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NCCN Guidelines for Patients® are developed by the National Comprehensive Cancer Network® (NCCN®)

These NCCN Guidelines for Patients are based on the NCCN Guidelines® for Management of Immunotherapy-Related Toxicities (Version 1.2020, December 16, 2019).

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NCCN Guidelines for Patients® Immunotherapy Side Effects: Immune Checkpoint Inhibitors, 2020

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# Checkpoint inhibitors and immune-related adverse events (irAEs)

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Immune checkpoint inhibitors have become the standard of care for some cancers. Like all cancer treatments, ICIs have side effects. A number of inflammatory reactions, or immune-related adverse events (irAEs), are possible.

Immune checkpoint inhibitors (ICIs) are a type of immunotherapy. Immunotherapy is a modern approach to cancer treatment that harnesses the power of your own immune system to kill cancer cells. Scientists have discovered different ways to use the immune system against cancer. In addition to ICIs, other types of immunotherapy include:

- CAR T-cell therapy
- Monoclonal antibodies
- Cancer vaccines
- Oncolytic virus therapy

ICIs are the focus of this patient guide. *NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy* is also available:

The immune system’s main job is to distinguish normal, healthy cells from abnormal cancer cells. Proteins on the surface of cancer cells—PD-L1 for example—interact with proteins on immune cells. These interactions are called immune checkpoints. The cancer cell proteins prevent attack by “blindfolding” the immune cells. ICIs remove the blindfold, allowing the immune system to see and attack cancer cells.

The two main types of ICIs currently used for cancer immunotherapy are:

- PD-1/PD-L1 inhibitors
- The CTLA-4 inhibitor ipilimumab (Yervoy®)

PD-1 inhibitors include:

- Cemiplimab (Libtayo®)
- Nivolumab (Opdivo®)
- Pembrolizumab (Keytruda®)

PD-L1 inhibitors include:

- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)
- Durvalumab (Imfinzi®)

What are irAEs?

“Boosting” the immune system with immunotherapy can cause your immune cells to attack healthy cells in the body. This results in inflammation and side effects known as immune-related adverse events (irAEs). These side effects are similar to those of autoimmune disorders, in which the immune system sees healthy cells as a threat and attacks them.
Immune-related side effects can range from mild to life-threatening. They can occur at any time during or even after treatment is over, and may affect one or more organ systems. Some side effects may worsen over the course of treatment, with each dose of immunotherapy. Most irAEs can be managed effectively if found and treated early. The side effects of ICI therapy are generally more severe when being treated with both a CTLA-4 inhibitor and a PD-1/PD-L1 inhibitor.

**How common are irAEs?**

Inflammatory skin conditions are the most common side effects of ICI therapy. Rash and itching are very common. Blisters may be a sign of a rare and severe blistering disorder. Fatigue is also very common, followed by diarrhea and inflammation of the large intestine (colitis). ICIs can also cause inflammation of the thyroid, pituitary, and adrenal glands. These hormone-related, or endocrine, irAEs are somewhat common. Inflammation of the lungs (pneumonitis) is also possible, but does not always cause symptoms. Musculoskeletal, or rheumatic, irAEs are less common. They include inflammatory forms of arthritis and muscle pain and inflammation. Rare but potentially severe side effects include those affecting the nervous system, kidneys, pancreas, heart, and eyes.

**Monitoring for irAEs**

During ICI therapy it is important to stay in close contact with the center where you are receiving treatment. Symptoms that may seem unrelated (diarrhea and shortness of breath, for example) may be signs of an irAE.

Notify all of your health care providers (especially your primary care doctor), that you are receiving, or have received, immunotherapy. You will be monitored closely to detect potential irAEs and to see how well immunotherapy is working against your cancer.

Monitoring includes having blood and other laboratory tests on a regular basis, including before each immunotherapy treatment. You can also expect to have physical exams on a regular basis. These exams will check your vital signs, including your blood oxygen level (oxygen saturation), and how well your major organ systems are working.

**Managing irAEs**

Treating irAEs is a team effort. Your cancer doctor (oncologist) and care team will work closely with specialists in the type of side effect you are experiencing.

Some irAEs affect more than one of your major body systems or functions. These “multi-system” irAEs and other hard-to-treat irAEs may require full-time (inpatient) treatment at a specialized care center.

Your health care provider may provide you with a wallet card that states the type of immunotherapy you are receiving, potential side effects, and contact numbers for your cancer care team. Carry it with you at all times.
Checkpoint inhibitors and irAEs

Treatment with corticosteroids

Corticosteroid (“steroid”) therapy is the most effective and widely used treatment for most irAEs. Steroids work best when started early. If you notice any new or worsening symptoms, don’t wait to tell your care team.

Steroids provide short-term relief of inflammation. If steroid therapy is needed, often prednisone or methylprednisolone will be used. They have similar side effects, including:

- Increased appetite
- Weight gain
- Mood changes
- Water retention
- High blood pressure

The main difference between the two is that methylprednisolone is available in an injectable form. This means it can be put directly into the bloodstream, rather than having to ingest a pill.

Stopping steroid therapy

Corticosteroid therapy should not be stopped suddenly. Your care team will instruct you in how to lower the dose slowly, over the course of several weeks. This is called tapering. Stopping steroid therapy too quickly can cause withdrawal symptoms such as anxiety, sweating, nausea, and insomnia.

Health care during steroid therapy

Preventing infection

Oral corticosteroid therapy can weaken your immune system’s ability to fight fungal infection. If you are taking the equivalent of prednisone 20 mg or more daily for at least 4 weeks, your doctor may prescribe an antifungal medicine, such as fluconazole (Diflucan).

You may also receive medication to prevent pneumocystis jirovecii pneumonia (PJP), a fungal infection of the lungs. Symptoms of PJP include shortness of breath, fever, night sweats, weight loss, and dry cough.

Stomach inflammation (gastritis)

Inflammation of the stomach lining is called gastritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants can increase the risk of gastritis. You may be prescribed a proton pump inhibitor (PPI) or H2 blocker if you have a higher risk of gastritis. H2 blockers reduce the amount of acid produced by the cells in the lining of the stomach.

Effect on blood sugar level

Corticosteroids can raise your blood sugar level. This is especially problematic for people whose blood sugar is already high due to diabetes or pre-diabetes. Blood sugar monitoring and treatment may be needed during steroid therapy.

Osteoporosis

Long-term treatment with steroids increases the risk of osteoporosis. Vitamin D and calcium can help prevent osteoporosis. Your doctor may also recommend physical therapy and weight-bearing exercises.

When steroids are not enough

If you have a serious irAE that hasn’t started to improve after 2 to 3 days of steroid therapy, or has resulted in an immediate life-threatening issue, treatment with additional types of medication that suppress the immune system may be needed. These are called immunosuppressants. The most commonly...
used immunosuppressants for this purpose are described next. The choice of immune-suppressing therapy will depend on the type of irAE and how severe it is.

**Infliximab (Remicade®)**

Infliximab is a prescription medicine called a tumor necrosis factor (TNF) blocker. It works by blocking a protein in your immune system that can cause inflammation (TNF-alpha).

Infliximab is given intravenously, meaning it is put directly into the bloodstream through a vein. You will be monitored closely after receiving an infusion of infliximab. If needed, two extra doses may be given 2 weeks and 6 weeks after the first infusion.

If you have immune-related hepatitis, you should not receive infliximab or any other TNF blockers. However, other immunosuppressants may be helpful for managing certain side effects. For example, a different type of medication called vedolizumab (Entyvio®) may be an option for treating immune-related colitis in people with hepatitis.

Infliximab can re-activate the hepatitis B virus. Your blood will be tested for the hepatitis B and C viruses. If you are a hepatitis B or C carrier, you will be monitored during treatment and for a few months after finishing treatment.

Infliximab can also re-activate tuberculosis. You will be tested for tuberculosis before starting treatment with infliximab. It is not necessary to have the results before starting treatment.

**Immunoglobulin replacement therapy**

In immunoglobulin replacement therapy infusions of antibody-containing plasma from blood are given to help your body fight infection and disease. Immunoglobulins are usually given intravenously. This is called intravenous immunoglobulin therapy (IVIG).

**Mycophenolate mofetil (CellCept®)**

While originally used in the management of patients with organ transplants, mycophenolate mofetil is now used to treat a variety of autoimmune diseases. It is the preferred immunosuppressant for treating liver inflammation (hepatitis) caused by ICI therapy that does not respond to steroid therapy. It is taken by mouth.

**Rituximab (Rituxan®)**

Rituxan is an antibody therapy. It works by destroying B cells (a type of white blood cell) that make autoantibodies. Autoantibodies are antibodies that attack your own cells by mistake. Rituximab destroys B cells that are carrying the CD20 marker.

