**INTRODUCTION**

A vigilant immune system is necessary for the survival of all human beings, playing multiple and complex functions on a day-to-day basis. At the most basic level, our immune system is able to recognize self from foreign substances, organisms, or transplanted organs and tissues. The immune system also maintains basic vigilance over abnormal cell growth providing essential protection from tumors.

A central physiologic role of the immune system is the protection of the host from infection, a function that is essential for the survival of the critically ill patient. In addition, the immune system has the essential task, in concert with neurologic and endocrine systems, in coordinating a physiologic metabolic response, reprioritizing energy utilization, and protein anabolism and catabolism that leads to the reorganization of biologic functions necessary for the patient to survive an acute life-threatening illness. A normal immune response is vital for tissue remodeling and adequate wound healing. In essence, thus, an adequate immune response is central for the survival of all acutely ill and critically ill patients (1).

Universally, immune activation occurs in all illnesses. A physiologic immune response (also known as an inflammatory response) is conducive to survival of the patient, with the eventual resolution of the illness, adequate healing of wounds, and a restoration of normal metabolism. It is not surprising that there are instances where the immune responses are maladaptive, further aggravating the illness and even leading to the demise of the patient.

In the 1970s, it was recognized that excessive inflammatory responses (mostly of the innate immune system) in response to infections, burns, or injury, could set up severe metabolic and hemodynamic alterations associated with fever, hyperglycemia, metabolic acidosis, accumulation of lactate, hypotension, multiple organ failure and eventually death. In this model, it was predicted that the magnitude of the systemic inflammatory response was proportional to the severity of the infection or injury. Furthermore, it was thought that this early systemic inflammatory response (SIRS) would lead to a proportional compensatory anti-inflammatory response (CARS), which was proportional to the severity of the systemic inflammatory response characterized by dysfunction of adaptive immune responses, mainly observed T-lymphocyte dysfunction. T-lymphocyte dysfunction was, in turn, associated with increased susceptibility to infection by opportunistic organisms such as fungi. Accordingly, CARS could also have led to death from overwhelming infections (1,2) (Fig. 18.1).

Significant basic research, leading to multiple human observational studies, was based on understanding the sequential SIRS/CARS paradigm with an aim at identifying key triggers that led to early activation of the immune system. Clinical trials based on the premise of controlling excessive innate immune activation with the use of antibodies against cytokines such as tumor necrosis factor (TNF), or targeting toxins released by microorganisms such as endotoxin (lipopolysaccharide-LPS) uniformly failed to demonstrate a significant benefit in acutely ill/critically ill patients. Only one study utilizing activated protein C suggested a benefit, and then only in a subset of patients. However, even this failed to demonstrate a benefit in a phase IV postmarketing trial. Furthermore, in general, a focus on “enhancing” adaptive T-lymphocyte responses has also failed.

These humbling results demonstrate that the complexity of immune response is such that targeted intervention by blocking the action of a single cytokine is most probably going to fail to demonstrate clinical benefit. In this process, investigators have been forced to realize that the initial paradigm of the SIRS/CARS response, while extremely useful as a research tool, has significant flaws. Xiao et al. have demonstrated that both inflammatory and anti-inflammatory responses occur simultaneously which, in a patient that has a successful immune response, ultimately resolves. However, patients may have early severe immune dysfunction creating self-injury through uncontrolled innate immune responses—for example, excessive production of nitric oxide leading to vasodilation and hypotension—while having significant and simultaneous T-lymphocyte dysfunction. In addition, it is now recognized that “smoldering” and continued inflammation may persist for a long time leading—the so-called persistent inflammation–immunosuppression catabolism syndrome (PICS)—to prolonged illness with the ultimate demise of the patient after several months (3) (Fig. 18.2).

There is simply no “magic bullet” to normalize immune responses in the intensive care unit (ICU). A careful understanding of immune response, along with attention to detail at controlling the initial disease process and careful adherence to the prompt initiation of evidence-based therapy are all necessary as they remain the best mechanism to prevent and/or control on unregulated immune response.

**STRUCTURAL AND FUNCTIONAL ORGANIZATION OF THE IMMUNE SYSTEM**

**Innate and Adaptive Immunity**

The immune system is structurally and functionally divided into innate and adaptive immunity, which have evolved teleologically to provide sophisticated surveillance and coordinated responses (Table 18.1). Innate immunity—also called natural or native immunity—consists of cellular and biochemical defense mechanisms that are in place and are poised to respond rapidly to immune activation. There are several components of innate and primary immune responses including (a) physical and chemical barriers; (b) phagocytes (neutrophils, macrophages) and natural
Section 2  Physiology of Critical Illness

Innate immune responses are non-specific and, in acute illness, are typically activated by infections and may also be activated by tissue injury that can result from trauma, surgery, ischemia, and necrosis. Early recognition of invading organisms occurs through the recognition of pathogen-associated molecular patterns (PAMPs) by “microbial sensors” of which the best studied include the toll-like receptors (TLRs). Interestingly, TLRs also recognize molecules released from dead or dying tissues (alarmins and damage-associated molecular patterns). Thus, an immune response in response to infection shares common elements to that of immune responses induced after trauma or burns.

In contrast to innate immunity, the adaptive immune response is highly specific and is activated by exposure to infectious agents or molecules. The defining characteristics of adaptive immunity are exquisite specificity for distinct molecules and an ability to “memorize” and respond more vigorously to repeated exposure. Because of its specificity for a particular antigen, adaptive immunity is also referred to as antigen-specific immunity. Memory increases the rapidity, magnitude, and defensive capabilities with each successive exposure to a particular molecule.

### Cellular Components of the Immune Response

Two cell families compose the cells of the immune response; myeloid cells and lymphocytes. Myeloid cells constitute

<table>
<thead>
<tr>
<th>TABLE 18.1 Structural Division of Immune Responses</th>
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<tbody>
<tr>
<td><strong>Innate immune responses</strong></td>
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<tr>
<td>• First line of defense</td>
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<tr>
<td>• Nonspecific to the antigenic stimulus</td>
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<tr>
<td>• Responds to both bacterial and tissue injury alike</td>
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<td>• Provides cues to an adaptive immune response</td>
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<td><strong>Adaptive immune response</strong></td>
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<tr>
<td>• Also called antigen-specific response</td>
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<tr>
<td>• Exquisite capacity to recognize foreign antigens</td>
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<tr>
<td>• Tolerance to self (antigens)</td>
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<td>• Development of memory responses</td>
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</tbody>
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![Image 1](image1.png)

**Figure 18.1** A historic paradigm was created to depict immune activation after injury or sepsis. It was thought that initial innate inflammatory response was followed by a compensatory anti-inflammatory adaptive immune response, which was proportional to the initial innate activation. Under physiologic circumstances, both the inflammatory and anti-inflammatory responses were self-contained (blue line). However, an excessive maladaptive inflammatory response would lead to self-injury, followed by increased susceptibility to infection from an equally maladaptive anti-inflammatory response (red line). This paradigm, dominant among investigators, led to the development of multiple clinical trials aimed at curtailing innate responses and/or enhancing adaptive immunity.

