

# An AP Perspective on Infusion Reactions in the Era of Immunotherapy

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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## Abstract

As cancer care advances, creative uses for immunotherapy continue to be developed, but it is also important to be cognizant of the risk for infusion reactions. At JADPRO Live Virtual 2021, Carrie Peterson, DNP, RN, AGNP-c, reviewed the different classes and pathophysiology of immunotherapy, how to anticipate potential infusion reactions for each class of immunotherapy, and how to identify and treat infusion reactions during infusion of immunotherapy so that patients can stay on treatment.

**A**lthough rare, infusion-related reactions to immunotherapy can lead to longer infusion times, medical interventions, hospitalizations, treatment discontinuations, and even death. According to Carrie Peterson, DNP, RN, AGNP-c, knowing how these medications work and how the body responds to these medications can be instrumental in the treatment and prevention of adverse events.

During JADPRO Live Virtual 2021, Dr. Peterson, a nurse practitioner at Dignity Health Cancer Institute at St. Joseph's Hospital and Medical Center, in Arizona, identified the different classes and pathophysiology of immunotherapy and discussed potential infusion reactions for each class of immunotherapy.

“As cancer care advances, we are seeing so many exciting, creative,

and amazing uses for immunotherapy,” said Dr. Peterson. “It's great to be mindful of how these therapies affect our patients and the potential reactions they can have. Let's keep them safe so that they can continue their treatment.”

## TYPES OF IMMUNOTHERAPY

Immunotherapy works by stimulating or suppressing the immune system to help the body fight disease, but not all immunotherapy drugs are the same. Immune checkpoint inhibitors, adoptive cell therapies, monoclonal antibodies, cancer vaccines, and immune system modulators have different mechanisms of action and are associated with different potential adverse reactions.

### Immune Checkpoint Inhibitors

Immune checkpoints are a normal part of the body's immune system

that prevent the immune response from killing healthy cells. As Dr. Peterson explained, immune checkpoints engage when T cells bind to proteins on cells, and when the checkpoint and the proteins bind together, they form an “off” switch to the T cells that prevents them from destroying cancer cells. Immune checkpoint inhibitors block the proteins from binding together, allowing the T cells to kill the cancer cells.

Types of immune checkpoint inhibitors include CTLA-4 inhibitors (e.g., ipilimumab [Yervoy]); PD-1 inhibitors (e.g., pembrolizumab [Keytruda], nivolumab [Opdivo], cemiplimab [Libtayo]); and PD-L1 inhibitors (e.g., atezolizumab [Tecentriq], avelumab [Bavencio], and durvalumab [Imfinzi]).

### **Adoptive Cell Therapies**

Adoptive cell transfer is a form of immunotherapy that utilizes the patient’s own immune cells to target and destroy cancer cells. Types of adoptive cell therapies include tumor-infiltrating lymphocytes (TILs), T-cell receptor (TCR) therapy, and chimeric antigen receptor (CAR) T-cell therapy.

### **Monoclonal Antibodies**

Antibodies are proteins produced by the immune system that target a specific foreign object called an antigen. Monoclonal antibodies are produced by clones derived from a single parent cell. They can restore, mimic, or enhance the immune system’s attack on cancer. Types of monoclonal antibodies include murine (rodent source), chimeric (both rodent and human), humanized (mostly human source), and human (entirely human source).

### **Cancer Vaccines**

Cancer vaccines can be manufactured in several ways: they can be made from a patient’s own tumor to cause an immune response against features unique to specific cancer cells; they can be made to cause an immune response to a specific antigen (tumor-associated antigens); and they can use dendritic cells to stimulate the immune system to respond to an antigen on a tumor cell.

### **Immune System Modulators**

Immune system modulators enhance the body’s immune response against cancer. Examples of this therapy include cytokines, interferons, interleu-

kins, and hematopoietic growth factors. Cytokines are proteins made by white blood cells. Interferons activate certain white blood cells (natural killer cells and dendritic cells), slow growth, and promote death of cancer cells. Interleukins such as IL-2 boost the number of white blood cells and help B cells target cancer cells. Finally, hematopoietic growth factors help with side effects from cancer treatment.

## **INFUSION REACTIONS**

An infusion-related reaction is any sign or symptom experienced by patients during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration. As Dr. Peterson explained, these are objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.

