How is it suppressed, and what does it mean for EMS?

The immune system is a complex yet essential system that constitutes our body’s infection defense. One of this system’s unique abilities is its constant adaptation and modification so that it continuously recognizes the world’s ever-changing bacteria, viruses, fungi, cancer cells and other organisms that attack the human body.

While these modifications are essential to continued health, improper modifications can leave the immune system attacking its own body.

The immune system’s first levels of defense are the physical barriers of the innate immune system. These include the skin, tears, and respiratory and digestive tract secretions. Should a foreign organism penetrate one of these barriers and enter the body, the innate immune system begins fighting it off by triggering inflammation and encouraging natural killer cells and macrophages to isolate the foreign antigen and kill it, a process known as phagocytosis.

The responses of the innate immune system are the same for any infectious process and are independent of any antigen. The adaptive immune response is antigen-dependent and designed to eliminate specific antigens; it develops throughout life as an individual is exposed to organisms. Antigens can be a whole cell or organism (e.g., bacteria) or may be a protein, nucleoprotein, lipid or polysaccharide within the foreign material. Once an antigen is recognized, the adaptive immune system can respond in one of two ways: humoral or cellular. Epitopes are the features of antigens that determine which immune response pathway is followed.

Both the humoral and cellular pathways rely on lymphocytes, which are the major cells of the immune system. Lymphocytes are classified as either T- or B-cells, both of which can only identify antigens. The immune system also has natural killer (NK) cells, which attack foreign organisms and abnormal cells without prior stimulation. Lymphocytes and NK cells originate in the bone marrow. B-lymphocytes and NK cells are mature when they leave the bone marrow.
meaning they are ready to provide defense for the body. T-cells leave the bone marrow not fully developed and must travel to the thymus gland to mature (Figure 1). Mature T- and B-lymphocytes and NK cells circulate constantly throughout the body in the bloodstream and lymph organs, including the spleen and lymph nodes.

T- and B-lymphocytes have different functions. B-lymphocytes are designed for easy stimulation by antigens and rapid proliferation of antibodies. T-lymphocytes can be helpers that identify different antigens and release cytokines (proteins) that stimulate the appropriate B-lymphocytes. This specification allows the immune system to trigger only the response necessary for the specific invading organism. Cytotoxic T-lymphocytes play a key role in the inflammatory response against antigens. In addition to contributing to inflammation (to isolate the antigen), cytotoxic T-lymphocytes also destroy organisms by causing cell destruction and apoptosis, or programmed cell death.

A cellular immune system response is driven via a T-lymphocyte-mediated reaction, and infected cells are attacked. During these responses, the body’s actual infected cells are targeted by T-lymphocytes and isolated and then eliminated via cytokotic T-lymphocytes. Cellular immune responses are the primary mechanisms for eliminating viruses, parasites and some bacteria. This mechanism is also the pathway by which transplanted organs are attacked.

Humoral immune responses occur from recognition of an antigen itself, sometimes before it impacts the body’s cells. In these responses, macrophages ingest the antigen and alert B-lymphocytes to release antibodies to fight off the invading antigen. Antibodies, also known as immunoglobulins (Igs), are the functional structure of the humoral immune response. Produced by B-lymphocytes and plasma cells, immunoglobulins bind to specific antigens as determined by the antigen’s epitope. There are five classes of immunoglobulins: IgG, IgA, IgM, IgE and IgD. IgE is the antibody responsible for most allergic reactions but is otherwise outside of the scope of this article.

Patients with improperly functioning immune systems are highly susceptible to attack from foreign organisms. Patients can either have an illness that impairs the immune system or be placed on medicines that inhibit its function.

**HIV**

The human immunodeficiency virus is a bloodborne infection of either the HIV-1 or HIV-2 virus. According to the CDC there are more than 1.1 million U.S. citizens with HIV, and more than 18% do not know they are infected. \(^1\) HIV-1 is much more common in the developed world than HIV-2 and is the strain on which most research is performed.

