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Immune-based Therapies—What the Emergency Physician Needs to Know

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KEYWORDS
- Immunotherapy
- Autoimmune
- Monoclonal antibody
- Checkpoint inhibitor
- Immune-related adverse event

KEY POINTS
- Patients on immune-based therapies are encountered frequently in the emergency department.
- Adverse effects from immunotherapies must be considered in the differential diagnoses for acute illness, although often must be diagnoses of exclusion.
- Key considerations for patients on monoclonal antibody treatment are infusion and hypersensitivity reactions as well as infection.
- Key considerations for patients on cancer immunotherapy include immune-checkpoint inhibitor toxicity, cytokine release syndrome, and chimeric antigen receptor–T-cell therapy neurotoxicity.
- Indications for immune-based therapies continue to expand, including treatment of severe acute respiratory syndrome coronavirus 2 infection.

INTRODUCTION

Immunotherapy refers to a class of biopharmaceutical agents that act by activating or suppressing the immune system. Immunotherapy also is referred to as biologic therapy and has been applied in the treatment of autoimmune disease, malignancies, and infections. Its mechanism can range from being very targeted to very broad, leading to a spectrum of possible side effects and adverse events. Overall, immunotherapies have been effective and well tolerated, leading to exponential growth in their development and use. The cancer immunotherapy market alone generated $75 billion globally in 2019 and is projected to generate more than $143 billion in 2025. Their expanding role in the treatment of many disease processes makes it imperative to have an understanding of the mechanisms, adverse effects, and other considerations for management in the acute care setting.
MECHANISM OF ACTION

In order to understand the mechanisms of action of various immunotherapies, it is important to review the adaptive immune responses, composed of the humoral and cellular immune responses. The humoral immune response consists of antibody production by mature B lymphocytes. Each B lymphocyte expresses an immunoglobulin against exactly 1 antigen on its surface. If the B-lymphocyte immunoglobulin recognizes an antigen, it binds and becomes activated. Once activated, these B lymphocytes differentiate into various cells, including antibody-producing plasma cells and memory cells. Many antigens require costimulation by CD4+ helper T cells for the B lymphocyte to differentiate. Only with T-cell help can the B lymphocytes undergo immunoglobulin gene rearrangements to produce higher-affinity IgG antibodies. The other component of the immune system, the cellular immune response, consists of cytotoxic (CD8+) and helper (CD4+) T cells. CD8+ T cells are responsible for killing of host cells and are activated via a major histocompatibility complex (MHC) class I process. MHC class I is a molecule expressed on all nucleated cells and is responsible for presenting peptide fragments (including tumor peptides) to the CD8+ T cells to induce a cytotoxic response. CD4+ T cells are responsible for cytokine synthesis and are activated via the MHC class II process. MHC class II is a molecule expressed by antigen-presenting cells (APCs), such as dendritic cells, and is responsible for presenting phagocytosed peptide fragments to the CD4+ T cells to induce cytokine synthesis. T_{H}1 helper T cells produce cytokines that promote cell-mediated immunity (like interleukin [IL]-2, interferon [IFN]-γ, and tumor necrosis factor α), and T_{H}2 helper T cells secrete B-cell stimulatory cytokines (like IL-4, IL-5, and IL-10) to help differentiate and proliferate plasma cells. In order for these T cells to become activated (to proliferate and differentiate), they require binding of the antigen-MHC complex by the T-cell receptor (TCR) and binding of a costimulatory molecule (CD28) on the T cell to its B7 ligand (CD80/86) on the APC. Without this costimulation, tolerance to the antigen develops.

The activity of the immune system is regulated by complex pathways. If the immune system is overactive, autoimmune conditions develop. If underactive or evaded, tumors can grow. Some of the mechanisms by which tumors evade the immune system include the loss of MHC class I expression, manipulation of cytokines that inhibit cytotoxic T-cell function and suppress proliferation of CD4+ and CD8+ T cells (secretion of IL-6 and IL-10 and consumption of IL-2), and up-regulated expression of immune checkpoint molecules, such as programmed cell death 1 receptor (PD-1) and programmed cell death ligand 1 (PD-L1).