**Tocilizumab (Actemra®)**

Interleukin-6, or IL-6, is an immune protein called a cytokine that can cause inflammation. Tocilizumab is a prescription medicine that inhibits, or blocks, IL-6. Tocilizumab is given intravenously. It may be used to treat lung inflammation (pneumonitis) that does not respond to steroid therapy.

**Anti-thymocyte globulin (ATG)**

ATG may be used to treat heart inflammation (myocarditis) that does not improve with steroid therapy. Myocarditis is an uncommon but serious irAE. ATG is serum from blood that contains antibodies that attach to human T cells. It is most often used to lower the risk of graft-versus-host disease (GVHD) after a stem cell transplant, and after a kidney transplant to help keep the body from rejecting the kidney.
After a severe irAE

After experiencing a serious irAE that required stopping ICI therapy, there are many factors to consider when deciding whether to resume immunotherapy. Upon completion of a steroid taper, often around 4 weeks or longer, repeat assessment of the organ affected by the irAE off steroids is required prior to considering resuming immunotherapy. Should this be a reasonable option, it is important to make an informed decision. Discuss the potential benefits and risks with your doctor.

If you experience a severe irAE, it may be necessary to permanently stop treatment with the type of checkpoint inhibitor immunotherapy you were receiving. Sometimes this is the case even for less severe irAEs.

Is other cancer treatment working?
When considering whether to resume immunotherapy, it is important to determine if other cancer treatment is working. Your doctor will do testing to see how well the cancer is responding to treatment without immunotherapy. If the cancer is responding to treatment (even partially), it may not make sense to restart immunotherapy and risk the side effect returning. Discuss the benefits and harms of restarting immunotherapy with your doctor. The anti-cancer benefits may not outweigh the risk of having another serious irAE.

Review

- Immunotherapy is a type of cancer treatment that uses the immune system to kill cancer cells.
- ICIs are a commonly used type of immunotherapy.
- The two main types of ICIs are PD-1/PD-L1 inhibitors and a CTLA-4 inhibitor.
- Boosting the immune system with ICI therapy can cause immune cells to attack healthy cells, causing side effects known as immune-related adverse events (irAEs).
- Corticosteroid (“steroid”) therapy is the most effective and widely used treatment for most irAEs.
- Steroids provide short-term relief of inflammation. Prednisone and methylprednisolone are commonly used steroids.
- Side effects of corticosteroid therapy include increased appetite, weight gain, mood changes, fluid retention, and high blood pressure.
- Stopping corticosteroid therapy abruptly can cause withdrawal symptoms such as anxiety, sweating, nausea, and insomnia.
- You may receive medication to prevent fungal infection during ICI therapy.
- Other immune-suppressing medications may be needed for irAEs that do not improve with steroid therapy.
2

Skin irAEs

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15 Itching
16 Blisters
18 Review
Skin disorders are the most common side effect of immune checkpoint inhibitor (ICI) therapy. Most are mild and can be managed without stopping immunotherapy. While rare, very serious skin reactions can occur.

Inflammatory skin conditions triggered by immunotherapy usually start within the first few weeks of treatment. Some ICIs are more likely to cause skin problems than others. The risk of getting a very serious skin problem is low, however, no matter which ICI you are taking.

If you develop symptoms of a skin disorder such as rash, itching, or blisters, your doctor will perform a broader skin exam. It is important to identify all problem areas and to determine how much of your body is affected.

A comprehensive total body skin exam includes:

- The inside of your mouth (“oral mucosa”)
- Hair and scalp
- Fingernails and toenails

In order to help track healing progress, your doctor may take photographs of the inflamed areas.

Tell your doctor if you’ve had an inflammatory skin disorder in the past. If you have, it is a good idea to see a dermatologist on a regular basis.

Your will also be asked about how your symptoms are affecting your ability to do everyday tasks, called activities of daily living (ADLs). Essential tasks such as bathing and dressing are “self-care” ADLs. Higher level tasks and activities such as grocery shopping, managing finances, and home maintenance are known as “instrumental” ADLs.

**Rash**

A rash that has both flat patches (macules) and bumps (papules) is called a maculopapular rash. It is one of the most common skin irAEs. You may or may not have other symptoms, such as itching, burning, and tightness.

Your doctor will consider the following in order to determine if the rash is mild, moderate, or severe:

- How widespread is the rash? How much of your body does it cover?
- Do you have any other symptoms, such as itching, burning, or tightness?
- How much is the rash impacting your ability to do day-to-day tasks?

**Treatment**

**Mild rash**

A maculopapular rash covering a small area of the body (less than 10 percent) is considered mild. You can continue immunotherapy. A moderate-strength steroid cream or gel should be applied to all areas of the rash. If the rash is itchy, taking an oral antihistamine can help.
Moderate rash
A rash covering a larger area of the body (10 to 30 percent) that is interfering with instrumental ADLs is considered moderate. You can continue immunotherapy. Your doctor may prescribe a steroid cream or gel, an oral steroid, or both.

If a topical steroid is used, a moderate- to high-strength dose is recommended. If treatment with an oral steroid is planned, prednisone 0.5 to 1 mg/kg/day is recommended. If the rash is itchy, taking an oral antihistamine can help reduce the itchiness.

Severe rash
A rash covering more than 30 percent of your body that is interfering with self-care ADLs such as bathing and dressing is considered severe. In-hospital care may be needed. ICI therapy will be stopped until further notice. A tiny piece of inflamed skin may be removed and tested (a biopsy).

Treatment with both a high-potency steroid cream or gel and an oral steroid is recommended. A dose of 0.5 to 1 mg/kg/day of oral prednisone is given to start. If there is no improvement, your doctor may increase the dose up to 2 mg/kg/day.

Maculopapular rash
Maculopapular rash is a common side effect of treatment with immune checkpoint inhibitors. They can vary greatly in appearance, but will have both flat patches (macules) and raised areas (papules).
Itching

Intense itching is called pruritus. It may occur with or without a rash. The itching may be widespread or limited to one or more small areas.

Your doctor will consider the following in order to determine if the itching is mild, moderate, or severe:

- How much of your body itches?
- Is the itching constant?
- Do you have skin changes from scratching?
- Is the itching impacting your ability to do everyday tasks?

Treatment

Mild pruritus
Itching that is mild and only affects a small area is considered mild. You can continue immunotherapy. Oral histamines can help reduce the itching. A moderate-strength steroid cream or gel can be used on itchy areas. Lidocaine patches are also an option for relieving itching in small areas.

Moderate pruritus
In moderate pruritus, intense or widespread itching comes and goes. There are skin changes from repeated picking and scratching, including lesions, bumps, swelling, oozing, crusting, or thickening of the skin (lichenification). The itching may be preventing you from doing certain non-essential tasks and activities.

Most people will be able to continue immunotherapy. Oral antihistamines can help reduce the itching. A high-strength steroid cream or gel should be applied to itchy areas. Your doctor may recommend a type of drug called a GABA agonist. Gabapentin and pregabalin are GABA agonists.

Severe pruritus
Constant intense or widespread itching that is interfering with sleeping or performing essential self-care tasks (eg, bathing and dressing) is considered severe. Immunotherapy will be stopped until further notice. Corticosteroid therapy will be started. Oral antihistamines are recommended. Your doctor may also recommend therapy with a GABA agonist. Gabapentin and pregabalin are GABA agonists.

If your itching does not improve with a combination of the treatments discussed above, your doctor may prescribe one of the following medications:

- Oral aprepitant (Emend®)
- Omalizumab (Xolair®), if there is a high level of immunoglobulin E (IgE) in your blood

If you are being treated as an outpatient (you are not in a hospital), your doctor may recommend light therapy (narrow-band UVB phototherapy).
Blisters

A blister is a fluid-filled sac in the outer layer of skin. Blistering, especially in the mouth or genital area, is a medical emergency. It could be a sign of a life-threatening blistering disorder called Stevens-Johnson syndrome (SJS).

Your doctor will consult with an expert in skin disorders (a dermatologist) right away. If a dermatologist is not available, testing will not be delayed. You may have a skin biopsy, blood testing, or both.

The contents of an intact (unbroken) blister are usually removed and tested. It is also common to have your blood tested for antibodies often found in people with autoimmune blistering disorders.

Your doctor will consider the following in order to determine if the blistering is mild, moderate, severe, or life-threatening:

➢ How much of your body do the blisters cover?

➢ Are the blisters painful? Do you have any other symptoms?

➢ Are the blisters impacting your ability to do everyday tasks?