When an individual is infected with an HIV, the virus binds itself to helper T-lymphocytes. Once attached it invades the lymphocyte, replicates itself by combining its viral DNA with the cell’s DNA, and then destroys the T-lymphocyte. Untreated, the patient’s T-lymphocyte count rapidly depletes. Even with treatment the infected patient experiences chronic decreases in both helper and cytotoxic T-lymphocytes.

HIV infections have three phases: acute seroconversion, asymptomatic HIV and AIDS. Acute seroconversion occurs in the 4–11 days following exposure. During this phase infection is established and a reservoir of persistently infected cells develops. As the viral reservoir rapidly builds, the patient’s T-lymphocyte count becomes dangerously low. Over time anti-HIV antibodies develop, and the viral load stabilizes. This stabilization, occurring over several weeks to months, allows the patient’s T-lymphocyte levels to stabilize, often back to normal ranges. Once stabilized, the disease progresses into an asymptomatic HIV infection. Do not mistake this for an inability to transmit the disease, however. HIV can remain asymptomatic for years to decades, although the virus continues to replicate in the body. The rate of viral load increase is inversely linked to the T-lymphocyte count. Antiviral drugs during this time can slow the role of progression but not eliminate the disease.

HIV progression is monitored by measuring a patient’s CD4 T-lymphocyte count. Healthy individuals will have 500–2,000 cells/μL of blood. Each individual has their own baseline, so serial measurements are required to monitor changes over time. Following seroconversion, most patients have a T-lymphocyte count of less than 700 cells/μL. A count of less than 200 CD4 T-lymphocytes/μL is considered diagnostic for AIDS, the third phase of the disease. For patients with the disease, AIDS is not what ultimately kills them; rather, their lack of ability to fight infections puts them at risk for acquiring opportunistic infections they’re unable to fight as a result of the lack of T-lymphocytes.

With proper treatment, patients may not develop AIDS for years. Although some patients continue to experience T-lymphocyte count decline, some never develop AIDS and may even see their counts normalize. Expect these patients to be on both antiretroviral drugs and prophylaxis for opportunistic infections.

One common side effect of antiretroviral drugs is diarrhea. Crotelamer has been approved for management of this diarrhea provided the patient does not have a GI infection. Remember, continuous diarrhea can lead to dehydration.

A physical on a patient with HIV will reveal no specific findings characteristic of the disease. Rather, it is essential to look for signs of infection. During acute seroconversion the patient may complain of flu-like symptoms and have a fever, malaise and generalized rash. Once seroconversion is complete, the physical findings of an opportunistic infection are the only external signs a patient may be infected. \(^2\)

**Organ Transplants**

According to the Organ Procurement and Transplantation Network, more than 44,000 organ transplants occurred in the U.S. since January 2012. \(^3\) In the United States, the kidney is the most commonly transplanted organ, followed by the liver, heart and lungs. \(^4\)

Following organ transplant, the recipient is placed on immunosuppression drugs to decrease the chances of transplant rejection. With aggressive management, one-year graft (the transplanted organ) survival is over 90%. However, this high success rate comes with an increased risk for infection. \(^5\) Unfortunately, without this aggressive management, graft success is nearly impossible.

Organ transplant success began with the release of two drugs, Purinethol and azathioprine, in the early 1960s; prior to that all patients had experienced organ rejection.
rejection. After these drugs it wasn’t until the 1980s that survival increased as cyclosporines, which inhibit the function and production of T-cells, were introduced and replaced Purinethol in the two-drug combo. Then in 1994 mycophenolate mofetil was introduced and replaced azathioprine as a primary immunosuppressant. Mycophenolate (MCA) slows B- and T-cell proliferation by slowing their cell division through enzyme inhibition.

Without immediate immunosuppression and long-term management, the patient’s body will eventually reject and attack a foreign organ like any other antigen. While physicians make every effort to match organ donors and recipients as best they can, only identical twins will have identical tissue antigens. Thus most organ recipients receive organs that have different proteins (antigens). Should the recipient’s body recognize these antigens as foreign, the immune system will attack.