![Image 2](image2.png)

**Figure 18.2** The possibility of studying the genomic response using new technologies has allowed a better understanding of the complexity of immune activation. A gargantuan effort performed by multiple centers studying the genomic response in different peripheral blood immune cells from both patients after injury and burns, as well as in normal volunteers receiving endotoxin. A virtual “genomic storm” was reported by Xiao and colleagues (2). Both innate inflammatory and adaptive anti-inflammatory responses occur simultaneously. Physiologic responses are self-contained and lead to resolution of illness (blue lines). On the other hand, maladaptive responses lead to a persistent inflammatory and immunosuppressive syndrome that is also associated with severe muscle wasting and progression to malnutrition (red lines).
the most abundant nucleated hematopoietic cell lineage in humans. Classic ontogenetic studies describe common myeloid progenitors (CMPs) eventually differentiate into three distinct mature cell lines: macrophages (derived from monocytes), dendritic cells (DCs), and granulocytes. Each of these cell lines play classic roles during immune activation directly functioning as effectors—such as in bacterial killing—while modifying immune and nonimmune physiologic functions.

Recently, an important group of mostly immature myeloid cell subpopulations have been identified playing key roles in immune responses in healthy individuals and during illness. These immature myeloid cells suppress lymphocyte function through two metabolic pathways involving the metabolism of arginine. Due to their suppressive functions, these cells are now called myeloid-derived suppressor cells (MDSCs). There are at least two subpopulations of MDSC, but it is possible there are more. MDSCs accumulate during pregnancy and appear to play an important role in preventing T-cell activation against the growing fetus. MDSCs also accumulate in certain cancers, during infection, and after physical injury (surgery or trauma) where they can cause severe immune suppression, worsening overall prognosis (4).

The main cells of adaptive immunity are lymphocytes; the two main subpopulations of which are designated B and T lymphocytes, which refer to the organs in which those cells are found to mature, bursa of Fabricius in birds (equivalent to bone marrow in mammals) and thymus, respectively. Lymphocyte responses are aided and modified in their provision of physiologic immunity by other cells, including myeloid cells (DCs, macrophages, monocytes, and others). Substances and molecules that induce specific immune responses, or are the targets of such responses, are termed antigens. There are two types of adaptive response: humoral immunity mediated by antibodies and B lymphocytes, and cell-mediated immunity, which involves T lymphocytes. The cardinal features of adaptive immune responses, besides specificity and memory, are diversity, which is the ability to respond to a large variety of antigens; specialization, considered as the optimal response for a particular antigen; self-limitation, allowing a regulated and finite immune response also known as immune homeostasis; and self-tolerance, a nonreactivity to self.

Both innate and adaptive immune responses can be divided into distinct phases: recognition of antigen, activation, and the effector phase of antigen elimination, followed by the return to homeostasis; and in the case of adaptive response, the maintenance of memory.

Lymphoid tissues are classified as generative or primary lymphoid organs, and as peripheral or secondary lymphoid organs. Primary lymphoid organs are bone marrow, where all lymphocytes arise and also where B lymphocytes mature, and the thymus, where T lymphocytes mature and reach a stage of functional competence. The peripheral lymphoid organs and tissues include lymph nodes, spleen, and the cutaneous and mucosal immune system. Specialized microenvironments within primary immune organs support immune cell growth and maturation, while secondary lymphoid organs are sites in which optimal adaptive immune responses are initiated and developed. Lymph nodes are sites of immune response to lymph-borne antigens, and the spleen is the major site of immune response to blood-borne antigens. Similarly, cutaneous and mucosal immune systems are specialized for the best response to potential antigens coming through skin and mucosal surfaces, respectively. Although some cells are permanently resident in one tissue, lymphocytes continuously “traffic” through the bloodstream and lymphatic system, from one peripheral (secondary) lymphoid tissue to another. Lymphocyte recirculation and migration to particular tissues are tightly regulated and mediated by adhesion molecules, chemokines, and their receptors, and depend on the cell maturation and activation stage.

The main cells of the immune system involved in the adaptive immune response are: antigen-specific lymphocytes, specialized antigen-presenting cells (APCs) that display antigens activate lymphocytes, and effector cells that function to eliminate antigens (microbes). Lymphocytes are exclusively capable of specifically recognizing and distinguishing different antigens; no other cell types are able to do so in our body. Lymphocytes consist of subsets that are different in their function, but are morphologically indistinguishable.

B lymphocytes are the only cells capable of producing antibodies. They recognize extracellular (soluble or cell surface) antigens and differentiate into antibody-secreting cells, thus functioning as the mediators of humoral immunity. T lymphocytes, the mediators of cellular immunity, consist of functionally distinct subpopulations. A growing complexity in the number of T-lymphocyte subpopulations is now recognized playing key distinct roles during health and disease. Attempts at understanding the role of T-lymphocyte subpopulations include identification of a functional state (naive, memory, effector cells) and phenotypic differentiation based on the presence of specific receptors. Yet other mechanisms of differentiation of T-cell subsets are that of the production of specific cytokines and telomere length. There is a significant amount of controversy in the attempts to determine the biologic roles of T-lymphocyte subsets during health and disease. Furthermore, this area of knowledge is changing rapidly as new receptors, cytokines, and functional roles are identified. To complicate things further there are significant interspecies differences including different nomenclatures.

It has emerged that there is a significant overlap between the different T-cell subpopulations suggesting a continuum of differentiation. Nevertheless, it is important to understand the historically established subpopulations, how they are identified, and the biologic roles that these can play under different circumstances. The classic classification of T cells, divides them into helper T cells, cytolytic or cytotoxic T cells (CTLs), and regulatory T cells. NK cells are a third population of lymphocytes with receptors different from those of B and T cells and with major function involving innate immunity.