Mild blistering

If blisters are covering only a small area of your body and you have no other symptoms, the blistering is considered mild. Immunotherapy will be stopped until all blisters have healed. You will be prescribed a high-potency steroid cream or gel. It should be applied to all inflamed and blistered areas.

Activities of Daily Living (ADLs)

Self care

• Eating
• Dressing and grooming
• Toileting
• Bathing
• Transferring

Instrumental

• Managing finances
• Managing transportation
• Shopping and meal preparation
• Home maintenance
• Managing medications
Moderate blistering
Blistering affecting a larger area of your body (10 to 30 percent) is considered moderate. The blisters may be painful, making it hard to do certain tasks or activities.

Immunotherapy will be stopped until all blisters have healed. Corticosteroid therapy will be started. If there is no improvement after 3 days, or for long-term management, your doctor may recommend treatment with rituximab (Rituxan®).

Rituximab is an anti-CD20 monoclonal antibody. It is given intravenously, meaning it is put directly into your bloodstream. This is called an infusion. One infusion is given first, followed by a second infusion 2 weeks later.

Continue taking the corticosteroid until all blisters have healed. You will be instructed on how to lower the dose gradually, over a 4- to 6-week period. If needed, you may have one or two more infusions of rituximab at 12 and 18 months. These “maintenance” infusions provide a lower dose of rituximab (500 mg).

Severe or life-threatening blistering
Blistering covering more than 30 percent of your body that is interfering with basic self-care tasks is considered severe. Extensive blistering accompanied by fluid or electrolyte problems that requires treatment in an ICU or burn unit is considered life-threatening.

Stevens-Johnson syndrome is a rare and serious skin disorder in which the outer layer of the skin separates from the layer of connective tissue beneath it. If left untreated, SJS becomes a life-threatening condition called toxic epidermal necrolysis (TEN).

SJS often starts with a fever, maculopapular rash, and other flu-like symptoms. Shortly thereafter a painful rash with blisters forms and the skin becomes raw and separated. SJS can also affect mucous membranes throughout the body, including:

- The lining of the mouth and airways
- The urinary tract and genitals
- The eyes

In-hospital care is needed for severe or life-threatening blistering. Immunotherapy will be stopped. Corticosteroid therapy will be started right away. If there is no improvement after 3 days, treatment with one of the following may be added:

- Rituximab (Rituxan®)
- Intravenous immune globulin (IVIG)
Review

- Inflammatory skin conditions are the most common side effect of ICI therapy. Possible reactions include rash, itching, and blisters.

- Most are mild and can be managed without stopping immunotherapy. While rare, very serious skin reactions can occur.

- A rash that has both flat patches and bumps is a maculopapular rash.

- Mild maculopapular rash is treated with a moderate-strength topical steroid.

- Moderate maculopapular rash is treated with a topical steroid, an oral steroid, or both.

- In-hospital care may be needed for a severe rash. ICI therapy will be temporarily stopped. Treatment with both a high-potency topical steroid and an oral steroid is recommended.

- Intense itching is called pruritus. It may occur with or without a rash. Oral antihistamines can help reduce itching.

- Mild itching is treated with a moderate-strength topical steroid. Lidocaine patches are also an option.

- Moderate itching is treated with a high-strength topical steroid. You may also be prescribed a GABA agonist.

- Blistering, especially in the mouth or genital area, is a medical emergency. It could be a sign of a life-threatening blistering disorder called Stevens-Johnson syndrome (SJS).

- If you develop blisters, ICI therapy will be stopped, possibly permanently.

- Mild blistering is treated with a high-potency topical steroid.

- Moderate blistering is treated with oral corticosteroids. Rituximab may be prescribed if there is no improvement, or for long-term management.

- In-hospital care is needed for severe or life-threatening blistering. Corticosteroid therapy will be started right away.
3

Fatigue

20 Testing and assessment
20 Managing fatigue
22 Review
Testing and assessment

Evaluating fatigue includes a physical exam, blood tests, and a review of medications you are taking.

Blood tests
Blood tests can provide helpful information about fatigue. See Guide 1 for a listing and description of the recommended blood tests.

Medication review
It is important to tell your doctor about all the prescription and over-the-counter medications you are taking. Certain medications—and the way certain medications interact—can cause fatigue or make it worse. Your doctor will consider whether making changes to the types or dosages of your medications may help with your fatigue.

If your doctor finds anything of concern during your physical exam or in your test results, he or she will discuss these findings with you. Your doctor may consult with a specialist, depending on the type of abnormal finding.

Using the information gained from the physical exam, blood tests, and medication review, your doctor will classify your fatigue as mild, moderate, or severe.

Managing fatigue
Managing fatigue may include:

- Hydration
- Adjusting your medications
- Learning about ways to offset or prevent fatigue
- Changes to your diet
- Practicing good sleep hygiene.

Mild fatigue
For mild fatigue that is relieved by rest, it is not necessary to stop immunotherapy. If your fatigue becomes worse and does not improve after resting, call your doctor.

Moderate fatigue
Fatigue that does not improve with rest and that limits you from doing certain tasks or activities is considered moderate.

It may be possible to manage or relieve your fatigue so that it doesn’t interfere with your ability to do everyday tasks. If your doctor feels this is possible, you can continue immunotherapy. Your doctor may prescribe low-dose steroid therapy. Call your doctor if your fatigue gets worse or if you notice other, new health issues.

Severe fatigue
Fatigue that does not get better with rest and that is preventing you from carrying out essential self-care tasks such as bathing and dressing, is considered severe.

Immunotherapy will be stopped temporarily, possibly permanently. Your doctor will consider
other possible causes of fatigue, include cancer-related fatigue, other medical conditions, or other side effects of immunotherapy.

Guide 1
Blood tests recommended for fatigue

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<th>Description</th>
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<tr>
<td><strong>Complete blood count (CBC)</strong></td>
<td>A CBC measures the levels of red blood cells, white blood cells, and platelets in your blood. It can detect a range of diseases and disorders and provides information on your overall health.</td>
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<tr>
<td><strong>TSH test</strong></td>
<td>This test measures the amount of thyroid-stimulating hormone (TSH) in the blood. It is used to learn how well your thyroid gland is working.</td>
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<tr>
<td><strong>Cortisol test</strong></td>
<td>Cortisol is a hormone that helps you respond to stress, fight infection, regulate blood sugar, and other functions. Cortisol should be measured in the morning, when the level is at its highest.</td>
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<tr>
<td><strong>Morning testosterone test</strong></td>
<td>This test is used to detect an abnormal testosterone level. Testosterone should be measured in the morning, when the level is at its highest.</td>
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Review

- Fatigue, or tiredness, is a common side effect of checkpoint inhibitors.
- Evaluating fatigue includes a physical exam, blood tests, and a review of medications you are taking.
- Immunotherapy can be continued for mild fatigue, but might be temporarily stopped for moderate fatigue.
- ICI therapy will be stopped temporarily—possibly permanently—for severe fatigue.
- Severe fatigue may be a sign of a hormone-related (endocrine) problem. Urgent testing and treatment may be needed.
4 Gastrointestinal irAEs

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ICI therapy can cause digestive, or gastrointestinal, side effects. Diarrhea and inflammation of the colon are very common. Liver inflammation (hepatitis) is also possible, but does not typically cause symptoms.

Diarrhea and colitis

The most common irAEs affecting the digestive system are diarrhea and colitis. Diarrhea is an increase in the number of bowel movements compared to normal, which may be watery. Colitis refers to inflammation of the inner lining of the large intestine (the colon).

Symptoms typically develop within 6 to 8 weeks of starting treatment. Symptoms of colitis include watery diarrhea, cramping, and needing to go to the bathroom suddenly (“urgency”). See Guide 2.

In order to evaluate your symptoms, it is important to determine your starting, or baseline, bowel habits. Because everyone’s bowel habits are somewhat different, it’s the increase in the number of bowel movements per day that’s important, along with other symptoms.

If you have chronic constipation or constipation due to opioid pain medication, your symptoms may be different. You may have colitis that presents as a daily bowel movement and abdominal cramping. It is important that you have a good understanding of your baseline.

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<td>Cramping</td>
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<td>Urgency</td>
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<td></td>
<td>Abdominal pain</td>
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<td></td>
<td>Blood (if severe)</td>
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<tr>
<td></td>
<td>Mucus in the stool</td>
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<td></td>
<td>Fever</td>
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<td>Nighttime bowel movements</td>
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</table>

Testing

Your doctor will order a stool (poop) evaluation in order to rule out infection (ie, *C. difficile*) as the cause of your symptoms. Testing will look for an infection of your digestive tract due to disease-causing bacteria, parasites, or viruses.

Your doctor may also order a lactoferrin test. Lactoferrin is a protein found in milk (human and cow), saliva, tears, mucus, and bile. It may help fight infection and inflammation.

