inflammation using corticosteroids and other immunosuppressants, such as methotrexate. Antagonists against tumour necrosis factor (TNF) is a targeted treatment that reduces inflammation and slows joint destruction.

IMMUNODEFICIENCY DISORDERS

Immune deficiency disorders occur when there is failure of the immune system to function normally, resulting in an increased susceptibility to infections. This is either genetically determined (primary) or an acquired (secondary) disorder caused by another condition, such as **cancer**, infection or ageing.

Primary (congenital) immunodeficiencies

Most **primary immunodeficiency** disorders are the result of a single gene mutation that results in immune dysregulation, autoimmunity and recurrent infection (Battersby and Cant, 2017). The onset of symptoms can occur early in life between 6 months and 2 years old and is manifested by recurrent infections and failure of the infant to gain weight or grow normally, which is also known as **failure to thrive** (Cant et al., 2013). Primary disorders vary depending on the component of the immune system that is affected, but the major groups include **combined immunodeficiency**, antibody deficiencies and complement deficiencies.

Combined

Combined immunodeficiency is when T-lymphocyte and/or B-lymphocyte development is impaired. This can be X-linked, where there is a defect in the gene coding for interleukin cytokines, and results in impaired maturation of T cells and **natural killer (NK) cells**. An autosomal pattern of inheritance is characterised by a deficiency in an enzyme called **adenosine deaminase (ADA)**, which causes the inhibition of DNA and immature lymphocytes (Shields and Patel, 2017). The most severe disorders are called severe combined immunodeficiencies (SCIDs) and serious life-threatening infections can develop frequently. **Pneumonia**, **meningitis**, chickenpox and gastrointestinal infections can be fatal. Immunisation using live vaccine, which is normally harmless in healthy children, may lead to infection in children with SCIDs. Di George syndrome is a form of SCID where there is a **congenital** defect in the formation of the thymus gland and the parathyroid gland fails to develop. This results in decreased T-cell numbers and function and abnormal calcium regulation. Muscle twitching and abnormal development of facial features are characteristic of this syndrome.

Antibody deficiencies

Defects in B cells, either in their development or in their activation, and synthesis of antibodies result in disorders where antibody production is abnormal. This results in lower levels of circulating **immunoglobulins**, most commonly IgA (Shields and Patel, 2017). People may be asymptomatic but clinical signs include recurring sinus, pulmonary or GI infections.

Complement deficiencies

Several complement deficiencies are known and can result in reduced resistance to infection and increased frequency of bacterial or viral infections. The complement system consists of a large number of plasma proteins, mainly synthesised in the liver, which play an important role in promoting phagocytosis

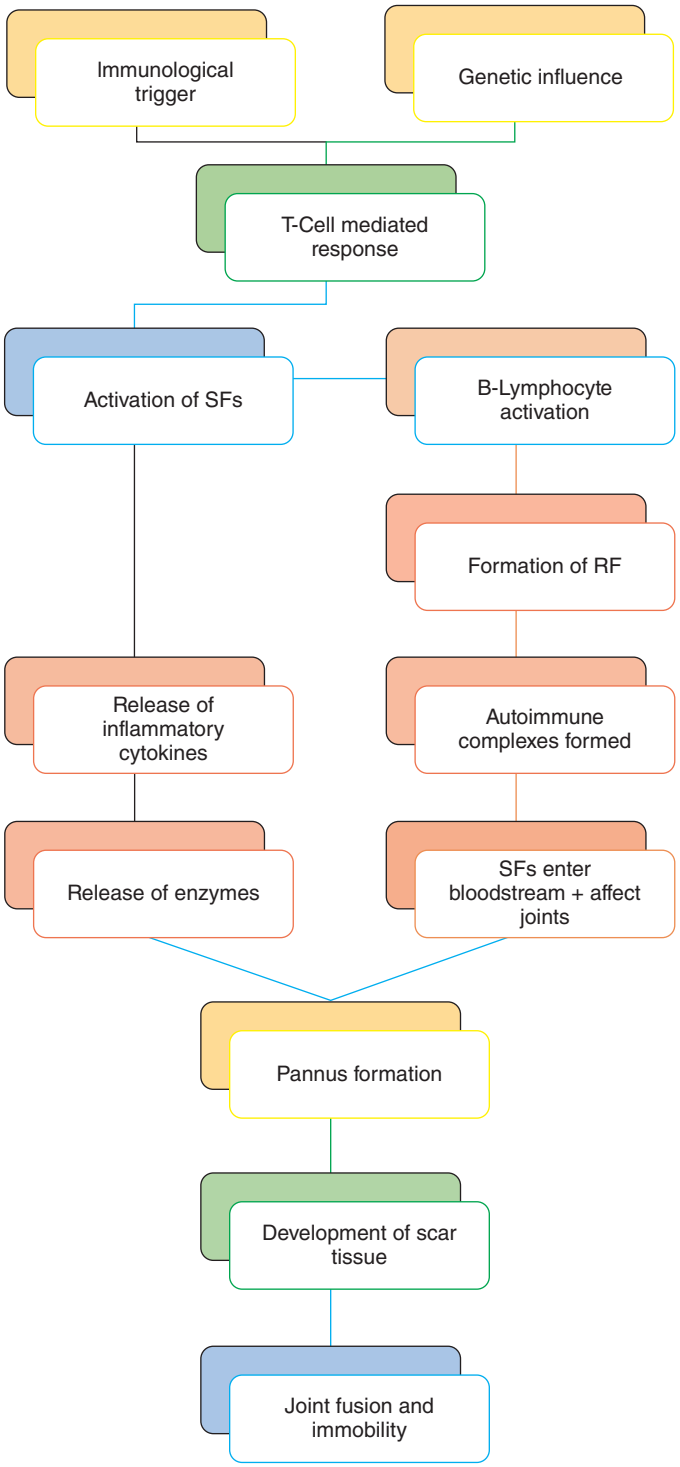

Figure 6.5 Pannus formation in rheumatoid arthritis

Note: SFs = synovial fibroblasts; RF = rheumatoid factors

through opsonisation (it does this by combining with the pathogen and making it more readily identified by cells of the immune system).

Components of the complement pathway are referred to by the letter C and a number, and C2 and C4 feature early in the complement pathway. Deficiency of these components results in reduced resistance to bacterial or viral infection and clearance of immune complexes, which can result in autoimmune features (Notarangelo, 2010). Deficiency in C5–C9 causes increased susceptibility to the **bacteria** genus *Neisseria*, which causes localised infections, meningitis or **gonorrhoea** (Notarangelo, 2010). C3 has a central role in the complement pathway and loss of this component is severe and results in life-threatening infections with *Haemophilus influenzae* and *Streptococcus pneumoniae* bacteria. Deficiency in regulatory proteins results in excessive inflammatory responses and cell injury (Battersby and Cant, 2017).

Secondary (acquired) immunodeficiencies

Deficiencies of the immune system more commonly develop as a result of other conditions acquired during life where **immunosuppression** occurs secondary to another disease, as a side-effect of therapy for other diseases or due to infection of the immune system (Table 6.3).

Table 6.3 Causes of secondary (acquired) immunodeficiencies

Cause	Mechanism
HIV infection	Depletion of $CD4^+$ helper cells
Protein-calorie malnutrition	Inhibition of lymphocyte maturation and function
Irradiation and chemotherapy for cancer	Decreased bone marrow leukocyte precursors
Involvement of bone marrow by leukaemia or metastasis	Reduced leucocyte development
Splenectomy	Decreased phagocytosis of microbes

Protein-calorie malnutrition adversely affects the maturation and functioning of cells of the immune system and is associated with increased susceptibility to infections and higher morbidity and mortality.

People with cancer affecting the bone marrow are susceptible to infections as the development and maturation of lymphocytes and leucocytes are affected. Treatment of cancer involves cytotoxic drugs, which also arrest the development of lymphocytes and leucocytes, thus causing immunosuppression. Some drugs are given to cause immunosuppression, for example in the treatment of inflammatory diseases, or to prevent the rejection of transplanted tissue. Removal of the spleen results in the defective clearance of microbes and defective antibody responses to infections by encapsulated bacteria such as *Streptococcus pneumoniae*. These are examples of **iatrogenic** immunosuppression.