The use of monoclonal antibodies has allowed the identification of unique surface proteins, which are present only in a particular cell population. These surface proteins have thus been used as their characteristic identification marker(s). The standard nomenclature for these proteins is the CD (cluster of differentiation) numerical designation that currently consists of over 350 different molecules. The majority of characterized molecules, however, are present on more than one cell population, where their presence defines maturation stage or particular effector function. The classification of lymphocytes by CD antigen expression is now widely used in clinical medicine and experimental immunology. T lymphocytes express the CD3 receptor on the cell membranes. According to the CD classification, helper T cells are defined as CD3+ and CD4+; most CTLs are CD3+ and CD8+, while regulatory
T lymphocytes are a subgroup of helper cells with an additional low expression of the CD25 activation marker—the α-chain of the surface receptor for interleukin-2 (IL-2Rα)—and are defined as CD3+, CD4+, and CD25+. B cells are characterized with the expression of CD19, while NK cells express the CD56 molecule (1).

APCs are a cell population that are specialized to capture microbial and other antigens, process and present the antigens to lymphocytes, and provide signals that stimulate the proliferation and differentiation of lymphocytes. The major type of APC is the DC, which is found under the epithelia and in most organs, where it is poised to capture antigens and transport them to peripheral lymphoid organs. There are two major subtypes of DCs: myeloid and plasmacytoid. DCs are the most potent APCs capable of stimulating “naive” T cells as they encounter antigens for the first time. Mature mononuclear phagocytes, tissue macrophages, also function as APCs in a T cell–mediated, adaptive immune response. Macrophages that have ingested microbes may activate “naive” T cells while, in turn, effector T cells may stimulate the macrophages to more efficiently kill ingested pathogens. Follicular dendritic cells (FDCs) are cells present in the lymphoid tissue that trap antigens in the complex with antibodies or complement products and display those antigens for recognition by B lymphocytes.

After being stimulated by APCs, lymphocytes differentiate into effector cells. Differentiated effector helper T cells secrete cytokines (see below: Cytokines) and interact with and activate macrophages and B lymphocytes. Effector CTLs develop granules containing proteins that kill virus-infected and transformed host (tumor) cells; B cells differentiate into plasma cells that actively synthesize and secrete antibodies. Some antigen-stimulated B and T lymphocytes differentiate into memory cells whose function is to mediate rapid and enhanced responses to second and subsequent exposures to antigens.

Cytokines

These are proteins secreted by the cells of innate and adaptive immunity that mediate many of the functions of those cells. Cytokines are produced in response to microbes and other antigens, and different cytokines stimulate diverse responses of cells involved in immunity and inflammation. In the activation phase of the adaptive immune response, cytokines stimulate growth and differentiation of lymphocytes; in the effector phase, they modulate different cells for a variety of functions including proliferation, cytotoxicity or, alternatively, downregulation.

The number of cytokines, like T-lymphocyte subpopulations, has grown significantly. In some cases, the production of a specific cytokine is characteristic of particular T-lymphocyte subsets. Thus, for example, the production of interferon gamma (IFN-γ) is characteristically generated by NK and TH1 (helper T1) T cells upon activation. In contrast, the production of IL-4 is produced by TH2 (helper T2) cells. Cytokines exhibit multiple potent biologic activities including mediating innate immunity (IL-1, IL-6, and TNF-α); cytokines that control (either stimulate or modulate) adaptive immunity (IL-2, IL-4, IL-5, and IFN-γ); and those that stimulate hematopoiesis (IL-3, IL-7, and some growth factors) among others. Although different cells produce cytokines of innate and adaptive immunity, and those cytokines act on different target cells, this distinction is not absolute because cytokines produced during such reactions often have overlapping actions (1).

Antigen Recognition and Processing

Antigen recognition is the first phase of the adaptive immune response. Antibodies, major histocompatibility complex (MHC), and T-cell antigen receptors (TCRs) are the three classes of molecules used in adaptive immunity to recognize antigens. Antibodies produced in a membrane-attached form function as B-cell receptors for antigen recognition. The interaction of antigen with membrane antibodies initiates B-cell activation and, thus, constitutes the recognition phase of the humoral immune response. B-lymphocyte differentiation, upon activation, proceeds along two pathways: one that requires stimulation by helper T lymphocytes, the T cell–dependent pathway, or a second T cell–independent pathway. The antigens recognized by B cells may be in their native, nondegraded form and not require prior processing of the antigen by other immune system cells. In order to get help from T cells, however, B cells need to internalize the membrane antibody–antigen complex, degrade protein, and display it back on the cell surface membrane in complex with the class II MHC molecule. As explained below, T cells can recognize antigens only if they are processed and presented on the membrane surface of APCs in complex with the MHC molecules. Antibodies are also produced in a secreted form by activated B cells. In the effector phase of the humoral immune response, secreted antibody binds to antigens and triggers several effector mechanisms that eliminate the antigens. Although of the same antigen specificity, membrane-bound antibodies are involved in antigen recognition and B-cell activation, while secreted antibodies are responsible for triggering the effector phase of the humoral immune response and antigen clearance.

In contrast to B cells and their secreted antibodies that can recognize soluble as well as cell-associated antigens in their native form, T cells can only recognize antigens that are displayed on other cell surfaces and are degraded into fragments by the body’s various APCs. The task of displaying (presenting) cell-associated antigens for recognition by T cells is performed by specialized proteins that are encoded by genes in a locus called the major histocompatibility complex. MHC molecules are integral components of the ligands that most T cells recognize, because the antigen receptors of T cells are actually specific for the complex of (foreign) peptide antigens and (self) MHC molecules.

MHC molecules are found on immune and nonimmune cells. There are two main types of MHC gene products: class I and class II MHC molecules, which sample different pools of protein antigens, cytosolic or intracellular antigens, and extracellular antigens that have been endocytosed, respectively. MHC class I molecules are present on virtually all nucleated cells where they display antigens to be recognized by CD8+ cytotoxic T lymphocytes. MHC class II molecules are found primarily on APCs and primarily activate CD4+ helper T cells. Once an antigen is engulfed by an APC, it is degraded to its peptide fragments. These antigen fragments are then integrated with the MHC molecule and transported to the cell membrane, where they are exposed to neighboring cells within a complex that includes either class I or class II MHC molecules. T lymphocytes subsequently recognize the MHC–antigen (MHC–Ag) complex and initiate antigenic response (1).
All T lymphocytes recognize an antigen by specific T-cell receptor (TCR) molecules expressed on their cell membrane. These TCR molecules function similarly to a lock and key with the MHC–Ag complex. Only a few T lymphocytes constituting one T-cell clone are specific for one particular antigen. In addition to T-cell receptor binding to the MHC–Ag complex, multiple membrane receptors are used in APC–T-cell interaction. Specificity of T-lymphocyte clones plays important physiologic functions. Specificity assures a graded T-cell response to infection, where upon activation, clonal expansion is sufficient to successfully eliminate the offending organism, cell, or foreign body. Typically, only one in a million T cells responds to a given antigenic stimulus.