Immunotherapy is defined as treatments designed to augment, reestablish, or suppress the immune system’s ability to prevent and fight disease. These treatments can be accomplished through passive or active immune mechanisms.

Passive immunotherapy includes agents that mediate tumor killing and consists of monoclonal antibody (mAb) administration and adoptive immunotherapy. mAbs, such as rituximab or alemtuzumab, are selective, minimally toxic, and easily mass produced. They can block a target protein’s function, trigger downstream signaling of target proteins, or deliver conjugated toxins to cells that express target proteins. Adoptive immunotherapy is the passive administration of cells with antitumor activity to the patient. It can take the form of tumor-infiltrating lymphocytes (TILs), modified TCR therapy, and chimeric antigen receptor (CAR)–T cells. TILs are lymphocytes that are isolated from tumor specimens or blood, expanded ex vivo in the presence of IL-2, and administered back to the patient (often after chemotherapy or radiation). In modified TCR therapy, T cells are transduced with a retrovirus that encodes for
TCRs that already recognize the cancer antigens. CAR–T-cell therapy consists of an infusion of T cells with a fusion molecule (intracellular TCR fused to the antigen-binding domain of a B-cell receptor)\(^9\) that recognizes tumor cells with tumor-specific antigens and attack independently of MHC recognition.

Active immunotherapy is the delivery of materials to augment and elicit an immune response. Active immunotherapy can be either specific or nonspecific. Specific active immunotherapy consists of vaccines that initiate and augment an immune response to a specific antigen.\(^9\) They can be tumor-specific peptide or protein antigens, autologous tumor cells (tumor is harvested, altered to be more immunogenic, irradiated, and returned to patient to stimulate a tumor-specific immune response), allogenic vaccines, and APC vaccines. Nonspecific active immunotherapy consists of immunomodulators that augment a preexisting immune response to an antigen. These include checkpoint inhibition and cytokines.

Checkpoint inhibitors interrupt negative feedback loops and re-engage an immune response. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is expressed by activated T cells, which competes with CD28 for B7 ligands on APCs.\(^10\) By delivering mAbs that bind to CTLA-4 and prevent it from binding to B7, the binding of CD28 to B7 (costimulation) increases, and T-cell responses are enhanced. PD-1 is a receptor expressed on the surface of activated mature T cells, B cells, and other cells. Binding of PD-1 to its ligand, PD-L1, suppresses T-cell function. This helps prevent autoimmune disorders, but some cancers use aberrant expression of PD-L1 to evade immune attack.\(^11\) Delivering anti–PD-1 or anti–PD-L1 antibodies can interrupt this T-cell suppression and restore T-cell function, allowing enhanced antitumor activity.

Cytokine therapy includes IFNs and ILs. IFNs (IFN-\(\alpha\), IFN-\(\beta\), and IFN-\(\gamma\)) increase MHC/antigen presentation and enhance antibody-dependent cell-mediated cytotoxicity. ILs either can enhance or suppress immune function. IL-2, for instance, is required for the differentiation and proliferation of activated T cells, and high-dose IL-2 promotes cytotoxic T-cell activity.\(^9\) IL-2 therapy, however, carries substantial toxicity because it is not specific against tumor only.

**MONOCLONAL ANTIBODIES FOR AUTOIMMUNE DISEASES**

The treatment of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, inflammatory bowel disease, and psoriasis, was transformed with the advent of mAb therapy. The first mAb therapy was approved for use in 1986,\(^12\) and, since then, the engineering of antibody therapies has evolved greatly. Many of the current targeted mAbs have minimal adverse effects because they have been engineered to be so highly specific. The applications of mABs also have expanded significantly to include oncologic, infectious disease, organ transplant, allergic, and neurologic indications.