Infection of the immune system is also a secondary cause of immunodeficiency and one of the most prominent is acquired immune deficiency syndrome (AIDS) caused by infection of the immune system by human immunodeficiency virus (HIV), which we will now discuss in more detail.

HIV and acquired immune deficiency syndrome (AIDS)

HIV is the human immunodeficiency virus which is transmitted by sexual activity, breast feeding, blood transfusion or injection. HIV infects and, if untreated, destroys the $CD4^+$ cells of the immune system

and suppresses the immune response, leading to the development of acquired immune deficiency syndrome (AIDS). AIDS is a syndrome characterised by immunosuppression and opportunistic infections, **malignant** tumours, **cachexia** and central nervous system (CNS) degeneration.

Epidemiology

HIV/AIDS is a global epidemic with 36.9 million people living with HIV worldwide in 2017 (World Health Organisation [WHO], 2018a). The African region is the most severely affected, with 4.1% of adults living with HIV infection, accounting for nearly two-thirds of people living with HIV worldwide. In 2017, 940,000 people died of HIV-related illness worldwide. In the same year, 1.8 million people were newly infected worldwide (WHO, 2018a). These statistics reflect the global impact of HIV/AIDS and the morbidity and mortality associated with it. National HIV programmes have helped to reduce the incidence of HIV, and between 2000 and 2017 new HIV infections fell by 36% and HIV-related deaths fell by 38% (WHO, 2018a). There is no cure for HIV/AIDS, but education, prevention and access to antiretroviral treatment have resulted in HIV infection now being recognised as a **chronic illness** and will help save lives.

Pathogenesis

HIV is a retrovirus, which means that genetic information is carried on the RNA strand rather than DNA. An enzyme known as **reverse transcriptase** converts two identical strands of RNA into double-stranded DNA once inside the host cell.

The HIV retrovirus is spherical and contains a cone-shaped core surrounded by a lipid envelope (Figure 6.6). The core contains proteins, RNA and enzymes, and the viral particle is covered in a lipid bilayer envelope with **glycoproteins (gp)** attached to its surface. The glycoproteins bind to receptors on the surface of the host cell and are essential for HIV infection. Glycoprotein gp120 (on the surface of the HIV envelope) binds to the CD4 molecule on the surface of T lymphocytes and promotes a secondary gp120 binding to a **chemokine receptor** on the cell surface. This induces gp41 to insert into the cell membrane, enabling the viral membrane to fuse with the target cell (Walker and McMichael, 2012). Once inside the cell, the enzymes become active and viral reproduction commences. RNA undergoes reverse transcription to become viral DNA and enters the nucleus. The enzyme integrase from the HIV virus also enters the host cell nucleus and induces the integration of viral DNA into the genetic material of the host cell. This leads to the production of **virons** and ultimately cell death. Activation of T lymphocytes by antigens or cytokines enhances the process of viral transcription and replication and loss of $CD4^+$ cells. Viral particles are released from the plasma membrane of the host cell and **lysis** occurs, causing destruction of the T cells. This is a cycle that ultimately results in the destruction of the immune system.

As viral production progresses, the rate of destruction of T cells is greater than they can be replaced, eventually leading to T-cell immunodeficiency. Macrophages and **dendritic cells** can also be infected with HIV and can act as reservoirs of infection as these cells are not killed on viral replication like $CD4^+$ cells.

Transmission of HIV infection

HIV is transmitted through body fluids that contain the virus via three major routes: sexual contact, inoculation with infected blood, and mother to baby transmission.

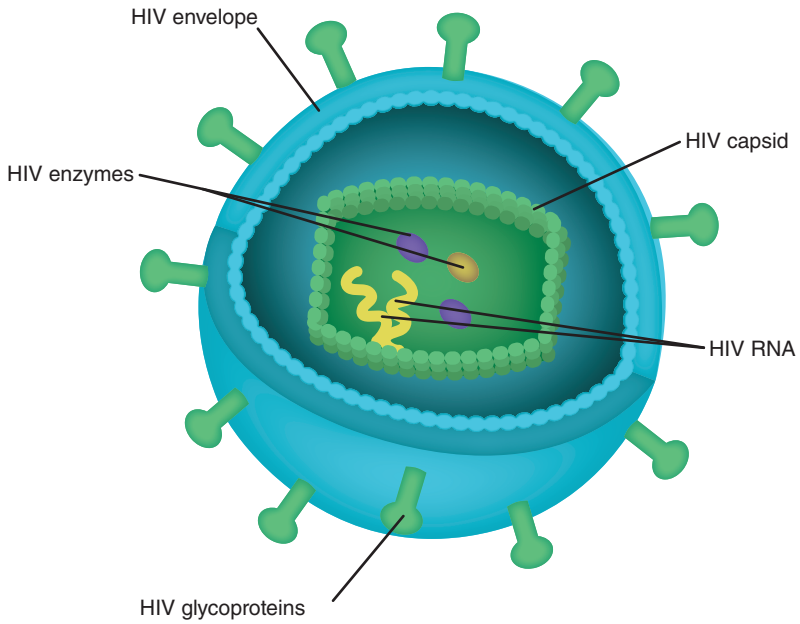

Figure 6.6 HIV virus

Sexual contact is the most frequent mode of transmission, where infected semen or vaginal fluid is exchanged and eventually gains entry to the bloodstream (e.g. through the mucosal lining of the vagina, anal mucosa, wounds or sores). Anti-retroviral treatment (ART) in an HIV-positive person can reduce the risk of transmitting the virus to an uninfected sexual partner (World Health Organisation, 2016).

Inoculation of infected blood or blood products is also a mode of transmission, particularly where needles are shared by intravenous drug users. The risk of transmission through blood transfusion is small as blood and blood products are screened for HIV in many countries. However, there is still a small risk due to a window where the infection is not detected; advanced testing of blood donors results in the risk as being 1 in 2 million. Mother to baby transmission occurs most frequently in utero, during childbirth or through breastfeeding.

Risk factors

Certain behaviour and conditions increase a person's risk of becoming infected, including having unprotected sex, having another sexually transmitted disease, sharing contaminated needles or any unsterile instrument that cuts or pierces the skin.

Diagnosis and testing

Blood serum tests can detect antibodies to HIV, although most people do not produce antibodies until around 28 days after infection. This period is known as the window, where the infection can still be transmitted but antibodies are not detectable. The person may be asymptomatic or present with general flu-like symptoms. Testing for the virus itself is used in newborn babies of infected mothers.

Clinical features

The following clinical features are characteristic of HIV (Kumar et al., 2018):

- *Acute phase*: During this period the virus is infecting $CD4^+$ T cells and progressing to the lymph tissue. The virus is disseminated through the blood and the host develops a response that manifests as a self-limiting acute illness with general flu-like symptoms, such as headache, fatigue and fever. This can occur 3–6 weeks after infection. The number of circulating $CD4^+$ cells falls. $CD8^+$ T cells are detected in the blood.
- *Chronic phase*: This phase may last for years, where the virus replicates and the destruction of $CD4^+$ T cells in the lymphoid tissue continues. $CD4^+$ T-cell count declines. The person is generally asymptomatic during this phase but may develop symptoms of acute viral infection. This can stimulate HIV production through the activation of cytokines such as TNF in response to microbial infections.
- *Final phase*: HIV progresses to AIDS when $CD4^+$ count drops below 200 cells/mm^3. The person is susceptible to opportunistic infections and cancers such as lymphomas or **Kaposi sarcoma**. Cachexia (wasting syndrome), kidney failure and central nervous system degeneration are features of this stage of the disease. The immune system cannot mount a response to infections or oncogenic viruses. A diagnosis of AIDS is based on clinical manifestations and CD4+ count.

Opportunistic infections and comorbidities

Tuberculosis (TB) is the most common cause of death in HIV-positive adults and children, and is responsible for about a third of deaths related to HIV (Gupta et al., 2015). Early diagnosis of TB through careful assessment of signs and symptoms and diagnostic tests can initiate anti-TB treatment as soon as possible and improve outcomes. Symptoms include fever, night sweats, cough and weight loss.

Cryptococcal meningitis is an opportunistic fungal infection that is not common in people with healthy immune systems. However, it is often seen in the later stage of HIV. It is diagnosed by lumbar puncture and treated with the antifungal drugs amphotericin B and fluconazole.