Clonal expansion can, in fact, fail in some instances being now recognized as a major pathophysiologic mechanism in different illnesses. Toxic shock syndrome (TSS) is a severe and often fatal disease that may occur in response to an infection by Staphylococcus aureus, although it can also occur as a response to other organisms. TSS was famously described with the use of certain types of tampons (now off the market). In contrast to appropriately processed antigens that stimulate a limited number of T cells (one clone) bearing the same TCR (approximately one in a million circulating T cells), some bacterial proteins and toxins are able to stimulate T cells without first undergoing endocytosis and degradation. Those molecules, characterized as superantigens, can simultaneously stimulate T cells with different antigen specificity, and subsequently induce polyclonal activation with the extensive systemic release of cytokines. The stimulatory effect of superantigens is a consequence of direct binding to the class II MHC on APCs and the non–antigen-specific part of TCR on T cells, thus being able to activate 2% to 20% of all T cells. The massive T-cell activation results in the release of large amounts of inflammatory cytokines that induce T-cell anergy or death (apoptosis), which severely disturbs the ability of the immune system to respond appropriately to infection. As a consequence of the systemic effects of released cytokines, infected patients develop systemic effects including fever, endothelial damage, profound hypotension, disseminated intravascular coagulation, multiple organ failure, and death.

Clonal deletion and clonal inactivation are essential processes that eliminate some T-cell clones or prevent them from reacting to an antigenic stimulus. Some clones of T lymphocytes recognize self-antigens in local cells and tissues, and these need to be eliminated to avoid self-injury. Clonal deletion is a process that occurs under physiologic circumstances and is responsible for self-tolerance. However, clonal elimination may fail and is, indeed, what happens in some autoimmune diseases such as rheumatoid arthritis and possibly in inflammatory bowel disease (IBD) (1).

**Immune Effector Functions**

**Antigen Clearance and Initial Immune Activation**

Once the immune system recognizes an antigen, inflammation and clearance processes are initiated. Activation and the effector phase of the adaptive immune response are intended to eliminate antigen in the most appropriate and efficient way. For example, one set of components of the immune system is activated in response to the extracellular antigen (antibodies and helper T cells), while others are more effective in the elimination of the intracellular antigen (CTLs and NK cells). Regardless of the type of antigen, processes involved in the activation and effector phase of immune response induce changes in the surrounding tissue, defined as inflammation. The antigen clearance process is enhanced within inflamed tissues by increased vascular flow, altered vascular permeability, and the recruitment of immune cells. Those changes also produce four cardinal clinical signs of inflammation or ongoing immune response: warmth (calor), redness (rubor), swelling (tumor), and pain (dolor), often accompanied by malfunction of the involved organ (functio laesa).

Several physiologic mechanisms are involved in circulating inflammatory cell adhesion to vascular endothelium and subsequent traffic of immune cells from the circulation into tissues (diapedesis). The process of adhesion is governed by adhesion molecules such as L-selectin, LFA-1, and MAC-1 in immune cells and in endothelial cells (P-selectin, E-selectin, ICAM-1, and ICAM-2 molecules) after stimulation. Expression and function of these molecules is modulated by “early response” cytokines (TNF-α and IL-1) secreted by activated tissue macrophages and other APCs. Additionally, IL-8 production by endothelial cells and tissue fibroblasts is a major component of the chemotactic gradient facilitating neutrophil migration across the endothelial surface. Neutrophils are capable of direct recognition and phagocytosis of circulating antigens. After neutrophil phagocytosis, enzyme-laden lysosomes fuse with the antigen-containing phagosome, digesting and destroying the antigen. Neutrophils possess receptors for the Fc portion of immunoglobulins as well as receptors for complement components. Thus, opsonization or coating of antigens by immunoglobulins and complement markedly enhances phagocytic capability and antigen elimination (5).

The predominant mechanism for adequate reaction to, and rapid clearance of, extracellular antigen involves antibodies or immunoglobulins. Antibodies possess unique antigen specificity, thereby narrowing the inflammatory response to the specific antigenic target. Antibodies circulating in the bloodstream or interstitial fluid promptly recognize, and bind to, an antigen; but because antibodies do not directly perform any effector function, the elimination of antigen requires interaction of antibody with the components of innate immunity such as complement proteins or phagocytes and eosinophils. Antibody-mediated effector functions include neutralization of microbes or toxic microbial products, activation of the complement system, opsonization (coating) of antigens for enhanced phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and immediate hypersensitivity in which antibodies trigger mast cell activation.

**Antibodies**

Antibodies are highly specific to a particular antigen. The molecular site at which the antibody recognizes an antigen is called an epitope. Specificity and effector functions of antibodies depend on their basic structure. An antibody molecule has a symmetric core structure composed of two identical light chains and two identical heavy chains. Both heavy chains and light chains consist of amino terminal variable (V) regions and carboxyl terminal constant (C) regions. While light- and heavy-chain amino terminal variable regions together participate in
antigen recognition, only the constant regions of the heavy chains are involved in antibody effector functions.

Several different types of antibodies or immunoglobulins (Ig) exist and can be divided into distinct classes and subclasses on the basis of differences in the structure (heavy chain), tissue and biologic fluid distribution, functional capability, and timing of the immune response. In order from the highest to the lowest serum concentration, those classes of antibody molecules (also referred to as isotypes) are designated as IgG, IgA, IgM, IgD, and IgE.

