Pathophysiology: The Immune System

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- Complete the questions at the end of the course.
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Faculty

Jane C. Norman, RN, MSN, CNE, PhD, received her undergraduate education at the University of Tennessee, Knoxville campus. There she completed a double major in Sociology and English. She completed an Associate of Science in Nursing at the University of Tennessee, Nashville campus and began her nursing career at Vanderbilt University Medical Center. Jane received her Masters in Medical-Surgical Nursing from Vanderbilt University. In 1978, she took her first faculty position and served as program director for an associate degree program. In 1982, she received her PhD in Higher Education Administration from Peabody College of Vanderbilt University. In 1988, Dr. Norman took a position at Tennessee State University. There she has achieved tenure and full professor status. She is a member of Sigma Theta Tau National Nursing Honors Society. In 2005, she began her current position as Director of the Masters of Science in Nursing Program.

Faculty Disclosure

Contributing faculty, Jane C. Norman, RN, MSN, CNE, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses working in critical care and general and specialty medical-surgical units in which patients with multiple organ system problems are found.

Accreditations & Approvals

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Course Objective

As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing management of their autoimmune or immune system disorder.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review the general characteristics of active and passive immunity.
2. Describe the role of cytokines in human immunity.
3. Identify the cells of the innate immune system and their functions.
4. Discuss the cells of the adaptive immune system and their functions.
5. Analyze features of immunity in special populations.
6. Evaluate the manifestation, diagnosis, and treatment of allergic conditions, including allergic rhinitis.
7. Outline the clinical manifestations and management of anaphylaxis.
8. Identify signs and symptoms of food allergy.
9. Review the diagnosis and management of asthma in various patient populations.
10. Describe the presentation and medical management of rheumatoid arthritis.
11. Discuss key points in the recognition and management of systemic lupus erythematosus.
12. Compare and contrast features of various other autoimmune rheumatic disorders, including Sjögren syndrome, spondyloarthropathies, and vasculitis.
13. Analyze tools available to diagnose and treat Lyme disease.
14. Describe the manifestations of acquired immune deficiency syndrome (AIDS) and available treatment options.
15. Evaluate other immune system disorders, including sepsis.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The human body is constantly exposed to potentially deleterious micro-organisms and foreign substances. Therefore, it has evolved a complete system composed of complementary and inter-related mechanisms to defend against invasion by bacteria, viruses, parasites, and other foreign substances. Through recognition of molecular patterns, the body's immune system is able to distinguish itself from these foreign substances and discriminate potentially harmful from non-harmful agents. In addition, it can defend against abnormal cells and molecules that periodically develop. The skin and its epithelial layers, in conjunction with the body's normal inflammatory processes, make up the first line of the body's defense and confer innate or natural immunity to the host. After these protective barriers have been crossed, the body relies on a second line of defense known as the adaptive immune response to eradicate infection by invading organisms. The adaptive immune response evolves slowly over time but results in the development of antibodies capable of targeting specific micro-organisms and foreign substances should a second exposure occur [1; 2].

This course will cover immunity and the immune system, including a discussion of innate and adaptive immunity. Concepts related to key cellular functions, recognition systems, and effector responses integral to the immune system are also presented. In addition, developmental aspects of the immune system are discussed.

OVERVIEW OF IMMUNITY

Immunity can be defined as the body's ability to defend against specific pathogens and/or foreign substances in the initiation of disease processes. The multidimensional response initiated by the body's various defense systems is known as the immune response. Some of these responses become active almost immediately, while others develop slowly over time. It is the coordinated interaction of these mechanisms that allows the body to maintain normal internal homeostasis. However, when these mechanisms are either depressed or overactive, they become responsible for many of the pathophysiologic processes encountered in health care [1; 2].

In order for a host organism to remain healthy, the immune system must function properly. A weakened immune response may lead to immunodeficiency, but an inappropriate or excessive response can cause allergic/hypersensitivity reactions or autoimmune diseases. Therefore, the immune system must be capable of regulating itself. The process by which this regulation occurs is poorly understood but involves all aspects of the innate and adaptive immune responses.

Intact innate immune mechanisms are essential for the initiation of the adaptive immune response, and therefore, a successful immune response depends upon cooperation between the two systems. Dendritic cells are an essential component of both innate and adaptive responses and act through the release of dendritic cell-derived substances, such as cytokines and chemokines. Innate immune cells are capable of communicating important information regarding key characteristics of the invading micro-organism or foreign substance to the B and T lymphocytes involved in adaptive immunity. The adaptive immune response is also capable of increasing its efficiency by recruitment and activation of additional phagocytes and molecules of the innate immune system. Each system is thus essential for an effective immune response and occurs in concert in the fight against infection [1; 2].

Each exposure to an antigen elicits a predictable response from the immune system. After activation, the response is amplified until it peaks and eventually subsides. This occurs because the body's normal immune responses are self-limiting. After the antigen is destroyed and the action of chemical mediators terminated, the immune response ceases. It is believed that anti-inflammatory cytokines and regulatory T lymphocytes play a role in this process [4].

Tolerance, or the ability of the immune system to react to foreign antigens but remain nonreactive to self-antigens, also plays a role in the self-regulation of the immune response. Tolerance to self-antigens protects the body from harmful autoimmune responses. This is exquisitely important in vital organs such as the brain, testes, ovaries, and eyes, where immunologic damage could be lethal [4].

ACTIVE VERSUS PASSIVE IMMUNITY

The goal of the immune system is to protect the host against invasion by potentially dangerous pathogens, foreign substances, and other sources of harmful antigens. Adaptive immune responses accomplish this goal though the activation of cell-mediated and humoral responses. This type of protection can be induced in one of two ways [3]:

- After exposure to the offending substance and activation of B and T lymphocytes (active immunity)
- Through the transfer of antibodies against an antigen directly to the host (passive immunity)

Active immunity is acquired when the host mounts an immune response to an antigen, either through the process of vaccination or from environmental exposure. It is called active immunity because it requires the host's own immune system to develop an immunologic response, including the development of memory. Active immunity is usually long-lasting but requires a few days to weeks after first exposure to sufficiently develop an appropriate immunologic response that culminates in the destruction of the presenting antigen. With subsequent exposures, the immune system rapidly becomes fully activated because of the presence of memory B and T lymphocytes and circulating antibodies. The process by which active immunity is acquired through the administration of a vaccine is termed immunization. An acquired immune response can improve on repeated exposures to an injected antigen (booster vaccines) or natural infections [3].

Passive immunity is immunity transferred from another source. The most common form is immunity conferred from mother to fetus. During fetal development, maternal immunoglobulin G (IgG) antibodies are transferred to the fetus via the placenta. After birth, the neonate also receives IgG antibodies from the mother in breast milk or colostrum. Therefore, infants are provided with some degree of protection from infection for approximately three to six months, giving their own immune system time to mature. Some protection against infectious diseases can also be provided by the administration of immunoglobulins pooled from human or animal sources. Passive immunity produces only short-term protection that lasts weeks to months [3].

CYTOKINES AND THEIR ROLE IN IMMUNITY

The ability of the cells of both the innate and adaptive immune systems to communicate critical information with each other and initiate end effector responses is dependent upon the secretion of short-acting, biologically active, soluble molecules called cytokines. Cytokines are an essential component of host defense mechanisms and the primary means by which cells of innate and adaptive immunity interact. Chemokines are a subset of cytokines that consist of small-protein molecules involved in both immune and inflammatory responses. They are responsible for directing leukocyte migration to areas of injury and to locations where primary immune responses are initiated, such as lymph nodes, the spleen, Peyer patches, and the tonsils [6].

General Properties of Cytokines

Cytokines are low-molecular-weight, regulatory, pro- or anti-inflammatory proteins that are produced by cells of the innate and adaptive immune systems and that mediate many of the actions of these cells. The majority of the functionally important cytokines are interleukins, interferons, and tumor necrosis factor-alpha (TNF-α). Cytokines generate their responses by binding to specific receptors on their target cells and activating G-protein-coupled receptors [6; 7].

Interleukins are produced by macrophages and lymphocytes in response to the presence of an invading micro-organism or activation of the inflammatory process. Their primary function is to enhance the acquired immune response through alteration of molecular expression, induction of leukocyte maturation, enhanced leukocyte chemotaxis, and general suppression or enhancement of the inflammatory process [1; 6; 7].

Interferons are cytokines that primarily protect the host against viral infections and play a role in the modulation of the inflammatory response. Interferons are cell-type specific, with IFN-α and IFN-β produced primarily by macrophages and IFN-γ produced primarily by T lymphocytes.

TNF-α, a cytokine in a class by itself, is one of the most important mediators of the inflammatory response and is produced by macrophages when surface toll-like receptors recognize pathogen-associated molecular patterns (PAMPs) on the surface of micro-organisms. TNF-α acts as an endogenous pyrogen (i.e., fever producer) and induces synthesis of preinflammatory substances in the liver. With prolonged exposure, it has the ability to cause intravascular coagulation and subsequent thrombosis production [1; 6; 7].

Despite the diverse functions of the cytokines, they all share certain important properties. All cytokines are secreted in a brief, self-limited manner. They are rarely stored as preformed molecules but rather are synthesized through transcription as a result of cellular activation. The actions of cytokines are often pleiotropic, meaning that a single cytokine has the ability to act on a variety of different cell types. For example, the interleukin IL-17 is produced by T-helper 17 ($T_{17}H$) cells and acts on several cell types, including leukocytes, epithelial cells, mesothelial cells, vascular endothelial cells, and fibroblasts. As a result, $T_{17}H$ cells play a critical role in host defense against pathogens that infiltrate the mucosal barrier. Although pleiotropic action allows cytokines to mediate diverse effects, it greatly limits their use for therapeutic purposes. Because of this redundancy, antagonists against a single cytokine may not have functional consequences; other cytokines may compensate. Redundancy refers to the ability of different cytokines to stimulate the same or overlapping biologic functions [1; 6; 7].

In addition to being pleiotropic and redundant, cytokines can have broad activity. Several different cell types are capable of producing a single cytokine. For example, IL-1 is a preinflammatory cytokine that is primarily produced by macrophages but can be produced by virtually all leukocytes, endothelial cells, and fibroblasts.

Cytokines also function to initiate cascade functions, with one cytokine influencing the synthesis and actions of other cytokines. Often, the second and third cytokines will mediate the biologic effects of the first cytokine. These effects may be localized, acting on a single cell or group of cells in the area surrounding the effector cell, or systematic, with the cytokines secreted into the bloodstream and transported to their site of action. TNF-α is an example of a cytokine with wide-reaching systemic effects. Cytokines may also serve as antagonists to inhibit the action of another cytokine and as a result act as anti-inflammatory cytokines. For example, IL-10 is an anti-inflammatory cytokine that down-regulates the inflammatory and adaptive immune response [1; 6; 7].

Chemokines

As noted, chemokines are small-protein molecules (consisting of 70 to 130 amino acids) that are involved in immune and inflammatory cellular responses and function to control the migration of leukocytes to their primary site of action in the immune response. There are four distinct classes of chemokines (C, CC, CXC, and CX3C), each named for the number and location of cysteine residing on the terminal amino acid of the protein. Currently, 47 distinct chemokine molecules have been identified within the four different classes. The vast majority of these are classified as either CC or CXC chemokines. The CC chemokines have the first two cysteine molecules adjacent to each other, while these molecules are separated by an amino acid in the CXC chemokines. The CC chemokines attract monocytes, lymphocytes, and eosinophils to sites of chronic inflammation. The CXC chemokines attract neutrophils to sites of acute inflammation [8; 9].

Functionally, chemokines may be categorized as either homeostatic or inflammatory. Homeostatic chemokines are produced in relatively constant amounts (constitutively) regardless of cellular environmental conditions, while inflammatory chemokines are produced in response to proinflammatory stimuli. However, there is some overlap in the actions of specific chemokines.

Colony-Stimulating Factors

Colony-stimulating factors (CSFs) are a subset of cytokines that participate in hematopoiesis by stimulating bone marrow pluripotent stem cells and progenitor or precursor cells to produce large numbers of mature platelets, erythrocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils, and dendritic cells. The CSFs are named according to the type of target cell on which they act. Macrophages, endothelial cells, and fibroblasts produce granulocyte colony-stimulating factor (G-CSF) during times of stress or inflammation, and this factor promotes growth and maturation of neutrophils. Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the mononuclear phagocyte progenitor. While CSFs are necessary for normal blood cell production and maturation, excess production has been implicated in several disease processes and in the development of corticosteroid-resistant chronic obstructive pulmonary disease (COPD). Impaired macrophage function and subsequent impairment of G-CSF activity have been associated with the development of neutrophilia in animal studies [8]. In clinical practice, recombinant CSF is being used to increase the success rates of bone marrow transplantation and to treat chemotherapy-induced neutropenia and myelosuppression. The availability of recombinant CSFs and other cytokines offers the possibility of clinical therapy in which stimulation or inhibition of the immune response or cell production is desirable [8; 9].

PATHOGEN RECOGNITION

The innate immune response plays a crucial role in the proinflammatory response to infection and relies on the ability of host defenses to differentiate self from non-self, so only invading organisms are targeted. The leukocytes involved in this response recognize certain evolutionarily retained patterns present on the surface of pathogens and in response bind to the membrane and destroy the invading organism through the process of phagocytosis [3].

Invading pathogens contain conserved structures in their cell membranes termed PAMPs, which are recognized by the cells of the innate immune system because they possess a limited number of germline-encoded pattern-recognition receptors (PRRs). Upon PAMP recognition, PRRs come in contact with the cell surface and/or send intracellular signals to the host that trigger proinflammatory and antimicrobial responses, including the synthesis and release of cytokines, chemokines, and cell-adhesion molecules. The PAMPs recognized by host PRRs are made up of a combination of sugars, lipid molecules, proteins, and/or patterns of modified nucleic acids. Because PAMPs are essential for the functioning and infectivity of the micro-organism, mutation cannot help it avoid immune recognition. The human complement of PRRs is extensive (approximately 1,000), so the

classes of pathogens recognized are diverse. Pathogens of very different biochemical composition are recognized by relatively similar mechanisms by host PRRs, and no single class of pathogens is sensed by only one type of PRR; the host genetic code allows for the unique receptors involved in both innate and adaptive immunity to recognize fine details of molecular structure [3].

The ability of the innate immune response to limit microbes early in the infectious process results from the binding of pathogens to the PRRs on leukocytes, which in turn initiates the signaling events that lead to complement activation, phagocytosis, and autophagy. Once initiated, white blood cells, neutrophils, and monocytes migrate from the blood to the tissues, along with other body fluids, causing peripheral edema. Blood monocytes mature into macrophages as they traverse the tissues and join the macrophages already present in the tissues. PRRs present on these cells become activated, which amplifies the inflammatory response through enhanced secretion of all chemical mediators, including cytokines and complements [3].

INNATE IMMUNITY

The innate immune system is comprised of two separate but inter-related lines of defense: the epithelial layer, which acts as a physical barrier to invading substances and organisms, and the inflammatory response. The innate immune response utilizes the body's natural epithelial barriers along with phagocytic cells (mainly neutrophils and macrophages), natural killer (NK) cells, and several plasma proteins, including kinins, clotting factors, and those of the complement system, to maintain internal homeostasis. The response of the innate immune system is rapid, usually within minutes to hours, and prevents the establishment of infection and deeper tissue penetration of micro-organisms. The innate immune response is effective against most pathogens. However, when the innate response is overwhelmed or ineffective, adaptive immune responses become activated as the final line of defense against invading organisms. Innate immune mechanisms are always present in the body and are rapidly activated, so the body's defenses have responded before the adaptive immune response is triggered. The innate immune system also interacts with and directs adaptive immune responses [9; 10].

Under normal conditions, the innate immune response is essential to the continued health and well-being of the body. However, during times of hyper-responsiveness or hyporesponsiveness, the innate immune system plays a role in the pathogenesis of disease. One of the main functions of the innate immune system is the initiation of the inflammatory response, which involves activation of a complex cascade of events and chemical mediators. However, inflammation plays a key role in the genesis of many common pathophysiologic states, including atherosclerosis and coronary artery diseases, bronchial asthma, diabetes, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus [9].

Epithelial Barriers

Physical, mechanical, and biochemical barriers against microbial invasion are found in all common portals of entry into the body, including the skin and the respiratory, gastrointestinal, and urogenital tracts. The intact skin is by far the most formidable physical barrier available because of its design. It is comprised of closely packed cells that are organized in multiple layers that are continuously shed. In addition, a protective layer of protein, known as keratin, covers the skin. The skin has simple chemicals that create a nonspecific, acidic environment (acid mantle) and antibacterial proteins, such as the enzyme lysozyme, that inhibit the colonization of micro-organisms and aid in their destruction. The complexity of the skin becomes evident in cases of contact dermatitis, whereby increased susceptibility to cutaneous infection occurs as the result of abnormalities of the innate immune response, including defects in the epithelial layer itself and defects in both signaling and expressing of innate responses [3].

Sheets of tightly packed epithelial cells also line and protect the gastrointestinal, respiratory, and urogenital tracts and physically prevent micro-organisms from entering the body. These cells destroy invading organisms by secreting antimicrobial enzymes, proteins, and peptides. Specialized cells in the lining, such as goblet cells in the gastrointestinal tract, secrete a viscous material comprised of high-molecular-weight glycoproteins known as mucins, which form mucus when hydrated. Mucins bind to pathogens, trapping them and washing away potential invaders. In the lower respiratory tract, hair-like mobile structures called cilia protrude through the epithelial cells and move microbes trapped in the mucus up the tracheobronchial tree and toward the throat. The physiologic responses of coughing and sneezing further aid in their removal from the body [3; 4].

Micro-organisms that are trapped by mucus are also subjected to various chemical defenses present throughout the body. For example, lysozyme is a hydrolytic enzyme found in tears, saliva, and breast milk capable of cleaving the walls of bacterial cells by hydrolyzing the 1,4 beta-lineages between residues in peptidoglycan.

In the stomach and intestines, microbes may be eliminated by the action of digestive enzymes, acid conditions, and secretions of defensins, small cationic peptides that kill both gram-positive and gram-negative micro-organisms within minutes by disrupting the microbial membrane [3; 4].

When pathogens overcome the epithelial defenses, the adaptive immune response is initiated by the body's leukocytes via the recognition of common surface receptors present on the invading micro-organisms [6; 11].

Cells of Innate Immunity

The cells of innate immunity are capable of recognizing microbes that share common surface receptor characteristics. In response, they initiate a broad spectrum of responses that target the invading micro-organisms. The key cells of innate immunity include neutrophils, macrophages, dendritic cells, NK cells, and intraepithelial lymphocytes [4].

Neutrophils and Macrophages

The leukocytes (white blood cells) involved in the innate immune response are derived from myeloid stem cells and subdivided into two distinct groups based on the presence or absence of specific staining granules in their cytoplasm. Leukocytes that contain granules are classified as granulocytes and include neutrophils, eosinophils, and basophils. Cells that lack granules are classified as lymphocytes or monocytes [4].

Neutrophils, which are named for their neutral-staining granules, are the most abundant granulocytes found in the blood and make up approximately 55% of all white blood cells. They are also known as polymorphonuclear neutrophils. Neutrophils are phagocytic cells capable of amoeboid-like movement and function as early responder cells in innate immunity. They are rare in the tissues and in body cavities and lay predominantly dormant in the blood and bone marrow until they are needed in the immune response.

Eosinophils have large, coarse granules and normally comprise only 1% to 4% of the total white cell count. In contrast to neutrophils, these cells ingest antigen-antibody complexes and viruses rather than cellular debris. They frequently become active in parasitic infections and allergic responses.

Basophils make up less than 1% of the total white cell count and contain granules that release a multitude of substances, including histamine and proteolytic enzymes. Their function is not completely understood, but they are believed to play a role in allergy and parasitic infection as well [4].

Monocytes are the largest in size of all the white blood cells but make up only 3% to 7% of the total leukocyte count. They are released from the bone marrow into the bloodstream, where they migrate into tissues and mature into macrophages and dendritic cells. These cells participate in the inflammatory response and phagocytize foreign substances and cellular debris. Macrophages have a long life span, reside in the tissues, and are the first phagocyte that invading organisms encounter upon entering the body. Neutrophils and macrophages work in concert with each other and are crucial to the host's defense against all intracellular and extracellular pathogens [4].

Macrophages are essential for the clearance of bacteria that reach the epithelial barrier in the intestine and other organ systems. They also have remarkable plasticity that allows them to efficiently respond to environmental signals and change their functional characteristics. This makes them more efficient than the more abundant neutrophils. Once activated, macrophages engulf and digest microbes that attach to their cell membrane. The ability of these cells to initiate this response is dependent upon recognition of pathogenic surface structures (i.e., PAMPs or PRRs), of which the toll-like receptors have been the most extensively studied. Phagocytosis of invading micro-organisms helps to limit the spread of infection until adaptive immune responses can become fully activated [4; 5].

In addition to phagocytosis, macrophages process and present antigens, acting as major initiators of the adaptive immune response. These cells secrete substances that initiate and coordinate the inflammatory response on active lymphocytes. Macrophages can also remove antigen-antibody aggregates or, under the influence of T cells, can destroy malignant host or virus-infected cells [5].