Kaposi sarcoma (KS) is a malignancy of the endothelial cells of blood and lymphatic vessels that initially manifests as a lesion on the skin and mucosal membrane of the mouth. It invades other organs, including the GI tract, causing pain, bleeding and obstruction of the lungs with symptoms of dyspnoea, cough and haemoptysis. Kaposi sarcoma is caused by an oncogenic virus called Kaposi sarcoma herpes virus (KSHV), which is a latent herpesvirus infection. When HIV suppresses the immune system, the KSHV becomes active and widespread, leading to KS.

Treatment and prevention

Major advances in the treatment of HIV have reduced the devasting effects of the progression of the disease. Treatment involves the administration of **antiretroviral drugs** that interfere with the viral life cycle and stop the progression of HIV. Once the virus is suppressed, the $CD4^+$ count gradually increases. Antiretroviral therapy (ART) is recommended for all people with HIV as soon as possible after diagnosis. Drugs used in combination are more effective and act in several ways (Table 6.4).

Table 6.4 Drugs used in HIV treatment

Class of drug	Mechanism of action
Nucleoside analogue	Inhibit the action of the enzyme reverse transcriptase
Viral protease inhibitors	Block the processing of viral proteins
Integrase inhibitor	Inhibit the viral entrance into the target cell
Entry inhibitor	Prevents viral attachment to the host cell by targeting CCR5 or CD4 molecules

Testing and counselling

Testing for HIV is advised for anyone exposed to the risk factors. This allows people to access treatment early and reduce the risk of transmission of the virus. When a person is diagnosed with HIV, it is recommended that they inform their sexual partner so that they too can be tested and commence treatment or preventative treatment. Antiretroviral therapy in non-infected high-risk individuals can block the acquisition of HIV and is used in pre-exposure prophylaxis (PrEP) in individuals who are at substantial risk of acquiring the virus (Ghosn et al., 2018).

HIV self-testing is a way to encourage people who do not know their HIV status to get tested. It has increased the uptake of testing among those at risk and should help to identify more HIV-positive individuals (Johnson et al., 2017). Testing for TB early in a person with HIV infection is essential as TB is a leading cause of death. Prompt commencement of TB treatment and ART can reduce this.

Individuals can change their behaviour to limit exposure to risk factors, such as practising safe sex with consistent use of condoms and taking precautions against becoming infected through the use of single sterile needles and syringes. Mother to child transmission can be prevented if both mother and baby are commenced on ARV drugs as early as possible in pregnancy and during breastfeeding (Payne et al., 2015).

Activity 6.2: Apply

HIV testing

Listen to this podcast about early testing for HIV.

The video can be accessed by **scanning the QR code** with your smartphone camera or via **https://study.sagepub.com/essentialpatho2e**.

HIV TESTING (50:24)

Alloimmunity: transplant rejection

Alloimmunity refers to the immune system reacting against the tissue of another individual and can be observed in blood transfusion reactions and transplanted tissue or in the fetus during pregnancy.

The immune system recognises antigens on foreign tissue and mounts a response. The ABO and Rhesus (Rh) systems for blood groups are antigens expressed on the surface of red blood cells and can be targets of alloimmune reactions (Cook et al., 2021).

Revise: A&P recap

Blood transfusion and potential reactions

Revise Chapter 12, The Cardiovascular and Lymphatic Systems, in *Essentials of Anatomy and Physiology for Nursing Practice* (2nd edition) (Cook et al., 2021) to refresh your knowledge about antibodies, and blood transfusion and the Rhesus system and pregnancy.

Transplanted tissue and organs are at risk of rejection due to the response of the immune system and rejection involves several of the immunological pathways that are seen in inflammatory diseases. Replacement of damaged non-functioning organs or tissues by healthy ones from a donor is a way of treating disease and prolonging life. Cells, tissues and organs can be transplanted from one person (the donor) to another person (the recipient). This process is known as transplantation and this type of transplanted tissue is known as an allograft. The immune system of the recipient can recognise the transplanted tissue as foreign and mounts a response to destroy the tissue. This is known as rejection and is a major barrier to transplantation.

Rejection is complex, involving a cellular response from T lymphocytes and antibodies and a humoral response, leading to inflammation and tissue necrosis. Major histocompatibility complex (MHC) molecules are expressed on the surface of all cells and are known as human leucocyte antigens (HLA). Their function is to enable the T lymphocytes $CD4^+$ and $CD8^+$ to recognise antigens. Donor tissue HLA can be recognised as foreign by host T lymphocytes and is the basis of rejection. The more similar two individuals are in their HLA types, the less risk of rejection. The recipient T lymphocytes recognise the donor antigens either directly or indirectly.

Direct pathway

Major histocompatibility complex (MHC) molecules on the surface of cells in the graft activate $CD4^+$ and $CD8^+$ cells and cause a type IV hypersensitivity reaction. Cytokines secreted by $CD4^+$ cells cause increased vascular permeability and accumulation of macrophages, resulting in graft tissue damage.

Indirect pathway

T-cell lymphocytes recognise MHC antigens of the graft tissue when they are presented by the recipient's own antigen-presenting cells in the same way as in the recognition of other foreign antigens, such as microbes. This pathway also produces antibodies.

Bone marrow transplantation involves the transplantation of stem cells harvested from donor bone marrow or blood. This is used to replace cancerous blood cells and immunodeficiency disorders and involves the recipient requiring treatment to destroy malignant cells and create an environment where the grafted stem cells will develop. This type of transplant grafts immunological competent cells into an immunosuppressed individual. Rejection is mediated by T cells and natural killer cells (NK). Graft-versus-host disease (GVHD) is a condition where the donor T cells recognise the recipient tissue as foreign and react against it (Choi and Reddy, 2014). This involves the activation of $CD4^+$ cells and $CD8^+$ T cells in a type IV delayed-type hypersensitivity (DTH). Symptoms include skin rash and GI involvement with nausea, diarrhoea and abdominal pain.

Transplant rejection may be hyperacute, acute or chronic. Hyperacute rejection occurs immediately due to pre-existing antibodies to HLA antigens in the vascular **endothelium** of the grafted tissue. Acute rejection occurs within days to weeks following transplantation when the recipient develops a cell-mediated response to HLA antigens. Chronic rejection occurs over months and years and often involves damage to the vascular supply to the graft (Perkey and Maillard, 2018).

INFECTION

Infectious diseases are in the top 10 leading causes of death worldwide, with lower respiratory tract infections, HIV/AIDS and diarrhoeal diseases the top three leading causes of death in low-income countries. Overall, the global mortality rates due to infectious diseases have dropped (Global Health Estimates, 2018). Improvements in sanitation, the availability of clean drinking water, vaccination programmes and the use of antibiotics have played an important role in reducing the risk of infection occurring and improving the outcome if someone acquires an infection.

Infectious diseases are caused by pathogens such as bacteria, viruses, fungi and protozoa (Table 6.5). Humans have contact with these microorganisms every day but, due to our finely tuned defence systems, we do not often acquire an infectious disease. Microorganisms that cause disease in humans are referred to as pathogens.

Revise: A&P recap

Microbiome

Some microbes are beneficial to humans. You may find it useful to revise Chapter 4, The Human Microbiome and Health, in *Essentials of Anatomy and Physiology for Nursing Practice* (2nd edition) (Cook et al., 2021).

General characteristics of microorganisms that cause disease

The microorganisms that cause infectious disease need to be capable of avoiding the immune system. They also need to be able to spread from one infected person to another. This is known as communicability. Certain microorganisms have high communicability and spread easily, making them difficult to control.