Fewer than 5% of patients receiving immunotherapy will have an infusion reaction, and many of these reactions can be predicted based on the class of agent being administered. According to Dr. Peterson, however, these reactions can cause significant distress to patients and interfere with treatment.

Immune responses can be innate, adaptive, or both (Vogel, 2010). The innate response is the body’s first line of defense: a rapid, nonspecific response that is activated by the chemical properties of an antigen.

“Innate immunity is present even before you’ve ever been exposed to the foreign substance and is not affected by exposure,” said Dr. Peterson. “An adaptive response, on the other hand, is an acquired response. It’s more specific and involves memory.”

With adaptive immunity, each successive exposure to a foreign substance increases the defensive response of your immune system. The adaptive response involves T cells, B cells, antigen-presenting cells, and antibodies (Keselowsky et al., 2020). The innate response involves macrophages, neutrophils, natural killer cells, dendritic cells, basophils, eosinophils, antimicrobial peptides, and proteins.

Infusion reactions can be antibody-mediated (e.g., anaphylaxis) or non-antibody mediated (e.g., standard infusion reactions and cytokine release syndrome).

### **Anaphylaxis**

Anaphylaxis is an acute, potentially life-threatening, generalized, or systemic allergic reaction that is mediated by the degranulation of mast cells and basophils. It is a serious allergic reaction that involves more than one organ system. As Dr. Peterson explained, anaphylaxis begins very rapidly (within minutes or hours), and symptoms may be severe or life-threatening.

The criteria for anaphylaxis are an acute onset of illness with involvement of skin/mucous membranes (hives, itching, swollen lips/tongue) and one of the following: (1) respiratory compromise (e.g., dyspnea, wheeze, stridor, hypoxemia) or (2) reduced blood pressure or signs and symptoms of end-organ dysfunction (e.g., syncope, incontinence).

“If you’ve seen anaphylaxis, you know what it looks like, and it’s very scary,” said Dr. Peterson, who also noted that premedication does not prevent anaphylaxis.

Risk factors for anaphylaxis include the following: female sex; older age; systemic mastocytosis (43% of mastocytosis patients have had at least one episode of anaphylaxis); severe, uncontrolled asthma; underlying cardiovascular and respiratory disease (COPD); preexisting allergies; previous exposure to drug; and newly diagnosed, untreated patients (Castells et al., 2020).

### **Standard Infusion Reactions**

Commonly referred to as “hypersensitivity reactions,” standard infusion reactions describe an excessive or pathogenic immune response to either foreign or self-antigens. These reactions can affect any organ system in the body, but most are mild. The signs and symptoms can mirror anaphylaxis, said Dr. Peterson, so it’s important to understand the difference between the two. Symptoms of standard infusion reactions include the following: flushing, itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, back or abdominal pain, fever and/or shaking chills, nausea/vomiting, diarrhea, skin rashes, throat tightening, hypoxia, seizures, and dizziness (Castells et al., 2020).

Risk factors for standard infusion reactions include previous allergic reactions, asthma, female sex, higher drug doses, iodine and seafood allergies, preexisting cardiac or pulmonary dysfunction,

previous exposure to the drug, concomitant  $\beta$ -adrenergic blocker therapy, and concurrent autoimmune disease.

### **Cytokine Release Syndrome**

Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. It clinically manifests when large numbers of lymphocytes and/or myeloid cells become activated and release inflammatory cytokines. This systemic inflammatory response can be triggered by CAR T-cell therapy, therapeutic antibodies, allogeneic transplant, and infections.

Signs and symptoms of CRS range from mild and flu-like (e.g., fever, fatigue, headache, cough, and shortness of breath) to life-threatening (e.g., hypotension, cytopenias, acute respiratory distress syndrome, hypoxemia, renal failure, cardiac dysfunction, and neurotoxicity).

“The key to treating these symptoms is to identify them quickly,” said Dr. Peterson. “CRS usually occurs in the first infusion and then subsides with subsequent infusions.”

The type of therapy can be a major risk for CRS as well as the severity of underlying disease (Rombouts et al., 2020). Higher disease burden at initiation of treatment is associated with greater risk of CRS, said Dr. Peterson, who noted that children are also at increased risk.