Dendritic Cells

Dendritic cells are specialized, bone marrow-derived leukocytes found in lymphoid tissue and are the bridge between the innate and adaptive immune systems. These cells take their name from the dendrites within the central nervous system (CNS), because they have surface projections that give them a similar appearance. Dendritic cells are relatively rare and are found mainly in tissues exposed to external environments, such as the respiratory and gastrointestinal systems. They are present primarily in an immature form that is available to directly sense pathogens, capture foreign agents, and transport them to secondary lymphoid tissues. Once activated, dendritic cells undergo a complex maturation process in order to function as key antigen-presenting cells capable of initiating adaptive immunity. As noted, dendritic cells are responsible for the processing and presenting of foreign antigens to the lymphocytes and, like macrophages, also release several communication molecules that direct the nature of adaptive immune responses [4; 5].

Natural Killer Cells and Intraepithelial Lymphocytes

NK cells and intraepithelial cells are other cell types involved in the innate immune response. NK cells are so named because of their ability to spontaneously kill target organisms. Both types of cells rely on the recognition of specific PAMPs associated with the micro-organism cell type [5].

NK cells are a heterogeneous population of innate lymphocytes that mediate spontaneous cytotoxicity against infected cells. They resemble large granular lymphocytes and are capable of killing some types of tumor and/or infectious cells without previous exposure to surface antigens. NK cells have been shown to play an equally important role in limiting the spread of infection and assisting in the development of adaptive immune responses through the production of cytokines. NK cells assist in dendritic cell maturation and innate immune control of viral

infections. These cells are capable of directly killing host cells infected with intracellular (viral) or bacterial pathogenic organisms. They comprise approximately 10% to15% of peripheral blood lymphocytes but do not bear T-cell receptors (TCRs) or cell surface immunoglobulins. Two cell surface molecules have been identified—CD16 and CD56—and are widely used to identify NK cell activity. CD16 serves as a receptor for the IgG molecule, which provides NK cells with the ability to lyse IgG-coated target cells [5].

NK cells can be divided into two main subsets based upon their ability to excrete proinflammatory cytokines. In addition, they differ in their expression of inhibitor versus activating receptors. Cells that express activating receptors (NKG2D) are induced in response to pathogen-infected or stressed cells, whereas the inhibitor receptors on NK cells recognize patterns (e.g., major histocompatibility complex [MHC]-1, lectins) on normal host cells and function to inhibit the action of the cells. This assures that only "foreign" cells are destroyed. In addition to their role as phagocytes, NK cells assist in T-cell polarization, dendritic cell maturation, and innate immune control of viral infection through the secretion of immune modulators and antiviral cytokines. Investigations of the potential role of these properties for the development of vaccines that can modulate and direct the immune response though enhanced cytokine activity are ongoing [5].

Complement System

The complement system is a primary effector system that functions as part of both the innate and adaptive immune responses. It is comprised of a group of proteins that are activated by three distinct but convergent pathways: the classical, the lecithin, and the alternative pathways. The primary function of the complement system is the promotion of inflammation and the destruction of microbes [10].

The complement system is found in the blood and is essential for the activity of antibodies. It is comprised of 20 different proteins, many of which act as precursors of enzymes. An antigen-antibody complex initiates this system. Activation of the complement system increases bacteria aggregation, which renders them more susceptible to phagocytosis through activation of mast cells and basophils through the direct release of C3 and C5 from dendritic cells.

ADAPTIVE IMMUNITY

The adaptive immune response involves a complex series of interactions between components of the immune system and the antigens of a foreign pathogen. It is the final line of defense against infection and is activated after the innate immune response initiates the inflammatory process. In contrast to innate immunity, the adaptive immune response is capable of targeting specific cells or organisms that it recognizes as foreign to the body through activation of various lymphocytes and their products, including antibodies. The lymphocytes involved in adaptive immunity have the unique ability to remember specific pathogens and mount a heightened immune response during repeat exposures. Each exposure results in a more rapid and aggressive response. Substances present on the surface of pathogens are called antigens [10; 12].

Adaptive immunity is comprised of two distinct but inter-related processes: cell-mediated and humoral immunity. Together, they respond to foreign antigens, amplify and sustain immunologic responses, distinguish self-from non-self, and confer "memory" so a heightened response can be initiated on subsequent exposures to an organism. Antigens are usually a substance foreign to the host that can stimulate an immune response. They possess specific antigenic binding sites (epitopes) for the cells of the immune system. Epitopes allow the adaptive immune system to distinguish foreign antigens from normal cellular substances whose destruction would be detrimental to the organism [5].

Humoral immunity is mediated by B-lymphocyte activation and subsequent antibody production. It is the primary defense against extracellular microbes and toxins. In contrast, cell-mediated immunity involves the activation of specific T lymphocytes (i.e., T-helper and T-cytotoxic lymphocytes), which are responsible for the body's defense against intracellular microbes such as viruses [10].

Antigens

Antigens, or immunogens, are substances or molecules that are foreign to the body that trigger the production of antibodies by B lymphocytes, leading to the ultimate destruction of the invader. They are usually large macromolecules (>10,000 Da) such as proteins, polysaccharides, lipids, and free nucleic acids. Antigens are recognized by specific receptors present on the surface of lymphocytes and by the antibodies or immunoglobulins secreted in response to the antigen. Antigens can take the form of any foreign substance, including bacteria, fungi, viruses, protozoa, parasites, and non-microbial agents such as plant pollens, insect venom, and foreign materials (including transplanted organs) [12].

Antigens possess immunologically active sites called antigenic determinants or epitopes. These are smaller, discrete components of the antigen that have a unique molecular shape that can be recognized by and bound to a specific immunoglobulin receptor found on the surface of the lymphocyte or by an antigen-binding site of a secreted antibody. It is not unusual for a single antigen to possess several epitopes and, therefore, be capable of stimulating several different T and B lymphocytes. For example, different proteins that comprise the influenza virus may function as unique antigens (A, B, C, H, and N antigens), each of which contain several epitopes. Hundreds of epitopes are found on structures such as a bacterial cell wall [12].

Low-molecular-weight molecules (<10,000 Da) may contain epitopes but alone are usually unable to stimulate an immune response. These molecules are known as haptens. When they are complexed with an immunogenic carrier (usually a protein), they function as antigens. Many haptens exist in nature and frequently create problems for humans. One example of a hapten is urushiol, a toxin found in the oils of poison ivy that is responsible for initiating an allergic contact dermatitis. An allergic response to the antibiotic penicillin is an example of a medically important reaction due to hapten-carrier complexes. The penicillin molecule is very small (350 Da) and usually non-antigenic. However, in susceptible people it can complex with carrier proteins in the body, which are then recognized as "foreign," initiating an antigen-antibody reaction [12].

Cells of Adaptive Immunity

The principal cells of the adaptive immune system are the B and T lymphocytes, antigen-presenting cells, and effector cells that are responsible for the elimination of antigens [5]. The functions of these cells will be discussed at length in the following sections.

Lymphocytes

Lymphocytes make up approximately 36% of the total white cell count and are the primary cells of the adaptive immune response. They arise from stem cells in bone marrow. B lymphocytes are responsible for forming the antibodies that provide humoral immunity, whereas T lymphocytes provide cell-mediated immunity. T and B lymphocytes are unique in that they are the only cells in the body capable of using cellular "memory" to assess the surfaces of microbial agents and other pathogens to recognize specific pathogens. These processes make the adaptive immune processes organism-specific [5]. Many autoimmune diseases, such as Hashimoto thyroiditis and type 1 diabetes, are caused by impairment in both B and T lymphocyte (specifically

cytotoxic lymphocyte) functions, resulting in direct cellular damage because the body's immune system is no longer capable of distinguishing "self" from "non-self" [4].

The recognition of specific surface antigens by lymphocytes is made possible because of the presence of specific receptors or antibodies on the surface of B and T lymphocytes. Scientists have been able to identify these specific proteins and correlate them with a particular cellular function. This has led to the development of a classification system for surface molecules known as the cluster of differentiation (CD). The nomenclature for the surface proteins utilizes the letters CD followed by a number that specifies the surface proteins that define a particular cell type or stage of cell differentiation and are recognized by a cluster or group of antibodies. Use of this nomenclature has spread to other immune cells and cytokines, all of which contribute to the acquired immune response [5].

Lymphocytes involved in the innate immune response, such as macrophages and dendritic cells, also play a key role in adaptive immunity because they function as antigen-presenting cells. These cells are capable of processing complex antigens into epitopes, which are then displayed on their cell membranes in order to activate the appropriate lymphocytes. Functionally, there are two types of immune cells: regulatory cells and effector cells. The regulatory cells assist in orchestrating and controlling the immune response, while effector cells carry out the elimination of the antigen. In the body, helper T lymphocytes activate the other lymphocytes and phagocytes, while regulatory T cells keep these cells in check so that an excessive immune response does not occur. Cytotoxic T lymphocytes, macrophages, and others function as effector cells in different immune responses [5].

While T and B lymphocytes are generated from lymphoid stem cells in the bone marrow, they do not stay there to mature. Undifferentiated, immature lymphocytes migrate to lymphoid tissues, where they develop into distinct types of mature lymphocytes. The T lymphocytes first migrate to the thymus gland, where they divide rapidly and develop extensive diversity in their ability to react against different antigens. Each T lymphocyte develops specificity against a specific antigen. After this differentiation occurs, the lymphocytes leave the thymus gland and migrate via the bloodstream to peripheral lymphoid tissue. At this time, they have been preprogrammed not to attack the body's own tissues, but it is believed that this process may go astray in the pathogenesis of autoimmune diseases. High concentrations of mature lymphocytes are found in the lymph tissue throughout the body including the lymph nodes, spleen, skin, and mucosal tissues [12].

T and B lymphocytes engage in all of the processes necessary for the adaptive immune response—specificity, diversity, memory, and self/non-self-recognition. When antigens come in contact with lymphocytes in the lymphoid tissues of the body, specific T cells become activated and specific B cells are stimulated to produce antibodies. After the first encounter occurs, these cells can exactly recognize a particular micro-organism or foreign molecule. Cell-mediated and humoral immunity are capable of responding to millions of antigens each day because there is an enormous variety of lymphocytes that have been programmed and selected during cellular development. Lymphocytes capable of "remembering" the presenting antigen are called "memory" T and B lymphocytes. They remain in the body for a longer period of time than their predecessors and as a result can respond more rapidly on repeat exposures. The system usually can respond to commonly encountered micro-organisms so efficiently that it is undetectable [12; 13].

The antigen receptor present on the B lymphocyte consists of membrane-bound immunoglobulin molecules that can bind a specific epitope. However, in order for B lymphocytes to produce antibodies, they require the assistance of helper T cells. While B lymphocytes bind to one determinant (or hapten) on an antigen molecule, the antigen-specific helper T cell recognizes and bonds to another determinant known as the "carrier." The carrier is an antigen-presenting cell that has previously picked up the specified antigen. This interaction (B cell-T cell-antigen-presenting cell) is restricted by the presence of cellular products genetically encoded by a self-recognition protein, called an MHC molecule. This allows the lymphocyte to differentiate between self and foreign peptides [12; 13].

After the B and T lymphocytes are activated and amplified by cytokines released as part of the innate response, the lymphocytes divide several times to form populations or clones of cells that continue to differentiate into several types of effector and memory cells. In the adaptive immune response, the effector cells destroy the antigens and the memory cells retain the ability to target antigen during future encounters [13].

Major Histocompatibility Complex (MHC) Molecules

The lymphocytes are designed to respond to a limitless number of antigens, but at the same time, they need to be able to ignore self-antigens expressed on tissue; MHC molecules enable the lymphocytes to do just this. The MHC is a larger cluster of genes located on the short arm of chromosome 6. The complex occupies approximately 4 million base pairs and contains 128 different genes, only some of which play a role in the immune response. The MHC genes are divided in three classes (I, II, and III) based on their underlying function [13].

The class I and II MHC genes are responsible for encoding human leukocyte antigens (HLAs), which are proteins bound on cell surfaces that define the individual's tissue type. These molecules are present on cell-surface glycoproteins that form the basis for human tissue typing. Each individual has a unique collection of MHC proteins representing a unique set of polymorphisms. MHC polymorphism affects immune responses as well as susceptibility to a number of diseases. Because of the number of MHC genes and the possibility of several alleles for each gene, it is almost impossible for any two individuals to have an identical MHC profile [13].

The class I and II MHC genes also encode proteins that play an important role in antigen presentation. Protein fragments form inside the cell and are displayed on the cell surface, allowing the immune system to differentiate between the body's own tissues and foreign substances. Cells, which present unfamiliar peptide fragments on the cell surface, are attacked and destroyed by the B and T lymphocytes. Class III MHC genes encode for many of the components of the complement system and play an important role in the innate immune process [13].

MHC-I complexes contain a groove that accommodates a peptide fragment. T-cytotoxic cells can only become activated if they are presented with a foreign antigen peptide. MHC-I complexes may present degraded viral protein fragments from infected cells. MHC-II molecules are found only on phagocytic antigen-presenting cells, including the macrophages, dendritic cells, and B lymphocytes, which communicate with the antigen receptor and CD4s molecule on T-helper lymphocytes [13].

Like MHC-I proteins, MHC-II proteins have a grove or cleft that binds a fragment of antigen. However, these bound fragments form pathogens that have been engulfed and digested during the process of phagocytosis. The engulfed pathogen is degraded into free peptide fragments within cytoplasmic vesicles and then complexed with the MHC-II molecules on the surface of the cells. T-helper cells recognize the complexes on the surface of antigen-presenting cells and become activated [13].

B Lymphocytes and Humoral Immunity

The humoral immune response is mediated by antibodies produced by the B lymphocytes. The primary functions of the B lymphocytes are the elimination of extracellular microbes and toxins and subsequent "memory" for a heightened response during future encounters. Humoral immunity is more important than cellular immunity in defending against microbes with capsules rich in polysaccharides and lipid toxins, because only the B lymphocytes are capable of responding to and producing antibodies specific for many types of these molecules. The T cells, which are the mediators of cellular immunity, respond primarily to surface protein antigens [14].

As discussed, B lymphocytes are produced in the bone morrow and are classified according to the MHC-II proteins, immunoglobulins, and complement receptors expressed on the cell membrane. During development, immunoglobulin gene rearrangement takes place to ensure that only B lymphocytes are capable of producing antibodies. At each stage of development, a cell-specific pattern of immunoglobulin gene is expressed, which then serves as a phenotypic marker of these maturational stages. The B lymphocyte progenitors are known as pro-B and pre-B cells, and both develop into mature B cells. They can be functionally removed from the body as a result of interaction with a self-antigen, by undergoing programmed cell death (apoptosis), or by the process of energy metabolism, whereby they become nonresponsive in the presence of the antigen. When B lymphocytes become fully mature, they become capable of expressing IgD, in addition to the IgM on the cell membrane surface. Mature B lymphocytes are fully responsive to antigens and are capable of interacting with T cells' membrane surface [14].

T Lymphocytes and Cellular Immunity

T lymphocytes serve many functions in the immune system, including the activation of other T cells and B cells, control of intracellular viral infections, rejection of foreign tissue grafts, activation of autoimmune processes, and activation of delayed hypersensitivity reactions. These processes make up the body's cell-mediated or cellular immunity. The effector phase of cell-mediated immunity is carried out by T lymphocytes and macrophages [14].

As discussed, T lymphocytes arise from lymphoid stem cells and migrate to the thymus gland to undergo the process of maturation. The thymus gland is richly innervated and produces several peptide hormones (e.g., thymosin, thymopoietin) believed to be involved in T-cell maturation. T-cell precursors are abstracted to the thymus by thymotaxin, a chemotactic factor secreted by the epithelial cells. After the prothymocyte enters the cortex of the thymus, terminal deoxynucleotidyl transferase is expressed, causing gene rearrangement and increased TCR diversity. The pre-T lymphocytes are designated CD3, CD4, CD8, and double-negative cells. The majority of these cells go on to rearrange their alpha and beta chain gene segments. The beta segment is expressed first, resulting in the formation of a pre-TCR. This halts further gene rearrangement, enhances alpha chain gene arrangement, and causes full maturation and expression of CD4 (helper) and CD8 (cytotoxic) lymphocytes. Mature T lymphocytes leave the thymus and migrate to peripheral lymphoid tissues, where they multiply and differentiate into memory T cells and various other mature lymphocytes upon encountering an antigen [14].

The majority of TCRs recognize antigenic peptides that are bound to MHC-derived molecules. CD4 and CD8 help stabilize the TCR-antigen-MHC complex during T-cell activation. The TCR is also characterized by their surface molecules (the CD3 complex), which aid in cell signaling [14].

Lymphoid Organs

The central and peripheral lymphoid organs are responsible for the production, maturation, and storage of large numbers of immune system cells, including the B and T lymphocytes. These organs and tissues are widely distributed throughout the body and provide different, but often overlapping, functions. The central lymphoid organs are comprised of the bone marrow and the thymus and are responsible for immune cell production and maturation. The tissues and cells of the peripheral lymph node system store the cells of the immune system, where they function to concentrate and process antigens as well as support cellular processes necessary for the development of fully functioning adaptive immune responses. These peripheral lymphoid tissues are comprised of the lymph nodes, spleen, tonsils, appendix, Peyer patches in the intestine, and mucosa-associated lymphoid tissues in the respiratory, gastrointestinal, and reproductive systems. Networks of lymph channels, blood vessels, and capillaries connect the lymphoid organs and transport immune cells, antigens, and cellular debris throughout the body [7].

Thymus

The thymus is an elongated, bilobed structure located in the mediastinum above the heart and serves as a specialized immune system organ. Each lobe is surrounded by a connective tissue capsule layer and is further divided into lobules. The lobules can be divided into an outer cortex and a central medulla, each of which plays a different role in the process of T-lymphocyte maturation. The outer cortex contains densely packed immature T lymphocytes (thymocytes). The inner medulla is a less dense area of tissue that contains fewer but more histologically mature lymphocytes. The medulla is comprised of Hassall corpuscles but also stores dendritic cells and macrophages [7].

The thymus is essential to the development of the immune system because it is responsible for the production of mature, immunocompetent T lymphocytes. The thymus is a fully developed organ at birth, weighing up to 15 g. It is most active in the neonatal and preadolescent periods. At puberty, when the immune cells are well established in peripheral lymphoid tissues, the thymus begins to atrophy and is replaced by adipose tissue. Nevertheless, residual T-lymphocyte production continues throughout adult life. Pre-T cells enter the thymus as functionally and phenotypically immature T cells. They then mature during different cycles and then move from the cortex to the medulla. After full maturation, they are released into the peripheral lymphoid tissues. Rapid cell division, maturation, and selection occur in the cortex under the influence of thymic hormones and cytokines. As T cells mature, they develop the TCRs that differentiate them. The majority of thymocytes die in the cortex during the process of gene arrangement and maturation because they fail to develop the appropriate receptor types on their cell membranes. Only those T cells capable of recognizing foreign antigen displayed by self MHC are allowed to mature. This process is called thymic selection. Mature, immunocompetent T-helper and T-cytotoxic cells leave the thymus in two to three days and enter the peripheral lymphoid tissues through the bloodstream [7].

Lymph Nodes

Lymph nodes are small aggregates of lymphoid tissue located along lymphatic vessels throughout the body. The lymphatic vessels carry lymph, which is a clear or yellow-tinged fluid that contains a variety of white blood cells (predominantly lymphocytes) and transports cellular debris and organisms to the nodes to be removed from the body. Each lymph node processes lymph from a discrete, adjacent anatomic site. Lymph nodes are congregated in the axilla and groin and along the great vessels of the neck, thorax, and abdomen. These nodes receive lymph from the collecting ducts, which ultimately drain into the thoracic duct in the left side of the chest at the level of the subclavian vein. Lymph nodes have two functions: removal of foreign material before it enters the bloodstream and proliferation and organization of immune cells [7].

Lymph nodes are bean-shaped, encapsulated tissues, approximately 0.5 – 1 cm in diameter. Lymph enters the node through afferent lymph channels and leaves through the efferent lymph vessels located in the deep indentation of the hilus. Lymphocytes and macrophages move slowly through the lymph nodes so they have adequate time to engulf microorganisms and interact with circulating antigens. The lymphatic system provides a large surface upon which macrophages and dendritic cells can more easily present antigens to T lymphocytes [7].

Lymph nodes are divided into three distinct and specialized areas: an outer cortex, a paracortex, and an inner medulla. T lymphocytes predominate in the paracortex. Within the follicles, the lymphocytes continue to mature, replicate, and interact with the antigen-presenting cells in the nodes (e.g., macrophages, follicular dendritic cells). Activated B cells then migrate to the medulla of the lymph node, where they complete their maturation to plasma cells. Large quantities of antibodies are then released into systemic circulation [7].