If you have moderate or severe colitis, you may have computed tomography (CT) of your abdomen and pelvis.

Treatment

Mild symptoms

Your doctor might recommend temporarily stopping the ICI for mild symptoms. For some people, mild symptoms may mean 1 to 3 bowel movements above normal per day and no colitis symptoms.
Gastrointestinal irAEs

**Diarrhea and colitis**

Treatment with anti-diarrheal medication for 2 to 3 days is recommended. Loperamide (Imodium®) and diphenoxylate/atropine (Lomotil®) are commonly used anti-diarrheal medications. It is important to stay hydrated. Drinking lots of fluids is recommended.

You will be closely monitored. If there is no improvement after 2 to 3 days, your doctor may test your stool for infection and lactoferrin.

If testing does not find infection, you can continue anti-diarrheal medication and fluids. Treatment with mesalamine (Pentasa®) or cholestyramine (Prevalite®) may be added. Mesalamine is an anti-inflammatory medicine; cholestyramine is a cholesterol-lowering medicine.

**Moderate symptoms**

If you’re having 4 to 6 bowel movements above normal per day and also have colitis symptoms, your symptoms are considered moderate. Immunotherapy will be stopped. Corticosteroid therapy (1–2 mg/kg/day) will be started. If your symptoms haven’t improved after 2 to 3 days of steroid therapy, your doctor may add treatment with one of the following:

- Infliximab (Remicade®)
- Vedolizumab (Entyvio®)

Both are given intravenously. You will have a tuberculosis test before receiving either of these, but it is not necessary to have the results before starting treatment.

If you receive either of these, your doctor may advise you to slowly stop steroid therapy in less than 4 weeks. This may reduce the chance of getting an infection. There is no standard length of treatment with Remicade® or Entyvio®. You may have up to three doses.

Endoscopy may be used to monitor how well you are healing and to help determine how long to continue treatment.

**Severe symptoms**

For more severe symptoms, ICI therapy should be stopped. Severe symptoms may include:

- More than 6 bowel movements above normal per day
- Colitis symptoms
- Symptoms interfering with activities of daily living (ADLs)

Very severe symptoms and complications are also possible. In-hospital care may be needed. Depending on your symptoms, immunotherapy with the type of ICI you are receiving may be permanently stopped.

Corticosteroid therapy will be started. If your symptoms haven’t improved after 2 days of steroid therapy, your doctor may add treatment with one of the following:

- Infliximab (Remicade®)
- Vedolizumab (Entyvio®)

Endoscopy may be used to monitor how well you are healing and to help determine how long to continue treatment.

A stool (fecal) transplant may be an option for colitis that does not respond to immune-suppressing treatment, or that returns after treatment. This will be based on the center where you are receiving treatment and the expertise of the health care providers.
Hepatitis

A less common gastrointestinal side effect of checkpoint inhibitors is liver inflammation (hepatitis). Unlike diarrhea and colitis, hepatitis does not typically cause symptoms. It is most often found by blood tests used to monitor the levels of two liver enzymes—alanine transaminase (ALT) and aspartate transaminase (AST). Having higher-than-normal levels of ALT and AST is called transaminitis. It may be a sign of liver inflammation or damage.

Treatment will depend on how high above normal your liver enzymes are. Corticosteroid therapy may be used for moderate transaminitis, and is essential for severe or life-threatening transaminitis.

Bilirubin is a yellowish substance found in blood. Any type of liver function problem can cause it to build up in your blood. If you have transaminitis and a higher-than-normal bilirubin level, immunotherapy should be permanently stopped. In-hospital treatment is needed. This excludes people with a genetic condition called Gilbert’s syndrome, which causes high levels of bilirubin in the blood.

Steroid therapy will be started (2 mg/kg/day). Your liver enzymes will be closely monitored. If there is no improvement after 3 days of steroid therapy, your doctor may add mycophenolate mofetil (CellCept®), an immune-suppressing medication. Infliximab is not used for liver problems.

Review

- Diarrhea and colitis are among the most common irAEs.
- Diarrhea refers to having more bowel movements than normal, which may be watery.
- Colitis is inflammation of the inner lining of the large intestine (the colon). Symptoms include watery diarrhea, cramping, and urgency.
- Anti-diarrheal medication is used to treat mild diarrhea. Treatment with mesalamine (Pentasa®) or cholestyramine (Prevalite®) may be added if there is no improvement.
- Immunotherapy will be stopped for moderate colitis. Corticosteroid therapy will be started. If your symptoms do not improve, treatment with infliximab or vedolizumab may be added.
- Hepatitis is inflammation of the liver. Higher-than-normal levels of liver enzymes (transaminitis) may be a sign of liver damage.
- Depending on how high above normal your liver enzymes are, it may be necessary to stop immunotherapy, possibly permanently.
- Corticosteroid therapy may be used for moderate transaminitis, and is essential for severe or life-threatening transaminitis.
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Endocrine irAEs

- 28 High blood sugar and diabetes
- 29 Thyroid problems
- 31 Primary adrenal insufficiency
- 32 Review
Immune checkpoint inhibitor (ICI) therapy can adversely affect your body's hormone-producing organs and glands (endocrine system). Endocrine irAEs are fairly common during ICI therapy.

High blood sugar and diabetes

Your body needs glucose, or sugar, to work properly. Insulin is a hormone that absorbs glucose into cells for use as energy. When the body doesn’t make or use enough insulin, the level of glucose in the blood becomes too high. This is called high blood sugar, or hyperglycemia.

High-dose corticosteroids can cause or worsen hyperglycemia. Your blood sugar level will be checked each time you receive immunotherapy. A blood sugar reading of more than 180 mg/dL is generally considered too high. A blood sugar reading of 300 mg/dL or more can be dangerous.

A slightly high blood sugar level may be due to corticosteroid therapy, or to pre-existing type 2 diabetes. If steroid therapy (or diabetes) has caused your blood sugar level to go up, but it is still below 200 mg/dL, you can continue immunotherapy.

You may benefit from changes to your diet and lifestyle. Eating healthy and exercising can help keep blood sugar under control. If needed, medications may also be an option for managing your blood sugar.

If you have a blood sugar level of 200 mg/dL after fasting, or a random (non-fasting) measurement above 250 mg/dL, you may have testing for diabetic ketoacidosis (DKA). DKA is a serious and potentially life-threatening condition. It occurs when the body starts breaking down fat too quickly and toxic acids (ketones) build up in the blood and urine. Symptoms of DKA are listed in Guide 3.

Your doctor will also consider the possibility of type 1 diabetes. Type 1 diabetes usually starts during childhood or adolescence. While rare, it is possible to develop it as an adult. This can be life-threatening if you do not get insulin.

Guide 3
Symptoms of diabetic ketoacidosis

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<td>Abdominal pain</td>
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<td>Dry skin</td>
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<td>Dry mouth</td>
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<td>Increased heart rate</td>
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<td>Fruity odor on the breath</td>
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</table>
Thyroid problems

The thyroid is a gland in the lower, front part of your neck. The thyroid makes thyroid hormone, a substance that regulates how fast food becomes fuel for the body (metabolism).

If thyroid hormone levels are too low, metabolism will be slow. This is hypothyroidism, or underactive thyroid. Symptoms of hypothyroidism include:

- Weight gain
- Constipation
- Dry skin
- Sensitivity to the cold

If the thyroid hormone levels are too high, the metabolic rate will be high. This is known as thyrotoxicosis. Signs and symptoms of thyrotoxicosis include:

- Weight loss
- Fatigue
- Rapid or irregular heartbeat
- Sweating
- Anxiety

Your thyroid hormone levels will be monitored with blood tests during ICI therapy. If the thyroid hormone level becomes too low, your doctor may prescribe levothyroxine. Levothyroxine is a medicine that replaces thyroid hormone.

If the thyroid hormone level becomes too high (thyrotoxicosis), treatment to slow your metabolism will be needed. Your doctor may start treatment with a type of medication called a beta-blocker. Treatment for thyrotoxicosis is usually temporary.
Hypophysitis

The pituitary gland is an important hormone-producing gland in the brain. While rare, the pituitary gland can become inflamed. This is called hypophysitis. Permanent damage to the pituitary gland can occur. The symptoms of hypophysitis are listed in Guide 4.

Testing for suspected hypophysitis includes a number of blood tests, and possibly magnetic resonance imaging (MRI) of your brain.

Immunotherapy will be stopped until new-onset symptoms are gone. If you have symptoms, corticosteroid therapy will be started. If your new symptoms are severe, high-dose steroids are recommended.