Different classes of antibodies perform different effector functions. Among the most notable functions of immunoglobulins are opsonization and the capacity to activate complement. IgG, IgM, and IgA are also crucial for phagocytic cells to recognize an antigen (known as opsonization). Opsonization by IgG and IgM expedites the clearance of circulating antigens, whereas the secretion of IgA onto mucosal surfaces facilitates the clearance of invading organisms by mucosal surface macrophages and neutrophils. Because of its larger size, the function of IgM is confined primarily to the intravascular clearance of antigens, whereas IgG readily diffuses into the extravascular space. After being coupled with an antigen, antigen–antibody complexes—also termed immune complexes—are normally cleared by phagocytic and red blood cells. The clearance of immune complexes from the circulation is dependent on effective opsonization, binding of the immune complex–bound C3b fragment to CR1 on erythrocytes, and subsequent transport to the liver and spleen. IgD is primarily found on the surface of naive B cells where it functions as the receptor for antigen recognition; a small amount of IgD is also secreted, generally along with IgM. The physiologic function for IgD appears that of activation of basophils. In contrast to other immunoglobulin classes, once secreted, IgE is present free in the serum for a very short time, since it binds rapidly to the specific receptor on basophils, eosinophils, and mast cells. Antigen activation of cell-bound IgE results in the immediate release of various mediators, including histamine, serotonin, and leukotrienes. Although IgE is commonly connected to the allergic reactions, the physiologic function of IgE seems to be an immediate response to antigen and the induction of vascular dilation, increased vascular permeability, and the recruitment of immune cells; another important immune function of IgE is to protect the host against parasites.

The complement system is capable of generating a broad series of inflammatory actions associated with antigen clearance. These actions include lysis of cells bearing antigen–antibody complexes, opsonization of antigens, chemotaxis of inflammatory cells, and generation of anaphylactic reactions. Complement activation may be accomplished by either the classic pathway, initiated by antigen–antibody complexes, or the alternate route initiated by antigeneric protein aggregates, endotoxin, or insoluble compounds with certain surface characteristics. With sequential proteolysis of complement substrates, various complement fragments with neutrophil and eosinophil chemotactic properties, as well as vasodilatory effects, are generated that produce the previously mentioned cardinal signs of inflammation (6).

Cellular Involvement in Immune Response

The major cells involved in antigen clearance include APCs and lymphocytes, neutrophils, and various organ-specific structural cells or tissue macrophages. Although many antigens may be destroyed within mononuclear phagocytic cells by intracellular enzymes, some antigens may become sheltered within these cells. Elimination of these antigens requires additional activation from helper T cells, which predominates in the case of bacterial infection. In general, the helper population of T lymphocytes (CD4+) supports the function of mononuclear phagocytic cells and enhances antibody production by B lymphocytes, thus supporting the clearance of extracellular antigens. Activated T cells increase the secretion of cytokines that are crucial for regulation of the immune response.

On the basis of the pattern of cytokines secreted, CD4+ lymphocytes are subdivided into two major classes: Th1 or Th2. The cytokines secreted by the Th1 group of CD4+ cells, including IL-2 and IFN-γ, are potent stimulants of the cell-mediated immune response. Th2 CD4+ cells secrete cytokines such as IL-4 and IL-10 and IL-13 that stimulate humoral responses including the secretion of antibodies while exerting a regulatory role on cellular immune responses.

It is apparent that Th1 and Th2 responses are carefully orchestrated for successfully overcoming illness as could be seen in critically ill patients. A Th1 response is essential for the survival against infection, while a Th2 response prevents an excessive inflammatory response and sets the stage for healing of tissues. While understanding helper T cell responses as a dichotomous response is a significant oversimplification of immune response, it has served to understand how an imbalance between Th1 and Th2 can be a cause of illness. Thus, caution has to be exercised while interpreting the role of Th1 and Th2 cellular responses in complex processes such as seen in critically ill patients.

Increasing attention is being paid to the presence of different Th1 and Th2 subpopulations during health and disease. Predisomance (also known as polarization) of Th1 responses appear to be a causative factor in continued unabated inflammation and self-injury in patients with Crohn disease; on the other hand a predominance of Th2 responses and the subsequent regulation of Th1 functions may worsen outcomes in patients with certain cancers, HIV, and tuberculosis (7).

The CD8+ population of T lymphocytes (CTLs) is essential for combating infection generating, for example, lysis of the infected cell such as is observed during viral infections. In a carefully orchestrated process, after exposure to processed antigen, and under the influence of the lymphokines IL-2 and IFN-γ, activated CD8+ cells proliferate, synthesize, and secrete membrane attack molecules, which result in lysis of the antigen-bearing cell. Besides the important role of the T lymphocyte in clearing microbial pathogens, CTLs are crucial for recognizing and eliminating self-transformed tumor cells. Tumor cells may express new antigens, which are presented on the cell surface within class I MHC molecules antigenic complexes. When functioning adequately, recognition of tumor cells arising in tissues is considered to be an essential and, in most cases, successful mechanism that of tumor surveillance and killing.

Similar to the cell lysis by CTLs, NK cells lyse neighboring cells by secreting membrane attack molecules (perforin and granzymes). Unlike the CTL response, the NK cell lysis of antigen-bearing cells does not seem to be antigen specific. Killer lymphocytes, the third major cytolytic cell population, are coated with surface receptors for antibodies. Killer lymphocytes may localize to antigen–antibody-coated cells, where
they release their cytotoxic granules. Antibody recognition is crucial to this system, and killer lymphocyte function seems to be a component of antibody-dependent cytotoxicity.

NK cells and killer lymphocytes can be activated and made to proliferate in vitro under the influence of cytokines. These lymphokine-activated killer (LAK) cells may be reinfused into the body and have been investigated as cancer immunotherapy (8).

In addition to the primary immune APCs or professional APCs, structural cells, such as those of the endothelium, epithelium, and connective tissue, are also important to an effective immune response. Not only are these cells capable of secreting cytokines and inflammatory mediators, but after stimulation, they also express class II MHC molecules and may function in antigen presentation to T lymphocytes. Those cells, termed nonprofessional APCs, can play important physiologic roles. However, the activation of nonprofessional APCs by particular cytokines (IFN-γ) may underlie the organ dysfunction associated with chronic immune stimulation and inflammation (1).

### Additional Factors and Mediators

Multiple additional inflammatory mediators from migrating leukocytes, such as proteases, oxygen radicals, leukotrienes, platelet-activating factors are released early on upon infection or after tissue injury, expanding the local inflammatory process. Conversely, several cytokines and soluble cytokine receptors are normally present to downregulate or limit the inflammatory response. Among these “anti-inflammatory” factors are IL-4, IL-10, IL-13, transforming growth factor (TGF)-β, other growth factors, and IL-1 receptor antagonist.