Spleen

The spleen is a large, ovoid, secondary lymphoid organ located high in the left upper quadrant of the abdominal cavity, between the diaphragm and the stomach. The spleen filters antigens from the blood and is important in the response to systemic infections. It is divided into two distinct areas: the white pulp and the red pulp. The red pulp is well-supplied with arteries and venous sinusoids and is the area where senescent and injured red blood cells are removed. The white pulp contains lymphatic nodules and diffuse lymphoid tissues. This is where concentrated areas of B and T lymphocytes permeated by macrophages and dendritic cells exist. The lymphocytes (primarily T cells) that surround the central arterioles form the periarterial lymphoid sheath. There is also a diffuse marginal zone that contains the follicles and germinal centers and is rich in B cells. This separates the white pulp from the red pulp and allows lymphocytes to move easily between the blood and the lymphatic tissue. A sequence of activation events similar to that seen in the lymph nodes occurs in the spleen [7].

Other Secondary Lymphoid Tissues

Other secondary lymphoid tissues include the mucosa-associated lymphoid tissues, which are nonencapsulated clusters of lymphoid tissue located around membranes lining the respiratory, digestive, and urogenital tracts. These organ systems constantly come in contact with pathogens and toxins and therefore require the presence of immune cells in order to respond to the potential invasion. In some tissues, the lymphocytes are organized in loose, nondescript clusters, but in other tissues (e.g., the tonsils, Peyer patches in the intestine, the appendix) their structure is better organized. These tissues contain all the cellular components (i.e., T cells, B cells, microplates, and dendritic cells) required to mount an immune response. Immunity at the mucosal layers helps to exclude many pathogens from the body and, as a result, protects the more vital internal structures [7].

IMMUNITY IN SPECIAL POPULATIONS

TRANSFER OF IMMUNITY FROM MOTHER TO INFANT

Development of the immune system begins early in fetal life, at approximately 5 to 6 weeks' gestation, when the fetal liver actively begins hematopoiesis. At about the same time (6 weeks' gestation), the thymus arises from the third branchial arch, with the cortex arising from its ectodermal layer and the medulla from the endoderm. Over the next two to three weeks, lipoid cells initially migrate from the yolk sac and fetal liver and then from the bone marrow to colonize the fetal thymus. Development of the secondary lymphoid organs (spleen, lymph nodes, and mucosa-associated lymphoid tissues) begins soon after. The secondary lymphoid organs are rather small but well-developed at birth and mature rapidly after exposure to microbes during the postnatal period. The thymus is the largest lymphoid tissue in the neonate relative to body size and normally reaches its mature weight by 1 year of age [5].

Neonates are protected against antigens in early life as result of passive transfer of maternal IgG antibodies through the placenta and IgA antibodies in colostrum. Maternal IgG antibodies readily cross the placenta during fetal development and remain functional in the newborn for the first few months of life, providing passive immunity until immunoglobulin production is well established in the newborn. IgG is the only class of immunoglobulins able to cross the placenta. Maternally transmitted IgG is effective against most micro-organisms and viruses that a neonate encounters. The largest amount of IgG crosses the placenta during the last weeks of pregnancy and is stored in fetal tissues. Infants born prematurely may be deficient in maternal antibodies and, therefore, more susceptible to infections. Because of transfer of IgG antibodies to the fetus, an infant born to a mother infected with human immunodeficiency virus (HIV) has a positive HIV antibody test result, although the child may not be infected with the virus [3].

Cord blood does not normally contain IgM or IgA. If present, these antibodies are of fetal origin and represent exposure to intrauterine infection. Normally, the neonate begins producing IgM antibodies shortly after birth, as a result of exposure to the antigens normally found in the surrounding environment. However, this IgM is of lower binding affinity and is effective only against a limited range of antigens. It has been demonstrated that premature infants can produce IgM as well as term infants. At approximately 6 days of age, the IgM level rises sharply, and this rise continues until approximately 1 year of age, when the adult level is achieved against a limited range of antigens [3].

Serum IgA is typically not present at birth but is detected in the neonate approximately 13 days after birth. The levels of IgA increase during early childhood and reach a normal range between 6 and 7 years of age. While maternal IgA is not transferred in utero, it is transferred to the breast-fed infant in colostrum and breast milk. Because IgA antibodies are associated with mucosal membranes, these antibodies provide local immunity for the intestinal system during early life [3].

IMMUNE RESPONSE IN THE OLDER ADULT

As people age, the ability of the immune system to protect the body from pathogenic organisms and environmental toxins declines in relation to an overall decline in both cell-mediated and humoral immune responses. Therefore, older adults are more susceptible to infections, have more evidence of autoimmune and immune complex disorders, and have a higher incidence of cancer than younger people. In addition, the immune system of older adults is less likely to respond appropriately to immunization, resulting in a weakened response to vaccination. Older adults also frequently have comorbid conditions that impair normal immune function and compromise the immune response [10].

Many changes occur with aging, but the exact immunologic mechanisms are not completely understood and are believed to be multifactorial. There is a continued decrease in the size of the thymus gland, which begins during puberty and affects overall T-cell production and function. Later in life, the size of the thymus diminishes to 15% or less of its maximum size. There may also be a decrease in the number of the lymphocytes in the peripheral lymphoid tissue. The most common finding is a slight decrease in the proportion of T cells to other lymphocytes and a decrease in CD4 and CD8 cells [10].

Aging also produces qualitative changes in lymphocyte function. Lymphocytes seem to exhibit altered responses to antigen stimulation, with an increased proportion becoming unresponsive to activation. It appears that CD4 T lymphocytes are most severely affected, because there is a decreased rate of synthesis of the cytokines that stimulate the proliferation of lymphocytes and expression of the specific receptors that interact with the circulating cytokines. Specifically, IL-2, IL-4, and IL-12 levels decrease in older adults. While actual B-cell function is compromised with age, the range of antigens that can be recognized by B cells does not change [10].

IMMUNE HYPERSENSITIVITY DISORDERS

ALLERGIES

An immune system that is malfunctioning predisposes an individual to the development of a wide variety of diseases ranging from severe infection to autoimmune disease and the resultant tissue injury [12]. Nurses care for patients with allergic conditions far more often than might be suspected. Allergic rhinitis, asthma, and dermatitis are a few examples of these immunologic diseases [11].

The genetic predisposition to develop allergies that involve IgE antibody formation is known as atopy. The terms atopic, allergic, and hypersensitive are frequently used interchangeably. Allergy (or, more appropriately, hypersensitivity) describes the increased immune response to the presence of an antigen. Between 20% and 30% of the population have allergies. Although it is not possible to predict who will have allergies, there is a higher incidence of allergies among children of parents with allergies [11; 15].

The development of allergy is a two-step process. Step one is sensitization. Sensitization occurs when one develops IgE antibodies against a substance that is inhaled, ingested, or injected. Newly formed IgE antibodies stick to basophils and mast cells, which are found in the skin's mucosal surfaces and in the respiratory and gastrointestinal tracts. Hypersensitivity develops only after IgE antibodies against a certain foreign substance and have formed and are bound to the surface of tissue mast cells and circulating basophils [11; 15].

Sensitization does not produce any of the manifestations typically associated with allergic disease. It is not until step two—re-exposure to the allergen—that allergic manifestations and anaphylaxis occur. Although the cellular events for all immediate allergic reactions tend to be similar, differences are found in the clinical sequelae, based on the state of the individual's host defenses, the nature of the allergen, the concentration and amount of the allergen, the route of exposure, and which organ is affected [11; 15].

Etiology and Risk Factors

Host Defenses

Some people are more susceptible to hypersensitivity than others for reasons that are unclear. The increasing prevalence of allergic disease suggests that environmental factors acting either before or after birth contribute to the regulation of the development of the T helper type 2 cells or their functions. T helper type 2 cells play a triggering role in the activation and recruitment of IgE antibody-producing B cells, mast cells, and eosinophils, the cellular triad involved in allergy. The decrease in the number of reported childhood infectious diseases that has resulted from vaccination programs, antimicrobial therapy, and changing lifestyles is an important factor in an individual's response to an allergen. Specific IgE formation can be influenced by viral infections, especially those caused by cytomegalovirus (CMV) and mononucleosis. Other factors, including sex, age, and exposure to secondhand smoke and other air pollution, can influence the manifestation of allergies [15].

Researchers believe that IgE once helped individuals ward off common ancient parasites; although IgE is not needed today, the body continues to manufacture it [16]. Most individuals are unaffected by the presence of IgE, as it only accounts for about 1% of all antibodies [16]. However, millions of individuals have inherited the genetic predisposition to overproduce IgE; in some cases, B cells release up to 20 times the normal amount of IgE. If an excess of the antibody is produced, the immune system may over-react to routine substances. Each substance to which an individual is sensitive triggers a different IgE antibody; any one of these substances could result in allergies.

Nature of the Allergen

Allergens are proteins that are capable of inducing IgE antibodies, thus triggering an allergic response. Haptens, along with other environmental allergens, are carried on vectors that may become airborne (e.g., pollen, molds, dust particles, animal dander). Contact with these allergens causes sensitization and evokes the acute manifestations of allergy. Some haptens (e.g., penicillin) are highly antigenic [15].

Concentrations of the Allergen

Higher concentrations of an allergen in an initial exposure usually result in hypersensitivity responses of greater intensity. Lower concentrations of the allergen may then cause severe manifestations when a re-exposure occurs [15].

Routes of Exposure

Routes by which allergens may enter the body include inhalation, injection, ingestion, and direct contact. Most allergens are inhaled [17].

Exposures to the Allergen

Factors that influence the likelihood of allergy development include a person's age at the time of exposure (i.e., exposure early in life), the type of allergen (e.g., house dust mite, cockroach, various medications, pollen), the allergen load, and the month of a person's birth (as a greater affinity for allergies is seen in those born in the spring and fall) [17; 18].

Types of Hypersensitivity Reactions

Hypersensitivity relations are divided into four main types [19]:

- Type 1: Immediate or anaphylactic
- Type 2: Cytolysis or cytotoxic
- Type 3: Immune complex
- Type 4: Cell-mediated or delayed

Type 1 (Immediate or Anaphylactic) Hypersensitivity

Examples of type 1 hypersensitivity reactions include anaphylaxis, allergic rhinitis, asthma, and acute allergic drug reactions [19]. The immediate (antigen-antibody) reaction occurs within minutes after exposure to the allergen. The resultant IgE production induces the immediate response by activating mast cells and basophils, causing them to degranulate and release mediators such as histamine, leukotrienes from basophils and prostaglandins, and platelet-activating factors from eosinophils. The mediators, whether preformed or formed after activation, are able to increase vascular permeability, dilate vessels, contract smooth muscle, and ignite other inflammatory cells [18].

Manifestations of mediator release vary, depending on the organ where the mediator's receptors are found. For example, histamine is a preformed mast cell mediator that has receptors in the skin, oral and nasal mucosa, lungs, and smooth muscle in the gastrointestinal tract. After histamine binds to its receptor, it can cause many reactions. Vasodilation causes edema; smooth muscle contraction results in dangerous airway narrowing; and glandular stimulation leads to increased secretion of mucus in the nose, lungs, and gastrointestinal tract [18].

Newly formed mediators, including lipid mediators and cytokines, are made after the mast cell had been activated and have similar actions to those of histamine. However, their effects tend to last much longer. Once released into the blood and after binding to their receptors, these mediators cause more bronchial smooth muscle contraction, vasodilation, nasal congestion, and edema [18].

Type 2 (Cytolysis or Cytotoxic) Hypersensitivity

Cytolysis or cytotoxic reactions are complement-dependent and thus involve IgG or IgM antibodies. The antigen-antibody binding results in activation of the complement system and destroys the cell on which the antigen is bound (usually a circulating blood cell), causing tissue injury. Examples of tissue injury caused by type 2 hypersensitivity include hemolytic anemia, Rh hemolytic disease in newborns, autoimmune hyperthyroidism, myasthenia gravis, and blood transfusion reactions [19].

During a blood transfusion, blood group incompatibility causes cell lysis, which results in a transfusion reaction. The antigen responsible for initiating the reaction is a part of the donor red blood cell membrane. Manifestations of a transfusion reaction result from intravascular hemolysis of red blood cells and include headache, flank pain, chest pain similar to angina, nausea and vomiting, tachycardia, hypotension, hematuria, and urticaria [19].

Transfusions of more than 100 mL of incompatible blood can result in severe, permanent renal damage, circulatory shock, and death. Therefore, if manifestations develop, the transfusion should be stopped at once [19]. However, routine blood typing prior to transfusion makes this complication very unlikely. More commonly, hemolytic disease develops in newborns whose blood type is incompatible with the mother's. In these cases, the newborn may display edema, jaundice, anemia, enlarged liver or spleen, and hydrops. Treatment usually consists of antibody (intravenous immunoglobulin) and fluid administration. In severe cases, exchange transfusion may be necessary.

Type 3 (Immune Complex) Hypersensitivity

Immune complex reactions result when antigens bind to antibodies, leading to tissue injury. The molecular size of the antigen-antibody complex is an important factor, as larger complexes are rapidly cleared by phagocytic cells. The smaller complexes formed in antigen excess persist longer in the circulation because they are not so easily captured by phagocytic cells in the spleen and liver. Inflammation results and leads to acute or chronic disease of the organ system in which the immune complexes were deposited [19; 20].

Immune complex-mediated inflammation is produced by IgG or IgM antibodies, antigens, and complements. The mediators of inflammatory injury include the complement peptides, which can activate mast cells, neutrophils, monocytes, and other cells. The release of lysosomal granules from white blood cells and macrophages causes further tissue injury [19; 20].

The antigen may be tissue-fixed or released locally, as in Goodpasture syndrome. In this syndrome, circulating antibodies react with autologous antigens in the glomerular basement membranes of the kidneys, causing inflammation of the glomerulus [19; 20].

Antigen-antibody complexes are formed in the bloodstream and get trapped in capillaries or deposited in vessel walls, causing urticaria, arteritis, or glomerulonephritis. Alternatively, antigen-antibody complexes may form in the joint space, with resultant synovitis, as in rheumatoid arthritis and systemic lupus erythematosus. An Arthur reaction is a localized area of tissue necrosis that results from immune complex hypersensitivity [19; 21].

The antigen may also be circulating, as in serum sickness. Serum sickness develops 6 to 14 days after injection with a foreign serum. Deposition of complexes on vessel walls causes complement activation, with resultant edema, fever, inflammation of blood vessels and joints, and urticaria. Classic serum sickness is rare because large doses of heterologous serum (horse antiserum to human lymphocytes) are seldom used today [19; 21]. A serum sickness-like reaction may occur, however, after administration of such medications as penicillin, sulfonamides, streptomycin, thiouracils, and hydration compounds. Rather than being dominated by cutaneous vasculitis, these reactions more often manifest with fever, arthralgia, lymphadenopathy, and urticaria. The illness is usually benign and self-limiting, and it reverses after discontinuation of the offending medication(s) [19; 21].

Type 4 (Cell-Mediated, Late-Phase, or Delayed) Hypersensitivity

In cell-mediated hypersensitivity, sensitized T cells respond to antigens by releasing lymphocytes, some of which direct phagocytic cell activity. This reaction occurs 24 to 72 hours after exposure to an allergen. Delayed hypersensitivity is induced by chronic infections or by contact sensitivities (e.g., contact dermatitis) [21; 22].

A type 4 reaction is used to test for tuberculosis infection. An injection of tuberculosis antigen or purified protein derivative is given, and if the patient has been sensitized to tuberculosis, T cells react with the antigen at the injection site. The reaction leads to local edema and fibrin deposits, which result in the induration characteristic of a positive tuberculosis reaction [21; 22].

Graft-versus-host disease and transplant rejection are also type 4 reactions. In graft-versus-host disease, donor immune cells (the graft) react against various antigens in the recipient (host). It is particularly common after allogeneic bone marrow transplant. Various clinical manifestations result, including dermatitis, hepatitis, and enteritis [21; 22].

Contact dermatitis is a type 4 reaction that occurs after sensitization to an allergen, commonly a cosmetic, adhesive, topical medication, drug additive (e.g., lanolin added to lotions), or plant toxin (such as poison ivy). With the first exposure, no reaction occurs, but antigens are formed. On subsequent exposures, hypersensitivity reactions are triggered, which lead to pruritus, erythema, and vesicular lesions [21; 22].

Diagnosis

The diagnosis of an allergic disease is based on the patient's history, manifestations experienced during or after allergen exposure, and the results from allergy testing. Common allergy tests include [22]:

- Skin testing
- Blood testing with radioallergosorbent test (RAST), enzyme-linked immunosorbent-assay (ELISA), or fluoroenzyme immunoassay (FEIA) to measure IgE levels to certain allergens in vitro
- Pulmonary function tests to diagnose asthma
- Blood assays for IgE levels

Patient History and Nursing Assessment

Nurses play a crucial role in obtaining a detailed medical history of the patient and ensuring that appropriate diagnostic tests are performed. The most important part of evaluating a patient with suspected allergy is the history. The history should elicit all the patient's current manifestations and triggers. It is important for clinicians to know whether the manifestations are always present or if they worsen at specific times of the day or year [23].

Indoor allergens can cause significant distress. House dust mites, cockroaches, and animal allergens are problematic and are present year-round in many homes. Nurses should assess whether animals are present in the home and, if so, how many. Is the house filled with plants that could harbor mold spores? Is the patient exposed to moist rooms, such as a basement that is constantly damp [23]?

Environmental factors (e.g., smoke) can exacerbate allergic manifestations. Determining where and when these manifestations present is very important. Many occupations involve exposure to certain allergens (e.g., smoke, latex, chemicals, animals), and manifestations may be reported as worse during the workweek compared with the weekend. A careful search for environmental factors should be undertaken, with the patient questioned in detail regarding the home environment, including location and type of heating, insulation, humidity, bedding, carpeting, and method of house cleaning [24]. Inquiries such as these help to narrow possible causes of allergy symptoms [23].

Skin Testing

With intradermal or injection skin testing, the healthcare practitioner introduces a small quantity of allergen into the skin by quickly pricking, scratching, or puncturing it or by using intradermal injections. A wheal and flare reaction usually occurs soon after the allergen is introduced if the patient is allergic. This type of skin testing is the most accurate, but it is linked to a higher incidence of severe allergic reactions. Therefore, it should be used with caution and under close supervision. A patch test can be used to evaluate contact allergies; the allergen is applied directly to the skin and then covered with a gauze dressing [25]. Skin testing is generally considered safe, but it always carries a risk of causing a systemic reaction such as anaphylaxis [25].

Nurses often administer skin tests and interpret test results. An immediate reaction (appearing within 10 to 20 minutes after exposure), marked by erythema and wheal formation greater than 3 mm of the positive control (usually histamine), denotes a positive reaction. Positive reactions indicate antibody response to previous exposure to this antigen and suggest that the patient is allergic to the particular substance. Negative reactions may be inconclusive, requiring further assessment. Negative results may indicate antibodies have not formed to this antigen, the antigen was deposited too deeply into the skin (subcutaneously), the patient is immune suppressed from disease or therapies (e.g., steroids, chemotherapy, radiation therapy), or the patient has taken antihistamines within the past 72 hours [25].

Problems that arise from skin testing range from minor itching to anaphylaxis. Itching and discomfort at the site are common and can be relieved by the application of cool compresses, topical steroid or antihistamine creams, and/or oral antihistamines such as diphenhydramine (Benadryl). Ulceration of the injection site is best treated by keeping the area clean and dry. Anaphylactic shock is a rare but potentially lethal complication of skin testing. A patient with a history of an anaphylactic reaction to a substance should never undergo skin testing for an allergy to that substance, particularly if the allergen is known to cause severe reactions (e.g., penicillin) [25].

Radioallergosorbent Test

The RAST uses the principle of immune absorption and reveals elevated levels of allergen-specific IgE associated with atopy. The allergen of interest is first bound to an insoluble material, which is then incubated with the patient's blood. If the patient has antibodies specific to the allergen being tested, they bind to that allergen. The unbound antibodies are washed away, and the level of antigen-specific IgE can be measured. This test is somewhat less sensitive than skin testing and is more time-consuming and costly [24]. It has generally been replaced by FEIA or ELISA tests.

ELISA and ImmunoCAP FEIA

Immunometric blood assays, also known as sandwich ELISAs, measure the total amount of IgE normally present in the circulation. Most studies have shown that blood concentrations of IgE are increased in the presence of allergic disease; however, a normal or even decreased level may occur in IgE-mediated sensitivities. Elevated serum eosinophil levels also may suggest hypersensitivities [24].

ImmunoCAP FEIA uses a flexible, hydrophobic cellulosic disk to which an allergen has been linked. The advantage of this system is that it has a very high antigen-binding capacity and minimal nonspecific binding, with high total IgE output. This test is more widely used today than RAST based on its increased sensitivity and equal specificity [24].

Pulmonary Function Tests

Pulmonary function tests calculate the amount and rate of air expelled during a single breath, helping to discern whether constricted airways are responsible for blocked airflow [16]. Guidelines for normal breathing are based on analysis of data obtained from large segments of the population. A patient's information is plotted on a continuum, allowing comparison to average breathing patterns for healthy individuals of the same sex, age, and size. Two common methods of measuring airflow assess forced expiratory volume (FEV_1) and peak expiratory flow (PEF) [16; 26].

