Immune-related adverse events from checkpoint inhibitors

December 19, 2018 by Josh Farkas

CONTENTS

- Introduction to checkpoint inhibitors
- Core principles of immunotherapy-related adverse events
- Specific organ-system involvement
  - Cardiac
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Nephritis
  - Endocrine
  - Neurologic
  - Hematologic
  - Dermatologic
- Algorithm
- Podcast
- Questions & discussion
- Pitfalls

Introduction to checkpoint inhibitors

We are entering a new era of immunotherapy in cancer. Although this is very promising, it also creates novel and unexpected side-effects.

Agents & mechanism of action of checkpoint inhibitors
These agents prevent inhibition of T-cell responses, thereby up-regulating the anti-tumor immune response. There are three subsets of checkpoint inhibitors as shown above. This distinction isn't terribly important clinically, but it's worth being familiar with the nomenclature.

**common indications for checkpoint inhibitors**

- Melanoma, squamous-cell carcinoma of head and neck
- Lung cancer (both non-small cell and small-cell carcinomas)
- Renal cell carcinoma, urothelial cancer
- Hepatocellular CA, Colorectal carcinoma, Gastric cancer
- Hodgkin’s lymphoma

**rapidly expanding world of checkpoint inhibitors**

- The number of indications for these drugs is currently exploding on a monthly basis.
- Most studies have extensive exclusion criteria (often excluding patients with a history of rheumatologic disorders; see example below).
- When utilized broadly among a more diverse patient population in actual practice, the incidence of toxicity of checkpoint inhibitors may increase. Combination therapy (two checkpoint inhibitors together, or a checkpoint inhibitor plus traditional chemotherapy) may also increase toxicity.
- There are precisely zero RCTs evaluating the treatment of checkpoint inhibitor toxicity, so ideal treatment remains unknown.

---

13 Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient’s participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

14 Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15 Patient is, at the time of signing informed consent, a regular user (including recreational use) of any illicit drugs or has a recent history (within the last year) of substance abuse (including alcohol).

Oncology RCTs often include extremely broad exclusion criteria (example from PMID 25891173).

---

**core principles of immune-related adverse events**

**immune-related adverse events (irAEs)**

- Checkpoint inhibitors lead to dysregulated, hyperactive immune responses which **mimic** autoimmune diseases (e.g. inflammatory bowel disease, interstitial lung disease).
- These events are usually discrete, involving only one organ. However, some tend to occur together (e.g. myocarditis and myositis).
- Any organ can be involved, with the most common sites being the skin, colon, adrenals, lungs, and liver.
Events usually develop within the first few weeks to months after treatment initiation, but can occur at any time. They may even occur months to years after the discontinuation of therapy.

**differential diagnosis, in broad strokes:**
- Acute illness totally unrelated to malignancy.
- Complications of the malignancy itself:
  - Direct progression of disease (e.g. compression of spinal cord, superior vena cava)
  - Indirect complications from malignancy (e.g. venous thromboembolic disease).
- Complications of conventional chemotherapy/radiotherapy in patients exposed to this:
  - Drug toxicity (e.g. radiation pneumonitis)
  - Opportunistic infections
- Complications of immunotherapy
  - Immune-related adverse events
  - Flare of any underlying rheumatologic disease
  - Immune reconstitution inflammatory syndrome (IRIS) causing previously latent tuberculosis to manifest clinically.

**basic evaluation**
- Lab panel: consider, depending on the clinical presentation:
  - CBC with differential, electrolytes
  - Coagulation studies (INR, PTT)
  - Liver function tests
  - Cortisol level
  - TSH & free T4
  - Urinalysis
- Physical examination may include:
  - Bedside echocardiography to evaluate for myocarditis or pericardial effusion
  - Lung ultrasonography (bilateral B-lines with spared areas in between may suggest pneumonitis)

**treatment**
- Treatment varies, depending on the organ involved, but the general rubric is as follows.
- Immune checkpoint inhibitor should be discontinued for any critically ill patient with possible immune-related adverse event.
- 1st line therapy is usually corticosteroid.
  - This doesn’t appear to impair the anti-tumor effect of these drugs.
  - Early initiation of steroid generally carries a favorable prognosis (e.g. ~1-2 mg/kg/day IV methylprednisolone or oral equivalent). Most patients will respond to steroids within 48-72 hours.
- 2nd line treatment is unclear.
  - Little evidence is available regarding this.
  - Various immunosuppressives are used, most often anti-TNF therapy (infliximab).
- For each organ involved, the severity may be graded in order to determine management. The general scheme tends to look something like this:

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Grade</th>
<th>Usual management steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>I</td>
<td>Continue checkpoint inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close monitoring</td>
</tr>
<tr>
<td>Moderate</td>
<td>II</td>
<td>Stop checkpoint inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close monitoring</td>
</tr>
<tr>
<td>Severe</td>
<td>III</td>
<td>Stop checkpoint inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~1 mg/kg/day prednisone/methylprednisolone</td>
</tr>
<tr>
<td>Very severe</td>
<td>IV</td>
<td>Stop checkpoint inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~2 mg/kg/day prednisone/methylprednisolone</td>
</tr>
</tbody>
</table>

**outcome**
- Most immune-related adverse events appear to be reversible, with the exception of endocrine side effects (which may require chronic hormone supplementation).
• Steroid is generally required for a long time (e.g. tapered down over several weeks). This places patients at risk for opportunistic infections, so prophylaxis against pneumocystis jiroveci may be considered.
• Recurrence can occur during steroid taper, even without re-exposure to checkpoint inhibitors.

**cardiac involvement**

**clinical presentations vary, including the following:**

• Myocarditis causing new-onset systolic heart failure, cardiogenic shock.
• Takotsubo cardiomyopathy
• Arrhythmias (heart block, supraventricular or ventricular tachycardias)
• Pericarditis, myopericarditis.

**differential diagnosis includes:**

• Dyspnea due to pneumonitis
• Arrhythmia due to hyperthyroidism
• Shock due to adrenal or pituitary dysfunction

**evaluation**

• EKG
• Echocardiography (may see reduced RV or LV function, with global or regional abnormalities)
• TSH, free T4, cortisol levels
• Troponin (only ~50% sensitive)²
• Creatinine kinase (cardiomyopathy may associate with generalized myositis)
• Cardiac MRI
• Cardiac catheterization

**treatment**

• Steroid therapy may be used for patients with myocarditis or ventricular arrhythmias. Mild-moderate illness can be treated with prednisone 1-2 mg/kg/day. However, if severe or not rapidly prednisone-responsive, consider early institution of pulse-dose steroid (methylprednisolone 1 gram daily) and either mycophenolate mofetil, infliximab, or antithymocyte globulin.
• Additional treatments depend on the clinical presentation, for example:
  • Treatment of heart failure with usual therapies (see chapter on [heart failure](https://emcrit.org/ibcc/chf/)).
  • Treatment of conduction disease may require pacemaker insertion.
  • Pericardial tamponade may require drainage.

more information


**pneumonitis**

**clinical presentation**

• Ranges in severity from sub-clinical to frank respiratory failure.
• Symptoms include dyspnea (53%), cough (35%), fever (12%), and chest pain (7%).²
• *Productive* cough usually doesn't occur, so this might suggest an alternative diagnosis.²

**differential diagnosis includes:**

• Heart failure (e.g. checkpoint inhibitor induced myocarditis)
• Infection (including opportunistic infection, if immunosuppressed by steroid or chemotherapy)
- Pulmonary embolism (both malignancy and checkpoint-inhibitors increase risk)
- Pneumonitis due to other therapies (e.g. radiotherapy, chemotherapy)
- Extension of malignancy (lymphangitic infiltration of the lung, lung metastases, or pulmonary tumor emboli)
- Flare of underlying interstitial lung disease
- Neuromuscular weakness (e.g., checkpoint-inhibitor induced myasthenia gravis)
- Diffuse alveolar hemorrhage (if severe chemotherapy-induced thrombocytopenia)

**Imaging Features**

<table>
<thead>
<tr>
<th>Radiologic Subtypes</th>
<th>Representative Image</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic organizing pneumonia-like (n = 5, 19%)</td>
<td>![Image]</td>
<td>Discrete patchy or confluent consolidation with or without air bronchograms. Predominantly peripheral or subpleural distribution</td>
</tr>
<tr>
<td>Ground glass opacities (n = 10, 37%)</td>
<td>![Image]</td>
<td>Discrete focal areas of increased attenuation. Preserved bronchovascular markings</td>
</tr>
<tr>
<td>Interstitial (n = 6, 22%)</td>
<td>![Image]</td>
<td>Increased interstitial markings, interlobular septal thickening. Peribronchovascular infiltration, subpleural reticulation. Honeycomb pattern in severe patient cases</td>
</tr>
<tr>
<td>Hypersensitivity (n = 2, 7%)</td>
<td>![Image]</td>
<td>Centrilobular nodules. Bronchiolitis-like appearance. Tree-in-bud micronodularity</td>
</tr>
<tr>
<td>Pneumonitis not otherwise specified (n = 4, 15%)</td>
<td>![Image]</td>
<td>Mixture of nodular and other subtypes. Not clearly fitting into other subtype classifications</td>
</tr>
</tbody>
</table>

Noldoo J et al. PMID 27646942

- Chest X-ray has a sensitivity of only ~75%. 
- CT scan is required. Consider using contrast to evaluate for pulmonary embolism.
- Radiographic patterns are variable, mimicking common interstitial diseases as shown above.
- Some features aren’t commonly seen (cavitation, pleural effusion). These should arouse suspicion for an alternative diagnosis.