## **GRADING INFUSION REACTIONS**

Grading the severity of an infusion reaction is essential to understanding how to proceed with current and future treatment options. The Common Terminology Criteria for Adverse Events (CTCAE) is an oncology-specific grading system. According to Dr. Peterson, however, there are no standard grading criteria and grading is subjective. The interchangeable terminology of the package inserts can also make grading difficult. Determining the type of reaction can be challenging because reactions can mimic each other, Dr. Peterson added.

## **INFUSION-RELATED REACTIONS TO IMMUNE CHECKPOINT INHIBITORS**

The risk of serious infusion reactions to immune checkpoint inhibitors is low except for the PD-

L1 inhibitor avelumab. Signs and symptoms include pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Infusion-related reactions to avelumab are most common in the first four infusions, and approximately 25% of patients have a reaction (Chin et al., 2017). Patients on avelumab are usually premedicated with an H<sub>1</sub> antihistamine and acetaminophen.

### INFUSION-RELATED REACTIONS TO MONOCLONAL ANTIBODIES

The most common reaction to monoclonal antibodies is CRS, which can mimic anaphylaxis. Unlike anaphylaxis, however, CRS symptoms appear to subside with each subsequent dose. The reaction is prevalent with the first dose because the tumor burden is the highest.

#### Cetuximab

Cetuximab is a chimeric mouse/human monoclonal antibody. Reactions to cetuximab are commonly during the first infusion, and approximately 3% of patients have a severe reaction (O'Neil et al., 2007). Dr. Peterson noted that reactions vary depending on geography. In Tennessee and North Carolina, for example, the infusion reaction rate is 22%, but in the Northeast, the rate is only 1%. People in specific geographic areas may have increased exposure to mouse antigen and develop IgE antibodies against cetuximab, said Dr. Peterson.

#### Rituximab

Rituximab is a chimeric/human monoclonal antibody indicated for hematologic malignancies. The incidence of hypersensitivity reactions to rituximab is 77% with the first infusion, but by the eighth infusion, the rate decreases to 14% (Giavina-Bianchi et al., 2017). Risk factors for infusion reaction include lymphocyte count greater than 50,000 and high numbers of circulating CD20-positive cells. The most common symptoms fever, chills, rash, and nausea. Reactions typically occur within 30 to 120 minutes.

#### Trastuzumab

A humanized monoclonal antibody, trastuzumab has significantly lower rates of infusion reactions than murine and chimeric monoclonal antibodies.

Premedication is often not required. Potential symptoms include fever, chills, nausea, vomiting, headache, dizziness, dyspnea, hypotension, rash, and asthenia (Giavina-Bianchi et al., 2017).

#### Alemtuzumab

Alemtuzumab (Lemtrada) is a humanized anti-CD52 monoclonal antibody used in chronic lymphocytic leukemia. Alemtuzumab is given in fractionated doses to lessen symptoms of CRS. Although 92% of patients have an infusion-related reaction with their first doses, only 3% are serious reactions (Giavina-Bianchi et al., 2017). Dr. Peterson noted that reactions can present up to 24 hours after infusion and the most common symptoms include rash, headache, pyrexia, flushing, and nausea. Patients are premedicated with steroids, and sometimes antipyretic, H<sub>1</sub>, and H<sub>2</sub> blockers are used.

### IMMUNE SYSTEM MODULATOR INFUSION REACTIONS

Common symptoms of infusion reactions to immune system modulators are headache, fever, chills, hypotension, and bradycardia. Patients can be premedicated with antihistamines, antipyretics, antiemetics, and analgesia.

“If patients are having a problem, we stop the infusion, let them settle down, and then slow the infusion rate,” said Dr. Peterson. “That usually helps with these drugs.”

### CANCER VACCINE INFUSION REACTIONS

Sipuleucel-T (Provenge), an immunotherapy for prostate cancer, is an autologous dendritic cell vaccine that is produced by exposure and activation of the patient's peripheral blood mononuclear cells to a tumor-associated antigen. Patients receiving sipuleucel-T are premedicated with antihistamine and acetaminophen. Common symptoms of a reaction include fever, chills, respiratory events, nausea, vomiting, fatigue, hypertension, and tachycardia.

Dr. Peterson reported that 71% of patients in clinical trials had an infusion reaction, with 3% grade 3 reactions and no grade 4 or 5 reactions. Patients with underlying cardiac or pulmonary disease should be closely monitored, said Dr. Peterson.