A spirometer is a simple machine used to determine both the total amount of air that can be forcefully exhaled after maximum inspiration, referred to as forced vital capacity (FVC), and how fully air can be expelled from the lungs, measured by the amount of air forced from the lungs in one second, which is expressed as FEV_1 [16; 26]. The spirometer is generally used in diagnosis to establish airflow obstruction and reversibility [27]. Obstruction may be ascertained if the FEV_1 is less than 80% of the predicted value or if FEV_1 divided by FVC is less than 65%. Normally, the FEV_1 should account for more than 75% of the FVC; anything less than 75% indicates a possible obstruction and 65% or less may indicate a diagnosis of asthma [27].

A peak flow meter measures the speed of exhalation. The highest speed or best flow is PEF or peak flow. The peak flow meter is less sophisticated than a spirometer, which provides a more thorough assessment of lung function. However, the meter has the advantages of being less expensive, portable, and easy to use [26]. The severity of a patient's asthma can be determined by careful and consistent monitoring of peak flow and comparison of a patient's best peak flow to standard measurements. Studies confirm that short-term peak flow measurements assist healthcare providers in assessing asthma severity [16].

Studies have shown that measuring exhaled nitric oxide is also helpful in evaluating and diagnosing asthma [27]. Nitric oxide is a mediator for the inflammation that occurs during an asthma episode; the amount of nitric oxide measured during exhalation will directly correlate with the inflammation in the bronchial tubes [28].

Prognosis and Medical Management

Allergies are among the most common disorders in medicine. Patients often require a combination of treatments, ranging from avoidance of known allergens and environmental control to pharmacotherapy, immunotherapy, and follow-up [24].

It is expected that patients will obtain relief from allergic manifestations when the treatment regimen is followed. This assumes that the patient will be able to avoid or control risk factors for allergic manifestations, avoid anaphylactic events, and obtain treatment before serious problems develop [29]. However, this is not always possible.

Some patients will experience anaphylaxis as a result of an uncontrolled allergic reaction. While foods and food additives are the most common causes of anaphylaxis, it may also develop in response to other triggers, including latex and exercise. The management of anaphylaxis is detailed later in this course.

Allergen Avoidance

Avoidance of the allergen is often the easiest, most cost-effective, and safest way of managing allergies. However, identification of the specific allergen may be difficult, especially if the patient refuses, cannot afford, or cannot locate allergen-testing services. Even if an allergen is identified, complete avoidance may not be possible, as with pollens and occupational exposures [24].

Environmental Control

Environmental control can help to eliminate airborne allergens. Changing offending objects in the home, deep cleaning, pest control, and air filters that remove small particles from the air can eliminate many allergens [30].

Pharmacotherapy

Patients with atopy benefit greatly from select prescription and over-the-counter medications. Usually, patients self-administer these agents, although in some settings the nurse or a family member administers them [30]. Common medications include antihistamines, decongestants, leukotriene antagonists, and bronchodilators.

Immunotherapy

Immunotherapy (desensitization therapy) is designed for the treatment of type 1 (IgE-mediated) hypersensitivity. With this approach, precise doses of allergens are injected at intervals over a prolonged period with the goal of altering (decreasing) the immune system's response to the allergen. The doses are increased gradually over time or injections may be given several times per day in increasing doses in "rush" protocols. Immunotherapy increases IgG antibody levels and may increase suppressor T-cell functions. Specific IgG interferes with IgE binding to allergens and thus mitigates the hypersensitivity response. Immunotherapy is widely used in the treatment of allergic rhinitis (hay fever), for which its greatest success has been achieved because immunotherapy blunts the seasonal rise in specific IgE antibody levels. It has also been used for Hymenoptera (bee, yellow jacket, wasp, hornet) venom sensitivity with reportable success. There is some controversy regarding the efficacy of this treatment in the management of asthma [30].

Nurses often administer these injections and assess and treat side effects. Patients are asked to wait at least 30 to 40 minutes after receiving the injections so immediate reactions can be identified and treated. Side effects are similar to those seen in skin testing [30].

Patient Teaching

Although patients usually self-administer allergy medications, nurses are responsible for instructing patients and their families about their use. The patient should receive education on the medications available, their actions, how and when to take them, and possible side effects. Patients should also receive instruction on management of an anaphylactic reaction [29].

Some patients will need information on performing desensitization injections themselves, including proper injection technique and potential untoward reactions, such as shortness of breath, hoarseness, urticaria, and generalized flushing. Patients at risk for anaphylaxis should carry epinephrine with them at all times and should wear a medical-alert bracelet [29].

Allergic Rhinitis

Manifestations of allergic rhinitis are persistent and show seasonal variation. Nasal manifestations are often accompanied by eye irritation, which causes pruritus, erythema, and excessive tearing. Numerous allergens may cause these manifestations, including tree pollens (spring), grasses (summer), ragweed (fall), or dust mites and animal dander (year-round) [17].

When the nasal mucosa is exposed to an allergen, a series of events is set in motion. Allergen exposure increases the production of IgE, which binds to the receptors on mast cells and basophils and eventually causes a release of mediators. Mediator release leads to increased swelling (nasal blockage), watery discharge, sneezing, and nasal itching [17].

Medical Management

Nasal glucocorticoid sprays are used with good results for the treatment of allergic rhinitis. Nonsedating antihistamines are beneficial in maintaining control over allergic rhinitis and are a crucial component of therapy [31].

Nursing Management

Educating patients is the most important component of therapy for allergic rhinitis. Patients should avoid allergens and use air filters and air conditioning, when feasible. Compliance with medication is essential. Education topics include daily medication use and strategies to adjust medication to control minor flare-ups and prevent progression of the disease [32].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The British Occupational Health Research Foundation recommends that healthcare providers provide more frequent health surveillance to workers who develop rhinitis when working with agents known to cause occupational asthma and ensure that the workplace and working practices are investigated to identify potential causes and implement corrective actions.

(https://www.bohrf.org.uk/downloads/OccupationalAsthmaEvidenceReview-Mar2010.pdf. Last accessed October 25, 2022.)

Level of Evidence: ** (One study with high quality and at least two studies with medium quality)

Atopic Dermatitis

Atopic dermatitis occurs in about 10% of the population [11]. Patients typically have a history of and/or complaints about itchy skin in addition to a history of rashes in the area of skin creases. Other common complaints are of generally dry skin (often initially experienced in children younger than 2 years of age) accompanied by manifestations of asthma, hay fever, or dermatitis. Lesions of atopic dermatitis are red and pruritic, contain exudates, and are maculopapular in younger patients, becoming drier and thicker as patients age. Lesions are typically found on the cheeks, scalp, and forehead; in later years, they may occur on the trunk and extremities [11; 15].

Medical Management

Treatment is aimed at controlling and reducing the manifestations of atopic dermatitis because there is no true cure. Antihistamines are used with good results to help alleviate the itch-scratch cycle common to the condition. The mainstay of therapy is topical corticosteroids, which control inflammation of the skin lesions. Gels penetrate more effectively but are drying. Ointments should be used in more severe cases because they promote hydration; however, they can be oily and become messy in the heat. Creams and lotions are the least penetrating but are preferred by most patients. They are absorbed quickly and promote control. Antibiotics may be needed to treat superficial skin infections caused by intense pruritus and scratching [15].

Nursing Management

Nurses should teach patients with atopic dermatitis the importance of environmental control. A key strategy is to minimize allergen exposure and avoid conditions or situations that exacerbate pruritus. Patients can reduce itching by wearing loose cotton clothing, using gentle detergents, rinsing clothing completely, and avoiding extreme changes in temperature. Patients should be advised to avoid chemical irritants, emotional stress, aeroallergens (e.g., dust, animal dander), and dietary allergens. Patients should be instructed on general skin care measures, such as [31]:

- Maintaining good skin hydration by bathing in lukewarm water
- Using gentle soaps
- Applying moisturizer immediately after bathing
- Avoiding scratching
- Keeping fingernails trimmed to avoid infection

CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS
Anaphylaxis is highly likely if any one of the following three criteria is fulfilled: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips/tongue/uvula) *And at least one of the following:* a) Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient: a) Involvement of the skin/mucosal tissue (e.g., generalized hives, itch, flush, swollen lips/tongue/uvula) b) Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) c) Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence) d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) 3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a) Infants and children: Low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure[a] b) Adults: Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline
[a]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than 70 mm Hg +(2 x age) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.
Source: Reprinted from Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Ann Emerg Med. 2006;47:373-380, with permission from The American College of Emergency Physicians. *Table 1*

Urticaria

Urticaria (or hives) is a cutaneous reaction associated with several different causes. It occurs in as many as 25% of all people at some time [33]. Urticaria that is present daily or intermittently over a period of less than six weeks is considered acute, while hives present for more than six weeks are chronic [33].

Urticaria is characterized by transient erythematous, raised, well-demarcated plaques that are often intensely pruritic. The plaques frequently have central pallor and blanch when pressure is applied. The lesions are round or oval and range in size from a few millimeters to several centimeters; they typically fade within 24 hours [33]. They are usually the result of an inflammatory reaction [34; 35]. Approximately 20% of cases of acute urticaria are caused by IgE-mediated reactions [34].

Mast cells and their mediators may play a key role in urticaria, causing pruritus and vascular changes. A biopsy of the lesion may be done to identify the types of inflammatory cells present, which can inform treatment planning. The most common causes of urticaria are medications, foods and food additives, and infections; insect bites and stings, contact irritants, inhalants, heat, cold, light, and pressure may also be triggers [33].

Medical Management

Although management of urticaria focuses on identifying and eliminating any known causative factors, in about 80% of chronic cases no cause is found [36]. All patients with urticaria should be cautioned about aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), which may exacerbate existing hives. Opioids should be used cautiously as well because they are typically mast cell degranulators [33].

Antihistamines are the mainstay of therapy for urticaria. Nonsedating antihistamines are recommended during the day; sedating antihistamines may be preferred at night. Doxepin (Sinequan), a tricyclic antidepressant, is sometimes used in refractory cases because of its actions on both H1 and H2 receptors. Corticosteroids should not be used except for short-term amelioration of symptoms [33].

Adults and adolescents 12 years of age and older with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment may be prescribed omalizumab. The usual dosage is 150 mg or 300 mg every four weeks [37].

Nursing Management

Urticaria tends to evoke anxiety and frustration in both patients and clinicians. The most effective treatment is to eliminate triggers, and patients should be helped to identify factors that may be triggers. Elimination diets and challenges are indicated if foods or food additives are thought to provoke manifestations. Patients should also avoid factors that cause pruritus, such as pressure from tight clothing, heat, vibration, sunlight, and rubbing of the skin. Maintaining good skin hydration is necessary. Patients should be advised to avoid harsh soaps and irritants and to apply moisturizing lotions after bathing while the skin is still damp [32].

Anaphylaxis

Until 2006, there was no universal agreement on the definition of anaphylaxis or the criteria for its diagnosis. The National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) held two symposia to collaborate with representatives from 16 organizations and government bodies to develop a universally accepted definition of anaphylaxis as well as criteria for its diagnosis. They defined anaphylaxis as, "a serious allergic reaction that is rapid in onset and may cause death" [38]. The collaborative effort also led to the establishment of clinical criteria for diagnosis (***Table 1***) [38; 39; 40].

Clinical Manifestations

Early recognition of the clinical signs and symptoms of anaphylaxis is necessary to ensure immediate, appropriate treatment. In most cases, these signs and symptoms will occur within one hour after the accidental exposure (ranging from less than one minute to a few hours) and will vary in terms of presence, sequence, and severity [41]. In 1% to 20% of anaphylaxis cases, there will be a biphasic response, with recurrence of symptoms 8 to 12 hours later, after the individual had seemed to recover [41]. The interval between the initial reaction and the recurrence has ranged from 1 to 72 hours [38; 42]. A biphasic reaction occurs in approximately 6% to 11% of children; such reactions typically occur within 8 hours after the first reaction but may occur as long as 72 hours later [43].

As with less severe allergic reactions, cutaneous manifestations are the most common, followed by respiratory and gastrointestinal symptoms [42; 44; 45; 46]. In one study of more than 600 children, cutaneous manifestations were documented in 87% to 98% of children; respiratory manifestations, in 59% to 81%; and gastrointestinal manifestations, in 50% to 59% [46]. The cardiovascular system is less frequently involved and is more often involved in adolescents [43; 46]. Still, cutaneous manifestations may be absent in about 10% to 20% of cases of anaphylaxis, which may contribute to underrecognition [44].

Medical Management

Appropriate treatment of anaphylaxis must be immediate, as death can occur within 30 to 60 minutes [44]. Guidelines for the treatment of anaphylaxis have been developed jointly by the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology as well as by the NIAID and by the World Allergy Organization [38; 39; 42; 44; 47]. The drug of choice for the treatment of anaphylaxis is epinephrine, and several studies have shown that the lack of early epinephrine is associated with an increase in biphasic reactions as well as greater morbidity and

mortality [43; 44; 48]. Yet, healthcare professionals often fail to use epinephrine, with geographic variations in practice patterns [47; 49; 50; 51; 52; 53]. Antihistamines (H1 and H2 blockers) and corticosteroids have been used to treat anaphylaxis, and the use of antihistamines is the most common reason given for not administering epinephrine [44; 48]. However, three systematic reviews have demonstrated that there are few or no data to support the effectiveness of antihistamines or corticosteroids and that epinephrine is the only first-line treatment for anaphylaxis [54; 55; 56]. The recommended dose of epinephrine is 0.01 mg/kg (maximum dose: 0.3 mg for children and 0.5 mg for adults), given intramuscularly every 5 to 15 minutes as necessary to control symptoms and maintain blood pressure [38; 42; 43; 44; 57]. Peak plasma concentrations are highest and achieved fastest when epinephrine is administered intramuscularly in the thigh (versus the arm) [57].

Treatment of anaphylaxis must begin before the individual is transported to an emergency care facility. The NIAID expert panel recommends that the following steps be carried out concurrently as soon as an anaphylactic reaction has started [44]:

- Eliminate additional exposure to the allergen
- Call for help (emergency response team or 911)
- Inject epinephrine intramuscularly

When the patient arrives at the emergency care facility, the first action is to assess the airway, breathing, and circulation. In the emergency care setting, additional injections of epinephrine may be necessary. There are multiple other components to treatment that vary according to many factors, most notably the individual's symptoms, the type of reactions that have occurred in the past, and the response to epinephrine [38; 41; 57].

Food Allergy

True food allergy affects approximately 5% to 9.3% of children and approximately 1% to 5% of adults in the United States, and the prevalence has been rising (>50% increase from 1997 to 2011) [44; 58; 59; 60; 61; 62]. Despite the overall low prevalence of food allergy, particularly in comparison to skin or respiratory allergy, there is cause for concern, as allergic food reactions can be severe. It is estimated that 200,000 individuals require emergency medical care for food-induced allergic reactions, and the number of medical procedures to treat anaphylaxis from food allergy increased by 380% between 2007 and 2016 [63]. In addition, 150 to 250 deaths caused by food-related anaphylaxis occur annually [43; 44; 64]. Food-induced anaphylaxis is also the most frequent cause of anaphylactic reaction outside of the hospital setting and has been estimated to cost $500 million per year [43; 65]. More than 40% of children and 50% of adults with food allergy have experienced anaphylaxis or another severe allergic reaction [63].

Food allergy is defined in the NIAID-sponsored guidelines as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" [44]. Adverse reactions to food are usually classified in two broad categories: IgE-mediated allergy or hypersensitivity (true food allergy) and non-IgE-mediated reactions; the latter group includes cell-mediated reactions and disorders that are a combination of IgE-mediated and cell-mediated reactions [44]. Non-IgE-mediated reactions include primarily gastrointestinal food allergies such as celiac disease, food protein-induced enteropathy and enterocolitis/proctitis, and eosinophilic disorders [44]. Allergic sensitization (presence of allergen-specific IgE) to a food can occur without clinical signs and symptoms on exposure to that food, but both sensitization and clinical symptoms are needed for a definition of food allergy [44].

With an IgE-mediated response, food-specific IgE antibodies are produced after exposure to certain proteins that bind to tissue mast cells and basophils, leading to the release of mediators such as histamines and leukotrienes [66]. The resultant reaction typically manifests in symptoms or disorders related to the skin, gastrointestinal tract, and respiratory system [66]. Symptoms occur within minutes to one to two hours after the causal food has been ingested and vary from mild (oral or cutaneous symptoms only) to a life-threatening systemic reaction [44; 66]. Sensitization without clinical symptoms is common; for example, approximately 1% of the population has a true allergy to peanut (sensitization plus symptoms), whereas approximately 8% will have sensitization to peanut (a positive test result) but no symptoms [67; 68].

In general, eight allergens account for approximately 85% to 90% of IgE-mediated food allergies: cow's milk, hen's egg, peanut, tree nuts (walnuts, cashews, etc.), fish (fin fish), shellfish, soy, and wheat [44; 63]. With shellfish, allergy to crustaceans (shrimp, crab, and lobster) is more common than allergy to mollusks (clams, oysters).

The understanding of non-IgE-mediated reactions is not as clear as that of IgE-mediated reactions [69]. Most adverse food reactions have no immunologic basis. However, for many adverse reactions that affect primarily the gastrointestinal tract, a cell-mediated response is involved [69]. Several mechanisms have been suggested to play a role in these reactions, including an abnormal mucosal immune response and responses involving mast cells, eosinophils, macrophages, and T-cells [69; 70]. In contrast to IgE-mediated reactions, the symptoms associated with non-IgE-mediated reactions are delayed, often not occurring for hours or days after the suspected food was ingested [69].

Clinical Manifestations

Food-induced adverse reactions vary from mild to severe and life-threatening. Most reactions are mild to moderate, with the exception of reactions to peanut, which are often severe [44; 71]. The rate of severe reactions to food allergens overall has ranged from 11% to 51% [58; 71; 72].

Food allergy manifests itself primarily through the skin, gastrointestinal tract, and respiratory system, and symptoms are categorized as acute or delayed (***Table 2***) [44]. Cutaneous symptoms are typically the most common.

Diagnosis

Many individuals seek medical attention for evaluation of reactions to food, interpreting the reactions as food allergy. However, studies have indicated that 50% to 90% of food-related adverse reactions are not true food allergies [44]. Even when medical attention is sought, diagnostic testing is not always done. In one survey, among children with physician-diagnosed allergies, one-third did not have diagnostic testing [73]. The NIAID guidelines recommend a detailed history or physical examination as an essential first step in the diagnosis of food allergy but note that they alone cannot provide a definitive diagnosis of food allergy, and an objective evaluation should be carried out to confirm or disprove a suspected food allergy [44]. The history will suggest whether the reaction was IgE-mediated or non-IgE-mediated and can guide the selection of the most appropriate diagnostic testing.

Medical Management

There is currently no cure for food allergy, and the mainstay of management is avoidance of the offending food. The NIAID-sponsored guidelines recommend the following [44]:

- Individuals with IgE-mediated and non-IgE-mediated food allergies should avoid ingesting their specific allergen or allergens.
- Individuals with food allergy and their caregivers should be given information on avoiding their food allergen and emergency management that is age- and culture-appropriate.
- Individuals with food allergy and their caregivers should receive education and training on how to interpret ingredient lists on food labels and how to recognize labeling of the food allergens used as ingredients in foods.

SYMPTOMS OF FOOD-INDUCED ALLERGIC REACTIONS		
Target Organ	**Immediate Symptoms**	**Delayed Symptoms**
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry, staccato cough	—
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough Dyspnea Wheezing
Gastrointestinal (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	—
Gastrointestinal (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	—
Miscellaneous	Uterine contractions Sense of "impending doom"	—

Source: Reprinted with permission from Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergies: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126:S1-S58. With permission from Elsevier. *Table 2*

- All children with food allergy should have nutritional counseling and regular growth monitoring.
- Follow-up diagnostic testing should be done to monitor a child's allergy status, especially for those food allergies that are most likely to be lost during later childhood (milk, egg, soy, and wheat).

Nursing Management

Parents of children with food allergy have expressed a desire for comprehensive information on the management of food allergy and have noted the following specific topics: early signs and symptoms, cross-contamination, reading of food labels, self-injectable epinephrine, and becoming a teacher and advocate [74]. Studies and surveys of children with food allergy and their families have also shown that improved education is needed in these areas [71]. Every healthcare professional involved in an individual's care should collaborate to ensure that patients with food allergy and their families understand these topics. The NIAID expert panel coined the SAFE mnemonic for patient education [44]:

- **S**eek support
- **A**llergen identification and avoidance
- **F**ollow-up with specialty care
- **E**pinephrine for emergencies

The results of studies have shown that both children and adults may underestimate the severity of a food allergy, which means that education on the consequences of risk-taking behaviors is essential. Many individuals with food allergy or their parents fear that a severe reaction will occur in a setting where immediate help will not be available. However, according to a survey, most severe reactions occur in a setting that is considered to be "safe," such as home, work, or school [43; 75]. Although this fact should be reassuring, it does suggest that better education is needed to help individuals with food allergy and/or their parents be better able to avoid causal foods.