Adverse effects from these targeted therapies may precipitate a visit to the emergency department (ED) during or immediately after infusion. Adverse effects include nausea, dizziness, palpitations, and headache as well as serious hypersensitivity, anaphylaxis reactions, and serum sickness.\(^13\)–\(^15\) Acute reactions occur within 24 hours but occur most often within 10 minutes to 4 hours from the initiation of infusion.\(^16,17\) Treatment of mild to moderate infusion-related reactions is supportive, and patients generally can be discharged home after a period of observation.\(^14\) Delayed reactions manifest as serum sickness-like reactions or type IV hypersensitivity (cell-mediated) mucocutaneous reactions. Serum sickness reactions typically begin 5 days to 7 days after the infusion and may mimic infection and sepsis.\(^18\) From the standpoint of ED management, serum sickness should be a diagnosis of exclusion while infection
and other causes on the differential are investigated. The type IV cell-mediated reactions occur between 12 hours and several weeks from the infusion and range from mild maculopapular rash and erythema multiforme to the more serious severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS/TEN overlap syndrome, and drug reaction with eosinophilia and systemic symptoms. Patients experiencing these adverse reactions may experience distress and fear that they cannot continue receiving the inciting therapy; however, they can be reassured that, in most patients, treatment may continue under the guidance of their ordering physician with premedication, adjusted infusion rates, and desensitization.

The other relevant adverse effect of mAB therapy to be considered in the ED is reactivation or increased susceptibility of new infection with rare serious pathogens, including tuberculosis, other mycobacterial infections, herpes simplex virus, varicella zoster virus, hepatitis C, Pneumocystis jirovecii, cytomegalovirus, and Epstein-Barr virus. Progressive multifocal leukoencephalopathy due to the John Cunningham (JC) virus also may be triggered by mAB therapy. These infectious complications should be considered in any patient who has undergone recent therapy with mABs.

CANCER IMMUNOTHERAPY

Cancer immunotherapy is evolving rapidly as the most innovative application of immune system-based therapies. As with other immunotherapies, a patient’s innate immune system mechanisms are manipulated to act against the target, such as tumor cells or proteins. Multiple mechanisms are employed, including mAB treatment, immune checkpoint inhibition, adoptive cell therapy, and cancer vaccines. They are given as single-therapy treatment or in combination with each other or with traditional cytotoxic chemotherapy, radiation, and/or surgery. In general, this class of cancer treatment has been shown to be well tolerated and provide durable long-term survival for melanoma, lung cancer, and colon cancer. Even so, they are not without adverse effects that prompt ED visits during the acute phase of treatment. A majority of adverse events occur within 6 months of treatment, but long-term effects also should be considered in the ED setting for patients who have undergone immunotherapy treatments up to 2 years prior. A key clinical consideration for those caring for oncology patients in the modern era is recognition of the difference between immunotherapy and traditional chemotherapy. Side effects and complications manifest differently from those in traditional chemotherapy and are referred to as immune-related adverse events (IRAEs).

IFN and IL therapies are used to treat metastatic melanoma and solid tumor malignancies, such as renal cell and non–small cell lung cancer. High-dose IL-2 has been administered in the inpatient setting because it creates a marked systemic inflammatory response, but, because of its high toxicity and low rate of sustained remissions, the application of high-dose IL-2 is decreasing in favor of the recently developed checkpoint inhibitor therapies.

T-cell activation has become a cornerstone of modern cancer immunotherapy. There are 3 main categories or approaches to T-cell immunotherapy: immune checkpoint blockade, adoptive cellular therapy, and cancer vaccines.

Immune checkpoint therapy currently is the most commonly applied type of T-cell immunotherapy. This treatment modality activates the patient’s immune response by inhibiting negative T-cell–regulating molecules—checkpoint molecules that normally serve to limit hyperactivation of the immune system. mAbs are targeted specifically at checkpoint molecules—CTLA-4, PD-1, or PD-L1. Box 1 lists the US Food and
Drug Administration (FDA)-approved checkpoint inhibitor immunotherapies available as of 2021.