### Myeloid-Derived Suppressor Cells and Arginine Metabolism

Increased numbers of myeloid cells are observed accumulating in the tumor and in lymphoid organs in patients with certain cancers. Similarly, myeloid cells accumulate rapidly in the spleen and in the circulation within hours of an injury or after surgery (9,10). These cells generally exhibit markers of immature myeloid cells and, given the appropriate growth stimuli, appear to exhibit the potential to differentiate in macrophages, granulocytes, or APCs. In cancer and after injury, immature myeloid cells are capable of suppressing T-lymphocyte function through two different enzymatic pathways that utilize arginine as a substrate; hence the name myeloid-derived suppressor cells (MDSCs). Nitric oxide synthase (iNOS) expression can be induced in myeloid cells through classic inflammatory stimuli including IL-1, TNF, and IFN-γ. Nitric oxide (NO) generated by iNOS can profoundly inhibit T-lymphocyte function. Conversely, anti-inflammatory stimuli such as IL-4, IL-13, and prostaglandin E2 (PGE2) induce arginase 1, which efficiently destroys arginine, an essential amino acid during T-lymphocyte activation. Arginine depletion inhibits T-lymphocyte function by acting on protein translation targeting the mammalian target of rapamycin (mTOR) and the general control nondepressible 2 (GCN2) serine/threonine-protein kinase (11).

Phenotypic and functional characteristics of arginine depletion have been described in T lymphocytes. Zhu et al. (4) first described these changes in cell cultures of T cells grown with limited arginine availability, demonstrating a decrease in the number of T-cell receptors on the cell membrane, an incapacity to proliferate, and a modest capacity to generate IL-2. It was later observed that expression of the ζ-chain, a peptide dimer whose concentrations significantly decrease in certain cancers and after trauma was exquisitely sensitive to arginine deprivation.

Immune suppression caused by MDSC through arginine depletion can be profound. Under physiologic circumstances, by accumulating in the placenta, arginine depletion may prevent fetal rejection. Under pathologic circumstances, MDSC may be part of an elaborate mechanism of tumor evasion, significantly worsening the prognosis of these patients. Loss of T-cell function (also known as anergy) is characteristically observed after trauma or after major surgery, and is associated with increased susceptibility to opportunistic infections such as Candida albicans and other fungal species (12).

### Metabolic Effects of Immune Responses

Cytokines released into the systemic circulation as a consequence of either localized or systemic inflammation have been directly implicated in the pathophysiologic mechanisms of the organ dysfunction associated with major trauma, sepsis, and burns. If high plasma concentrations are achieved, IL-1, TNF-α, and IL-6 have been shown to have profound effects on body metabolism and are capable of inducing hypotension, fever, and cachexia. Their functions have been implicated in the manifestations of septic shock, and their concentration correlates with mortality. In response to TNF-α, NO is produced by endothelial cells and, along with the other mediators, promotes smooth muscle relaxation and vasodilation.

### HYPERSENSITIVITY REACTIONS INCLUDING ALLERGIES

Adaptive immunity serves the important function of host defense against microbial infections. However, the immune system is also capable of causing tissue injury and disease. Hypersensitivity reactions are a group of illnesses caused by immune responses leading to tissue injury and even death. Hypersensitivity is a term that arose from the clinical observations that an individual who has been exposed to an antigen instead of developing tolerance created a detectable clinical reaction becoming “sensitized” to subsequent encounters with the antigen. A common cause of hypersensitivity diseases is failure of self-tolerance, which, under physiologic conditions, ensures that the individual’s immune system does not respond to his or her own antigens. Hypersensitivity diseases also result from uncontrolled or excessive responses against foreign antigens such as microbes and noninfectious environmental antigens (13).

Hypersensitivity diseases represent a clinically heterogeneous group of disorders that have been classified into four different types based on the nature of the abnormal immune response, the tissue injury caused, and the clinical manifestations that arise from these (Table 18.2).

### Type I Hypersensitivity

Type I hypersensitivity reaction, also called immediate hypersensitivity, is the most prevalent type of hypersensitivity diseases and is characterized clinically as an allergic reaction. Type 1 hypersensitivity occurs when the patient has become “sensitized” to an otherwise innocuous antigen (also known...
sensitivity can cause disease by three main mechanisms. Antibodies against tissue antigens observed in type II hypersensitivity are deposited in the tissues or extracellular matrix (generated in our own tissues). These antibodies cause tissue injury by recruiting and activating inflammatory cells other than IgE. Antibodies that react to an antigen can typically mediate type II hypersensitivity reactions.

Type II Hypersensitivity

Type II hypersensitivity is also mediated by antibodies other than IgE. Typical examples include asthma and allergic rhinitis.

Type III Hypersensitivity

Type III hypersensitivity is characterized by immune complex disease (antigen-antibody complex). Secondary damage occurs through deposition of immune complexes in tissues. An example of Type III hypersensitivity is serum sickness.

Type IV Hypersensitivity

Type IV hypersensitivity is delayed-type hypersensitivity. Examples include type I diabetes mellitus, rheumatoid arthritis, and inflammatory bowel disease.

3. Some antibodies to a hormone, hormone receptors, blood-clotting factors, growth factors, an enzyme, or a drug might cause disease or treatment failure by inactivating or activating vital biologic function of these molecules without inducing any inflammation and tissue damage. Diseases mediated by this mechanism include myasthenia gravis and hyperthyroidism.

Type III Hypersensitivity

Immune complex disease, or type III hypersensitivity, is caused by antibody–antigen complexes formed in tissues. In certain disease states, immune complexes may freely circulate or be deposited within tissues, stimulating inflammatory reactions throughout the body. Immune complexes easily activate and recruit neutrophils that cause tissue injury. In contrast to the type II diseases, type III hypersensitivity diseases are often systemic, and include serum sickness and systemic lupus erythematosus (SLE) among others.

Serum sickness is characterized by the formation of circulating antigen–antibody complexes 7 to 10 days after injection of an antigenic protein into the body. With systemic deposition of the immune complexes, complement is activated and edema, rash, arthralgia, and fever result. Serum sickness can be observed after treatment with antithymocyte globulin (equine or rabbit origin) or snake antivenom (equine origin).

Type IV Hypersensitivity

Tissue injury may be due to T lymphocytes that activate the effector mechanisms of delayed-type hypersensitivity (DTH) or directly kill target cells. Such conditions are type IV hypersensitivity disorders. In those diseases, tissue injury results from the products of activated macrophages, such as hydrolytic enzymes, reactive O₂ species, NO, and proinflammatory cytokines. Many organ-specific autoimmune diseases are caused by hypersensitivity reactions induced by T cells, such as insulin-dependent diabetes mellitus, multiple sclerosis, rheumatoid arthritis, contact sensitivity, and IBDs.