Patients and their families need help in identifying so-called hidden sources of food allergens to avoid inadvertent ingestion of a food allergen by cross-contamination. For example, some deli meats may have trace amounts of dairy product if the meat was cut on a slicer also used to cut cheese. Particular emphasis should be placed on nonfood items as potential sources of allergens; for example, many cosmetics may contain milk, tree nut oils, wheat, or soy; modeling dough may contain wheat; and beanbag stuffing often includes nut shells [76; 77].

ASTHMA

In 2018, 1.6 million individuals in the United States visited an emergency department and received a primary diagnosis of asthma [78]. In addition, 5.9% of patients seen by their primary care physician in 2018 had a diagnosis of asthma in their medical records [78]. The costs associated with healthcare usage related to asthma put a tremendous burden on healthcare systems and professionals as well as on patients and public organizations.

The pathogenesis of an asthma attack can be described as an inflammatory cascade composed of triggered, acute inflammation and chronic inflammatory changes. In the body of a person without asthma, the immune responses in the bronchi (e.g., swelling, excretion of mucus, recruitment of inflammatory cells) are present in a lesser degree to protect the body against any infectious agents or foreign objects (as discussed). However, a person with asthma produces an extreme reaction to otherwise relatively harmless irritants, referred to as asthmagens or triggers. Exposure to a trigger causes inflammatory mast cells to release specific inflammatory mediators, including histamine and interleukins, resulting in an acute response. Histamine causes local tissue edema; interleukins generally act as chemotactic factors and activate other inflammatory cells. Studies reveal that leukotrienes, another chemical released by mast cells, prolong bronchial muscle and airway constriction [16].

After the inflammatory cells are activated, bronchospasm occurs. Bronchospasm and local tissue edema cause narrowing of the airways. Release of interleukins and other chemotactic substances causes migration of other inflammatory cells, including eosinophils, airway macrophages, and neutrophils. The physical presence of these cells can also cause airway narrowing. The migration of the inflammatory cells starts within 30 minutes of exposure and may take hours to reach peak levels. Several different types of antibodies contribute to the inflammation process, but IgE is particularly harmful in patients with asthma.

The actual cause of the hyper-reaction by the immune system in persons with asthma is unclear. While many cases may be attributed to a reaction in response to exposure to an allergen/asthmagen, the possibility of nervous system involvement is also an accepted theory. Generally, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) work in harmony to balance the body's functions; the PNS stimulates the bronchial tubes to constrict while, at the same time, the SNS stimulates the bronchial tubes to dilate [16]. Ideally, these two systems coordinate to maintain open airways, allowing an effortless flow of air during inhalation and exhalation. In the lung of a person with asthma, it is thought that the balance may be tipped toward the PNS and that this imbalance may result in narrowed bronchial tubes and asthma symptoms [16]. There was once a belief that the PNS was solely responsible for airway sensitivity; however, studies now seem to indicate that, although the PNS is involved, it is not the major reason for inflammation in asthma [16]. Researchers continue to study the importance of these neurotransmitters relative to bronchial muscle tone.

Additionally, there is a proposed theory that some people with asthma have abnormal beta receptors and the proper neurotransmitters are blocked from reaching the appropriate receptors [16]. When the nervous system becomes unbalanced due to this blockage, the parasympathetic nerves over-react and constrict the bronchial tubes. For some researchers, the "beta blockage theory" offers a better explanation of the cause(s) of asthma symptoms present in some patients after exposure to what are known as non-specific triggers, such as viruses and extreme weather changes [16]. However, it is still not understood how and when beta receptors would become defective.

Clinical Manifestations

Asthma is marked by recurrent episodes of wheezing, breathlessness, chest tightness, and/or coughing. Usually, these periods are associated with widespread but variable airflow obstruction followed by a period of relief, either spontaneously or in response to treatment [79].

Clinical signs of airway narrowing generally consist of wheezing, increased respiratory rate, retractions, nasal flaring, and grunting. Later signs can include tripoding (using accessory muscles to breathe) and altered mental status. In general, asthma symptoms are revealed in different combinations and varying intensities.

Asthma has many puzzling aspects, and its symptoms may wax and wane, especially seasonally [16]. Unlike other respiratory diseases, such as COPD and emphysema, in which air trapping and hyperinflation of the lungs also occur, asthma is reversible with the use of proper medications and therapies.

Diagnosis

In some instances, a physical examination and a thorough exploration of a patient's medical history offer enough information for an accurate asthma diagnosis. There are several main criteria that should be present for a diagnosis of asthma to be ascertained. It is vital that a history of episodic asthma symptoms, characterized by airflow obstruction, be established. Symptoms that increase the probability of an asthma diagnosis include episodic wheeze, chest tightness, allergic rhinitis, atopic dermatitis, shortness of breath, and cough. It should also be

noted if symptoms worsen at night or in the presence of aeroallergens, irritants, or exercise. A family history of asthma, allergies, sinusitis, or rhinitis is also an indication of potential asthma. According to the National Institutes of Health, most recurrent episodes of coughing and/or wheezing may be attributed to asthma [27].

Most physicians order tests to confirm an asthma diagnosis or to rule out any complications and evaluate the severity of the condition. The objectivity of pulmonary tests allows for a reliable analysis of lung function that patient history and physical examination may not provide; this information may be valuable to the diagnosis process. The most critical tests for evaluating asthma assess pulmonary function. As discussed, common methods of measuring airflow in patients with asthma assess FEV_1 and PEF [16; 26].

Medical Management

The National Asthma Education and Prevention Program (NAEPP) advocates the use of a stepwise approach to asthma management [27]. In this program, the asthma classifications are treated as separate steps, beginning with mild intermittent at step 1 and advancing to severe persistent at step 6.

Asthma is classified based on symptom severity and frequency [27; 81]. Patients for whom symptoms occur more frequently (i.e., more than two times per week) and who experience interference with normal activity as a result of asthma symptoms are classified as having persistent asthma. Patients who experience asthma fewer than two times per week, have fewer than two night-time awakenings due to asthma per month, use rescue inhalers fewer than two times per week, have no interference with normal activity, and have "normal" peak FEV_1 are categorized as having intermittent asthma. The asthma is then further classified as mild, moderate, or severe based on the extent of interference in daily life, lung function tests, and use of rescue medications. After asthma severity has been classified, the treatment step is determined and begun (***Table 3***).

When considering pharmacologic treatment of asthma, the dosage, timing, and type of medication should be tailored to individual needs. Optimal treatment should include methods to reverse airflow barriers, stop symptoms from occurring, prevent serious attacks and need for emergency care and hospitalization, keep asthma from interfering with activities of daily living, minimize side effects, and control symptoms with the least amount of medication [16]. As with the approach to management, medication therapy generally adheres to two possible uses: to relieve symptoms quickly with the use of bronchodilators, or to reduce chronic airway inflammation with anti-inflammatory medications, preventing asthma from recurring in the future.

Bronchodilators are used to address the acute symptoms of an asthma attack. They act by relaxing the muscles surrounding airways, thereby dilating bronchial tubes. The primary categories of bronchodilators are beta2 agonists, theophylline derivatives, and anticholinergics [16]. Most often, bronchodilators are prescribed in inhaler or aerosol form. They are also available in liquid, tablet, and capsule forms, but these are generally not used due to gastrointestinal side effects. The bronchodilator inhaler is usually the first line of defense in an asthma attack [16].

In 2007, a panel of experts, under the guidance of the NAEPP, noted that the critical role of airway inflammation in asthma has been further substantiated since the 1990s, when this inflammatory role was first acknowledged and treatment was shifted away from calming acute flare-ups to engaging in preventative measures [16; 27; 82]. The NAEPP also noted that bronchodilators work best for acute asthma situations and for preventative treatment before exertion or exercise, but it emphasized anti-inflammatory medications as the foundation for long-term treatment of asthma; this was reaffirmed in the 2020 Global Initiative for Asthma guidelines [27; 82]. This approach relies on daily medication to maintain healthy lungs. Patients who require regularly administered bronchodilators should switch to longer-acting drugs designed to reduce airway inflammation [16; 27; 82].

STEPWISE APPROACH FOR MANAGING ASTHMA IN PATIENTS 12 YEARS OF AGE AND OLDER			
Step	**Preferred Treatment**	**Alternative Treatment**	**Indication**
1	Short-acting beta$_2$ agonist as needed	—	Intermittent asthma
2	Low-dose inhaled corticosteroid	Cromolyn, leukotriene antagonist, nedocromil, or theophylline	Persistent asthma (Consider subcutaneous allergen immunotherapy for patients who have allergic asthma)
3	Either low-dose inhaled corticosteroid and long-acting inhaled beta$_2$ agonist OR medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid AND either leukotriene antagonist, theophylline, OR zileuton	
4	Medium-dose inhaled corticosteroid AND long-acting inhaled beta$_2$ agonist	Medium-dose inhaled corticosteroid AND either leukotriene antagonist, theophylline, OR zileuton	
5	High-dose inhaled corticosteroid AND long-acting inhaled beta$_2$ agonist Consider omalizumab for patients with allergies	—	
6	High-dose inhaled corticosteroid, long-acting inhaled beta$_2$ agonist, AND oral corticosteroids Consider omalizumab for patients with allergies	—	
Quick relief of asthma exacerbations in all patients with short-acting beta$_2$ agonist, up to three treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed. Use of short-acting beta$_2$ agonists more than two days per week for symptom relief generally indicates inadequate control and the need to step up treatment.			
Source: [27]			*Table 3*

Anti-inflammatory medications block production of substances from cells involved in inflammation, such as mast cells; this action reduces or reverses the swelling that causes asthma symptoms [16]. Equally important, these medications lessen airway sensitivity, which prevents edema [16]. If asthma symptoms appear more than once or twice per week and less powerful options cannot control them, anti-inflammatory medication is indicated [16]. Before newer drugs were developed, the only anti-inflammatory asthma medication available was an oral corticosteroid, such as prednisone. Long-term treatment with oral corticosteroids is associated with serious side effects, including stunted growth in children, hyperlipidemia, thinning skin, and immune system impairment, making patient compliance difficult. As a result, several inhaled anti-inflammatory drugs were developed, which greatly reduced negative reactions [16]. The four primary types of anti-inflammatory drugs are corticosteroids, mast cell stabilizers, antiallergic medications, and antileukotriene medications [16].

The most effective nonpharmacologic intervention for the treatment and/or prevention of asthma at this time is trigger avoidance. Knowing and eliminating any possible asthma triggers is one of the most important elements of any management plan. Additionally, peak flow meter use and increased patient education contribute to an enhanced understanding and control of asthma symptoms. Immunotherapy and complementary medicine modalities have also been used by patients with asthma. Strong patient education and communication is vital to the successful management of the disease.

Nursing Management

It is important that nurses are able to discuss the different aspects of asthma symptoms as well as treatment and management to ensure that patients are able to understand and follow the established plan. In addition to the treatment plan and common symptoms associated with asthma episodes, patient education should outline the importance of compliance, trigger avoidance, and the continuous monitoring of their condition.

The main problem seen in both adult and pediatric asthma populations is compliance with a prescribed treatment plan and control of asthma symptoms. It is important that, as a part of patient education, adherence to the treatment plan is stressed. Much of the treatment and management responsibilities associated with controlling asthma and asthma symptoms falls on the patient. The more patients understand their treatment and the value of each aspect, the more likely they will be to adhere to the established treatment plan. Nurses should take into account the possible barriers to care, such as income level, education, language, and cultural beliefs.

There are many different types of triggers; some act in isolation, and others work together. The severity of an asthma attack depends upon the number of irritants, allergens, or other stimuli in the environment and the degree of lung sensitivity to these triggers [16; 83]. If a patient has known asthma triggers, avoidance of these items, substances, or situations may greatly improve, or even eliminate, asthma symptoms. Information regarding these asthmagens, where they may occur, and ways to avoid triggering an attack should be incorporated into initial patient education.

RHEUMATIC DISORDERS

Rheumatic disorders are inflammatory disorders and have been called the primary crippling diseases of the developed world. They are the most prevalent chronic conditions and a leading cause of disability in the United States [18].

The triad of pain, fatigue, and stiffness is common in rheumatic disorders and must be controlled so function is enhanced or maintained. If this triad, which represents a runaway inflammatory response, is not controlled, essential self-care deficits develop. Difficulty with self-care is usually accompanied by sleep disturbances, altered nutrition, and impaired mobility. All of these problems can adversely affect an individual's self-concept and self-esteem and lead to social isolation.

Although rheumatic conditions have different clinical patterns, pain and impaired mobility are commonalities. Chronic pain and progressive physical impairment of the joints and soft tissues are typical characteristics. When caring for patients with rheumatic disorders, the ultimate goals are to reduce pain and other physical manifestations, assuage psychologic distress, improve physical function, and generally aid in the well-being of the patient [18].

Systemic manifestations can be as devastating as musculoskeletal manifestations, and patients may experience acute exacerbations. The unpredictable nature of these disorders results in considerable uncertainty, which in turn leads to a cycle of ineffective coping, disturbed self-esteem, helplessness, and powerlessness. In many respects, the psychologic and social problems associated with these chronic illnesses are more disabling than the physical complaints.

Because of the chronicity of these disorders, patients require skilled, knowledgeable nursing care that draws on the disciplines of rehabilitation, counseling, and self-care. The unique role of the nurse is one that assumes accountability and responsibility for guiding and directing the patient through the healthcare system. Patients with chronic and often systemic illnesses require multiple therapies and follow-up appointments for pharmacologic adjustments, nutritional counseling, lifestyle assessment, physical and occupational therapy, and psychologic support. The personal and financial costs of rheumatic disorders can exhaust a patient's enthusiasm, job security, support systems, and sense of purpose in life. The nurse can provide a sense of consistency, hope, and reassurance, and the patient can learn to cope with, and positively adapt to, the demands of a chronic illness.

Rheumatic disease is often, but not always, the result of autoimmune dysfunction. Autoimmune diseases are defined as conditions in which immunologic self-tolerance has been disrupted, with resultant damage to body tissues. Rheumatic autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma, and mixed connective tissue disease [19]. Another important aspect of autoimmune disease is familial aggregation (or clustering), which suggests that there is a genetic predisposition to the development of specific disorders [19].

RHEUMATOID ARTHRITIS

An estimated 1.5 million American adults are affected by rheumatoid arthritis [84]. The yearly incidence of rheumatoid arthritis is approximately 53 per 100,000 for women and about half that (27.7 per 100,000) for men [84]. These figures vary significantly based on the age of the cohort. The data show that the incidence of rheumatoid arthritis increases steadily with age in both sexes, until approximately 65 to 74 years of age, when incidence peaks [84]. However, women in all age groups have a much higher incidence compared with men.

Rheumatoid arthritis is defined as a chronic inflammatory disease characterized by uncontrolled proliferation of synovial tissue and a wide array of multisystem comorbidities [85]. In its most common presentation, rheumatoid arthritis affects the joints, causing inflammation of the synovium and cartilage and bone loss. The precise etiology of rheumatoid arthritis is presently unknown. Most likely it has an autoimmune origin (whereby an individual's immune system confuses healthy synovial tissue for foreign substances, thereby attacking the synovial joint surfaces) given that autoantibodies (e.g., rheumatoid factor, anti-citrullinated protein antibody) are present and often precede the clinical manifestation of rheumatoid arthritis by many years [86; 87; 88].

Clinical Manifestations

Findings on general physical examination of the patient with rheumatoid arthritis are normal except for an occasional low-grade fever (38°C) and a slightly elevated pulse rate. The characteristic patient initially presents with complaints of pain and stiffness in multiple joints. There is prominent and prolonged morning stiffness (lasting more than one hour) that usually begins gradually with fatigue, loss of appetite, widespread muscle aches, and weakness [86; 89; 90].

After this initial presentation, joint pain appears. When the joint is not used for some time, it can become warm, tender, and stiff. After inflammation of the joint, increased synovial fluid is produced and the joint becomes swollen. There is accompanying soft tissue swelling, and joint pain is often felt bilaterally, affecting the fingers, wrists, elbows, shoulders, hips, knees, ankles, toes, and neck [86]. Though the joints are tender, the small joints of the hands and feet are not usually painful when the patient is at rest. Palmar erythema and prominent veins on the dorsum of the hand and wrist indicate increased blood flow. Distal interphalangeal joints are rarely involved. The temperature over the involved joints (except the hip) can be elevated, but there is usually no accompanying erythema. There are limitations in the range of motion, muscle strength, and function around inflamed joints.

In addition, soft, poorly delineated subcutaneous nodules (rheumatoid nodules) are often found in the extensor surface of the forearm. Soft, small lymph nodes are found occasionally in epitrochlear, axillary, and cervical areas [85]. Other symptoms that may present include anemia due to deficits in bone marrow production; eye burning, itching, and discharge; or lung inflammation (pleurisy) [85; 86; 89; 90]. Joint destruction may occur within one to two years after the appearance of the disease.

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with chronic extremity joint pain and suspected rheumatoid arthritis, the American College of Radiology recommends x-ray as the imaging study of choice for evaluation.

(https://acsearch.acr.org/docs/3097211/Narrative. Last accessed October 25, 2022.)

Strength of Recommendation: 9 (Usually appropriate)

Diagnosis

The history and physical examination are the most sensitive and specific tools for rheumatoid arthritis diagnosis. In addition, the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) joint working group recommends several laboratory tests for the diagnosis of rheumatoid arthritis, including rheumatoid factor, erythrocyte sedimentation rate, C-reactive protein, and anti-cyclic citrullinated peptide antibody [88].

Medical Management

Rheumatoid arthritis has no known prevention or cure. Lifelong treatment is usually required, including medication, physical therapy, exercise, and possibly surgery. The 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis is now a well-established diagnostic and prognostic tool; as such, guidelines (e.g., the 2019 update of the EULAR Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs) recommend that patients start treatment with a disease-modifying antirheumatic drug (DMARD) immediately following a rheumatoid arthritis diagnosis [91]. Therapeutic goals include preservation of function and quality of life, minimization of pain and inflammation, joint protection, and control of systemic complications, with the ultimate aim being low disease activity or remission [85; 89; 90; 91; 92].

Today, the recommended standard of treatment is a tightly controlled, aggressive strategy tailored to each patient, with modifications to the individual medication regimen to achieve a particular target (remission, or alternatively, low disease activity) in a specific period of time (usually six months) [91; 93]. The "treat-to-target" approach for a patient with early high disease activity and poor prognostic features typically involves initiation of methotrexate and/or another DMARD(s) immediately upon diagnosis [91; 92; 93]. Initial combination therapies with DMARDs, particularly those including a biologic anti-TNF agent, appear to provide earlier clinical improvement and less joint damage progression in patients with early moderate or highly active disease; they can be withdrawn successfully, and fewer treatment adjustments are needed than with initial monotherapies [91; 93; 94; 95; 96]. Patients with active disease are monitored closely (every one to three months), and it is recommended that treatment adjustments be made if there is no improvement at three months (or if the six-month target has not been reached) [91; 93]. Patients with low-to-moderate disease activity or high disease activity without poor prognostic features are typically started on DMARD monotherapy. NSAIDs, glucocorticoids, or cyclooxygenase-2 (COX-2) inhibitors are often used concurrently to treat rheumatoid arthritis-associated joint pain and inflammation. However, they do not alter the disease course and should not be used as single therapy.

Occasionally, surgery is needed to correct severely affected joints. Surgeries serve to relieve joint pain, correct deformities, and modestly improve joint function [85; 89; 90]. The most successful locations of surgery are those performed on the knees and hips [85; 89; 90].

Range-of-motion exercises and individualized exercise programs prescribed by a physical therapist can also delay the loss of joint function. Joint protection techniques, heat and cold treatments, and splints or orthotic devices to support and align joints may be of assistance [85; 89; 90]. Some therapists will use specialized devices to apply deep heat or electrical stimulation to reduce pain and improve joint mobility [85; 89; 90]. Occupational therapists can construct splints for the hand and wrist and teach patients with rheumatoid arthritis how to protect and use their joints most effectively. In addition to physiotherapy, occupational therapists can also show patients with rheumatoid arthritis how to better cope with limitations that can affect their daily tasks at work and at home. For example, many clinicians have recommended frequent rest periods between activities and proper sleeping habits (e.g., 8 to 10 hours of sleep per night) [97].

Nursing Management

In order to provide the best outcomes, patients should be educated regarding the most appropriate treatment regimens for their disease manifestations, as earlier rheumatoid arthritis diagnosis can assist in aggressive early treatment (when indicated), thereby delaying joint destruction. In addition to the medical management of rheumatoid arthritis, several lifestyle changes may improve symptom severity and decrease the number of flare-ups. The National Institute of Arthritis and Musculoskeletal and Skin Disorders recommends advising patients regarding rest and exercise, use of orthotic devices, stress reduction, and healthful diet [89].

As most patients with rheumatoid arthritis will be utilizing pharmacotherapy, regular blood or urine tests may be necessary to evaluate the efficacy and incidence of adverse effects related to medication. Because rheumatoid arthritis may cause eye complications, patients should have regular eye exams. In addition, patients with rheumatoid arthritis should have yearly cardiovascular assessment examinations.