Immediately following an organ recipient’s surgery, immunosuppression begins. The initial immunosuppression phase typically lasts around three months, after which patient enters into their long-term immunosuppression maintenance phase. This is accomplished with the same drugs used for initial suppression, but the doses and patient’s serum levels (concentration in the blood serum) are reduced.

For the rest of a transplant recipient’s life, their immune system must remain suppressed, and they are also at risk for acute organ rejection. Inadequate immunosuppression can cause acute rejection. However, if the patient’s immunosuppressive drugs are already in their therapeutic range, increasing their doses is unlikely to help during acute rejection. Instead, corticosteroids are the primary intervention for acute rejection, as they prevent the release of macrophages and block the synthesis of helper T-cells. The net effect is a near depletion of the immune system, yet reversal of rejection in 75% of cases.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (lupus) is a multifaceted autoimmune disease that affects all organ systems. It is considered a chronic condition that has acute symptomatic flare-ups and is followed by a relapse-type period.

The specific cause of lupus is not known, but research shows a combination of immune system dysfunctions leads to the generation of autoantibodies and microvascular inflammation. Autoantibodies, antibodies that attack the body, are suspected to develop as a result of a defect in apoptosis that results in increased cell death and immune intolerance; however, this is unproven. During a lupus activation, immune antibody-antigen complexes form in the microvasculature, triggering adaptive system activation and inflammation. These complexes also become deposited along the base of the skin and kidney membranes. As tissue damage becomes more widespread, lupus can cause antibody-mediated cytotoxicity, which results in thrombocytopenia, hemolysis and organ dysfunction.

There are about 250,000 individuals with lupus in the United States. Cases may be benign for years or progress rapidly and become fatal. Cases tend to be less serious when the primary organs affected are the skin and muscle groups; it has more serious symptoms when the renal and central nervous systems are affected. Currently 10-year survival exceeds 90%.

The presentation of lupus varies widely, as all organ systems can be affected at different times. A new diagnosis will not be made by prehospital providers. Patients with a history of lupus experiencing flare-ups may complain of fatigue, mild fever, weight changes or joint discomfort. Of these, fatigue is the most common. Patients may also experience mood swings, migraines and difficulty focusing. Some may also say they notice rashes that develop when their skin is exposed to sunlight for an extended period. Patients may complain of chest pain or shortness of breath when inflammation occurs in the pulmonary system. Nausea and vomiting are common complaints during a flare-up but do not specifically indicate gastrointestinal inflammation. Physical exams are nonspecific, as complaints are often vague.

One specific physical finding of lupus is a facial rash. Inspect the face for a malar rash, an erythematous rash spreading across both cheeks and the nose. On occasion the malar rash can be slightly painful. When patients complain of rashes following sun exposure, inspect the skin for discoid lesions, which are often plaquelike lesions in the follicles. Long term, the lesions can cause scarring. On occasion oral ulcers can be noted. Nonspecific findings on the skin can include a broken mottled and erythematous pattern, Raynaud’s phenomenon, bullous lesions, purpura and urticaria. Raynaud’s phenomenon is the spontaneous excessively reduced circulation in the periphery (typically fingers or toes) during sudden exposure to cold or stress. Additionally, joints become swollen when lupus affects them; the most frequently affected are the hands and wrists, as well as the knees. Pain within the joints often seems disproportionate to the swelling.

Infections in patients with lupus are not uncommon. Patients often complain of chest pain; evaluate this carefully, as pericarditis is common and often presents with relief when the patient leans forward. Listening to heart tones may reveal a friction rub or murmur. Rales are often heard when auscultating lung sounds; this suggests pneumonia, particularly when the rales or decreased lung sounds are one-sided. Patients with lupus are medicated based on the severity of their symptoms and the organ systems affected. If only the integumentary and skeletal systems are involved, the patient may be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and low-potency immunosuppression drugs. With the more central organ systems, such as the renal, digestive, respiratory and circulatory systems, patients are likely to be on corticosteroids and immunosuppressive drugs such as azathioprine and mycophenolate mofetil.