Immune Defects as a Cause of Critical Illness

Life-threatening diseases can also occur when the immune system is incapable of mounting an immune response rendering the patient susceptible to recurrent and often unusual infections, increased susceptibility to tumors, and impaired wound healing. Immune defects can be congenital or acquired. Congenital diseases are not frequently observed in clinical practice; nevertheless, a short review of some of the common problems is discussed below to familiarize the critical care physician of their nature. In addition, due to the specialized nature of illnesses, suggested therapies are avoided in this chapter and the reader is encouraged to seek specialized information and early consultation with clinical immunologists.

Defective Complement Response

Defects of the complement system include deficiencies of individual complement component proteins, regulatory proteins, or complement receptors. Complement component deficiencies...
may be broadly grouped into early (C1–C4) or late-component (C5–C8) deficiencies. A predisposition to Streptococcus pneumoniae and Haemophilus influenzae infections are observed in patients deficient in early complement components. In contrast to patients with late-component deficiencies, patients with early-component deficiencies possess a uniquely higher incidence of autoimmune disease, especially SLE. In these patients, it has been suggested that the complement deficiency impairs effective clearance of circulating immune complexes, predisposing to autoimmune diseases. Neisseria meningitidis infections are recognized as sequelae of late-component deficiencies.

**Complement Activation in Critical Illness**

Complement activation is a central component to the innate immune response to injury. In addition, both the alternate and classic pathways of complement activation have been shown to be activated in septic shock. Like all immune functions, complement activation plays key physiologic roles. Nevertheless, a maladaptive complement response and also be observed. For example, an exaggerated immune response associated with complement activation has been observed in patients with H1N1 pneumonia (14). Complement depletion is observed in patients with septic shock and is associated with elevation of the dimer and coagulopathy. The correlation of complement depletion and other complement abnormalities with mortalities is however unclear (15).

**Alterations in Immunoglobulin Production**

Abnormalities of immunoglobulin production manifest most commonly as deficiencies, although the excessive production of immunoglobulins occasionally results in severe sequelae, as may occur in Waldenström macroglobulinemia. Infectious consequences result from most forms of immunoglobulin deficiency. The most common adult type of primary immunoglobulin deficiency is a selective deficiency of IgA. Although IgA deficiency has been associated with recurrent infections of the paranasal sinuses, pneumonia, and Giardiasis, many of these patients remain asymptomatic. The clinical consequences of hypogammaglobulinemia are more frequent in patients with the heterogeneous disorders that compose common variable hypogammaglobulinemia. Common variable hypogammaglobulinemia includes a group of disorders characterized by low or absent serum immunoglobulin levels and clinical manifestations that may be similar to IgA deficiency. Because the infections are usually recurrent and generally responsive to treatment, these patients may present in adulthood with bronchiectasis and lung destruction. Infections with encapsulated bacteria, such as Haemophilus and Streptococcus, are especially prevalent. The most frequently diagnosed immunoglobulin deficiency pattern in these patients is a decrease in all classes of immunoglobulins (16).

Among the many disorders associated with elevated serum concentrations of immunoglobulins, diseases associated with excessive IgM production are especially notable for acute clinical sequelae. Because of their size and structure, IgM globulins possess unique properties, including cold insolubility (cryoglobulins) and the potential to greatly increase blood viscosity. Excessive IgM production may result from a response to mycoplasma and viral infections; alternatively, it can be a neoplastic-like B-lymphocyte response (Waldenström macroglobulinemia). The cold agglutinin response to infections rarely results in more than a mild hemolytic anemia, but the IgM levels associated with Waldenström macroglobulinemia may produce life-threatening consequences. Viscosity-related sequelae include confusion, coma, visual impairment, and congestive heart failure (17).

**Illnesses Associated with Impaired Neutrophil Function**

The most common abnormalities of phagocytic function are related to either an abnormal number or function of circulating neutrophils. The consequence of almost all neutrophil defects is infection, primarily bacterial and fungal, and, less commonly, viral. The incidence of infection among neutropenic patients correlates with the depression of the circulating neutrophil count and the duration of neutropenia. Neutropenia is graded based on absolute neutrophil count as mild (1,000 to 1,500 cells/μL), moderate (500 to 1,000 cells/μL), or severe (<500 cells/μL). The risk of infection increases proportionally as the circulating neutrophil count falls and is greater when the neutropenia persists over several days. Universally, patients with an absolute neutrophil count below 1,000 cells/μL have a substantially increased risk of infection over time, while serious infections are uncommon until more severe neutropenia develops with counts less than 500 cells/μL. With neutrophil counts below 100 cells/μL, the incidence of severe infection increases dramatically (1,18).

**Acquired Defects in Immune Function**

Acquired defects in lymphocyte- and macrophage-regulated immunity are the most common immunodeficiencies encountered in adults. Three major groups of disorders account for most of these disorders: acquired immunodeficiency syndrome (AIDS), lymphoid and hematologic malignancies, and iatrogenic immunosuppression. These diseases are associated with enhanced susceptibility to infections with common pathogens, as well as a unique predisposition to infections with opportunistic microorganisms.

As of 2013, some 37 million patients were living with AIDS, 1.2 million of these in the United States. HIV was identified as the cause of AIDS almost 35 years ago, spreading rapidly around the world. HIV targets CD4+ cells, eventually resulting in their depletion. Clinical manifestations of AIDS, mostly characterized by opportunistic infections and certain cancers (Kaposi sarcoma), are observed when CD4+ counts drop below 200 mm³. Other immunologic abnormalities in patients with HIV include an accumulation of MDSCs, though their clinical significance is unknown. Severe pulmonary infections, frequently by organisms such as Pneumocystis jirovecii, Listeria monocytogenes, Nocardia sp., Mycobacteria sp., Cryptococcus neoformans, and cytomegalovirus are observed. Attempts to create a successful vaccine against HIV have failed so far. However, antiretroviral therapy has significantly prolonged the life of patients with HIV effectively preventing millions of deaths worldwide (19,20).