Another management trend for patients with rheumatoid arthritis has been toward self-assessment. For the individual patient, health assessment questionnaires may be a more useful means of evaluating disease progression. Examples include the EULAR response criteria for rheumatoid arthritis (which classifies trial participants as "good," "moderate," or "non-responders" using individual change from baseline in disease activity score), disease activity indices, and various daily activity score surveys [93; 98]. Outcome measures, some based on patient-reported outcomes (such as the Rheumatology Assessment Patient Index Data), some based on a combination of laboratory and physician-derived measures (such as the Disease Activity Score, Simplified Disease Activity Index, and Clinical Disease Activity Index), should be used routinely to ensure that nurses are providing optimum care for patients with rheumatoid arthritis. (Various versions of the Disease Activity Score are available online at https://www.das-score.nl/en.)

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus, often referred to simply as lupus, is a chronic inflammatory autoimmune disorder of the connective tissue, primarily affecting the skin, joints, blood, and kidneys [99; 100; 101]. In this autoimmune disorder, antibodies are formed within the body that target healthy body systems, causing inflammation and structural changes. The word lupus means "wolf" in Latin, while erythematosus means "redness." The disease is named for the characteristic red rash that appears on the face and is thought to resemble a wolf's face [100; 101]. The term "lupus erythematosus" was coined in 1851 by Pierre Cazenave, a French dermatologist, but writings describing lupus date to ancient Greece [101; 102].

In patients with lupus, the body produces an accelerated inflammatory response, resulting in the production of autoantibodies, causing immune complexes [101; 103]. These autoantibodies and complexes assault the body's own healthy cells and tissues [100; 101; 102; 104]. Antigen-antibody complexes can

attack or suppress the body's normal immunity and cause damage to tissues. Symptoms of lupus are the result of the damage to the body's tissues secondary to the immunologic response.

A shortage or functional failure of T lymphocytes is believed to be partially responsible for this autoimmune reaction. Red blood cells, neutrophils, platelets, lymphocytes, or almost any organ or tissue in the body may be attacked. One of the hallmark indicators of lupus is the formation of autoantibodies, and the presence of autoantibodies in the blood is a key factor to the diagnosis of lupus [100; 101; 104].

Clinical Manifestations

Lupus has been characterized as a multidimensional, unique, complex, challenging, unpredictable, and often elusive disease [100]. It is a non-organ-specific systemic disease with a varying prognosis that can be mild, serious, life-threatening, or even fatal. The disease is characterized by recurring remissions and exacerbations, often called flares, that occur most commonly in the spring and summer [99; 104]. Periods of remission vary considerably among those diagnosed with lupus [100].

The onset of lupus may be acute or insidious, vague, or even nonspecific. On average, individuals with lupus have symptoms of the disease for two to three years before a diagnosis is made [101].

Common symptoms of lupus include fever, weight loss, malaise, fatigue, skin rashes, polyarthralgia, vasculitis, Raynaud syndrome, patchy alopecia (hair loss), and painless ulcers of the mucous membranes [104]. Fatigue is probably the most universal symptom, described as a persistent complaint of a paralyzing fatigue that normal rest may not relieve [100]. Vague symptoms of lupus include aching, fatigue, low-grade or spiking fever, chills, and malaise. Episodic fever is reported by more than 80% of all patients with lupus, with a low-grade fever most often noted [100]. Infection is certainly a major concern and is a potential symptom for patients with lupus. Those with lupus are more susceptible to opportunistic infections due to alterations in their hematologic system, especially in white blood cells. Women with lupus may also experience irregular periods or amenorrhea due to the disease process [100; 101].

Skin rashes are very common among patients with lupus; approximately 80% of patients report skin involvement [100]. A red, raised rash over the nose and cheeks characterizes the classic "butterfly rash" of lupus. The butterfly rash is reported by 55% to 85% of all patients with lupus at some point during their disease process [100]. Discoid lupus lesions may also be seen. Ultraviolet light often aggravates skin eruptions, and approximately one-third of all patients with lupus are found to be photosensitive [100; 105]. Oral, nasal, and vaginal ulcers may occur. Conditions such as alopecia, pruritus, alteration in wound healing, and bruising are other common dermatologic symptoms.

Diagnosis

The diagnosis of lupus can be facilitated with a physical examination, extensive patient history, various laboratory tests, and radiographic evaluations [101; 104]. There are several laboratory procedures that help to diagnose and monitor individuals with lupus; these various tests have different implications for the patient, but the antinuclear antibody (ANA) test is the most specific and sensitive test for lupus and is therefore the most commonly used autoantibody test. Ninety-seven percent of patients with lupus have a positive ANA blood test. The titer and patterns of the blood sample are reported. A titer greater than 1:80 is usually considered positive [106]. It is important to note that a positive ANA test is found in 97% of patients with lupus, but alone, it does not indicate a conclusive diagnosis of lupus [106]. A positive ANA test, although not always found, satisfies one of the four typical clinical characterizations required for a definitive diagnosis of lupus. ANA tests may also be positive in patients with other connective tissue diseases, chronic infectious diseases, and autoimmune diseases [106].

Other laboratory tests are available to assist in diagnosis or to monitor the effects of treatment. The anti-DNA blood test indicates disease activity, especially renal involvement. The anti-DNA test is most often used to monitor response to treatment. In remission, the anti-DNA test response is reduced or absent. In addition, the complement assay levels can assist with the diagnosis and monitoring of active lupus. The most common complements associated with lupus are C3, C4, and CH50. When these complement levels are decreased, they can indicate an increase in disease activity [107]. Skin and kidney biopsies can also be used.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Rheumatology Task Force Panel recommends that all patients with clinical evidence of active lupus nephritis, previously untreated, undergo renal biopsy (unless strongly contraindicated) so glomerular disease can be classified.

(https://www.rheumatology.org/Portals/0/Files/ACR%20Guidelines%20for%20Screening,%20Treatment,%20and%20Management%20of%20Lupus%20Nephritis.pdf. Last accessed October 25, 2022.)

Level of Evidence: C (Consensus opinion of experts, case studies, or standard of care)

Medical Management

There is currently no cure for lupus, and long-term disease management is required. Due to the variability of lupus symptoms, treatment protocols differ for each individual. The range of treatments, however, is increasing and becoming more effective; thus, the disease can be controlled reasonably well in most people. According to the U.S. Department of Health and Human Services, "the best way to treat lupus is to listen to the patient, whether she or he was diagnosed today or years ago" [100]. The ultimate goal of treatment is to suppress immune system abnormalities, prevent disease flares, and reduce inflammation and other complications secondary to lupus [104]. Treatment is based on such factors as symptoms and severity, overall general health, activity level, school and/or family schedule, age, family and social situations, other medical conditions, and financial and insurance considerations [102].

There are several types of drugs available to aid in the treatment and management of secondary symptoms. Among these drug classes are NSAIDs, corticosteroids, antimalarials, biologics, and immunosuppressives. In cases of severe lupus kidney disease not helped by pharmacologic intervention, dialysis or kidney transplant may be necessary.

In 2011, the U.S. Food and Drug Administration approved a new drug for the treatment of lupus—the first in more than 50 years [108]. The medication, belimumab, is a human monoclonal antibody that inhibits B-lymphocyte stimulator and acts to suppress abnormal B cells. In clinical studies, belimumab was more effective in lessening disease activity than placebo in patients with mild-to-moderate forms of the disease, although more research is necessary to determine if the drug is effective in patients with African American heritage and in patients with severe manifestations. The drug has been approved to treat patients with active, autoantibody-positive lupus who are receiving standard therapy [108]. It is administered via an intravenous infusion, and infusion reactions may occur. This can be prevented in most cases with pretreatment with an antihistamine. Other possible side effects of belimumab use include fever, diarrhea, and nausea [108; 109; 110].

Nursing Management

Individuals diagnosed with lupus should be encouraged to do all of the following [100; 101; 102; 104]:

- Get plenty of physical and emotional rest.
- Maintain a healthy diet.
- Establish an exercise regimen.
- Avoid sunlight.
- Seek prompt treatment of infection.
- Limit stress.
- Set realistic goals and priorities.
- Maintain effective communication with their healthcare providers.

- Develop a support system, including family, friends, healthcare professionals, community organizations, and organized support groups.
- Avoid triggering or aggravating factors.
- Seek regular health care.

SJÖGREN SYNDROME

Sjögren syndrome is a systemic chronic inflammatory condition characterized primarily by decreased function of lacrimal and salivary glands, enlargement of the parotid gland, and often, extraglandular manifestations. The syndrome is classified as primary when it develops in a previously healthy individual and as secondary when it is associated with an underlying rheumatic disease.

The pathogenesis of Sjögren syndrome primarily involves organ-specific autoantibodies—antibodies to cellular antigens of salivary ducts, the thyroid gland, the gastric mucosa, erythrocytes, the pancreas, the prostate, and nerve cells. In addition, non-organ-specific autoantibodies are found in approximately 60% of individuals with the disease [111].

Clinical Manifestations

The typical clinical features of Sjögren syndrome are dry eyes (xerophthalmia or keratoconjunctivitis sicca) and dry mouth (xerostomia), which have been reported to occur in 93% and 98% of cases, respectively [112]. In addition to dryness, symptoms related to xerophthalmia include grittiness, itchiness, and sensation of a foreign body in the eye. Symptoms related to xerostomia include difficulty eating, swallowing, and speaking and the premature and accelerated loss of teeth. As with other autoimmune diseases, nearly half of individuals report debilitating fatigue [111].

Among the most common manifestations of extraglandular involvement are joint pain and/or swelling (37% to 75%), gastrointestinal symptoms (54%), pulmonary disease (e.g., chronic cough, recurrent bronchitis, fibrosis) (29%), and Raynaud phenomenon (16% to 28%) [112; 113]. Occurring less frequently are cutaneous vasculitis, lymphadenopathy, and renal involvement (e.g., proteinuria, interstitial nephritis, glomerulonephritis) [112; 113]. Peripheral neuropathies are often associated with Sjögren syndrome, and the reported prevalence of this complication has ranged widely, from 10% to more than 60% [114; 115]. Cognitive dysfunction has been reported in about half of individuals [114].

Diagnosis

Diagnosing primary Sjögren syndrome is challenged by its slow, insidious onset, its variable course, its wide range of clinical features, and its symptoms, which are nonspecific and not always concurrent [111; 116]. These factors have led to delays in diagnosis, often over several years [111]. Early diagnosis is essential, however, to prevent complications and to allow for surveillance to detect serious systemic manifestations.

There is no single diagnostic characteristic of Sjögren syndrome. Although xerophthalmia and xerostomia are found in nearly all individuals with the syndrome, they may be symptoms of other conditions. As a result, the diagnosis should be based on a combination of characteristic symptoms, the history and physical examination, diagnostic testing, and the distinguishing of Sjögren syndrome from other conditions with similar signs and symptoms. Differentiating Sjögren syndrome from other autoimmune diseases with similar clinical features, such as systemic lupus, rheumatoid arthritis, and scleroderma, is important to ensure appropriate treatment [111]. Healthcare professionals should remember that if another rheumatic condition is diagnosed, Sjögren syndrome may still be present, given the high rate of secondary disease [111].

Medical Management

No evidence-based guidelines are available for the treatment of Sjögren syndrome. Treatment focuses on alleviating symptoms and preventing complications, as no cure is available.

Treatment of dry eye involves artificial tears to replace moisture, and a topical anti-inflammatory agent should be used for moderate-to-severe symptoms. Preservative-free artificial tears have been better tolerated than tear solutions with preservatives because of the irritation that can be caused by frequent use of the latter type [111]. Randomized

controlled trials have shown that topical ocular cyclosporine (0.05%) significantly improves objective measures of dry eye, blurred vision, and use of artificial tears in patients with moderate or severe dry eye [117]. In its guidelines for dry eye, the American Academy of Ophthalmology (AAO) includes topical cyclosporine as a level IA recommendation for moderate dry eye [118].

If symptoms are not relieved by artificial tears or anti-inflammatory agents, a muscarinic agonist can increase tear production by stimulating muscarinic receptors. These receptors are a type of cholinergic receptor and are present on exocrine glands as well as on heart muscle and smooth muscle [119]. The two muscarinic agonists shown to be effective for dry eye are pilocarpine (a nonselective agonist) and cevimeline (a selective muscarinic agonist). According to a review of the literature, placebo-controlled trials have provided evidence of improvement with these agents. In three trials, pilocarpine was associated with subjective and objective improvement of dry eye in 42% to 53% of patients (compared with 26% for the control), and in two trials, cevimeline was associated with improvement in 39% to 72% (compared with 24% to 30% for the control) [117]. Systemic cholinergic agents, such as pilocarpine and cevimeline, are a level IA recommendation for severe dry eye in the AAO guidelines [118].

Treatment of dry mouth involves stimulating production of saliva and using saliva substitutes; muscarinic agonists can be used for severe dry mouth. Saliva production can be stimulated with the use of sugar-free chewing gum and sour lozenges [119]. Saliva substitutes are available as over-the-counter and prescription products and are manufactured as lozenges, rinses, sprays, and swabs [111].

Nursing Management

Patient education should focus on the importance of careful eye and oral care. Oral care should include frequent dental examinations, use of fluoride, and daily rinsing with an antimicrobial solution [111; 120]. Nurses should emphasize the importance of maintaining general health, reporting any changes in symptoms, following the prescribed use of medications, and keeping appointments for follow-up visits.

SCLERODERMA

Scleroderma literally means "hard" (sclerosis) "skin" (derma), but the disease may present with internal organ involvement (diffuse scleroderma or systemic sclerosis) in addition to cutaneous signs. Systemic sclerosis is one of the least well understood of the rheumatic disorders. It occurs as a multisystem inflammatory disease characterized by skin thickening (scleroderma) and deposition of excessive quantities of connective tissue (particularly collagen), which eventually results in severe fibrosis. The skin, blood vessels, synovium, and skeletal muscles are affected along with the microvasculature of internal organs. Widespread vascular involvement, perhaps the earliest and most significant pathologic change, is also a prominent feature [24; 25].

Medical Management

Management of systemic sclerosis is typically complicated, as it can have many variations. In general, management focuses on treatment of each affected organ system, and there are a range of pharmacotherapeutic options for the various systems.

SPONDYLOARTHROPATHIES

The spondyloarthropathies are a group of interrelated disorders that include psoriatic arthritis, reactive arthritis, and ankylosing spondylitis [24].

Psoriatic Arthritis

Psoriasis is a common skin disorder characterized by stippled nails, pruritus, and silvery scales on bright-red plaques, usually on the elbows, knees, and scalp. Several types of psoriatic arthritis have been proposed. In asymmetrical oligo arthroplasty, there is asymmetrical involvement of both large and small joints, and sausage-shaped joints are common. With this type of arthritis, the asymmetrical pattern involves the interphalangeal and metatarsophalangeal joints of the feet and the distal interphalangeal joints of the fingers. The second type, symmetrical polyarthropathy, closely resembles rheumatoid arthritis. Arthritis mutilans, a severe form of destructive arthritis, is characterized by telescoping digits, also known as the "opera-glass hand." Psoriatic spondylitis is characterized by the sacroiliitis of ankylosing spondylitis [30].

The cause of psoriatic arthritis appears to be a complex combination of immunologic, genetic, and environmental factors. Immunologic changes seen in some patients include elevated titers of IgG and IgA and the presence of immune complexes [30].

Clinical Manifestations

The diagnosis of psoriatic arthritis is usually confirmed after a positive history of psoriasis and specific x-ray findings. However, it is important to realize that in some patients, particularly children, joint changes precede skin changes. Nevertheless, most rheumatologists agree that the diagnosis cannot be made without evidence of psoriatic skin or nail changes [30].

Medical Management

In 2018, the American College of Rheumatology and the National Psoriasis Foundation published updated guidelines for the treatment of psoriatic arthritis. The guideline "covers the management of active psoriatic arthritis in patients who are treatment-naive and those who continue to have active psoriatic arthritis despite treatment, and addresses the use of oral small molecules, tumor necrosis factor inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib)" [121]. Nonpharmacologic approaches to management include physical therapy, smoking cessation, weight loss, massage therapy, and exercise.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Rheumatology/ National Psoriasis Foundation recommend that patients with active psoriatic arthritis use some form or combination of exercise, physical therapy, occupational therapy, massage therapy, and acupuncture.

(https://www.rheumatology.org/Portals/0/Files/PsA-Guideline-2018.pdf. Last accessed October 25, 2022.)

Level of Evidence: Low

Ankylosing Spondylitis

Literally, ankylosing spondylitis refers to fusion (ankylosis) of inflamed vertebrae (spondylitis). The disease typically begins in the spine of young men in their late teens or early twenties. The average annual age-adjusted incidence of ankylosing spondylitis has been reported to be 6.6 per 100,000 population, with men being affected three times as frequently as women. Although the usual age of onset is set between 15 and 35 years, the age group with the highest incidence is those 25 to 34 years of age [24].

Most patients have bilateral sacroiliitis that causes pain and some degree of restricted motion in the lumbar spine. Peripheral arthritis of the large joints, usually the hips, shoulders, and more rarely the knees, occurs in 20% to 30% of persons with ankylosing spondylitis [24]. Chest expansion can also be decreased as a result of associated costovertebral arthritis. By the time the patient is 50 or 60 years of age, the fusion of the lumbar spine has proceeded to the cervical region. If ankylosing spondylitis is not treated, the disease tends to progress, with remissions and exacerbations, to a final stage of rigid lumbar and thoracic kyphosis that leaves the neck in a flexed position. Ankylosing spondylitis is associated with a shortening of the life span [24].

Clinical Manifestations

Initially, morning backache and stiffness begin during adolescence or young adulthood. The back pain and stiffness subside with movement but often return with inactivity. Back pain throughout the spinal column, difficulty sleeping, fever, and neurologic changes (e.g., bowel and bladder incontinence, paresthesia, numbness) may also occur. Several other systemic manifestations of ankylosing spondylitis can be seen, including uveitis, pulmonary fibroids, inflammatory bowel disease, and aortic insufficiency. Uveitis occurs in up to 25% of patients with ankylosing spondylitis [24].

Medical Management

According to current guidelines, in patients with active ankylosing spondylitis, the strongest recommendations include use of NSAIDs, use of TNF inhibitors when activity persists despite NSAID treatment, not to use systemic glucocorticoids, physical therapy, and hip arthroplasty for patients with advanced hip arthritis [122].

Nursing Management

The nurse plays a key role in teaching patients with ankylosing spondylitis about health promotion activities, exercise, and the management of pain. One of the most critical areas for skillful nursing intervention involves being attentive to and providing positive, unconditional regard for those persons with changing appearances. Another important area for nursing intervention, especially as the disease progresses, is the maintenance of effective breathing patterns and adequate oxygenation [29].

Reactive Arthritis

Reactive arthritis is a form of peripheral arthritis, often accompanied by one or more extra-articular manifestations, that appears shortly after certain infections [30]. Specifically, reactive arthritis occurs following exposure to a bacterial gastrointestinal or genitourinary infection [30].

Clinical Manifestations

Reactive arthritis may manifest in almost every system of the body; the most common features are polyarthritis, urethritis or cervicitis, and conjunctivitis. Urethritis can occur with clinical manifestations (e.g., discharge, slight burning on urination) or can be asymptomatic, which contributes to the difficulty in establishing a diagnosis. Reactive arthritis has also been associated with HIV infection [30].

Medical Management

Reactive arthritis runs a self-limited course of days or weeks in most patients. However, some studies suggest that many patients continue to be plagued by musculoskeletal manifestations [30]. This chronic form of the disease may require treatment with a DMARD.

IDIOPATHIC INFLAMMATORY MYOPATHY

Inflammatory diseases of muscle are a heterogeneous group of disorders characterized by proximal muscle weakness and nonsuppurative inflammation of skeletal muscle. The idiopathic myopathies are categorized more specifically as polymyositis (affecting both sides of the body), dermatomyositis (characterized by a distinctive rash), inclusion body myositis (the most common form in older adults), and necrotizing autoimmune myopathy. As a group, these are relatively rare diseases, and accurate estimates of their prevalence are difficult to obtain. Muscle weakness with an underlying malignancy develops in a subset of patients with inflammatory myopathies. Malignancy may precede or follow the onset of muscle weakness.

Clinical Manifestations

The most frequently occurring idiopathic myopathies in adults are diffuse, systemic, inflammatory connective tissue diseases. Although these disorders can have an acute onset and progress rapidly, more typically there is a slower progression. Patients gradually develop significant weight loss, fatigue, and weakness over a period of months. These diseases cause symmetrical progressive weakness of the proximal or limb-girdle muscles and occasional atrophy of the muscles of the limbs, neck, and pharynx. Decreased muscle strength occurs in the pelvic girdle first, followed by weakness of the legs, shoulders, and arms. Weakness of the flexor muscles of the neck occurs in about half of those affected with inflammatory myopathy. Falling and tripping may be early signs. With dermatomyositis, the first sign is often a violet or red rash developing on the face/eyelids, knuckles, elbows, knees, chest, and/or back.

Medical Management

Treatment of inflammatory myopathy usually begins with the daily administration of high doses of oral corticosteroids. Prednisone (1–2 mg/kg/day) is given until elevated muscle enzymes begin to decrease toward normal and patients show improvement in their ability to perform activities of daily living [123].