Table 6.5 Main types of microbial organisms

Microbe type	Class of organism	Structure	Metabolism	Additional information
Bacteria	Prokaryotes	DNA or RNA within cell without membrane surrounding organelles. No nucleus	Varied oxygen requirements	
Archaea	Prokaryotes			Much research still required
Viruses	'At the edge of life'	RNA or DNA (genetic material), surrounded by a protein coat, sometimes with lipid coat	Dependent on host cell metabolism for replication	Non-active outside host Replicate only inside living cells of host using cell materials to produce proteins encoded in RNA or DNA and form viruses Each virus restricted to specific number/type of cell. Those infecting bacteria are known as 'phages'
Fungi	Eukaryotes	Separate from animals and plants with some characteristics of both Cell nuclei surrounded by membrane	Rely on carbon fixed by other organisms	Most grow from their tips as tubular filaments (hyphae) which branch producing a network of hyphae. Some grow by budding or binary fission as single cells: include moulds, yeasts Some produce spores dispersed for reproduction. Further research to clarify role in microbiota needed
Protozoa/ protists	Eukaryotes	Eukaryote that is not animal plant or true fungus Independent cells or non-differentiated into tissues	Some use sunlight, others rely on organic compounds	Some are pathogens of animals, some of plants, some are non-pathogenic
Helminths	Eukaryotes	Worm-like **parasites** living in animal hosts	Feed on living hosts	Can cause weakness and disease but can also reduce incidence of allergy and autoimmune conditions. Uncommon in developed countries

Source: Cook et al., 2021

They also need to be able to gain entry to the host and multiply (infectivity) and cause disease (pathogenicity) (Rote, 2017). These are known as virulence factors and when a microorganism possesses these, it is said to be virulent.

Portal of entry

Microorganisms are able to gain entry through direct contact, inhalation, ingestion, penetration of the skin or by sexual transmission.

Direct contact

Some pathogens are transmitted directly from infected tissue or secretions to mucous membranes. Sexually transmitted infections are transmitted in this way.

Indirect contact

Microorganisms can gain access to the body via the gastrointestinal tract from the ingestion of infected food and water. The microorganism needs to overcome the acidic environment of the stomach, the resident microorganisms (flora), pancreatic enzymes and secreted IgA antibodies produced by plasma cells located in the mucosa-associated lymphoid tissue (MALT) (Brooks et al., 2013). Microorganisms can enter the host from the intestinal lumen.

Respiratory inhalation is another route of entry to the host and, like GI entry, the microorganism needs to overcome the defences of the respiratory system. The surface of the respiratory system is lined with ciliated mucous **epithelium** that sweeps any particles away from the lungs. The coughing mechanism removes particles form the lower respiratory tract and respiratory secretions contain antibodies and enzymes that can destroy invading microorganisms.

Penetration of the skin

A breach of the skin, the first line of defence, will allow microorganisms to enter and invade the tissue. Wounds, surgical incisions, burns, pressure ulcers, puncture of the skin with needles, sharp objects or insect or animal bites all breach the skin integrity.

Dissemination within the body

The portal of entry does not necessarily dictate the site of infection as once the microorganism has gained access it will either proliferate locally or cause infection at a distant site. The microbe may travel in the blood or lymph systems to spread to distant sites in the body. Viruses, bacteria, fungi and protozoa are transported in the plasma, although some viruses, such as herpes virus and HIV, are transported in leucocytes and some parasites, such as the *Plasmodium* species, use the red blood cells as a means of transport. Many viruses spread from cell to cell and some bacteria, fungi and helminths secrete enzymes that destroy tissue, allowing direct invasion (Kumar et al., 2018).

Transmission

Transmission of infections from one individual to another can occur via direct or indirect contact. For example, secretions from saliva, respiratory droplets from coughing and sneezing, faeces, blood, urine, genital mucosa and secretions, and vertical transmission from mother to fetus or newborn through the placenta, during childbirth or through breastfeeding.

Bacterial infection

Bacteria are single-celled prokaryotes (without membrane-bound organelles) that exist in a variety of shapes and sizes (see Cook et al., 2021, Chapter 4). They contain both DNA and RNA and many contain

small extra chromosomal pieces called **plasmids** that are associated with the development of resistance to antibiotics. The cytoplasm of the bacterial cell is surrounded by the cytoplasmic membrane and this is surrounded by a rigid cell wall. The physical and chemical structure of the cell wall differentiates bacteria based on the Gram stain. Bacteria will either stain gram positive (stain blue/green by the crystal violet dye) or gram negative (stain red) when the dark Gram stain is not absorbed by the cell wall. The Gram stain is the most widely used technique for staining and identifying bacteria according to the structure of their cell wall. (See Table 6.6 for characteristics of gram-positive and gram-negative bacterial cells.) Most bacterial cell walls have a distinctive polymer known as peptidoglycan which is a carbohydrate protein structure that is unique to bacteria. This is why many antimicrobial drugs target the cell wall.

Table 6.6 Relative characteristics of gram-positive and gram-negative bacteria

Gram-positive bacteria	Gram-negative bacteria
Stain blue	Stain red
Thick layer of peptidoglycan in cell wall	Thin layer of peptidoglycan in cell wall
No outer membrane	Cell wall has an outer membrane of proteins and phospholipids known as **lipopolysaccharides** (LPS)
Secrete proteins out of the cell (exotoxins)	LPS released from cell wall outer membrane on cell death (**endotoxin**)

Bacteria's pathogenicity depends on the effectiveness of the immune system and the ability of the bacteria to overcome it. Once bacteria have gained access to the host, they must attach to host cells through surface molecules called adhesins or by structures called **pilli** found on the surface of the bacterial cell. The bacterial cell can produce toxins which destroy normal functioning of the host cell. Toxins are classified into two main types: endotoxins, which are components of the bacterial cell, and exotoxins, which are proteins secreted by the bacteria.

An endotoxin is a lipopolysaccharide (LPS) component of the outer membrane in gram-negative bacteria. LPS binds to the surface of the host leucocytes and activates the inflammatory response. This response induces cytokine production and T-lymphocyte activation. However, in larger doses, LPS has detrimental effects through excessive levels of cytokines, as seen in **septic shock** (discussed later).

Exotoxins are proteins secreted from the bacterial cell that cause cell injury and death. They can be classified according to their mechanism of action. Some act as enzymes on specific tissue cells, for example proteases (break down protein), **lipases** (break down fats) and coagulases (cause blood clots). A–B toxins alter regulatory pathways; there is an active (A) component that is an enzyme and a binding (B) component that binds to the cell surface receptors and delivers the A protein into the cytoplasm. A–B toxins include the toxin of *Bacillus anthracis*, otherwise known as anthrax, and *Vibrio cholerae*. **Neurotoxins** are exotoxins produced by *Clostridium botulinum* and *Clostridium tetani* that inhibit the release of **neurotransmitters**, leading to paralysis. **Enterotoxins** are specific exotoxins that affect the gastrointestinal tract, causing vomiting and diarrhoea, for example the exotoxin produced by *Clostridium difficile*.

Some bacteria produce **endospores** when exposed to extreme conditions, such as lack of nutrients or water. Endospores are highly resistant structures that can remain dormant for many years and are resistant to desiccation, toxic chemicals and UV irradiation. When conditions become favourable, the

endospore exits the dormant stage to become a vegetative cell (germination). *Bacillus anthracis* (anthrax) and *Clostridium botulinum* (botulism) produce endospores when required.

Biofilms

Biofilms are complex multicellular masses consisting of interactive bacterial cells attached to a solid surface or to each other (Brooks et al., 2013). They are associated with urinary tract infections related to indwelling urinary catheters, foot ulcers, burns, pneumonia and infections of the oral cavity due to dental plaque. They offer a survival advantage for the microorganism as they can evade the immune system and exposure to antibiotics and show increased tolerance to nutrient deprivation and the host immune response (Scherr et al., 2015).

Viral infection

Viruses cause infection and disease in humans and some can transform normal cells into cancerous cells (oncogenic virus). A virus is an obligate intracellular parasite that depends on the cell machinery for its replication. It consists of a piece of genetic material (DNA or RNA which can be double- or single-stranded) inside a protein coat. Viruses are acellular and have no structures for metabolism/reproduction, and are therefore completely dependent on the host cells for existence. The host cell provides energy, synthetic machinery and materials for synthesis of viral proteins and nucleic acids. Viral replication takes place and new viral particles are released either by lysis of the host cell or by budding out through the host cell membrane, acquiring a new envelope in the process. This does not kill the host and so it continues to produce new viruses. Viruses account for a large number of infections and this can be manifested as a transient illness like the common cold or the virus may remain inside the cell, continuing to multiply, as in chronic infection with **hepatitis** B virus, or in a latent state with the possibility of reactivation at a later stage in response to stimuli such as stress or hormonal changes. An example of this is the herpes zoster virus. This virus causes chickenpox and can enter the dorsal root ganglia and reactivate as shingles, a painful nerve and skin condition, years later (Brooks et al., 2013). Influenza viruses change their viral surface antigens so they are not recognised by antibodies produced from a previous infection, hence the need for yearly vaccine against influenza. Influenza A and B circulate and cause seasonal epidemics (WHO, 2018b). Influenza A mutates quickly and distinct subtypes based on the haemagglutinin (HA) and the neuraminidase (NA) antigens have been identified. The A (H1N1) subtype caused the flu pandemic in 2009.