**Iatrogenic Immune Suppression**

A large number of medications affect immune function either as a side effect (e.g., chemotherapeutic agents) or as a targeted
therapy. Chemotherapeutic agents used for the management of cancer patients may suppress the bone marrow decreasing lymphocytes and myeloid cells. Bone marrow suppression can generate a life-threatening susceptibility to infection and is also a limiting factor in aggressively treating patients with cancer (4).

Regulation of immune responses is particularly important in autoimmune diseases. With the greater knowledge of the immune system, it has become increasingly possible to provide highly targeted therapies in illnesses such as rheumatoid arthritis, lupus, IBD, and others with the use of so-called disease-modifying biologic agents. There are several major classes of biologic agents in this category, including antibodies against cytokine and depletion of B lymphocyte with anti-CD20 antibodies and the modulation of the B-cell receptor. Biologic modifiers are also used as a targeted therapy in transplanted patients to prevent organ rejection; these target T lymphocytes (21).

**Corticosteroids**

An essential response to sepsis and other acute injuries is that of the elevation of cortisol. There are multiple observations that suggest that inadequate elevations of cortisol response in critical illness can be maladaptive and are associated with poor outcomes. This is particularly important in sepsis.

Over 33 clinical trials have been performed to determine the clinical role of corticosteroids in sepsis. In addition to the endocrine role, corticosteroids also suppress immune function at multiple levels providing significant anti-inflammatory effects. A recent meta-analysis of the existing clinical trials as well as other levels of evidence suggest that careful use of corticosteroids can lead to improved outcomes in patients with septic shock. Whereas initial clinical trials suggested some efficacy of certain anti-endotoxin antibodies, studies in larger patient populations clearly demonstrated no benefit and perhaps a harmful effect; these results are not surprising, considering the complexity of the immune system regulatory mechanisms in critical illnesses.

A gargantuan effort in the past 15 years was done by multiple investigators demonstrated a "global reprioritization affecting over 80% of the cellular functions and pathways of the immune system" (2). They called these massive changes as a "genomic storm." Interestingly, there is a significant overlap and similarity between the genomic response of injury, burns, and volunteers receiving endotoxin. These findings demonstrate that innate immune responses are activated while simultaneously activating anti-inflammatory responses.

Based on these observations, investigators have begun understanding the determinants of maladaptive immune responses. As there is progressive success at managing early multiple organ failure, there are a growing number of patients who now survive the ICU. However, at least a number of these patients continue to have a subacute or chronic illness characterized by progressive loss of muscle mass, continued susceptibility to infections, pool wound healing, and eventual death. This persistent inflammation-immunosuppression catabolism syndrome appears to be our next challenge. Interestingly, the biggest determinants of poor outcomes in these patients are the continued T-cell dysfunction and the elevation in the expression of MDSCs expressing arginase. It remains to be seen whether interventions aimed at improving T-cell function and regulating MDSC activity will result in improved outcomes (23).

**IMMUNE RESPONSES IN CRITICAL ILLNESS**

Immune activation plays a central role in the survival of all critically ill patients. Our understanding of immune responses has grown significantly in the past 15 years. From the early days of critical care, it was suggested that an abnormal immune response could cause systemic illness that affected multiple organs eventually leading to their failure. Significant progress at avoiding multiple organ systems failure (MOSF) has been made in critically ill patients with trauma or after surgery, and its incidence has decreased dramatically. No single intervention is responsible for this. Rather, the benefit has occurred with simple and clear attention to detail, early recognition of any issues, the avoidance of overly aggressive iatrogenic interventions, and a progressive knowledge of the organ physiology and adaptive responses.

Multiple organ failure continues to be observed in patients with sepsis. Sepsis has been recently redefined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection." Septic shock is considered as a subset of patients with sepsis, which can be identified by persistent hypotension requiring vasopressor to maintain a MAP of at least 65 mmHg and are at substantially increased risk of mortality.

Multiple immunomodulatory agents, including cytokines, antibodies to cytokines, and soluble cytokine receptors, have been tested for the management of critical illnesses with particular interest in the management of septic shock. Whereas initial clinical trials suggested some efficacy of certain anti-endotoxin antibodies, studies in larger patient populations clearly demonstrated no benefit and perhaps a harmful effect; these results are not surprising, considering the complexity of the immune system regulatory mechanisms in critical illnesses.

**SUMMARY**

Appropriate immunologic responses are crucial to recovery from most critical illnesses. All aspects of immunity are tightly integrated, such that cell-mediated immune responses...
and humoral responses do not function as independently of each other, as was once thought. Similarly, almost all nonimmune cellular and organ functions, such as those responsible for hemodynamic stability and body metabolism, have been shown to be partially modulated by networking cytokine messages from the multiple immune system cells. The complex intercommunication among immune and nonimmune system cells manifests itself as many of the systemic symptoms commonly associated with acute illness, such as fever, hypotension, and protein depletion. Perturbation of the immune defense systems, whether on a congenital or acquired basis, complicates the recovery process and commonly prolongs otherwise curable illnesses.

A better understanding of the immune system has allowed targeted interventional approaches in autoimmune diseases. Conversely, immunotherapy involves the manipulation of the immune system at specific target levels to induce an immune response against cancer. Significant improvement in outcomes has been observed using both approaches. Significant side effects may also be present and may land the patient in the ICU. Because of the specialized nature of these new therapeutic approaches, it is strongly suggested that the intensivist consult clinical immunologists for help when these cases arise.

While targeted immune modulation has failed so far in the management of critically ill patients, progressive understanding of the pathophysiology of illnesses such as sepsis and injury allowed better control in the progression of these patients to the development of early multiple organ failure and death. Long-term survival of these patients is not possible. However, continued adaptive immune suppression associated with significant metabolic abnormalities in amino acid regulation and severe muscle loss (cachexia) occurs in the so-called persistent inflammatory immunosuppression cachexia syndrome. In the future, we expect to find immunotherapeutic approaches to overcome adaptive T-cell dysfunction and improve protein anabolism, resulting in long-lasting cure.

**Key Points**

- Activation of both inflammatory and anti-inflammatory responses occurrence is simultaneous during illness in all critically ill patients.
- A balanced/physiologic response leads to a self-limited immune response. A maladaptive/pathologic immune response can lead to organ failure and increased susceptibility to infection.
- The best mechanism to manage immune activation during critical illness is to control the illness for which the patient was admitted, paying attention to detail, following guidelines and protocols, and impeccable timing.
- Iatrogenic immune dysfunction can occur as a result of the treatment of several illnesses. Iatrogenic immune dysfunction may lead to increased susceptibility to opportunistic infections.

**References**