Unfortunately, inclusion body myositis is refractory to any known treatments and does not respond to corticosteroid therapy. For these patients, palliative care and physical therapy are indicated.

VASCULITIS

Vasculitis encompasses a group of disorders leading to inflammation and neuritis of blood vessel walls. Soluble immune complexes are deposited in blood vessel walls in areas where capillaries have increased permeability. After deposition, the immune system is activated and the complex is destroyed along with the blood vessel wall. These disorders include Behçet disease, Kawasaki disease, polymyalgia rheumatica, and giant cell (temporal) arteritis. Inflammation and damage to large and small vessels result in end-stage organ damage [123].

Behçet Disease

Behçet disease is a chronic multisystem inflammatory disorder characterized by ulcers affecting the mouth and genitals, various skin lesions, and ocular abnormalities. In some people, the disease also results in arthritis, skin problems, and inflammation of the digestive tract, brain, and spinal cord [124]. The exact cause of Behçet disease is still unknown, but it is thought that it is an autoimmune disease, whereby the abnormal immune activity is triggered by exposure to an environmental agent (such as an infection) in people with a genetic predisposition to develop the disease. There is no known cure, and treatment is symptomatic and supportive.

Kawasaki Disease

Kawasaki disease is an autoimmune vasculitis typically diagnosed in young children. It begins with a fever that lasts at least five days. In 80% to 99% of patients, the following clinical signs/symptoms are present: cheilitis, conjunctivitis, erythema, lymphadenopathy, and proteinuria [125]. In some cases, the disease affects the coronary arteries and can lead to serious heart problems. An infection along with genetic factors may be involved in the pathogenesis [125]. Treatment includes intravenous gamma globulin and high doses of aspirin in a hospital setting.

Polymyalgia Rheumatica

Polymyalgia rheumatica is a clinical syndrome occurring more commonly in women than in men. It is a disease of aging, rarely occurring before 60 years of age. It is characterized by pain and stiffness in the neck, shoulder, back, and pelvic girdle, especially in the morning. Headaches or painful areas on the head may be present. The patient also may have a low-grade fever or temporal arteritis [123]. Rarely, the aorta is affected, increasing the risk for aortic aneurism. Treatment is corticosteroid therapy to reduce inflammation and pain. Effective treatment may take more than one year, and relapse is possible.

Giant Cell Arteritis

Giant cell (temporal) arteritis is systemic large- and medium-sized vessel vasculitis. Most often, it involves the external carotid arteries [126; 127]. It typically begins as an intermittent soreness or burning headache and steadily escalates over several weeks or months to become a constant, well-localized pain. On rare occasions, it can be explosive. Many patients report that the pain is worse at night. Although the pain is usually unilateral, it may also be bilateral. Pain is classically confined to the temples. Between 70% to 90% of patients with giant cell (temporal) arteritis complain of headache [127; 128].

Clinical Manifestations

The typical presentation is a new-onset headache in patients older than 50 years of age. Incidence is higher in women than men (ratio 3.7:1), as well as in persons of northern European descent. It represents the most common vasculitis in adults. Nearly 50% of patients with polymyalgia rheumatica also have giant cell arteritis [127].

On exam, the affected scalp artery is sometimes prominent. It may be tender and is often pulseless. The scalp itself is usually tender as well. Depending upon the progression, visual field defects and decreased acuity may be noted, although the patient does not usually exhibit focal neurologic deficits. Typically, the headache occurs in someone who is febrile, has malaise, and feels aches in the back and

shoulders. Claudication of the jaw occurs commonly and is virtually pathognomonic for this condition when present during talking or chewing [127].

Giant cell arteritis involves not only the arteries of the scalp causing headache, but also other vessels, including those supplying the eye and occasionally the brain. Nearly half of patients with giant cell arteritis develop blindness, if untreated, due to ischemia of the optic nerve or retina. Because blindness can be prevented by immediate steroid treatment, prompt and accurate diagnosis is critical [126; 127].

Medical Management

When ocular symptoms exist, emergency medical treatment is necessary. High-dose corticosteroids are an effective treatment. Headache usually resolves or greatly improves within three days of high-dose steroid treatment [126; 127]. A maintenance dose of prednisone may be required to be administered for one to two years in some patients [127].

LYME DISEASE

Lyme disease is the leading arthropod zoonosis reported in the United States [129]. The primary agent of Lyme disease is the spirochetal organism *Borrelia burgdorferi*; however, in the United States, there are at least one other bacteria (*Borrelia mayonii*), two other known genospecies, and as many as 40 disease-causing subspecies of *Borrelia* [130; 131; 132]. The primary Lyme disease vectors are the ticks *Ixodes scapularis* or *Ixodes dammini* in the eastern United States and *Ixodes pacificus* in the West [129]. Other *Ixodes* spp. ticks, also known as deer ticks, can carry the organism in some of the less disease-prevalent areas [133; 134].

Clinical Manifestations

The first signs of Lyme disease are usually flu-like symptoms and joint pain, which is why it is considered a rheumatic disease. In an elderly person, pre-existing arthritis may complicate early diagnosis. Three distinct stages have been described in patients with untreated infections [135]. Stage 1 (early localized stage) occurs 3 to 30 days after the tick bite and is associated with the appearance of the characteristic "bull's-eye" skin lesion of erythema migrans. Various sources estimate that approximately 70% to 80% of the documented infections will have the characteristic expanding rash [129]. This initial stage may show the nonspecific clinical signs of malaise, headache, arthralgia, fever, myalgia, and regional lymphadenopathy. If they never see a rash, many patients will not consider Lyme disease as the source of their symptoms.

Stage 2 (early disseminated stage) develops through hematogenous spread and is evident after days to weeks post-tick bite [129; 136]. Possible manifestations include subtle encephalitis with headache and cognitive difficulty, stiff neck, cranial neuropathy (with facial palsy being a common finding), cerebellar ataxia, motor and sensory radiculoneuritis, myelitis, and visual disturbances. This stage is associated with acute neuroborreliosis in a significant number of cases [129; 136]. Most patients with neuroborreliosis are affected by meningitis, facial nerve palsy, and/or radiculitis, with only a limited number having parenchymal spinal cord or brain involvement [137].

Stage 3 (late disseminated stage) is the chronic phase, which may appear months to years after the initial infection [129]. Various names for this stage have been proposed and are currently used, including post-Lyme syndrome, post-Lyme disease syndrome, post-treatment chronic Lyme disease, or chronic Lyme disease [137]. One of the most common findings in this stage is oligoarthritis, with the knee being the most frequently affected joint, although other joints can become inflamed [129; 136]. Pain is usually out of proportion to the swelling [129]. Musculoskeletal pain, spinal radiculopathy with paresthesias, encephalopathy, and the symptom complex of fibromyalgia or chronic fatigue syndrome may be present. This stage is associated with chronic borreliosis; consequently, cardiac arrhythmias, respiratory compromise, and spread to the entire nervous system are liable to occur. It is suspected that fibromyalgia may be a long-term sequela to chronic Lyme disease. If untreated, chronic expression results in potentially crippling arthritic changes as well as organ system involvement. The organism can establish itself in the bladder wall and reoccur with another exposure or stress from another illness [133].

Many of the symptoms of Lyme disease are caused by the body's immune system. Because the spirochete infects the cartilage cells intracellularly, the neutrophils concentrate in the region, resulting in a pain similar to the pain of rheumatoid arthritis. Damage to the cartilage cells and subsequent pain is caused by neutrophils attacking both infected and healthy cells. The amount of discomfort and joint destruction varies among patients depending upon their individual immune response.

Diagnosis

Clinical suspicion from history, signs, and symptoms is paramount in the diagnosis of Lyme disease [129]. Patients can present with a variety of clinical findings, and not all classic signs or symptoms are present in those with active Lyme disease. If patients have a rash and recognize it as visceral migrans, it may be too early for other symptoms to be noted or for testing to yield positive results. Additionally, early but inadequate antibiotic treatment may prevent full antibody development in patients who are still clinically ill [138]. Varying severity and expression can make Lyme disease difficult to diagnose in some patients. The criteria as set by the Centers for Disease Control and Prevention (CDC) do not always fit the signs, symptoms, and test results. This can be very frustrating for patients as well as medical professionals. A few good diagnostic procedures are available, although they require diligent interpretation.

The first test should include an ELISA or, rarely, an indirect immunofluorescence assay (IFA); however, false positives occur with cross reactions to other spirochetes, such as syphilis, mononucleosis, some autoimmune diseases, and oral cavity flora. If the first step is positive or indeterminate, the second step should be performed. The second step, the Western blot test, identifies antibodies for the different spirochetes [129]. The most definitive diagnosis is made with a combination of positive ELISA and specific Western blot results [129; 133].

Medical Management

Prompt and complete treatment with antibiotics is important to prevent the development of chronic Lyme disease and/or chronic neuroborreliosis and their troublesome sequelae. The International Lyme and Associated Diseases Society (ILADS) suggests that Lyme disease should be treated with doxycycline as the antibiotic of choice for prophylaxis following an *Ixodes* tick bite with known feeding, irrespective of the amount of tick engorgement or the local tick population infection rate [139]. Where doxycycline is contraindicated, antibiotics known to be effective for treating Lyme disease, such as amoxicillin, azithromycin, or cefuroxime, may be substituted. The recommended adult dose and prophylactic regimen is 100–200 mg doxycycline twice daily for 20 days [139].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the International Lyme and Associated Diseases Society, clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis.

(https://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900. Last accessed October 25, 2019.)

Strength of Recommendation/Level of Evidence: Recommendation, very low-quality evidence

Nursing Management

Patients with Lyme disease can frequently be frustrated with the long-term nature of the treatment and will need support, especially to maintain the antibiotic regimens. The long-term effects can also be very discouraging for the unfortunate patients who eventually develop the syndrome, which mimics fibromyalgia or chronic fatigue syndrome. Fortunately, it appears that early treatment, and in most cases even late treatment, can prevent or eliminate these sequelae [129; 133].

As with any disease, prevention is paramount. Educating people about how the disease is transmitted and its early signs will help reduce the overall incidence and lessen the severity in those who receive early treatment. The following advice should be given to patients, family, and friends.

If walking where ticks might be present, wear clothing that provides protection from tick exposure. Bare legs should not be exposed, and socks should be pulled up over pant legs. Ticks are not able to get through clothing to exposed skin, but they can climb up socks and reach exposed skin if the pant legs are not inside the socks. Long-sleeve tops and having long hair under control will help as well. Clothing should be removed and washed on arrival home. A thorough tick check should be completed, especially in body creases such as the groin and the axilla (armpit) [129]. Many people have been fooled into thinking ticks were freckles and have not removed them before they became engorged. It is most important that embedded ticks be removed promptly. If the capitulum, or head, is broken off, it may cause a local reaction. *Borrelia* is actually in the body of the tick, so transmission likelihood will decrease the faster the body is removed. It takes at least 24 to 36 hours of contact by the tick for the disease to be transmitted.

IMMUNE SYSTEM DISORDERS

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

HIV infects people worldwide and results in destruction of the body's host defenses and immune system. HIV has infected more than 42 million people throughout the world, with an estimated five million people newly infected each year. The CDC has reported an overall increase in new diagnoses of HIV in the United States. The greatest increases have been noted in black (55%) and Hispanic (26%) Americans. HIV kills more people than any other infectious disease and ranks fourth among the leading causes of death worldwide [123; 140].

For many years, because of a lack of understanding and effective treatment, HIV was considered a rapidly progressing fatal disease. Today, HIV infection is viewed as a chronic disease that can be controlled with appropriate health care. The cost of such health care ($12,000 yearly per person), however, can limit its accessibility. Because many parts of the world, such as Africa and Asia, lack adequate economic resources to treat this disease, HIV infection continues to be a rapidly progressing fatal illness in these areas [123; 140].

Etiology

The etiologic agent associated with AIDS was first isolated by French scientists in 1983 and named lymphadenopathy-associated virus. One year later, an American scientist claimed the discovery of the etiologic agent and named it the human T-cell lymphotropic virus type III. However, both scientists had actually identified the same virus, causing confusion. In 1986, the International Society in the Taxonomy of Viruses renamed the virus, calling it HIV. That same year, a second and distinctly different strain of the virus was discovered in Africa. Since 1986, the scientific names to distinguish the two viruses have been HIV-1 and HIV-2 [123; 140].

This was a major discovery because it was the first clue that HIV could change its appearance, or mutate, rapidly. This capability, called genetic promiscuity, has become the hallmark of the virus, creating a monumental challenge for scientists and researchers alike. HIV-1 is distributed worldwide but is most prevalent in Europe and the United States. HIV-2 is believed to be endemic to West Africa, although it is increasingly overtaken by HIV-1. A total of 242 cases of HIV-2 had been identified in the United States as of 2010; most of the cases were associated with immigration from, travel to, or a sexual partner from West Africa [123; 140].

HIV-1 has also mutated several times. It has two major subtypes, which are designated as HIV-1 major (group M) virus, and HIV-1 outlier (group O) viruses [123; 140].

Risk Factors

On the basis of newly reported cases, the transmission categories are [141]:

- Male-to-male sexual contact (MSM)
- Injecting drug users
- MSM who inject drugs
- Heterosexual contact
- Perinatal transmission
- Other (includes hemophilia, blood transfusion, and risk factor not reported or not identified)

The CDC has published guidelines for medical professionals to integrate HIV prevention into the regular medical care of those living with HIV. The three major components of the recommendation are: screening for HIV transmission risk behaviors and sexually transmitted infections; providing brief, behavioral risk-reduction interventions in the office setting and referring selected patients for additional prevention interventions and other related services; and facilitating notification and counseling for sex and needle-sharing partners of infected persons [142; 143].

Pathophysiology

HIV, known formerly as human T cell lymphotropic virus, is a member of the retrovirus group and as such carries an RNA genome and a reverse transcriptase enzyme (RNA-directed DNA polymerase) that enables the virus to replicate within infected host cells. Susceptibility in humans is determined by the binding affinity of virion envelope proteins for a specific cell surface receptor molecule (CD4+) found on tissue dendritic cells, macrophages, and CD4+ T lymphocytes. The pathogenesis of infection, and the subsequent perpetuation of the disease state, involves a complex set of interactions by which HIV is able to take advantage of cellular pathways while avoiding or neutralizing various components of the immune system [144; 145].

The most common mode of HIV infection is sexual transmission across exposed mucosal epithelium. Dendritic cells and macrophages are found beneath the mucosal epithelium of the anogenital and cervicovaginal tracts, as well as within tonsillar and adenoidal tissue. Studies in primates demonstrate that after the virus penetrates the mucosal epithelium, infection is initiated within nearby dendritic cells and macrophages. Infected dendritic cells then fuse with CD4+ T lymphocytes and the infection extends to deeper tissue and, shortly thereafter, to regional lymph nodes [145]. Within days, this proliferation of infected CD4+ T lymphocytes, combined with the migration of infected macrophages, leads to the appearance of viral RNA in the bloodstream. This is followed by widespread secondary amplification of infection within the lymphoid tissue of the gastrointestinal tract, spleen, and bone marrow.

After the virus enters the cell, it may replicate, induce cell fusion and propagation of infection, or lead to cell death [145]. The defining characteristic of HIV disease is the immune deficiency state caused by ongoing viral replication and cell-to-cell transmission within lymphoid tissue. With chronicity of infection there is a progressive depletion of CD4 (helper-inducer) lymphocytes, the very T lymphocyte cohort whose function it is to direct other cells in the immune system and to orchestrate the inactivation of virus antigen. The result is a depressed T lymphocyte functional capacity, characterized by depletion of helper T cells (T4), impaired killer T cell activity, and increased suppressor T cells (T8). In persons with intact lymphocyte immune systems, the normal number of CD4 T cells ranges from 600–1,200 cells/mcL, depending on the stage and duration of infection.

Clinical Manifestations and Disease Course

The clinical manifestations of HIV disease are determined by the stage of primary infection and the chronicity and degree of the resultant cellular immunodeficiency state. Acute, primary HIV infection may be asymptomatic, but most often it is manifest by a subacute viral syndrome of malaise and

fatigue, fever, sore throat, rash, myalgia, headache, and lymphadenopathy—clinical features similar in many respects to that seen with Epstein-Barr virus mononucleosis, CMV, and certain types of herpes simplex infections [145]. A variety of atypical symptoms and signs may be seen, including aseptic meningitis syndrome, genital ulcers, and ulcerations involving the gingiva, palate, or buccal mucosa. The acute illness usually resolves in less than 14 days but may follow a protracted course over many weeks [145].

Early in the chronic phase of HIV infection, when the CD4 lymphocyte population is only modestly depressed and declining slowly, patients are often asymptomatic or may exhibit generalized lymphadenopathy and recurrent oropharyngeal candidiasis (thrush). During this stage, a reservoir of HIV is established throughout the lymphoid tissue system, including the spleen. Gradually, wandering (infected) macrophages disseminate the virus to certain internal organs, notably the brain, kidney, and adrenal glands.

Chronic HIV disease follows a variable course but eventually leads to a variety of clinical manifestations, some of which are directly related to the impact of chronic infection on vital organs. Common syndromes include HIV encephalopathy and dementia, peripheral neuropathy, interstitial nephropathy, a variety of skin eruptions, and signs of adrenal insufficiency.

The late clinical manifestations of HIV disease are most frequently the result of AIDS that follows progressive depletion of CD4+ T lymphocytes to levels <200 cells/mcL. AIDS-defining illnesses include secondary, opportunistic infections and certain malignancies usually encountered only in clinical settings of severely impaired cellular immunity.

Opportunistic infections are very common in persons with undiagnosed or poorly treated chronic HIV infection and are of two types. The first type is infection newly acquired by exposure to microorganisms normally nonpathogenic, or of low pathogenicity, for persons with a healthy immune system. Examples are *Pneumocystis jiroveci*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and atypical mycobacteria, all of which are commonly associated with inhalational exposures and transient colonization of the respiratory tract in healthy individuals. The second type is reactivation of latent infection acquired earlier in life, which typically remains dormant throughout life. Examples of this type are CMV, *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *Histoplasma capsulatum*. The advent of an opportunistic infection may serve as the herald sign of unrecognized, undiagnosed chronic HIV infection/AIDS.

Clinically, these infections tend to present in one of several distinct syndromes, with useful differential diagnosis considerations:

- Pneumonia: *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium* complex (MAC), cryptococcosis, histoplasmosis
- Meningoencephalitis: Toxoplasmosis, cryptococcosis, tuberculosis
- Gastrointestinal disease (diarrhea): Common bacterial dysentery, cryptosporidium, fungal and atypical mycobacterial infection
- Fever of unknown origin (often with abdominal complaints, hepatosplenomegaly, and/or lymphadenopathy): CMV, MAC, tuberculosis, histoplasmosis

Late clinical manifestations related to HIV-induced malignancy include Kaposi sarcoma of the skin or respiratory tract and lymphoma presenting as lymphadenopathy, splenomegaly, or focal gastrointestinal disease.

Without satisfactory antiretroviral therapy, the usual patient with HIV/AIDS experiences a slow, inexorable wasting illness punctuated by periods of feverishness and diarrhea, becoming increasingly anorectic, malnourished, and lethargic. Late clinical signs include muscle wasting and weakness, anemia and thrombocytopenia, lymphadenopathy, pulmonary infiltrates, and neurologic abnormalities (such as dementia, peripheral neuropathy, and

tremors). The median survival of patients with advanced HIV/AIDS (CD4 count <50 cells/mcL) is approximately 12 to 18 months. Patients succumb to complications of uncontrolled infection, malignancy, or critical organ failure (such as uremia or adrenal insufficiency).

Medical Management

With early combination antiretroviral therapy (cART) and prophylaxis for opportunistic infections, HIV disease shares features of other multisystem, chronic diseases characterized by acute exacerbations and end-stage manifestations. cART combines six major classes of agents: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs), and chemokine (C-C motif) receptor 5 (CCR5) antagonists.

Initiated in 1995 in the United States, antiretroviral therapy regimens have been effective in dramatically decreasing HIV-related morbidity and mortality and should be considered for all HIV-infected persons who qualify for such therapy. In addition to combination therapy, the sequencing of drugs and the preservation of future treatment options are also important. Two types of combination regimens are recommended as initial therapy: INSTI-based regimens or a PI-based regimen. The goal of these regimens is to effectively reduce HIV-associated morbidity, prolong the duration and quality of survival, restore and preserve immunologic function, and prevent HIV transmission while also avoiding drug resistance [146]. A significant proportion of patients starting cART are infected with drug-resistant strains of HIV, which may lead to suboptimal virologic responses. Therefore, pretreatment genotypic resistance testing should be used to guide selection of the most optimal initial regimen [146]. Patient compliance may be improved with therapies that combine more than one drug into a single pill, making it easier for patients to comply with their medication regimen.