Coronaviruses are a group of viruses that circulate in animals and can cross over to humans, meaning they are zoonotic. They include the common cold virus, the SARS coronavirus (Severe Acute Respiratory Syndrome) and MERS coronavirus (Middle East Respiratory Syndrome). Coronaviruses are continually evolving and currently the SARS-CoV-2 coronavirus has circulated worldwide to cause the COVID-19 pandemic. This is discussed later.

Fungal infection

There are over 100,000 species of fungi with around 200 being pathogenic to humans. Fungi are very diverse in shape and size, being microscopic and macroscopic. Fungi have a rigid cell wall containing a

polysaccharide sugar known as **chitin** (Brooks et al., 2013). Fungal infections are known as **mycoses** and are classified according to the degree of tissue involved:

- *Superficial mycoses*: occur in the epidermis, nails and hair (e.g. ringworm, athlete's foot).
- *Subcutaneous mycoses*: confined to the dermis and subcutaneous tissue but may spread to underlying tissues. Caused by fungi that live in soil (e.g. sporotrichosis acquired by farmers and gardeners).
- *Systemic mycoses*: deep, often life-threatening, infections of internal organs. Usually caused by inhalation of spores from infected soil into lungs which then spread via the circulation to other tissues (e.g. histoplasmosis, a chronic respiratory disease). Immunocompromised people are particularly at risk of fungal infection.

Parasitic infection

Parasitic disease is where the parasite, an organism living within another organism, benefits at the expense of the host species. Parasites vary from unicellular protozoa to multicellular worms. Of the many parasites, only a few cause diseases in humans and this is mainly in tropical climates. Parasites have a complex life cycle involving different hosts. Some can form protective coats called cysts that offer protection while outside the host. Parasites can enter the body in various ways, such as through contaminated food, insect bites or direct penetration of the skin.

Pathogenic protozoa include *Plasmodium falciparum*, which is responsible for malaria. Malaria is one of the most common infections worldwide and the World Health Organisation estimates there were 216 million cases of malaria worldwide in 2016, resulting in 445,000 deaths (WHO, 2017). The mosquito insect (arthropod) is a vector for *Plasmodium*. There are four different *Plasmodium* spp. but *P. falciparum* is the most fatal. Plasmodium has a complex life cycle involving sexual reproduction in the mosquito and asexual reproduction in the human liver and erythrocytes. Destruction of erythrocytes results in anaemia and tissue **hypoxia**.

Helminths or worms are not microorganisms but are parasites and cause disease in people throughout the world. Three types cause disease in humans: nematodes (or roundworms), cestodes (or tapeworms) and trematodes (or flukes). They have a complex life cycle and are often ingested as eggs or larvae in contaminated food or water, or they enter directly through the skin. They are often identified in the faeces of an infected person.

Stages in the development of disease

Infectious disease progression can be identified in three distinct phases:

1. ***Incubation period***: This is the period between introduction of the microbe to the host and the onset of the symptoms of the illness.
2. *Illness*: During this phase the host experiences signs and symptoms of disease.
3. ***Convalescence***: This is the period of recuperation and recovery from disease.

The host can spread infection during all three stages.

SOME INFECTIOUS DISEASES

Sexually transmitted infections

Sexually transmitted infections (STIs) are caused by a range of pathogens that can be acquired through sexual contact. They can lead to infertility, **pelvic inflammatory disease** and malignancy. A range of pathogens cause STIs – bacteria, viruses and fungi, protozoa and parasites (Table 6.7).

Table 6.7 Pathogens that cause STIs

Infection	Microorganism
Bacterial	
Chlamydia (urogenital infections)	Chlamydia trachomatis
Gonorrhea	Neisseria gonorrhoeae
Syphilis	Treponema pallidum
Viral	
Genital herpes	Herpes simplex virus (HSV)
Genital warts, cervical cancer	Human papilloma virus (HPV)
Protozoa	
Trichomoniasis	Trichomonas vaginalis

Sexually transmitted infections affect the external genitalia, the rectum and oral pharynx and/or produce systemic effects. The spread of STIs is a problem as frequently they are asymptomatic, so people are unaware that they have the infection and do not take adequate precautions or seek treatment. Other challenges include recurrent infections, more than one infection present at a time, the emergence of drug-resistant microorganisms, and difficulty in notifying sexual partners who might have become infected.

Bacterial infections

Chlamydia

Chlamydia is one of the most common sexually transmitted infections and is caused by the bacterium *Chlamydia trachomatis*, a gram-negative obligate intracellular pathogen (Lehr et al., 2018). It is known as a polymicrobe because it behaves like both a virus and a bacterium. In the 'elementary' state, the bacterium can survive outside the cell and when it attaches to the susceptible host cell it is ingested. Once inside the host cell it transforms into a larger reticulate body which takes over the metabolic machinery of the cell and reproduces by binary fission. New elementary bodies are formed and released from the infected host cell (Lehr et al., 2018).

Chlamydial infections are often asymptomatic but non-specific symptoms such as urinary frequency, **dysuria** and vaginal discharge, or mucopurulent cervical discharge may be present. The cervix can become inflamed and more susceptible to further infection. The Fallopian tubes and **endometrium** can also become inflamed and there can be elements of inflammatory pelvic disease present. In men,

chlamydial infection causes **urethritis** with symptoms of dysuria, itching and penile discharge. A painful, swollen scrotum and fever may indicate the presence of **epididymitis**.

Gonorrhoea

This is a sexually transmitted infection caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus bacterium that is spread by direct contact with the mucosa of an infected individual. The portal of entry can be the genitourinary tract, eyes, oropharynx, rectum or skin. The bacteria attach to the mucosal epithelium and penetrate through to the deeper tissues, causing an inflammatory reaction (Sherrard, 2014). This is clinically manifested as dysuria with a **purulent** urethral discharge in males and, although often asymptomatic in females, dysuria can also occur with other features, such as vaginal discharge, pelvic pain or tenderness and fever. Ascending infection can lead to acute **prostatitis** and epididymitis in males and infection of the uterus, Fallopian tubes and ovaries in females.

Oro-genital contact may lead to **pharyngitis** or **tonsillitis**. Babies of infected mothers risk becoming infected during passage through the birth canal and can develop gonorrhoeal conjunctivitis which can lead to blindness if not treated. Strains of resistant gonorrhoea have been reported by the European Centre for Disease Prevention and Control (ECDC, 2018b).

Syphilis

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum*, an aerobic spirochete bacterium. *T. pallidum* is spread by direct contact with a skin or mucosal lesion through sexual activity. The microorganism gains entry through the mucosa or through breaks in the skin. The infection can also be transferred from infected mother to fetus through the placenta and this is referred to as congenital syphilis (Hook, 2017). Syphilis is a systemic infection with four clinically distinct stages (sometimes referred to as phases in other texts):

Primary: Occurs several weeks after infection and is characterised by a primary lesion (or lesions), called a chancre, at the point of contact on the skin or mucous. This is a painless, firm, ulcerated nodule. The immune response is initiated, and antibodies are formed at this stage. The infection is highly contagious and can often go unnoticed as the chancre heals spontaneously within 3–6 weeks.

Secondary: This stage, or secondary syphilis, occurs when the bacteria have already entered the general circulation and there is enlargement of the lymph nodes (lymphadenopathy). Highly infectious mucosal and cutaneous lesions full of bacteria develop and a widespread reddish **maculopapular rash** appears on the palms of the hands and the soles of the feet. Other general signs of infection, such as fever, sore throat, loss of appetite and inflamed eyes, are common.

Latent: After the second stage in an untreated infection, the person becomes asymptomatic for more than a year after the initial infection. This is known as the latent phase, which may last for many years.

Tertiary: If individuals become symptomatic, they enter the tertiary stage where the infection progresses and there is the formation of lesions known as **gummas**. These can occur anywhere in the body but are more common in the bone, skin and mucous membranes. Gummas are necrotic

fibrous lesions caused by tissue necrosis, which can lead to aneurysms in the aorta if formed in the cardiovascular system, bone destruction and damage to the central nervous system, leading to blindness, dementia and sensory/motor loss. This condition can lead to death.