T cells interact with tissues throughout the body, leading to the potential for checkpoint inhibitor toxicity to affect any system. The effects tend to be autoimmune/inflammatory in nature, for example, dermatitis, pneumonitis, or colitis. The severity of toxicity also may range from very mild to life-threatening. Box 2 is a comprehensive listing of IRAEs in patients with cancer treated with immune checkpoint inhibitors. The ED approach to cancer patients on checkpoint inhibitors is challenging because of the variable timing, severity, and vague or nonspecific presentations. Severe IRAEs also can mimic life-threatening disease processes, such as pneumonitis presenting like pneumonia or congestive heart failure.

CAR–T-cell therapy has been approved for use in patients with relapsed or refractory large B-cell lymphoma. It is known to have major side effects systemically with cytokine release syndrome (CRS) as well as CAR–T-cell–associated neurotoxicity, which generally occur early after infusion. Late toxicities of CAR–T-cell therapy include cytopenias and B-cell aplasia. CAR–T-cell therapy traditionally is administered in an inpatient, closely monitored setting, but an increasing number of cancer centers are beginning to administer CAR–T-cell therapy in the outpatient setting. CRS affects up to 90% of patients receiving this therapy and can be severe in 11% to 30%, requiring vasopressors and/or ventilation for supportive care. It is marked by a systemic inflammatory response with high cytokine levels (IL-6, IFN-γ, and others). Clinical symptoms range from mild fever and flulike symptoms to hypotension, hypoxia, and organ injury. In addition to supportive care, patients with high-grade CRS may be treated with an antibody that targets the IL-6 receptor, such as tocilizumab. Administration of this treatment must be in conjunction with oncology and intensive care specialists. CAR–T-cell–associated neurotoxicity, also known as immune effector cell-associated neurotoxicity syndrome (ICANS) and previously known as CAR–T-cell–related encephalopathy syndrome, is the second most common acute toxicity of CAR–T-cell therapy, occurring either concurrently with CRS or after CRS has subsided. It presents with symptoms of toxic encephalopathy, beginning with word-finding difficulty, aphasia, and confusion and can progress to depressed level of consciousness, seizures, coma, and cerebral edema. The pathophysiology of the toxicity is actively being researched, and, currently, treatment involves supportive care with the use of corticosteroids in high-grade cases. Consensus guidelines for grading and treatment of both CRS and ICANS were developed by the American Society for Transplantation and Cellular Therapy in 2018.
| Organ-based classification of immune-related adverse events in patients with cancer treated with immune checkpoint inhibitors |
|---------------------------------------------------------------|
| **Cardiac**                                                   |
| • Myocarditis<sup>a</sup>                               |
|   o Autoimmune myocarditis                                 |
|   o Myocardial fibrosis                                    |
| • Pericarditis                                               |
|   o Autoimmune pericarditis                                 |
|   o Pericardial effusion                                    |
|   o Pericardial tamponade                                   |
| **Dermatologic**                                            |
| • Alopecia areata/universalis                              |
| • Dermatitis herpetiformis                                 |
| • Erythema multiforme                                       |
| • Granuloma annulare                                        |
| • Lichen planopilaris/planus/lichenoid dermatitis           |
| • Panniculitis/erythema nodosum                             |
| • Pemphigoid/pemphigus                                      |
| • Psoriasis                                                 |
| • Pyoderma gangrenosum                                      |
| • Sweet syndrome                                            |
| • Vitiligo<sup>a</sup>                                       |
| **Endocrine**                                               |
| • Adrenalitis<sup>a</sup>                                   |
|   o Adrenal insufficiency                                   |
|   o Cortisol deficiency                                     |
|   o Hypercortisolism                                        |
|   o Hypoadrenalism                                          |
|   o Isolated adrenocorticotropic hormone deficiency         |
| • Autoimmune diabetes mellitus                             |
| • Hyperparathyroidism                                       |
| • Hypogonadism                                              |
| • Hypophysitis<sup>a</sup>                                 |
|   o Autoimmune hypophysitis                                 |
|   o Hypopituitarism                                         |
|   o Pan-hypopituitarism                                     |
| • Thyroiditis<sup>a</sup>                                   |
|   o Autoimmune thyroiditis                                  |
|   o Hyperthyroidism                                         |
|   o Hypothyroidism                                          |
|   o Graves disease                                          |
|   o Thyrotoxicosis                                          |
| **Gastrointestinal**                                        |
| • Enterocolitis<sup>a</sup>                                 |
|   o Ileitis                                                  |
|   o Ileocolitis                                             |
|   o Ischemic colitis                                        |
|   o Microscopic colitis                                     |
|   o Ulcerative colitis                                      |
| • Hepatitis<sup>a</sup>                                     |
|   o Autoimmune hepatitis                                    |
|   o Eosinophilic hepatitis                                  |
| • Lymphocytic gastritis                                     |
| • Pancreatitis                                              |
| **Hematological**                                           |
| • Aplastic anemia/pure red cell aplasia                      |
• Autoimmune hemolytic anemia
• Autoimmune neutropenia
• Hemophagocytic lymphohistiocytosis
• Immune thrombocytopenic purpura