**ADOPTIVE CELL THERAPIES  
INFUSION REACTIONS**

Reactions to adoptive cell therapies include CRS, tumor lysis syndrome, immune effector cell-associated neurotoxicity, anaphylaxis, coagulation disorders, infections, B-cell dysplasia, and hemophagocytic lymphohistiocytosis.

**TREATING INFUSION REACTIONS**

Several premedications are used to prevent infusion reactions. These include H<sub>1</sub> blockers such as Benadryl, cetirizine, and loratadine and H<sub>2</sub> blockers such as famotidine. Corticosteroids, acetaminophen, acetylsalicylic acid, and montelukast can also be used. Importantly, said Dr. Peterson, the infusion should not be started until 30 to 60 minutes after premedications have infused.

In the event of an infusion reaction, the first step is to stop the infusion and start intravenous fluids. Vital signs are taken, and the patient is assessed. The class and type of medication being infused will inform treatment of the reaction, as will previous premedications. According to Dr. Peterson, it's also important to be aware of the patient's allergies (e.g., some people are allergic to Benadryl).

Medications to treat infusion reaction include H<sub>1</sub> blockers, depending on the previous dose, pa-

tient age, and severity of the reaction. Steroids and H<sub>2</sub> blocks are also an option. Patients who need to be administered epinephrine should be watched in the emergency room in for rebound anaphylaxis (Figure 1).

“In the heat of the moment, it’s stressful,” said Dr. Peterson. “Your patient may be freaking out, but it’s very important for everybody to be calm and prepared.”

“At our institution, we have mock hypersensitivity reactions so that providers are always prepared and handle these situations professionally,” she added.

According to Dr. Peterson, the severity and nature of the reaction determine if there will be a re-challenge. After all symptoms have resolved and additional medications are given, re-challenge at a slower rate, she said. However, using the CTCAE grading scale, it is advised to not challenge for any grade 3 or above or anaphylaxis reaction. ●

**Disclosure**

The presenter had no conflicts of interest to disclose.

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DRUG	Dose	FREQUENCY	MAX DOSE	ONSET	PEAK	DURATION	Indication
Epinephrine	0.3mg IM	q 5-15 min until symptoms resolve	n/a	variable	unknown	1-4 hrs	anaphylaxis, airway obstruction
Albuterol	2.5mg - 5mg	q 20 min x 3 doses 1-4 hours		5-15 min	0.5-2 hrs	2-6 hrs	anaphylaxis, airway obstruction, wheezing, SOB
Benadryl (H1 Blocker)	12.5-50mg		100mg in single dose, max is 200 mg q day	immediate	1-2 hrs	6-8 hrs	allergic reactions
Famotidine (Pepcid) H2 blocker	20mg	q12 hrs (administer over 2 minutes)		1 hour	1-4 hrs	10-12 hrs	
Corticosteroids hydrocortizone (solucortef)	100mg - 500mg	q 6 hrs	500mg qday	variable	variable	variable	
cetirizine (Quzutti)	10mg (comparable to 50mg of benadryl)	once (administer over 2 minutes)	20mg qday	immediate	108 seconds	24 hours	itching, rash, allergic reactions

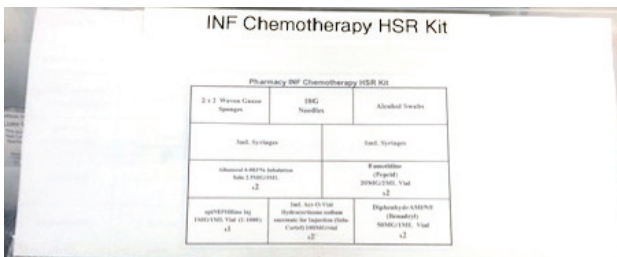


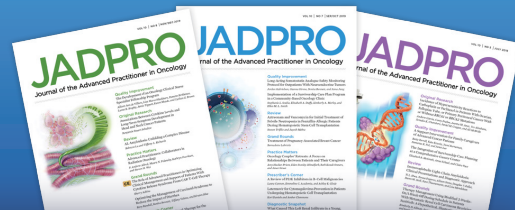
Figure 1. Infusion reaction kits

tions-to-systemic-chemotherapy?search=standard%20infusion%20reaction&source=search\_result&selectedTitle=1-150&usage\_type=default&dis%20play\_rank=1

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