The decision to initiate antiretroviral therapy is one that requires careful discussion with the patient, usually in consultation with an infectious disease specialist or other physician well versed in the use of cART. Physicians and patients alike should be aware of the advantages, potential toxicities, and complexity of monitoring therapy. At the present time, the most active triple-drug regimen in a previously untreated patient can be expected to reduce the viral load below detectable levels, increase CD4 counts by an average of 100–150 cells/mcL, reduce the risk of HIV-associated complications, and prolong survival. However, the ability to achieve this advantage depends on the patient's willingness to accept a complex medical regimen that requires "many pills," rigorous compliance, frequent follow-up, and moderate risk for drug toxicity. In reaching a decision it is helpful to bear in mind that prognosis is determined by viral load and the CD4 count. Patients having a viral load in excess of 60,000 copies/mL have a relatively rapid course and average survival of a little more than four years. In contrast, those with less than 6,000 copies/mL have an average survival of more than 10 years. The CD4 count is also a prognostic factor, as counts less than 350 cells/mcL indicate severe damage to immune function and corresponding risk for opportunistic infection.

According to the Panel on Antiretroviral Guidelines for Adults and Adolescents, antiretroviral therapy should be initiated in all patients with HIV infection regardless of CD4 count.

(https://clinicalinfo.hiv.gov/sites/default/files/guidelines/archive/AdultandAdolescentGL_2021_08_16.pdf. Last accessed October 25, 2022.)

Strength of Recommendation: AI (Strong recommendation based on one or more randomized trials with clinical outcomes and/or validated laboratory endpoints)

Antiretroviral therapy should be initiated immediately for all patients infected with HIV in order to reduce the risk of disease progression and limit transmission [146]. There is growing evidence that early initiation of cART is effective in preventing clinical events (e.g., non-AIDS malignancies, infection, AIDS-defining illness) regardless of pre-treatment CD4 count [147; 148]. Advances in the development of antiretroviral medications and combination tablets makes adherence to therapy more effective, more convenient, and better tolerated than regimens used in the past. Deferral of therapy may be considered in patients with high CD4 counts (e.g., more than 500 cells/mcL) if adherence will be very difficult or impossible, comorbidities complicate or prohibit antiviral therapy, or a patient is considered a long-term non-progressor [146].

For treatment-naïve patients, initial recommended therapy generally consists of two NRTIs in combination with a third active antiretroviral drug from one of three drug classes: an INSTI, an NNRTI, or a PI with a pharmacokinetic enhancer (cobicistat or ritonavir) [146]. These regimens result in maximum reduction of viral load for the longest period of time. When used as initial therapy, these regimens will achieve the goal of no detectable virus in the majority of patients after four to six months [146].

Prevention of Opportunistic Infections

Depending on the CD4 count and other risk factors, asymptomatic patients may benefit from treatment to prevent opportunistic infections. In many cases, cART is useful in the prevention and treatment of these infections. Antimicrobial prophylaxis of opportunistic infections should be conducted according to guidelines provided by the CDC, the National Institutes of Health, and the Infectious Diseases Society of America [149]. Prophylactic therapy for these conditions is strongly recommended because these infections are relatively common in patients with HIV, preventive therapy is simple and cost-effective, and efficacy has been established in clinical studies. In addition, all patients should be vaccinated with pneumococcal vaccine. Hepatitis B vaccination should be considered in patients whose serologic testing indicates susceptibility.

Nursing Management

To help a patient with HIV/AIDS adhere to health maintenance behaviors, nurses should not restrict assessments to the patient's immediate clinical status. Instead, focus on potential problems the patient may encounter during the illness. For example, it is of no value to tell patients they need regular health care follow-up if they have no insurance and no money to pay for it. In these cases, social work intervention is needed to find an alternative source of healthcare services, such as the federally funded AIDS Drug Assistance Program, which provides more than just drugs. If the patient lives alone and has no one willing to assist, he or she may need to be hospitalized if the illness progresses. As a coordinator of care, have information readily available to identify problems and plan ahead [150; 151].

Before performing any teaching, evaluate the patient's existing level of knowledge about HIV infection. Some patients may know little, whereas others may be knowledgeable. Try to assess exactly what the patient does and does not know about transmission and health-promoting behaviors instead of making any assumptions [150].

The psychologic burden to HIV disease can be overwhelming. Crisis points at which the nurse can anticipate anxiety, fear, or depression include [150]:

- Time of the initial HIV diagnosis
- Changes in treatment
- Development of new manifestations
- Recurrence of problems or relapse
- Terminal illness

Psychologic conflicts that patients commonly experience include fear of transmitting HIV to others, constant worry about developing an infection, guilt about a previous lifestyle, and changes in personal relationships. Social stressors may include disclosure of one's HIV status, stigma related to that status, insecurity about employment and insurance, and loneliness and social isolation [151].

Patient Education

Health teaching should be ongoing and repeated at frequent intervals. Patients with HIV can adopt several behaviors that not only improve immune function but also increase a sense of well-being. Teaching health maintenance for these individuals should include stress management, exercise, safer sex practices, pregnancy and HIV infection, nutrition, infection prevention (e.g., handwashing, food and water safety), skin care, routine mouth care, limiting alcohol consumption, risks of injection drug use, travel safety, importance of health care follow-up, and understanding and interpreting viral load tests and CD4 cell counts [151].

It is important to carefully explain viral load test results, because many people misunderstand the results. When successful therapy begins, the viral load drops from high levels (e.g., 750,000 copies/mL), down to what are called "undetectable" levels. Most laboratory tests can detect HIV copies down to only 400 copies/mL; an "undetectable level" indicates success of a prescribed regimen, but it does not mean that the person no longer has HIV infection. Patients with HIV infection should not interpret an "undetectable" result as cure or evidence that they are no longer at risk of spreading HIV. Emphasize that patients should still practice safer sex, avoiding sharing needles, and engage in other practices to prevent transmission [151].

Some patients may opt to try alternative or complementary treatments, including spiritual or psychologic interventions (e.g., guided imagery, mediation, faith healing), nutritional alternatives, (e.g., macrobiotic diet), drug and biologic therapies (e.g., homoeopathy, oxygen, ozone therapy), and physical therapies (e.g., acupuncture, acupressure, massage therapy). In most cases, these choices can have a positive effect on the person's emotional well-being with no adverse effects. But some approaches can be detrimental. For example, a macrobiotic diet can lead to vitamin and mineral deficiencies as well as weight loss. Herbal remedies may cause nausea, vomiting, diarrhea, or CNS depression [151].

Initiating and Maintaining Antiretroviral Therapy

One of the most important aspects of providing nursing care to patients with HIV is helping with the antiretroviral regimen. Studies suggest that, in general, patients with chronic diseases take their prescribed drugs about 50% of the time [151]. In contrast, to sustain the durability and efficacy of antiretroviral therapy, patients must maintain about a 95% compliance rate. This places high expectations on both the patient and his or her healthcare providers. Because therapy may last for many years, it is vital that the patient understand the potential benefits and drawbacks of any regimen and the potential consequences of not adhering to therapy. Benefits of cART include [151]:

- Control of HIV replication and mutation, with reduction in viral load
- Prevention of destruction of the immune system and loss of CD4 T helper cells
- Delayed progression to AIDS-defining illnesses
- Decreased risk for development of HIV resistance to drugs
- Decreased risk for drug toxicity
- Increased survival with HIV disease

Potential risks include [151]:

- Reduced quality of life from adverse drug effects and the inconvenience of a complex regimen
- A limited number of drugs available to respond to drug resistance
- Unknown long-term toxicity
- Unknown duration of the effectiveness of current therapies

The decision of whether to take cART is ultimately up to the patient. The regimen ordered is commonly complex and requires the patient to take many pills daily (although combination agents are addressing this issue), often at exactly spaced intervals and with differing requirements as to timing the pills related to food. All antiretrovirals have side effects and may

interact with numerous other drugs. These drug-drug interactions are usually not life-threatening [151].

Evaluation of a patient's ability to adhere to a prescribed drug regimen includes both subjective and objective techniques. Subjective evaluation is by self-report; patients and their care partner describe the patient's ability to take all prescribed medications. Objective analysis of the success of the plan of care is by laboratory evaluation of CD4 cell counts and viral load. "Pill counting" should only be performed if the patient wants this intervention and participates. In the past, pill counts have been used as a sort of policing activity, but today the practice is generally considered to be a waste of time, with leftover pills often simply discarded prior to the count [150].

Caring for the Patient with AIDS

In advanced HIV disease, the goal of nursing care is to diagnose and treat human responses to an actual or potential health problems related to the development of clinical manifestations and the diagnosis of AIDS. All efforts are directed at controlling manifestations. Issues that often arise include fever, fatigue, weight loss, nausea, diarrhea, dry and painful mouth, dry skin, skin lesions, pain, dyspnea, cough, impaired cognition, impaired vision, insomnia, and sexual dysfunction [32; 152]. Assessment of clinical manifestations should include both subjective and objective data. All clinical manifestations should be quantified [32; 152].

Because of the underlying immunodeficiency and impaired inflammatory responses, clinical manifestations of infection, including fever, may be greatly muted. Nonpharmacologic interventions include keeping the patient in a warm room to avoid shivering and applying a sheet and a light blanket. Avoid fanning the bed covers, exposing skin, or removing clothing, all of which might cause chilling [23]. Counterproductive treatments should be avoided, such as tepid water sponge bathing, which causes defensive vasoconstriction and has not been shown to be an effective coolant in fever [23].

Increase caloric and fluid intake by providing a plan for six feedings distributed over 24 hours and high-protein, high-calorie nutritional supplements, especially if the patient has anorexia. Provide 2–2.5 L of fluids daily. Maintain comfort and safety by providing dry clothes and bed linens made of natural fibers. Emollient creams may be useful for dry skin. Mental status should be monitored frequently, especially when the patient has a fever. Evaluate the patient's need for assistance with activities of daily living.

PRIMARY IMMUNE DEFICIENCY DISEASES

Primary immune deficiency diseases (PIDDs) are inherited genetic disorders and tend to cause chronic susceptibility to infection. There are more than 300 PIDDs, and almost all are considered rare (affecting fewer than 200,000 people in the United States) [153; 154]. They may result from altered immune signaling molecules or the complete absence of mature immune cells. For instance, X-linked severe combined immunodeficiency is caused by a mutation in a signaling receptor gene, rendering immune cells insensitive to multiple cytokines. Without the growth and activation signals delivered by cytokines, immune cell subsets, particularly T and natural killer cells, fail to develop normally.

Medical Management

Because there are many PIDDs, treatment options are targeted toward the specific immune defects [154]. Options include transplantation (e.g., bone marrow, stem cell, thymus), immunoglobulin replacement, preventive antibiotics, strategies to manage autoimmune disease, and in some cases, gene therapy.

SEPSIS

Sepsis is a systemic pathophysiologic and clinical syndrome caused by infection and manifest by signs of inflammation, host immune response, and organ dysfunction. The causes of sepsis are myriad, and the scope of illness is broad. Most cases of sepsis syndrome arise from bacterial infection, but certain viral (e.g., Ebola and other hemorrhagic fevers) and fungal (e.g., candidiasis, histoplasmosis) infections induce a sepsis syndrome as well.

Sepsis is defined clinically as a systemic inflammatory response arising from known or suspected infection, leading to widespread tissue injury and manifested by two or more of the following conditions [155; 156]:

- Fever (temperature greater than 38.3°C [100.6°F])
- Hypothermia (core temperature less than 36°C [96.8°F])
- Tachycardia (heart rate greater than 90 beats per minute in adults)
- Tachypnea (respiratory rate greater than 20 breaths per minute)
- Altered mental status
- Hyperventilation (partial pressure of carbon dioxide less than 32 mm Hg)
- Leukocytosis (leukocyte count greater than 12,000 cells per mm^3)
- Leukopenia (leukocyte count less than 4,000 cells per mm^3)

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Institute for Health and Care Excellence, risk factors for sepsis include very young (younger than 1 year) and older (older than 75 years) age; frailty; impaired immune systems and/or function; administration of chemotherapy, long-term steroids, or immunosuppressant drugs; history of surgery or other invasive procedures in the past six weeks; any breach of skin integrity; injection drug use; indwelling lines or catheters.

(https://www.nice.org.uk/guidance/ng51. Last accessed October 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Medical Management

The Society of Critical Care Medicine guideline emphasizes that sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately upon recognition. Intravenous fluid resuscitation of a patient with sepsis-induced shock (defined as tissue hypoperfusion) should be initiated as soon as the hypoperfusion is recognized (i.e., not delayed pending admission to an intensive care unit).

Intravenous antimicrobial therapy should be started as early as possible, ideally within the first hour of recognition of sepsis or septic shock. If hypotension persists after intravascular volume repletion, then vasopressors may be required to restore and maintain adequate blood pressure and tissue perfusion (goal mean arterial blood pressure ≥65 mg Hg). Such patients are considered to have the combination of vasodilation and reduced cardiac contractility, a condition best managed with a combined inotrope-vasopressor agent. In order to monitor arterial pressure accurately, it is suggested that all patients requiring vasopressors have an arterial catheter placed as soon as practical, if resources are available [157].

The Hour-1 Bundle consists of five elements that are intended to be initiated within the first hour after the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis or septic shock. The five elements are [80]:

- Measure lactate level. Re-measure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial blood pressure ≥65 mm Hg.

More than one hour may be required for resuscitation to be completed, but initiation of resuscitation and treatment should begin immediately [80]. The Hour-1 Bundle, based on the 2021 guideline, is evidence-based and intended for use by emergency department, hospital, and intensive care unit staff as a tool for improving the care of patients with sepsis and septic shock.

CONCLUSION

With knowledge of the immune system and function and the dynamic pathology that intrudes and impedes normal function, nurses are able to readily provide quality and often lifesaving actions. The awareness of pathology underlying symptoms leads to quicker reporting of changes in the patient's condition. Nurses can also perform immediate interventions based on standing orders and a recognition of appropriate actions to provide safe, quality care. This knowledge elevates technical care to professional care through use of decision-making skills built upon the knowledge of pathophysiology.

CASE STUDIES

SYSTEMIC LUPUS ERYTHEMATOSUS

Patient A is a married black woman, 47 years of age, with two children and an 18-year history of systemic lupus erythematosus. She has no known allergies. The patient takes an occasional naproxen for joint pain and antacid for heartburn but reports no other prescription or over-the-counter medications. She neither smokes nor drinks alcohol. Except for lupus, the patient's medical history is unremarkable.

Patient A is 5 feet 5 inches in height and weighs 102 pounds, a decrease in weight of 23 pounds since her last physical exam nearly one year ago. She has four brothers and three sisters. An older sister has rheumatoid arthritis, an aunt has pernicious anemia, and her deceased mother had hyperthyroidism (Graves disease).

At presentation, the patient's blood pressure is 110/70 mm Hg, heart rate is 70 beats per minute, and oral temperature is 99.9°F. Her respiration is unlabored at 15 breaths per minute.

Medical History

Eighteen years ago, Patient A complained to her primary care provider of multiple rashes that developed on her arms and legs whenever she went out into the sun. She also complained of several small patches of hair loss on her head that she attributed to stress and anxiety experienced during an airplane trip (as she has a fear of flying). Furthermore, she mentioned at that time she lacked energy, became tired very easily, and always needed to take at least one nap each day. She reported mild arthritic pain in her fingers and elbows but attributed the joint discomfort to "growing old." Her erythrocyte sedimentation rate was 25 mm/hour.

Patient A had been aware of these problems for approximately four months. A physical examination was conducted, during which the primary care provider noted multiple rash-like lesions on sun-exposed areas of the body, primarily on the arms and legs. A tissue biopsy of one of the lesions was taken and microscopic examination of the tissue revealed vasculitis (white blood cells within the walls of blood vessels). An ANA test was positive. The lungs were clear to auscultation, heart sounds were normal with a prominent S_1 and S_2, and there was no evidence of enlarged lymph nodes. Blood tests revealed a hematocrit of 23% and a red blood cell count of 3.5 million/mcL. She was also slightly jaundiced, with some yellowing within the sclera. Microscopic examination of a peripheral blood smear revealed that red blood cells were normal in shape, size, and color, ruling out iron, folate, and vitamin B12 deficiencies. The total white blood cell count was 5,500/mcL, and her pitted erythrocyte count was 350,000/mcL. Urinalysis was normal. She was placed on prednisone for two months, during which time all signs and symptoms of disease resolved.

Five years ago, Patient A presented again to her primary care provider, this time complaining of a productive cough and stiffness and pain in her hands and feet that seemed to come and go and to affect different joints (migratory polyarthritis). She was afraid that she was developing rheumatoid arthritis like her older sister.

Her blood pressure at this time was 140/90 mm Hg and heart rate 105 beats per minute, and she had a temperature of 100°F. Auscultation of the lungs revealed abnormal lung sounds, suggesting that she had bronchitis. A chest x-ray revealed mild pulmonary edema but no white blood cell infiltrates in the terminal airways. The primary care provider was concerned about susceptibility for developing pneumonia. Axillary and inguinal lymph nodes were slightly enlarged. Blood tests revealed a hematocrit of 43%, a platelet count of 330,000/mcL, and a total white blood cell count of 1,200/mcL. A urinalysis was essentially normal.

The patient was given a 10-day course of antibiotic therapy to prevent pneumonia and placed on prednisone again. All signs and symptoms resolved within three months.

Today, Patient A returns to her primary care provider complaining of fatigue, anorexia, weight loss, and significant swelling in the abdomen, face, and ankles. The primary care provider notes that a "butterfly-shaped" rash is present across the bridge of her nose and cheeks. Blood tests reveal a hematocrit of 24%. The white blood cell count is 2,400/mcL. A dipstick examination of the urine reveals an abnormal protein concentration, and microscopy shows the presence of significant numbers of red and white blood cells. A 24-hour urine protein collection reveals excretion of 2.5 g protein/24 hours.

Study Questions

1. What is the relevance of the current information to her disease?
2. What is the significance of the patient's family history?
3. Explain the pathophysiology that underlies hair loss in this patient and the relevance of the abnormal erythrocyte sedimentation rate.
4. What might have caused the lack of energy in this patient, and what type of tests might be ordered to support this conclusion?
5. Vasculitis in lupus results from the trapping of antigen-antibody complexes in blood vessel walls followed by an intense inflammatory response to the immune complexes. Why is prednisone effective in relieving vasculitis?
6. What is the most likely cause of jaundice in this patient?
7. What is the pathophysiology that underlies lymph node enlargement in this patient?
8. Which of the three blood test results would be of most concern? Give a likely cause for the abnormality.
9. The patient's white blood cell differential was 75% neutrophils, 15% lymphocytes, 5% monocyte/macrophages, 4% eosinophils, and 1% basophils. Which one of these five white blood cell types has been specifically targeted by the patient's immune system?
10. Give a reasonable explanation for the cause of tachycardia and elevated blood pressure in this patient.
11. Patients with systemic lupus erythematosus should receive an influenza vaccination every year and a pneumococcal vaccination every five years. Why?
12. Why is hypocomplementemia consistent with a diagnosis of systemic lupus erythematosus?

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

A white man, 32 years of age, presents to the emergency department with a fever of 102.5°F. He was diagnosed with HIV infection approximately three years previously, when he presented to his primary care provider with oral thrush. He was offered cART and stayed on this regimen until approximately 10 months ago, when he lost his job and insurance and could no longer pay for the drugs and discontinued all treatment. He has felt more "run down" recently.

For the past two to three weeks, he has had fever, a nonproductive cough, and shortness of breath with mild exertion, such as when cleaning his house. On examination, his blood pressure is 134/82 mm Hg, pulse 110 beats per minute, and respiratory rate 28 breaths per minute. His oxygen saturation on room air at rest is 89% but drops to 80% when he walks 100 feet, and his breathing becomes quite labored. His lungs are clear to auscultation, but white patches cover his buccal mucosa. Otherwise, his examination is unremarkable. Laboratory testing shows a leukocyte count of 2,800 cells/mcL. Serum lactic (acid) dehydrogenase is 540 IU/L.

Study Questions

1. What is the most likely diagnosis?
2. What is your next step?
3. What other diagnoses should be considered?

IMMUNE THROMBOCYTOPENIC PURPURA

A Hispanic woman, 26 years of age, presents to the emergency department on a Saturday afternoon with complaints of bleeding from her nose and mouth since the previous night. She also noticed small, reddish spots on her lower extremities when she got out of bed in the morning. She denies fever, chills, nausea, vomiting, abdominal pain, or joint pain. The patient reports she had developed an upper respiratory infection two weeks prior to the visit, but the infection has now resolved. She denies significant medical problems. Her menses have been normal, and her last menstrual period was approximately two weeks ago. She denies excessive bleeding in the past. Prior to this episode, she never had epistaxis, easy bruisability, or bleeding into her joints. There is no family history of abnormal bleeding. The patient does not take any medications.

On examination, the patient is alert, oriented, and somewhat anxious. Her blood pressure is 110/70 mm Hg, her heart rate is 90 beats per minute, and she is afebrile. No pallor or jaundice is noted. There is bright red oozing from the nose and the gingiva. Skin examination reveals multiple 1-mm flat, reddish spots on her lower extremities. The rest of the examination is normal. There is no lymphadenopathy or hepatosplenomegaly. Her complete blood count is normal, except for a platelet count of 18,000/mcL. Prothrombin time and partial thromboplastin time are normal.

Study Questions

1. What is your most likely diagnosis?
2. What is the best initial treatment?

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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