Genital herpes

Herpes simplex virus (HSV) causes genital herpes and is a highly contagious infection. There are two types of herpes simplex virus that are associated with STIs: these are HSV-1, associated with blisters and cold sores, and HSV-2, which causes most cases of genital herpes. Both viruses are genetically similar, and both can cause genital and oropharyngeal herpes, but it is now being seen more often in the genitalia due to the increase in frequency of oral sex. HSV-2 typically infects the genitalia (Garland and Steben, 2014).

HSV is transmitted by direct contact with infectious lesions and the incubation period is 2–12 days. Often the infected person is asymptomatic and viral shedding (expulsion and release of virus after successful reproduction within the host cell) can contribute to the spread of infection.

The initial symptoms include painful **vesicles** on the skin of the external genitalia, with itching and pain in the genital area. The vesicles rupture and form wet ulcers that are associated with dysuria, urethral discharge and local lymph node enlargement. Systemic symptoms of fever, muscle ache, headache and regional lymph node enlargement are a feature. Vesicles are found on the cervix, vulva and urethra in women. In men, lesions form on the penis, scrotum and urethra. Rectal and perianal lesions may also occur. Following the acute stage, HSV migrates along the peripheral nerve to the dorsal root ganglia where it can remain dormant in the latent phase. Reactivation of the virus may be triggered by many factors, such as **stress** and other infections, and recurrent episodes are usually milder and of shorter duration than the primary episode.

The vesicles contain the virus and the infection can spread to the eyes or skin through hand contamination. Lesions of the cervix and vagina can transmit the infection to the baby during vaginal delivery. Neonatal herpes infection can be fatal.

Human papilloma virus (HPV)

HPV is a nonenveloped, double-stranded DNA virus that affects the genital tract. There are several types of HPV, some of which are associated with cervical cancer. HPV types 6 and 11 infect the squamous epithelial cells, causing genital warts, also known as condylomata acuminata. These lesions occur on the penis and scrotum as well as the female genitals, perineum and perianal skin. They may also affect the mucous membrane of the vagina, urethra, anus or mouth. They vary in appearance from soft fleshy projections to cauliflower-like masses. The incubation period is 2–3 months. Vaccination against HPV is one of the most effective ways of controlling HPV-related diseases (Maver and Poljak, 2017).

Protozoan infection

Trichomoniasis is an STI caused by the protozoan *Trichomonas vaginalis*, an anaerobic flagellated protozoan. It is associated with other STIs and resides in the urethra in men and in the vagina in women. These protozoa attach easily and feed off the mucosa they inhabit. Active infection causes a copious,

malodourous yellow discharge with associated inflammation and itchiness of the mucosa. Systemic treatment with metronidazole or tinidazole is effective.

Other infectious diseases

Meningitis

Infectious agents can affect any part of the body including the nervous system. The coverings of the brain and spinal cord are susceptible to invasion by microorganisms that can access the nervous system in several ways. The most common means of access is via the arterial blood supply, but direct invasion through open trauma or, rarely, by invasive surgery or diagnostic tests can also occur. Local extension from an infected nearby structure may also occur, for example infected sinuses, teeth or the middle ear.

Meningitis is inflammation of the **meninges**, usually as a result of infection. However, the meninges can become inflamed in response to a non-infectious cause, such as carcinoma. Infectious meningitis can be caused by bacteria, often referred to as acute pyogenic meningitis, by viruses, referred to as aseptic meningitis, or by fungi and *Mycobacterium tuberculosis*. This last is usually a chronic form of the infection.

Bacterial meningitis (acute pyogenic meningitis)

Different bacteria cause bacterial meningitis, and this varies with age. *Escherichia coli* and group B streptococcal bacteria are the most common causative organisms in neonates. In adolescents and young adults *Neisseria meningitidis* (meningococcus) is the most common pathogen, and in older adults *Streptococcus pneumoniae* (pneumococcus) and *Listeria monocytogenes* cause most cases (Kim, 2010). Risk factors associated with developing meningeal infection include base of skull **fractures**, **otitis media**, sinusitis neurosurgery, systemic sepsis and a compromised immune system.

N. meningitidis is often carried in the nasopharynx of an asymptomatic carrier and is spread by respiratory droplet transmission, through kissing, coughing, sneezing or sharing utensils, food and drink. It is often epidemic in environments where there is close contact between people, such as educational institutions or where young people reside together. Six sub-groups of meningococcus have been identified – A, B, C, W-135, X and Y (Brooks et al., 2013).

Once the microorganism has crossed the **blood–brain barrier** it gains access to the cerebrospinal fluid (CSF), where it replicates and undergoes lysis. This releases toxins that cause alterations in cerebrovascular permeability, leading to oedema and inflammation of the pia and arachnoid maters. A purulent exudate is produced, and the meningeal vessels become engorged. Neutrophils can be found in the subarachnoid space and **phlebitis** can occur, leading to venous occlusion and **infarction** of the surrounding tissues. The meninges thicken and **adhesions** form which may obstruct the outflow of CSF, giving rise to **hydrocephalus** (obstructive hydrocephalus). Typical symptoms of acute bacterial meningitis result from meningeal irritation with sudden onset of headache, fever, irritability, neck stiffness, photophobia and altered mental state. Nausea, vomiting, seizures and reduced **consciousness** are an indication of raised intracranial pressure. A rose-coloured **petechial rash** with palpable **purpura** (bleeding into the skin) is a feature of meningococcal meningitis and can rapidly progress to haemorrhagic infarction of the skin, leading to systemic sepsis, shock and multiple organ failure.

Diagnosis is based on clinical signs and examination of CSF obtained by lumbar puncture and positive **Kernig sign** (resistance to knee extension in the supine position with the hips and knees flexed against the body) and **Brudzinski sign** (flexion of the knees and hips when the neck is flexed forward rapidly). Lumbar puncture reveals increased pressure and CSF examination shows neutrophils, increased protein and reduced glucose. Prompt treatment with antibiotics and supportive care increases chances of recovery and reduces risk of morbidity and mortality.

Aseptic meningitis (viral meningitis)

Viruses such as enterovirus (coxsackievirus, poliovirus, echovirus), herpes simplex virus (HSV) and Epstein–Barr and mumps virus can cause meningitis. The virus enters the nervous system by crossing the blood–brain barrier, by direct spread along peripheral nerves or through the **choroid plexus** epithelium (Doran et al., 2016). The inflammatory response is activated, and the clinical signs are similar to bacterial meningitis but milder and typically self-limiting. Lymphocytes rather than neutrophils are found in CSF, with moderate protein elevation and normal glucose levels. Viral meningitis is managed by treating symptoms and the administration of antiviral drugs.

Chronic meningitis

Chronic meningitis is defined as chronic inflammation in the cerebrospinal fluid, persisting for at least one month without spontaneous resolution (Baldwin and Zunt, 2014). *Mycobacterium tuberculosis* and *Cryptococcus* species are some of the most common causes of chronic meningitis.

Chronic meningitis is characterised by general symptoms of headache, malaise, mental confusion and vomiting. Protein levels in CSF are elevated and CSF glucose levels are normal or reduced. Infection with *M. tuberculosis* can lead to the development of a mass within the cerebral tissue that can block CSF resorption and lead to hydrocephalus. Cerebral vessels may be affected, causing **vasoconstriction** and eventually thrombosis with cerebral infarction (Baldwin and Zunt, 2014).

COVID-19 SARS-CoV-2 coronavirus infection

The SARS-CoV-2 virus emerged in 2019 and is similar to the SARS CoV virus but for changes on the spike glycoprotein (Rodriguez-Morales et al., 2020). It is spread through droplet and airborne transmission and an infected person can have no symptoms or experience the most common symptoms of fever, cough and fatigue. In severe cases of COVID-19, acute respiratory distress syndrome is present and hospitalisation is required. The severity of infection is associated with enhanced immune response (Long et al., 2020). The inflammatory response and release of cytokines has been shown to be similar to other cytokine mediated diseases, such as sepsis, and as such the direct role of cytokines is unclear (Wilson et al., 2020). Thromboembolism occurs frequently and is associated with increased mortality in COVID-19 (Malas et al., 2020).