Patient Management

These patients are likely to chronically be on drugs that minimize their infectious symptoms. Their drugs have the potential for toxicity, and multiple infections are common. Overall, these considerations create difficulty distinguishing underlying illness-related symptoms from new opportunistic infections.

These patients regularly complain of the side effects of immunosuppressive agents. Common side effects include loss of appetite, nausea and vomiting, trembling,
in the hands and feet, weakness and chills. Do not automatically assume patients with these symptoms are having side effects; be a detective and use an organ system-based approach to look for evidence of infection.

Evaluation of a potential solid organ transplant rejection requires laboratory data specific to that organ as well as ruling out other infections. Because rejection suppression is a true specialty of medicine, this management is best performed at the hospital where the transplant occurred. Anticipate that patients with solid organ transplants will want to be taken to the operating hospital; when this isn’t feasible (e.g., due to distance or illness severity) the patient will likely be transported interfacility as soon as an emergency department physician reviews and stabilizes them. Patients who have had a kidney transplant are at increased risk for urinary tract infections, lung recipients are at risk for pneumonias, and heart recipients are at risk for pneumonias, pericarditis and the rapid onset of sepsis.

Immunosuppression agents break down most of the major inherent barriers of a healthy immune system. Because of this patients constantly risk exposure to opportunistic infections. Use a thorough history and assessment to try to identify potential infection sources and affected organs. These infections generally follow one of these pathways:4

• Community-acquired infections such as colds, respiratory system infections, MRSA and pneumonias;
• Reactivation of a dormant infection, including from the donor of a transplanted organ; these infections can include herpes, parasites, hepatitis and tuberculosis;
• Epidemiologic exposure based on a patient’s habits, including travel, sexuality, workplace and animal exposure;
• Healthcare-initiated infections, especially a risk when the patient is seen by medical providers who see multiple patients in a given day;
• Travel-associated infections, especially when travel includes foreign countries.

Fever is an ominous symptom of illness in the immunocompromised patient, and at times it may be the only obvious symptom. Assume that any fever is associated with a high-risk infection and ensure safe transport to an emergency department. Even low-grade fevers are considered serious, as many of these patients are on corticosteroids, which can suppress fevers; these are not patients who should be referred to a primary care physician or urgent care.

As you look for evidence of infection within organ systems, be astute for exposures that prehospital providers can control or make worse. For example, an open wound should be cleaned with soapy water prior to transport and dirty pants may require removal, especially if a urinary or gastrointestinal infection is suspected.

Children require special consideration, especially when they are immunocompromised following a solid organ transplant. There are more than 2,000 children in the U.S. with transplanted organs, with the kidney, liver and heart the most common. As part of normal development, the immune system matures as we age. Young children have immature immune systems with greater risk for infection, and when they require organ transplants the immunosuppressive agents greatly increase their risk of infection.

Prevention is paramount when managing immunocompromised patients, as their infections are more easily prevented than eliminated. One of the most effective and important strategies for infection prevention is use of proper hand hygiene. In general, roughly 1 of 20 patients acquire an infection while hospitalized.2 Wearing gloves is not enough to prevent the spread of an infection from one patient to another. Proper hand washing—scrubbing all surfaces for 40–60 seconds—is the standard. Use enough soap to cover all of the hands’ surfaces before scrubbing and rinsing. When arriving on the scene of an ill immunocompromised patient, it is worth taking the time to ask permission and wash your hands prior to donning gloves to evaluate the patient.

Additionally, it may be beneficial when interacting with an immunocompromised patient to take a few minutes to ensure there is low risk for exposure inside the ambulance. While an ambulance should never allow these patients to be transported with other patients or extra passengers. Further, these patients must be managed with extra oral and intravenous fluids compared to healthy individuals. Don’t be surprised to find patients with neutropenia at home; their environment must be kept particularly clean and free of any plants or other materials that are bacteria-prone, their food thoroughly cooked, and clothing and sheets kept impeccably clean.