Muscular
• Myalgia
• Myositis
  • Antisynthetase syndrome
  • Bulbar myopathy
  • Dermatomyositis
  • Diaphragmatic lymphocytic polymyositis
  • Necrotizing myopathy
  • Orbital myositis

Neurologic
• Aseptic meningitis
• Encephalitis
• Cranial nerve involvement
  • Bilateral hearing loss
  • Facial palsy
  • Oculomotor paresis
• Motor neuropathy
  • Acute generalized motor neuropathy
  • Multifocal motor neuronopathy
• Myasthenia gravis
• Neuromyelitis optica spectrum disorders
  • Optic neuritis
  • Transverse myelitis
• Polyneuropathies
  • Axonal sensory motor polyneuropathy
  • Multiplex mononeuritis
  • Peripheral sensory neuropathy
• Polyradiculopathies
  • Chronic inflammatory demyelinating polyneuropathy
  • Guillain-Barré syndrome

Ocular
• Conjunctivitis
• Episcleritis/scleritis
• Orbital inflammation
• Uveitis
  • Anterior uveitis
  • Chorioretinopathy
  • Iridocyclitis/iritis
  • Panuveitis
  • Posterior uveitis
• Vogt-Koyanagi-Harada syndrome

Pulmonary
• Interstitial lung disease
  • Alveolitis
  • Organizing pneumonia
  • Pneumonitis
  • Pulmonary fibrosis
  • Pulmonary hemorrhage

Renal
• Acute tubulointerstitial nephritis/renal tubular acidosis
• Glomerulonephritis

Skeletal
• Arthralgia/polyarthralgia
Since December 2019, the world has been battling a novel viral infection caused by the severe acute respiratory syndrome (SARS)–coronavirus (CoV)-2, which leads to the development of the clinical syndrome, known as COVID-19. As of late summer 2021, there were more than 223 million confirmed cases and 4.6 million documented deaths globally.\textsuperscript{28} Cases range from asymptomatic to severe, with many deaths related to progression to severe respiratory failure, acute respiratory distress syndrome (ARDS), and multiorgan failure. The impact of COVID-19 has been profound, prompting a worldwide effort to understand the disease and develop effective treatments and vaccination. Understanding the immunopathogenesis of SARS–CoV-2 has allowed for the opportunity to utilize immunotherapies to target specific immune responses to assist with the management of patients with COVID-19, especially in those with severe disease.

The pathogenesis of viral infection involves first stimulating the innate immune cells to recognize the molecular pattern of the pathogen. The innate immune system consists of cytokine and chemokine of ILs, IFNs, and chemoattractant to activate a response from neutrophils, macrophages, and monocytes to recognize and eliminate...
the pathogen. Failure to eliminate the virus at this step leads to activation of the adaptive immune system and lymphocyte response. Dysregulation of the immune response can lead to the host’s failure to battle a viral infection. SARS–CoV-2 has been noted to be particularly virulent in many people, leading to critical illness and death.29 The severity of disease presentation is thought to be a result of over-activation of the innate and suppression of the adaptive immune systems.30

Based on the available literature, there are several proposed mechanisms leading to the immune system dysregulation. The main causes that have been identified and discussed include host immune system evasion, lymphopenia, T-cell exhaustion, and cytokine storm. These proposed causes often overlap and perpetuate the dysregulation noted in SARS–CoV-2 infections.