SEPSIS

It is estimated that sepsis affects more than 30 million people worldwide every year, potentially leading to around 6 million deaths (Fleischmann et al., 2016). One in 10 deaths associated with pregnancy and

childbirth is due to maternal sepsis (Say et al., 2014). In the UK, it is estimated that 48,000 people die from sepsis each year (Rudd et al., 2020). Certain age groups are more at risk of developing sepsis, such as the very young (under 1 year) and older people over 75 years. People who are immunocompromised because of drugs or illness, or who are receiving **chemotherapy** for cancer or taking immunosuppressant drugs are also at higher risk (NICE, 2016b).

Severe microbial infections can lead to **bacteraemia** (bacteria in the blood) and this can trigger what is known as **systemic inflammatory response syndrome (SIRS)**. This is associated with a massive release of inflammatory mediators from the innate and adaptive immune cells which results in cardiovascular abnormalities, leading to shock and often progressing to **multiple organ dysfunction syndrome (MODS)**. SIRS was defined in the 1992 international consensus conference based on deranged clinical findings in temperature, respiratory rate, heart rate and white blood cell count (Bone et al., 1992). A diagnosis of SIRS was based on meeting two of the four criteria outlined in Table 6.8.

Table 6.8 SIRS diagnostic criteria: diagnosis is based on any two or more of the criteria

Parameter	SIRS (systemic inflammatory response syndrome)
Tachypnoea	Respiratory rate >20 breaths/min
Tachycardia	Heart rate >90 beats/min
Hyperpyrexia	Body temperature >38°C or <36°C
Leucocytosis	White blood cell count >12,000 cells/mm^3 or <4000/mm^3

Until recently the SIRS criteria had been used to identify the signs and symptoms of sepsis. However, terminology has changed in recent years and the current definition of sepsis stems from the 2016 international consensus definition:

> life-threatening organ dysfunction caused by a dysregulated host response to infection. (Singer et al., 2016)

Septic shock is defined as:

> a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. (Singer et al., 2016)

Adults with suspected infection can be rapidly identified if they have at least two of the following clinical criteria:

- Respiratory rate of 22/min or greater
- Altered mentation
- Systolic blood pressure of 100 mmHg or less (Singer et al., 2016).

The National Institute for Health and Care Excellence (NICE, 2016b) has produced clinical guidance on sepsis recognition, diagnosis and early management. Table 6.9 provides a tool to identify risk of severe illness.

Table 6.9 Risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

Category	High risk criteria	Moderate to high risk criteria	Low risk criteria
History	Objective evidence of new altered mental state	History from patient, friend or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks	Normal behaviour
Respiratory	Raised respiratory rate: 25 breaths per minute or more New need for oxygen (40% FiO_2 or more) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)	Raised respiratory rate: 21–24 breaths per minute	No high risk or moderate to high risk criteria met
Blood pressure	Systolic blood pressure 90mmHg or less or systolic blood pressure more than 40mmHg below normal	Systolic blood pressure 91–100 mmHg	No high risk or moderate to high risk criteria met
Circulation and hydration	Raised heat rate: more than 130 beats per minute Not passed urine in previous 18 hours. Not catheterised patients, passed less than 0.5ml/kg of urine per hour	Raised heat rate: 91–130 beats per minute (for pregnant women 100–130 beats per minute) or new onset arrhythmia Not passed urine in the past 12–18 hours For catheterised patients, passed 0.5–1 ml/kg of urine per hour	No high risk or moderate to high risk criteria met
Temperature		Tympanic temperature less than 36° C	
Skin	Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound	No non-blanching rash

Source: NICE, 2016b

Pathophysiology of sepsis and septic shock

Sepsis is the result of a complex sequence of cellular activation and inflammatory mediators, associated with infection. Gram-positive bacteria, gram-negative bacteria and fungal pathogens are all associated with sepsis. The most common gram-positive pathogens are *Staphylococcus aureus* and *Streptococcus pneumoniae*, while *Escherichia coli*, *Klebsiella species* and *Pseudomonas aeruginosa* are the most common gram-negative organisms. The bacterial cell wall releases endotoxins (gram-positive cells) and exotoxins (gram-negative cells) that engage receptors on the cells of the immune system (macrophages).

These receptors are called Toll-like receptors (TLRs) and they recognise the molecules on the bacterial cell called 'pathogen-associated-molecular patterns' (PAMPs). Once activated, the immune cells produce cytokines, including tumour necrosis factor (TNF), Interleukin 1 (IL-1), IL-12 and IL-18. Other mediators, such as **platelet-activating factor (PAF)**, **prostaglandin** and **nitric oxide (NO)** are also released. Complement and coagulation are activated (Deutschman and Tracey, 2014) (Table 6.10).

A significant feature of sepsis is this proinflammatory state, which is counteracted with anti-inflammatory responses at the same time (Hotchkiss et al., 2013). As sepsis progresses, there is widespread vasodilation caused partly by NO being further released from damaged endothelial cells. This leads to **hypotension**, and compensatory tachycardia with increased cardiac output, which is the early stage of septic shock. Endothelial cell activation leads to widespread vascular leakage and subsequent tissue oedema, reducing the circulating blood volume. Derangement in coagulation leads to a decrease in the production of anti-coagulant factors and an increase in pro-coagulation factors. Tissue **perfusion** is reduced due to oedema and decreased blood volume and flow, and this in turn leads to the systemic activation of thrombin and the formation of thrombi in the microcirculation. Coagulation factors and platelets are consumed, resulting in bleeding and haemorrhage. This derangement of coagulation is known as **disseminated intravascular coagulation (DIC)**. Poor tissue perfusion leads to cellular hypoxia, eventually progressing to septic shock (Hotchkiss et al., 2013).

Table 6.10 Summary of mediators involved in sepsis

Mediator molecule	Function
Nitric oxide	Causes and maintains vasodilation. Contributes to increased permeability
Complement proteins	Neutralise pathogens, mobilise white blood cells and amplify the immune response
Thrombin	Promotes clot formation by changing fibrinogen into fibrin. Involved in nitric oxide production
Interleukins	Complex group of proteins which attract white blood cells to the area and modulate inflammation. Some cause inflammation and some suppress the inflammatory response
Tumour necrosis factor (TNF)	Pro-inflammatory cytokine

Stress-induced hormones drive **gluconeogenesis** and proinflammatory cytokines promote insulin resistance, leading to hyperglycaemia (Kumar et al., 2018). Septic shock can progress to **multiple organ dysfunction syndrome (MODS)**, where two or more organ systems fail due to the overwhelming uncontrolled inflammatory response.

Sepsis and septic shock are manifested by hypotension and flushed skin due to vasodilation. Compensatory tachycardia with a strong pulse is present in the early stages and there is an increase in respiratory rate. Temperature may be high or low and there may be alteration in mental state. Sepsis can progress rapidly to septic shock unless it is recognised early and appropriate treatment commenced.

Treatment

Treatment is focused on finding the causative agent and treating it with targeted antimicrobials. Early fluid resuscitation and the use of **vasopressors** to support the circulation and optimise tissue perfusion

and oxygen delivery to the cells are essential. Once sepsis is recognised, depending on the environment, there are six simple steps that can be performed by health care professionals within the first hour to improve the person's chances of survival (Daniels and Nutbeam, 2019). Table 6.11 provides an overview of the actions that should be completed for adults and young people over 12 years in an acute setting within one hour of identification of sepsis.