When your symptoms are gone—typically in about 1 to 2 weeks—you will be transitioned to hormone replacement therapy. Hormone replacement therapy for pituitary gland damage may be needed for the rest of your life.

Your doctor may temporarily increase your dose of hormone replacement therapy if you get an infection, become sick, or experience other trauma to your body. This is called “stress dosing.” A medical alert bracelet is recommended for people with hypophysitis.

Guide 4
Hypophysitis symptoms

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<td>Visual field cuts</td>
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<table>
<thead>
<tr>
<th>Long-term symptoms</th>
<th>Weight loss</th>
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<tr>
<td></td>
<td>Fatigue</td>
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</table>
Primary adrenal insufficiency

An adrenal gland sits on top of each kidney. These glands make hormones that are essential for the body to function properly, including cortisol. Cortisol helps you respond to stress, fight infection, and regulate blood sugar.

In primary adrenal insufficiency (also called Addison’s disease), the adrenal glands do not make enough cortisol, and often not enough of a different hormone called aldosterone.

Symptoms of adrenal insufficiency include:

- Weight loss
- Dark areas of skin (hyperpigmentation)
- Severe fatigue
- Gastrointestinal problems, such as nausea, vomiting, and diarrhea
- Lightheadedness or fainting

Addison’s disease is treated with medication to replace the hormones not being made by the body. This hormone replacement therapy typically includes:

- Oral hydrocortisone or prednisone to replace cortisol
- Oral fludrocortisone acetate to replace aldosterone

Immunotherapy can be restarted when hormone levels have returned to normal. Hormone replacement therapy is usually needed for the rest of your life. Your doctor will determine the lowest dose needed to prevent symptoms of adrenal insufficiency.

In people without Addison’s disease, the adrenal glands make significantly more cortisol in response to infection, illness, injury, or trauma to the body. Your doctor may

Cortisol

In primary adrenal insufficiency (also called Addison’s disease), the adrenal glands don’t make enough cortisol—a hormone that helps you respond to stress, fight infection, and regulate blood sugar. Symptoms such as weight loss, fatigue, and gastrointestinal problems are possible.
temporarily increase your dose of hormone replacement therapy in such situations. This is called "stress dosing."

A medical alert bracelet is recommended for people with Addison’s disease.

Review

- High-dose corticosteroids can cause or worsen hyperglycemia. Your blood sugar level will be checked each time you receive immunotherapy.
- Your thyroid hormone levels will be monitored with blood tests during ICI therapy.
- Levothyroxine may be prescribed if the thyroid hormone level is too low.
- Having too much thyroid hormone is thyrotoxicosis. Your doctor may start treatment with a beta-blocker. Treatment for thyrotoxicosis is usually temporary.
- Hypophysitis is inflammation of the pituitary gland. Long-term symptoms include weight loss and fatigue. Immunotherapy will be stopped if new, severe symptoms develop.
- In primary adrenal insufficiency (also called Addison’s disease), the adrenal glands do not make enough cortisol, and often not enough of a different hormone called aldosterone.
- Addison’s disease is treated with hormone replacement therapy, which is usually needed for the rest of your life.
6

Lung irAEs

34 Testing
35 Treatment
36 Review
Lung inflammation is called pneumonitis. The most common symptom is trouble breathing, with or without a dry (mucus-free) cough. Other symptoms include fever and chest pain. Pneumonitis can typically be seen on imaging tests, even if it’s not causing symptoms.

**Testing**

The first sign of pneumonitis is often a low level of oxygen in the blood. In addition to a physical exam, you will have a fast and painless oxygen saturation test. This is done using a small device called a pulse oximeter placed on your fingertip. The oxygen saturation level will be measured when you are at rest (not moving) and also after walking.

Depending on your symptoms (if any) and how severe they are, you may also have some or all of the testing described next.

**Testing for infection**

An important first step is to rule out infection. Testing for infection may include:

- Swabbing the inside of your nose to detect viruses, such as the flu
- Phlegm (sputum) culture test
- Blood culture test
- Urine test

**Bronchoscopy and BAL**

An additional test that can help confirm or rule out infection is bronchoscopy. Bronchoscopy is an imaging technique that allows your doctor to see inside your lungs.

A thin, flexible tube with a tiny light and camera (a bronchoscope) will be guided into your lungs through your nose or mouth. A small amount of sterile saline (saltwater) will be put through the bronchoscope into the lungs. The saline will wash the airway and is then be suctioned back through the tube. This is called

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**Pulse oximetry**

A pulse oximeter measures the amount of oxygen being carried by red blood cells by shining light through your finger.
a bronchoalveolar lavage (BAL). The collected fluid will be sent to a laboratory to be tested for infection. If there is a possibility that cancer has spread to the lungs, a biopsy will be performed during bronchoscopy.

**Computed tomography**
Your may also have computed tomography ("CT scan" or "CAT scan") of your chest. If so, a liquid called a contrast agent will also be used. It will either be put directly into your bloodstream through a vein, or given to you to drink. It will help make the CT images clearer.

**Treatment**

Pneumonitis that does not cause symptoms, but that can be seen on imaging tests, is considered mild. Your doctor may recommend temporarily stopping ICI therapy. Or, a watch-and-wait approach may be taken. If imaging suggests widespread pneumonitis, your doctor may prescribe steroids to prevent symptoms before they start.

If you have symptoms of pneumonitis (ie, shortness of breath, cough, chest pain, fever), immunotherapy will be stopped. Corticosteroid therapy will be started. If steroid therapy works well and you no longer have symptoms, you may be able to resume immunotherapy.

Pneumonitis is considered severe if you require extra oxygen to breathe and your symptoms are limiting your ability to do essential self-care tasks. An extremely serious respiratory crisis is considered life-threatening pneumonitis.

In-hospital care is needed for severe or life-threatening pneumonitis. Immunotherapy will be permanently stopped. Intravenous corticosteroid therapy will be started. If there is no improvement within 48 hours, treatment with one of the following may be added:

**Bronchoalveolar lavage**

During a bronchoscopy, a small amount of sterile saline (saltwater) may be put into one small area of the lungs. The saline “washes” the airway and is then suctioned back through the tube. The fluid is tested for infection.
Review

Symptoms of lung inflammation (pneumonitis) include trouble breathing, dry cough, fever, and chest pain.

Testing for infection often includes a nasal swab to detect viruses and testing of your phlegm, blood, and urine.

Other testing may include bronchoscopy with bronchoalveolar lavage and a chest CT.

Mild pneumonitis does not cause symptoms but can be seen on imaging tests. ICI therapy can often be continued.

Steroid therapy is needed for pneumonitis that is causing symptoms. ICI therapy will be stopped, at least until you no longer have symptoms.

In-hospital care is needed for severe or life-threatening pneumonitis. ICI therapy will be permanently stopped.

Follow-up

You will likely have a follow-up visit in 1 to 2 weeks to see if there is any change to the level of inflammation. If you had a CT scan initially, you may have another in about a month, or only if you develop symptoms. Your doctor may choose to monitor your lungs with a special lung function test or oxygen monitor.

Review

- Infliximab (Remicade®)
- Intravenous immunoglobulin (IVIG)
- Mycophenolate mofetil (CellCept®)
# 7 Musculoskeletal irAEs

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Immunotherapy with immune checkpoint inhibitors (ICIs) can cause inflammation of the joints, tendons, ligaments, bones, and muscles. This chapter describes these musculoskeletal (also called rheumatic) side effects and their treatment.

**Inflammatory arthritis**

Inflammatory arthritis is not a single disease. It refers to a group of disorders in which the immune system attacks the joints, causing inflammation. Major types include:

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Gout
- Lyme disease
- Lupus

Inflammatory arthritis is different from osteoarthritis, which is caused by physical use of the joint(s) over many years. Also unlike osteoarthritis, inflammatory arthritis often affects joints throughout the body, rather than one or two joints. Symptoms of inflammatory arthritis include:

- Joint pain and swelling
- Tendon pain and swelling
- Stiffness after rest/inactivity
- Improvement with heat

Your doctor will carefully examine the painful or swollen joint(s) in order to see if it functions properly. You may have an x-ray, ultrasound, or magnetic resonance imaging (MRI) of the affected joint(s).

**Treatment**

Immunotherapy can be continued for inflammatory arthritis that is mild or only affects one joint. Nonsteroidal anti-inflammatory drugs (NSAIDs) can help relieve the inflammation. If there is no improvement with NSAID therapy, your doctor may prescribe low-dose steroid therapy. Steroid injections may also be an option for relieving inflammation, depending on the number of inflamed joints and their location. This involves injecting steroids directly into the painful or swollen joint with a needle.