Similar to its viral predecessors, SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, SARS–CoV-2 has mechanisms that attempt to evade the host immune detection system.31 The innate immune response consists of a complicated cascade of receptor presentations, chemokine expression, and pathway activations in an attempt to recognize and eliminate a new pathogen. Type I INF is considered part of that first line of defense by attempting to suppress viral replication and spread. SARS–CoV-2 evades the innate immunity by antagonizing type I INF, suppressing its response and subsequent cascade of events to support the host’s immune system. Evasion of the host’s innate immune system leads to immunosuppression and unchecked viral replication.

This unchecked viremia progresses to an exaggerated inflammatory response and aggressive production of cytokines, leading to a cytokine storm. As a result of the infection, the body produces high levels of cytokines, leading to influx of immune cells, especially monocytes, macrophages, and neutrophils. These inflammatory cells perpetuate the response by continued and amplified secretion of proinflammatory cytokines, such as IL-2, IL-6, IL-10, and TNF-α. These markers in particular, have been associated with disease severity and specifically cytokine storm. This leads to lung-tissue damage, edema, alveoli fibrosis, and inflammatory exudate, ultimately causing ARDS. The cytokine storm also is associated with development of multiorgan failure.

Along with detection evasion and cytokine storm, SARS–CoV-2 also has affected the adaptive immunity by causing immunosuppression of lymphocytes, affecting CD8+ cells primarily. Lymphopenia has been a hallmark of the clinical presentation of COVID-19 patients, secondary to the dysfunction and exhaustion of T-cells. It is believed that the SARS-CoV-2 virus can infect the T cell directly by invading via angiotensin-converting enzyme 2 receptors, the same receptors that are used to invade the host through respiratory epithelial cells. Additionally, it is believed that the cytokine storm, in particular, elevated levels of IL-2 and IL-6, cause inflammatory dysfunction of T cells. Finally, COVID-19 results in T-cell exhaustion. Studies have found that both CD4+ and CD8+ T cells have increased expression of PD-1 and T-cell immunoglobulin and mucin domain 3 (Tim-3), which are markers for T-cell exhaustion. Expression of PD-1 and Tim-3 were noted to correlate with severity of the disease presentation.

Antivirals along with several immunotherapies are being used in an attempt to treat SARS–CoV-2 infections. These therapies are geared toward targeting the pathways, cell types, cytokines, chemokines, and mechanisms identified as key players in disease progression. As discussed previously, immune system evasion, cytokine storm, lymphopenia, and T-cell exhaustion have been identified as some of the key pathways associated with severe COVID-19. Many of the biologics available specifically attempt to target these mechanisms.
Convalescent plasma was granted emergency use authorization (EUA) by the FDA in August 2020 for patients hospitalized with COVID-19 infection. Plasma from COVID-19 convalescent patients contains antibodies that are postulated to block viral infection and improve clearance of cells infected with the virus.

mAbs have developed as a promising treatment modality in COVID-19 infection. LY-CoV555, or bamlanivimab, is a neutralizing antibody against the SARS–CoV-2 receptor-binding domain that was developed from the convalescent plasma of infected patients and received EUA from the FDA in November 2020. Another EUA was declared for casirivimab/imdevimab, a combination mAB therapy (REGEN-COV), in late fall 2020. Bamlanivimab’s EUA subsequently was revoked in April 2021 and replaced with an EUA for bamlanivimab given in combination with another mAB, etesevimab. The combination therapies are hypothesized to reduce rapid mutation and viral mutant escape. Although these therapies are promising, there remains much to be learned with ongoing investigations.