Table 6.11 Sepsis 6 screening and action tool

Action to be completed within 1 hour	Why we do this
1. Ensure senior clinician attends	Experience is essential to deliver the right care and confirm diagnosis
2. Give oxygen if required *Aim for oxygen saturation of 94–98%*	There is a critical imbalance between oxygen supply and demand in sepsis. Correcting low oxygen saturations helps to reduce tissue hypoxia
3. Secure IntraVenous access and take bloods *Include blood cultures, glucose, lactate, full blood count and biochemistry, CRP, clotting screen*	Lab tests help stratify risk and identify causative pathogen allowing more targeted antibiotic therapy
4. Give IV antibiotics *Maximum dose broad spectrum therapy*	To control the source of infection, reducing the stimulus to the immune system
5. Give IV fluids	Hypovolaemia contributes to shock in spesis. Restoring volume can help correct this
6. Monitor *Measure urine output and measure lactate*	Urine output and lactate measurements can help guide fluid therapy and determine need for Intensive care

CHALLENGES OF MICROBIAL INFECTIONS

Antimicrobial resistance

Antimicrobial resistance is a growing problem worldwide in treating and controlling infections (Khabbaz et al., 2014). Some bacteria, such as *Staphylococcus aureus*, have developed resistance to **broad spectrum antibiotics**, including methicillin-type antibiotics. Methicillin-resistant Staphylococcus aureus (MRSA) is the most important cause of health-care-associated infections worldwide and use of antibiotics is the main driver for this (Boswihi and Udo, 2018; den Heijer et al., 2013). While the prevalence of MRSA has decreased significantly in Europe between 2013 and 2016, it still remains a public health priority. There have been significant increases in the percentages of other types of bacterial resistance, such as *Enterococcus faecium*, resistant to vancomycin and also known as vancomycin-resistant enterococcus (VRE), and *Klebsiella pneumoniae*, resistant to third-generation cephalosporins and carbapenems (European Centre for Disease Prevention and Control [ECDC], 2018a).

Mechanism of bacterial resistance to drugs

There are several ways bacteria can develop resistance to antibiotics. Gram-negative bacteria produce enzymes that destroy the β-lactam component of penicillin-type antibiotics. A reduction in permeability, including closure of porin channels in the cell wall, prevents entry of the antibiotic into the cell and

the creation of a modified target so that the antibiotic no longer recognises its target receptor. Bacteria also use an export mechanism to actively pump the antibiotic out of the cell. This mechanism leads to resistance to multiple classes of antibiotics (Karam et al., 2016).

Resistance can also occur as a result of genetic mutations in the microorganism with 'resistance' genes found on a **chromosome** or a plasmid. Plasmids are small pieces of extrachromosomal DNA that use cellular proteins to replicate. By a process of selection, the cells with resistance genes will not be killed by the antibiotic and are passed on to daughter cells, thus maintaining resistance. Bacteria that contain the resistance gene can transfer the gene to other bacteria in the population that are sensitive to the antibiotic. These bacteria then become resistant, thus contributing to the spread of resistance (Bhattacharjee, 2016). The widespread use and misuse of antibiotics has resulted in the development of resistance in microorganisms, including the use of antibiotics in animals that are part of the food chain. A global action plan has been agreed to address the problem of microbial resistance, with a particular focus on the use of antibiotics (World Health Organisation, 2015). Prudent use of antimicrobials, for example avoidance of prescribing antibiotics for viral infection for which they have no effect, effective infection control measures to reduce spread, reduced use of antibiotics in farm animals, and screening and isolation of infected patients in hospitals are recommended (ECDC, 2018a).

Antibiotic stewardship

As antibiotic resistance is a global crisis, all health care providers should develop an antimicrobial stewardship programme in which the responsibilities and roles are clearly identified (NICE, 2015). A coordinated approach by all health care professionals is therefore required to establish, maintain and facilitate this process, and nurses have a key role to play. Infection control nurses can actively prevent infection through the use of their audit skills, analysing and reporting data. Nurse prescribers play a vital role in improving antimicrobial use by adhering to local and national antimicrobial prescribing guidelines. Nurses can also educate colleagues and patients on the appropriate use of antimicrobials and implement strategies to optimise their safe and effective use (CDC, 2021).

Activity 6.3: Understand

Antibiotic resistance

An interesting overview on antibiotic resistance has been produced by BBC *Future Now*. To read the article, type 'futurenow antibiotic resistance' into a search engine.

CHAPTER SUMMARY

In this chapter you have studied how the immune system defends the body against threats to homeostasis and the consequences of a malfunctioning immune system. Inappropriate responses leading to hypersensitivity, misdirected responses leading to autoimmunity and alloimmunity, and inadequate response leading to immune deficiency disorders were examined. How microorganisms cause infectious

diseases and how the immune system deals with them were also examined, along with some of the challenges we face in controlling the spread and treatment of infectious diseases. In considering these pathophysiological processes, it is essential to consider that people in your care can be vulnerable to such disorders of immunity, whether in a hospital situation or community setting. These disorders have the potential to make someone seriously ill, leave them with a lifelong illness and impact on their ability to function independently or have a family, and may even result in death. As nurses, people in our care are often experiencing some form of illness that may lead them to be vulnerable to an immune disorder, and we therefore need to ensure that we minimise such risks, particularly where our actions as health care professionals may be a link in the chain of infection. Handwashing is one of the most important factors in preventing cross-contamination, as is the use of aseptic non-touch techniques when there is a risk of introducing or contaminating with pathogens. Understanding the factors relating to disorders of immunity addressed in this chapter is central to your effectiveness as a person-centred practitioner.

Key points

- Disorders of the immune system result in homeostatic imbalances: hypersensitivity, where the immune system overreacts; autoimmunity, where the immune system attacks the body's own tissues; and immunodeficiency, where components of the immune system fail.
- Environmental and genetic factors play a role in immune system disorders.
- In autoimmune diseases, the mechanism of self-tolerance is lost, and almost any cell or tissue in the body can be affected.
- Immune deficiency disorders occur when there is failure of the immune system to function normally, resulting in an increased susceptibility to infections. This is either genetically determined (primary) or an acquired (secondary) disorder.
- Bone marrow transplantation involves the transplantation of stem cells harvested from donor bone marrow or blood. Graft-versus-host disease (GVHD) is a condition where the donor T cells recognise the recipient tissue as foreign and react against it, involving $CD4^+$ cells and $CD8^+$ T cells.
- HIV is a retrovirus transmitted through body fluids that spread the virus via three major routes: sexual contact, inoculation with infected blood and mother to baby transmission.
- Infectious diseases are caused by microorganisms such as bacteria, viruses, fungi and protozoa.
- The spread of sexually transmitted infections (STIs) is aided by the fact that they are often asymptomatic, so people are unaware they have the infection and do not take adequate precautions or seek treatment.
- *Neisseria meningitidis* is the most common cause of bacterial meningitis in young adults. It is often carried in the nasopharynx of an asymptomatic carrier and is spread by respiratory droplet transmission through kissing, coughing, sneezing or sharing utensils, food and drink.
- Sepsis occurs through a complex sequence of cellular activation and inflammatory mediators and results in life-threatening organ dysfunction caused by a dysregulated host response to infection.

- Bacteria develop resistance to antibiotics in several ways:
    - production of enzymes that destroy the β-lactam component of penicillin-type antibiotics
    - reduction in permeability, including closure of porin channels in the cell wall, preventing entry of the antibiotic into the cell
    - creation of a modified target so that the antibiotic no longer recognises its target receptor
    - use of an export mechanism to actively pump the antibiotic out of the cell. This mechanism leads to resistance to multiple classes of antibiotics.

Revise

Test your knowledge

In this chapter you have learned about disorders of immunity and their complexity. Use the questions below to check your knowledge and understanding.

Answers are available online at **https://study.sagepub.com/essentialpatho2e/answers**.

1. Explain the immunological mechanisms that are responsible for allergic reactions.
2. Explain why it is important that people with a known risk of anaphylactic shock need to carry an epinephrine 'pen' with them at all times.
3. Discuss the type of reaction triggered by a Mantoux test and why it is used.
4. Describe four clinical features of SLE.
5. Identify how HIV is transmitted.
6. Describe how HIV causes destruction of the immune system.
7. Outline the virulence factors that a microorganism needs to cause infectious disease.
8. Describe the stages of the sexually transmitted infection syphilis.
9. What are the risk factors for developing meningitis?
10. Outline the clinical signs of systemic inflammatory response syndrome (SIRS).
11. Explain how sepsis can lead to multiple organ dysfunction syndrome (MODS).
12. Explain the six steps of treatment once sepsis is suspected.
13. Explain how microorganisms become resistant to antimicrobial drugs
14. Identify what steps can be taken to reduce microbial resistance.

Revise

Ace your assessment

For additional revision resources visit **https://study.sagepub.com/essentialpatho2e**.

- Revise key terms relevant to this chapter with interactive flashcards.
- Test yourself with quizzes and multiple-choice questions.
- Access the glossary with audio to hear how complex terms are pronounced.

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