While ICI therapy can be continued for mild inflammation, it may be temporarily stopped if the arthritis is somewhat more severe (“moderate”). Corticosteroid therapy with prednisone for 4 to 6 weeks is recommended. If your symptoms haven’t improved by week 4 of steroid therapy, a specialist (rheumatologist) may be consulted.

If the arthritis is preventing you from carrying out activities of daily living (ADLs) and imaging tests show joint erosion, the arthritis is considered severe. Severe inflammatory arthritis can lead to irreversible joint damage.

Immunotherapy will be stopped until further notice. Steroid therapy (1 mg/kg/day) will be started. If there is no improvement by week 2, treatment with other disease-modifying anti-rheumatic drugs (DMARDs) may be added. Steroid injections may also be used.
Muscle pain and inflammation

Treatment with checkpoint inhibitors can cause muscle pain (myalgia) and inflammation (myositis). Muscle weakness is also a symptom of myositis.

Testing
Blood tests can provide helpful information about the cause of muscle pain. Recommended blood tests are described below.

Comprehensive metabolic panel (CMP)
A CMP is a group of over 10 different blood tests that provide an overall picture of your body chemistry and metabolism.

Creatine kinase and aldolase testing
Creatine kinase (CK) and aldolase are enzymes found in high amounts in the blood when there is muscle damage. Testing measures the amount of these enzymes in the blood.

Muscle strength testing
Muscle strength testing can help your doctor identify neurologic problems that may be causing your muscle weakness.

Treatment
If you are experiencing mild muscle pain, inflammation, or both, your doctor might recommend stopping the ICI temporarily. You will have blood tests on a regular basis to monitor the levels of creatine kinase and aldolase. NSAIDs and other medications can help to relieve muscle pain.

If the levels of creatine kinase and aldolase in your blood are higher than normal, stopping immunotherapy temporarily is recommended.

Your doctor may recommend magnetic resonance imaging (MRI) of your muscle (a “muscle MRI”) and/or an electromyogram.

Severe muscle pain and inflammation require treatment with steroid therapy. Oral prednisone 1–2 mg/kg/day is recommended. Continue steroid therapy until you don’t have symptoms, then gradually stop steroid therapy over a 4- to 6-week period. Your doctor will continue to monitor the levels of creatine kinase and aldolase in your blood during steroid therapy. Your doctor may also recommend intravenous immune globulin (IVIG).

Managing the pain associated with severe myalgia is important. Your doctor will make recommendations for treating severe muscle pain.

For muscle pain and inflammation that does not improve with steroid therapy, more testing and treatment are needed. In some cases, it is helpful to remove a tiny piece of muscle for testing (muscle biopsy). A procedure called plasmapheresis may be used to treat severe muscle pain and inflammation that does not improve with steroids. Treatment with one of the following may also be an option:

- Infliximab (Remicade)
- Mycophenolate mofetil (CellCept®)
Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory disorder that causes muscle aches, pain, or stiffness, especially in the shoulders. Signs and symptoms usually come on quickly and are worse in the morning.

PMR is closely related to another, less common condition called giant cell arteritis (GCA). Many people who have one of these conditions also have symptoms of the other. GCA causes inflammation and narrowing of blood vessels. The arteries on the sides of the forehead (“the temples”) are most often affected. These are called the temporal arteries. If left untreated, GCA can lead to stroke or blindness.

Symptoms of GCA include:

- Changes in eyesight
- Headache
- Scalp tenderness
- Jaw pain from chewing or prolonged speaking

Testing

Blood and laboratory tests are used to gather more information about possible PMR or GCA. Testing the erythrocyte sedimentation rate (ESR) and level of C-reactive protein (CRP) is recommended.

If your doctor suspects PMR based on your symptoms, you may have an ultrasound of your shoulders, hips, or both. If you are experiencing symptoms of GCA, such as headaches or vision problems, you may have an ultrasound and a biopsy of your temporal artery. This is a minor procedure performed under local anesthesia to remove a tiny piece of scalp artery for testing. In a temporal artery ultrasound, sound probes are on the sides of the head and under each arm.
PMR treatment
If you have mild symptoms of pain and/or stiffness that do not limit your ability to do everyday tasks, you can continue immunotherapy. Six weeks of treatment with steroid therapy (oral prednisone) is recommended.

If pain, stiffness, or both are limiting your ability to do everyday tasks, immunotherapy should be stopped until further notice. Steroid therapy with prednisone is recommended. A long steroid taper period of 8 to 12 weeks is needed. If there is no improvement, you may be referred to a specialist (a rheumatologist).

GCA treatment
Immunotherapy will be stopped. Steroid therapy with prednisone (1 mg/kg/day) is recommended. Steroid therapy should be continued until you no longer have symptoms. Steroid therapy should always be stopped slowly. When treating GCA, steroid therapy should be stopped extra slowly, over an 8- to 12-week period.

If you are having eye or vision symptoms, you may have “pulse therapy” with methylprednisolone. Pulse therapy refers to the use of very high doses of intravenous corticosteroids given intermittently (not continuously) over a short period, usually a few days. Pulse therapy can “boost” the helpful effects of steroid therapy while reducing its harmful effects. Your doctor may consult with both an ophthalmologist and a rheumatologist in order to guide treatment for GCA.

Review
- Inflammatory arthritis is a group of joint disorders that includes rheumatoid and psoriatic arthritis.
- Immunotherapy can usually be continued for mild inflammatory arthritis. NSAIDs can help relieve the inflammation.
- Steroid injections may be an option for relieving the symptoms of inflammatory arthritis.
- Severe muscle pain (myalgia) or inflammation (myositis) require treatment with steroid therapy.
- PMR causes muscle aches, pain, or stiffness, especially in the shoulders. ICI therapy may be paused, depending on how severe your symptoms are.
- GCA is a related but less common condition in which blood vessels in the temples are inflamed. Immunotherapy will be stopped. Steroid therapy is needed.
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Less common irAEs

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Treatment with immune checkpoint inhibitors (ICIs) can also have less common but serious effects on other organs. This chapter describes these uncommon but potentially severe irAEs.

**Neurologic irAEs**

Neurologic (nervous system-related) effects of ICI therapy are rare but very serious. Neurologic irAEs can affect the brain, spinal cord, and nerves throughout the body.

**Myasthenia gravis**

Myasthenia gravis is a disease that causes muscle weakness throughout the body. It can weaken muscles in the eyes, face, and throat. Symptoms of myasthenia gravis include droopy eyelids (ptosis), double vision, and problems with swallowing. See Guide 5.

Testing for suspected myasthenia gravis may include:

- Blood tests
- Lung function tests
- Heart function tests, such as an electrocardiogram (ECG)
- Nervous system tests (eg, electromyography; nerve conduction studies)
- Magnetic resonance imaging (MRI) of your brain and spine

In-hospital treatment is needed for moderate or severe myasthenia gravis. Immunotherapy will be permanently stopped.

Moderate myasthenia gravis is treated with pyridostigmine (Mestinon®). Mestinon® is a muscle strengthener. It works by increasing the levels of a neurotransmitter (acetylcholine) in your nervous system. Acetylcholine is a chemical that carries signals to muscle cells and other nerve cells. In addition to Mestinon®, your doctor may also prescribe low-dose oral prednisone (20 mg daily).

Severe myasthenia gravis is treated with intravenous corticosteroid therapy. In addition to steroids, plasmapheresis or intravenous immune globulin (IVIG) is recommended for severe cases or if steroids are not helping.

If your symptoms don’t improve from treatment with plasmapheresis or IVIG, your doctor may start therapy with rituximab (Rituxan®). You may receive two doses of rituximab two weeks apart, or four doses of rituximab given once a week for 4 weeks.

**Guide 5**

**Myasthenia gravis symptoms**

- Drooping of the upper eyelid (ptosis)
- Double vision
- Difficulty swallowing (dysphagia)
- Facial muscle weakness
- Respiratory muscle weakness
- Weakness in the arms and legs
Guillain-Barré syndrome (GBS)
GBS is a serious muscle weakness disorder. It can affect the arms and legs, face, breathing muscles, and eye nerves. The first symptom of GBS is often pain in the lower back and thighs.

Testing for immunotherapy-related GBS typically includes:

- MRI of your spine
- Lumbar puncture
- Blood tests
- Lung function and breathing tests

**Treatment**
In-hospital treatment is needed. ICI therapy will be permanently stopped. GBS triggered by ICI therapy is treated with intravenous corticosteroid therapy and intravenous immune globulin (IVIG) or plasmapheresis.

Steroids are not usually recommended for “classic” GBS, which starts for unknown reasons. However, it is appropriate to use steroids to treat immunotherapy-related GBS, in addition to IVIG or plasmapheresis.