Inflammatory modulators, such as the IL-6 inhibitor tocilizumab, discussed previously as a treatment of severe CAR–T-cell therapy CRS, are being investigated as a potential therapy for severe COVID-19 infection. Overall evidence appears to show treatment with tocilizumab reduced mortality and led to clinical improvement in patients with severe infection, but further studies are needed to confirm efficacy and safety for this indication.

Several other immune-based therapeutic strategies are being investigated for treatment of COVID-19. These include IFNs, intravenous immunoglobin, and stem cell therapies.

OTHER APPLICATIONS OF IMMUNE-MEDIATED DRUGS

Beyond the use of immunotherapeutics in autoimmune and oncologic conditions, immune-mediated drugs, specifically mAbs, are used for the treatment of numerous conditions. These include, but are not limited to, atopic states, infectious diseases, neurodegenerative diseases, immunosuppression, migraine headaches, hyperlipidemia, osteoporosis, hereditary conditions, and medication neutralization.

Dupilumab is an IL-4 receptor α-antagonist approved for the treatment of moderate to severe atopic dermatitis and uncontrolled asthma (through its reduction of the T_{H}2 helper T-cell inflammatory response). Omalizumab is an IgE antagonist also approved for the treatment of uncontrolled asthma and chronic idiopathic urticaria. Palivizumab is a mAB that binds to respiratory syncytial virus (RSV) and is approved for the prevention of RSV in high-risk infants. Raxibacumab and obiltoxaximab are mAbs approved for the treatment and prophylaxis of inhalational anthrax due to Bacillus anthracis spores, and bezlotoxumab is a mAB used to reduce the recurrence of Clostridium difficile infections. Ranibizumab and aflibercept are 2 vascular endothelial growth factor inhibitors approved for the treatment of diabetic macular edema, among other ocular conditions. Basiliximab is an IL-2 antagonist approved as immunosuppressive therapy after renal transplantation. Erenumab is a calcitonin gene-related peptide inhibitor approved for once-monthly subcutaneous injection to prevent migraine headaches. Alirocumab and evolocumab are 2 proprotein convertase subtilisin/kexin type 9 inhibitors approved for the reduction of low-density lipoprotein cholesterol. Denosumab is a mAB that binds to RANKL and inhibits the maturation of osteoclasts, approved for the treatment of postmenopausal women with osteoporosis at high risk of fracture. Emapalumab is a mAB that neutralizes IFN-γ and is approved for the treatment of hemophagocytic lymphohistiocytosis through its role in suppression of cytokine release. Lanadelumab is a mAB against plasma kallikrein.
approved for the prevention of hereditary angioedema.\textsuperscript{53} Idarucizumab is a mAb fragment that binds to and neutralizes dabigatran, approved to reverse the anticoagulant effects of dabigatran.\textsuperscript{54}

The indications for mAb therapies are vast. Given their widely differing mechanisms, their toxicities differ widely as well. When a patient presents to an ED, it is imperative to review the medication list and the side-effect profile of any immunologic agent prescribed, so that toxicities can be recognized and treated appropriately.

**SUMMARY**

The intersection of immunology and emergency medicine is not a simple crossroads but a complex weave of overpasses and tunnels. The array of indications for immune-based drugs is immense, and patients on these therapies are encountered daily in the ED. Recognition of the adverse effects allows for improved coordination and care for these complex patients. In addition, understanding the latest developments and indications puts a treatment team in the best position to provide the best care possible.

**CLINICS CARE POINTS**

- Immune-based therapies are wide ranging, with indications spanning chronic and acute disease, from autoimmune, to oncologic, to infectious, and more.
- mABs currently are the most common type of immune-based therapy and usually are well tolerated.
- Adverse effects of mABs include acute infusion reactions, acute and delayed hypersensitivity responses, and increased risk for severe rare infections.
- Immune checkpoint inhibitors are specific cancer mABs; their IRAEs affect all organ systems. Management is guided by severity of the symptoms.
- Immune-based therapies are actively being investigated for treatment of acute infections, such as SARS–CoV-2. Familiarity with these new treatments is critical.

**DISCLOSURE**

The authors have nothing to disclose.

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