**Monitoring**
Your lung function and mental status will be checked frequently in the hospital. You will also be monitored for autonomic dysfunction. The autonomic nervous system controls several basic body functions, including body temperature, heart rate, and breathing rate.

**Pain management**
You may be given gabapentin, pregabalin, or duloxetine for pain.

Aseptic meningitis
The thin layers of tissue that cover the brain and spinal cord are called the meninges (meh-NIN-jeez). Meningitis is inflammation of the meninges. Meningitis not caused by a bacterial infection is known as aseptic meningitis. Symptoms can include:

- Headache
- Sensitivity to light (photophobia)
- Neck stiffness
- Fever
- Nausea or vomiting

It is important to rule out bacteria and viruses as the cause of your symptoms. Your doctor may start you on an antiviral drug called acyclovir while waiting for all test results to come in. If infection has been ruled out, your doctor may start low-dose steroid therapy, or may take a watch-and-wait approach.

Testing used to assess meningitis may include:

- MRI of your brain
- Cortisol blood test
- Lumbar puncture

Immunotherapy will be stopped for mild or moderate aseptic meningitis. You may be able to restart it later. For severe aseptic meningitis, however, it is necessary to permanently stop immunotherapy.

In-hospital care is needed for severe meningitis, which means the disease is limiting your ability to take care of yourself (self-care) and you require aids/assistive devices.
Encephalitis

Encephalitis is inflammation of the brain. Symptoms can range from mild confusion to very serious brain function problems. See Guide 6.

It is important to rule out infection—especially viruses—as the cause of encephalitis. Testing typically includes:

- MRI of your brain
- Lumbar puncture
- Electroencephalogram (EEG) to detect seizures
- Blood and laboratory tests

Immunotherapy will be stopped until further notice for mild encephalitis, pending close medical evaluation and recovery. Immunotherapy will be permanently stopped for moderate or severe encephalitis.

If your symptoms are limiting your ability to do essential self-care tasks and you need assistive devices, encephalitis is considered severe. In-hospital care is needed to treat severe or life-threatening encephalitis.

While waiting for test results in the hospital, your doctor may start treatment with an antiviral drug called acyclovir. A trial of steroid therapy (methylprednisolone 1–2 mg/kg/day) is recommended. If your symptoms are severe or getting worse, your doctor may order intravenous immune globulin (IVIG) or plasmapheresis.

If your test results are positive for a particular antibody (autoimmune encephalopathy antibody) or if you are not improving with steroid therapy, your doctor may recommend treatment with rituximab (Rituxan®).

Transverse myelitis

Transverse myelitis is inflammation of the spinal cord. The spinal cord carries messages between the brain and nerves throughout the body. Transverse myelitis interrupts these messages, resulting in problems with sensation and nerve function.

Symptoms of transverse myelitis include:

- Pain
- Weakness in the legs and sometimes the arms
- Sensory problems
- Bladder and bowel problems, such as constipation or retaining urine

Testing for suspected transverse myelitis typically includes:

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Heart inflammation (myocarditis)

Treatment with immune checkpoint inhibitors can cause serious—and possibly deadly—problems affecting the heart and blood vessels. Cardiovascular irAEs include:

- Myocarditis
- Pericarditis
- Arrhythmias
- Impaired ventricular function
- Conduction abnormalities

**Myocarditis**

Myocarditis is a rare but serious condition in which the heart muscle (the myocardium) becomes thick and inflamed. It often affects people who also have myositis or myasthenia gravis.

Symptoms of myocarditis include:

- Chest pain
- Fatigue

If you have symptoms of myocarditis, you will be admitted to the hospital and evaluated by a cardiologist. A cardiologist is an expert in diagnosing and treating diseases of the heart and blood vessels. In-hospital testing typically includes:

- Telemetry monitoring
- Electrocardiogram (ECG)
- Magnetic resonance imaging (MRI) of the heart
- Blood and laboratory testing

Your doctor may order blood tests to rule out other possible causes of your symptoms, including viruses. Myocarditis that is not related to immunotherapy is often caused by a viral infection. You may also have an ultrasound of your heart (echocardiogram). For very serious symptoms, you may have a tiny sample of heart tissue removed for testing (a biopsy).

**Severe or life-threatening myocarditis**

You will be admitted to the hospital and have intensive care unit (ICU)-level monitoring. Immunotherapy will be permanently stopped.

You may be given intravenous corticosteroid therapy for 3 to 5 days. If there is no improvement within 24 hours, the cardiology and intensive care team may need to use a variety of powerful immunosuppressive drugs to reverse immune attack against the heart muscle. A pacemaker may be needed for people with a fast or abnormal heartbeat.
Eye irAEs

The most common side effects of immunotherapy affecting the eyes are dry eye and uveitis, a type of eye inflammation. A topical steroid is often all that is needed for mild eye issues. More severe symptoms may require intravenous steroid therapy and stopping immunotherapy.

The sclera is the white of the eye. It protects the eye and helps maintain its structure. Inflammation of the sclera is called episcleritis. Episcleritis does not usually affect eyesight and does not always need treatment.

The layer of tissue beneath the sclera is called the uvea. Uveitis is inflammation of one, two, or all three parts of the uvea. If left untreated, uveitis can lead to serious complications, including blindness.

A number of symptoms can be a sign of an ICI-related eye problem, including changes in vision and eye pain. See Guide 7.

For mild eye symptoms, you could continue immunotherapy. Use over-the-counter eye drops (“artificial tears”) to help relieve dryness and irritation. Artificial tears are saline (salt)-based eye drops designed to feel like real tears. They can moisturize and soothe the eyes. You may be referred to an eye specialist (an ophthalmologist).

Uveitis

The most common type of uveitis is iritis. Iritis is inflammation of the colored part of the eye that circles the pupil (the iris). The iris is the front part of the uvea. ICI therapy will be stopped until further notice. In addition to steroid eye drops, you may also be prescribed an oral steroid. Iritis is also called anterior uveitis.

More severe uveitis

Inflammation of the back of the uvea—or of all three parts—is less common and also more serious. Immunotherapy will be permanently stopped. Treatment with both steroid eye drops and an oral steroid is recommended. If your symptoms don’t improve, your doctor may prescribe one or both of following medications:

- Infliximab (Remicade®)
- An antimetabolite such as methotrexate

Episcleritis

While uncommon, it is possible for inflammation of the white of the eye (episcleritis) to impair your vision. If the inflammation causes your eyesight to worsen somewhat, but not drastically, immunotherapy will be stopped until further notice. You will be evaluated
by an ophthalmologist. Treatment with both steroid-based eye drops and an oral steroid is recommended.

If your eyesight worsens significantly, you should be seen by an ophthalmologist right away. Immunotherapy will be permanently stopped. Treatment with both steroid-based eye drops and an oral steroid is recommended.

Acute kidney failure

The kidneys filter blood to remove waste and extra water. Acute kidney failure (also called acute kidney injury) occurs when your kidneys suddenly lose their filtering ability. Wastes may build up, causing your blood’s chemical makeup to get out of balance.

One of the substances filtered out of blood by the kidneys is creatinine, a waste product of muscles. A high level of creatinine in the blood is often an early sign that the kidneys aren’t working well. Acute kidney failure develops rapidly, usually in less than a few days. Signs and symptoms may include:

- Not enough urine
- Swelling in your legs, ankles, or feet
- Shortness of breath
- Fatigue
- Confusion
- Nausea
- Chest pain or pressure
- Seizures or coma in severe cases

Avoiding use of contact lenses, eye makeup, and other irritants can help prevent or relieve eye irritation and discomfort

If you develop signs of acute kidney damage, your doctor will do a review of all medications you are taking, prescribed and over the counter. Certain medications can damage your kidneys if taken at high doses over a long period of time. Any medications that can damage your kidneys will be avoided or limited. The others will be adjusted according to how well your kidneys are working.

Treatment

If your creatinine level goes up slightly during ICI therapy, your doctor might recommend temporarily stopping immunotherapy. Your creatinine and urine protein levels will be monitored.

If your creatinine level goes up two to three times higher than before treatment, immunotherapy will be stopped until further notice. Your creatinine and urine protein levels will be monitored. It may be necessary to remove a small piece of tissue from your kidney in order to test it. This is called a
biopsy. If causes of high creatinine levels other than immunotherapy have been ruled out, corticosteroid therapy with oral prednisone is recommended.

In-hospital care is needed for severe or life-threatening acute kidney injury. Immunotherapy will be permanently stopped. Corticosteroid therapy will be started. You may have a kidney biopsy.

Pancreatitis

The pancreas is a large gland located behind the stomach. Among other jobs, the pancreas makes substances called enzymes that help digest food. Pancreatic amylase helps to digest sugars (carbohydrates). Pancreatic lipase helps to digest fat.

High levels of pancreatic enzymes can be a sign of acute pancreatitis. In autoimmune pancreatitis, the body’s immune system attacks the pancreas, causing inflammation. While rare, acute pancreatitis can occur during ICI therapy.

Mild symptoms include:
- Nausea
- Bloating
- Burping
- Abdominal pain
- Back pain

The levels of these enzymes will be monitored with blood tests during ICI therapy. Mild elevations do not typically cause symptoms and do not require treatment.

In-hospital care is needed for acute pancreatitis. ICI therapy may be stopped, possibly permanently.

The kidneys

The kidneys are a pair of organs found in the belly area (abdomen). Each kidney is about the size of an adult fist. Acute kidney failure is a rare side effect of ICIs.
Review

- ICI side effects affecting the brain, heart, eyes, kidneys, and pancreas are rare but potentially serious.
- Myasthenia gravis causes muscle weakness in the eyes, face, throat, and throughout the body.
- GBS is a serious muscle weakness disorder that can affect the arms and legs, face, breathing muscles, and eye nerves.
- The most common irAEs affecting the eyes are dry eye and uveitis, a type of eye inflammation.
- Myocarditis is a rare but serious condition in which the heart muscle (the myocardium) becomes thick and inflamed.
- High levels of pancreatic enzymes can be a sign of acute pancreatitis. While rare, acute pancreatitis can occur during ICI therapy.

The pancreas

The pancreas is a large gland found behind the stomach. In autoimmune pancreatitis the body’s immune system attacks the pancreas, causing inflammation.
9

Resources

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NCCN Guidelines for Patients® Immunotherapy Side Effects: Immune Checkpoint Inhibitors, 2020
Immune checkpoint inhibitors (ICIs) are the most commonly used type of immunotherapy for cancer treatment. This chapter includes resources for learning more about ICIs and their effects.

ICIs now play a major role in cancer care. They are used to treat advanced melanoma, lung cancer, urothelial cancers, kidney cancers, and others. While their anti-cancer benefits are important, they come with a unique range of side effects.

Understanding the possible side effects of ICI therapy can help you to spot symptoms early and report them to your care team.

Questions to ask

It is normal to have lots of questions about immunotherapy with ICIs. Possible questions to ask your doctor are listed on the following pages. Feel free to use these questions or come up with your own.

Following the questions is a listing of websites that provide information for patients about ICIs and their effects.

When to contact your cancer care team

- If you develop signs and symptoms, such as:
  - Severe fatigue
  - Headache
  - Rash
  - Cough
  - Shortness of breath
  - Chest pain
  - Abdominal bloating
  - Change in bowel habits
  - Weight loss
  - Vision changes or eye pain
  - Severe muscle weakness
  - Severe muscle or joint pains
  - Mood changes

- If you are seen by a new health care provider
- If you are prescribed any new medication
- If you are admitted to the hospital
- Before getting any immunizations or vaccinations
Questions to ask your doctor about immunotherapy with ICIs

1. Is immunotherapy the same as chemotherapy?
2. Am I a candidate for immunotherapy with ICIs?
3. What if I have a pre-existing autoimmune disorder?
4. What if I've had a stem cell transplant?
5. How do ICIs work? Are they safe?
6. Can ICIs be combined with other treatments?
7. Are any immunizations or vaccinations needed before ICI therapy starts?
8. Is it safe to get vaccinated during ICI therapy?
9. What health care is needed during ICI therapy?
10. What if I am pregnant, or planning to become pregnant?
11. Is breastfeeding safe during and after ICI therapy?
12. Should I join a clinical trial?
Questions to ask your doctor about immune-related adverse events (irAEs)

1. What are immune-related adverse events (irAEs)?
2. What are the irAEs of ICI therapy? When do they start? How long do they usually last?
3. Which side effects should I report right away? Who do I call?
4. Which side effects are most common? Which are rare?
5. What can be done to treat side effects?
6. What are the side effects of corticosteroid therapy?
7. What should I do if I get a rash?
8. What can I do about my fatigue?
9. Will I be sick to my stomach or have loose stools or diarrhea?
Websites

AIM with Immunotherapy
aimwithimmunotherapy.org/

Be the Match®
BeTheMatch.org/one-on-one

Good Days
mygooddays.org

Oncology Nursing Society
Immunotherapy Wallet Cards
ons.org/sites/default/files/2019-01/IO%20Card%201-sided_Vertical.pdf

Society for Immunotherapy of Cancer
Understanding Cancer Immunotherapy, 5th Edition
sitcancer.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=567abb47-c7f1-2fa3-b008-053953020940&forceDialog=0#page=1&zoom=auto,-91,783

Stupid Cancer
stupidcancer.org

The Leukemia & Lymphoma Society
lls.org/informationspecialists

The Myositis Association
myositis.org/

Immune-related adverse events can happen even after ICI therapy is over. You should stay alert for new symptoms for at least 1 year after finishing immunotherapy.

Understanding Immunotherapy Side Effects Infographic
National Comprehensive Cancer Network
nccn.org/images/pdf/Immunotherapy_Infographic.pdf

U.S. National Library of Medicine
Clinical Trials Database
clinicaltrials.gov
**Words to know**

**aseptic meningitis**
Inflammation of the membrane covering the brain and spinal cord that is not caused by a bacterial infection.

**blister**
A fluid-filled sac in the outer layer of skin.

**colitis**
Inflammation of the large intestine (colon). A common side effect of ICI therapy.

**CTLA-4**
A protein found on T cells that helps keep the body's immune responses in check. The immune checkpoint inhibitor ipilimumab is used to block CTLA-4.

**diabetes**
Frequent and watery bowel movements. A common side effect of ICI therapy.

**encephalitis**
Inflammation of the brain. A rare side effect of ICI therapy.

**episcleritis**
Inflammation of the thin layer of tissue that covers the sclera (the white part of the eye). A rare side effect of ICI therapy.

**gastritis**
Inflammation of the lining of the stomach.

**giant cell arteritis (GCA)**
Inflammation of the lining of the arteries, especially the arteries in the temples.

**Guillain-Barré syndrome (GBS)**
A rare autoimmune condition in which the body’s immune system attacks the nerves located outside the brain and spinal cord.

**hepatitis**
Inflammation of the liver.

**hyperglycemia**
A higher than normal amount of glucose (a type of sugar) in the blood. Also called high blood sugar.

**hypophysitis**
Inflammation of the pituitary gland.

**hypothyroidism**
A condition in which the thyroid gland does not make enough thyroid hormone. Also called underactive thyroid.

**inflammatory arthritis**
A group of joint inflammation disorders caused by an overactive immune system.

**immune checkpoint inhibitor (ICI)**
A type of cancer treatment that blocks interactions between immune cells and cancer cells.

**immune-related adverse event (irAE)**
A side effect of cancer immunotherapy.

**immunoglobulin replacement therapy**
Treatment for antibody deficiencies. Also called intravenous immunoglobulin (IVIG) when given intravenously.

**maculopapular rash**
A rash with both flat patches (macules) and bumps (papules). A common side effect of ICI therapy.

**myalgias**
Pain in a muscle or group of muscles.

**myasthenia gravis**
A disease in which antibodies made by a person’s immune system prevent certain nerve-muscle interactions. It causes weakness in the arms and legs, vision problems, and drooping eyelids or head.
Words to know

myocarditis
A rare condition in which the heart muscle becomes thick and inflamed and may also become weak.

myositis
Muscle inflammation causing weakness, swelling, and/or pain.

nonsteroidal anti-inflammatory drug (NSAID)
A drug that decreases fever, swelling, pain, and redness. Also called NSAID.

pancreatitis (acute)
Inflammation of the pancreas. A rare side effect of ICI therapy.

PD-1
A protein found on T cells that helps keep the body’s immune responses in check. Immune checkpoint inhibitors are used to block PD-1.

pneumonitis
Inflammation of one or both lungs.

polymyalgia rheumatica (PMR)
An inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders.

primary adrenal insufficiency
A condition in which the adrenal glands don’t make enough cortisol. Also called Addison’s disease.

pruritus
An itching sensation, with or without a rash. A common side effect of ICI therapy.

Stevens-Johnson syndrome (SJS)
A rare but very serious disorder of the skin and mucous membranes.

thyrotoxicosis
Having too much thyroid hormone in the body.

transverse myelitis
A neurological disorder in which both sides of one section of the spinal cord are inflamed.

uveitis
Inflammation of all or part of the middle layer of the wall of the eye (uvea). A rare side effect of ICI therapy.
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This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Immunotherapy-Related Toxicities. It was adapted, reviewed, and published with help from the following people:

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