**Basic Evaluation**

- Chest CT scan (see above).
- Bedside echocardiography to evaluate for myocarditis.
- Blood cultures, sputum culture & gram stain, procalcitonin, urine pneumococcal and legionella antigens.
- During influenza season: Viral PCRs.
- If concern for fungal infection: Beta-D-glucan serum assay, antigens for endemic fungi (e.g. histoplasma, blastomycoses, cryptococcus neoformans)
- If concern for neuromuscular weakness, check negative inspiratory force (NIF) and forced vital capacity (FVC)
The utility of bronchoscopy in checkpoint-inhibitor-associated respiratory failure is currently unknown. While some authors promote the use of bronchoscopy, others report treating patients empirically without bronchoscopy. There is no finding on bronchoscopy that proves the diagnosis of checkpoint inhibitor pneumonitis. The role of bronchoscopy is primarily to exclude infection (especially pathogens that require specific antibiotic therapy: fungus, tuberculosis, or pneumocystis jiroveci). Thus, bronchoscopy is most important among patients with immunocompromise or imaging features suggestive of fungal/mycobacterial infection (e.g. nodular infiltrates, cavitation).

Should unstable patients be intubated solely to facilitate bronchoscopy?

- Some patients are encountered who are doing OK, yet are too unstable for bronchoscopy (e.g. on 60-80% FiO2 via high-flow nasal cannula). A classic conundrum is whether to intubate such patients in order to facilitate bronchoscopy.
- For each patient, the benefits of bronchoscopy must be weighed against the risks of intubation and mechanical ventilation. This should involve an informed discussion with the patient including risks/benefits of various strategies.
- From an evidentiary standpoint, bronchoscopy has never been shown to improve mortality (not even among immunosuppressed pneumonia patients). Meanwhile, intubation of critically ill patients has repeatedly been demonstrated to carry a small, yet real mortality of ~2%. Intubation also increases the risk of delirium and ventilator-associated pneumonia. This makes intubation solely for the purpose of bronchoscopy difficult to justify.
- A reasonable compromise may be to initiate empiric therapy and consider delayed bronchoscopy after 1-2 days (by which point the patient will often have improved). Delaying bronchoscopy will reduce the yield for bacterial pathogens, but pneumocystis and fungal studies are likely to remain positive. Sometimes lab tests will return within this time frame, which make bronchoscopy unnecessary (e.g. positive urine pneumococcal antigen).
treatment overview

Patients with asymptomatic radiographic abnormalities may not require any therapy (aside from discontinuing the checkpoint inhibitor and closely monitoring). The remainder of this section refers to patients admitted to the hospital with respiratory failure (Grade 3-4 toxicity).

**treatment: antimicrobial**

- It is rarely possible to be entirely certain of the diagnosis of pneumonitis immediately, so patients will often be covered with antibiotics. As laboratory tests return and the diagnosis becomes clear, these antibiotics should be discontinued.
- 1) Antibacterial therapy
  - Most patients will be treated initially to cover pneumonia (e.g. ceftriaxone/azithromycin).
  - If procalcitonin and other microbiologic studies are negative, antibiotics can generally be discontinued.
- 2) Pneumocystis jirovici (PJP) therapy
  - PJP can cause radiographic patterns that look exactly like checkpoint-inhibitor pneumonitis (e.g. diffuse, patchy, ground-glass opacification).
  - Empiric therapy with trimethoprim-sulfamethoxazole may be reasonable if the patient is at risk for PJP and has a CT scan which is consistent with PJP.
- 3) Antifungal therapy (e.g. histoplasma, blastomycosis, cryptococcus neoformans)
  - Checkpoint inhibitor pneumonitis with a cryptogenic organizing pneumonia (COP) pattern may resemble fungal pneumonia (with dense nodules and patchy consolidation; image above).
  - For patients at risk for fungal pneumonia (due to immunosuppression or exposure) and with a CT scan consistent with fungal pneumonia, empiric coverage with isovuconazonium is reasonable while awaiting microbiologic studies. Isovuconazonium is a newer anti-fungal agent which lacks the toxicity of amphotericin.

**treatment: immunomodulatory**

- The mainstay of therapy is 1-2 mg/kg/day of prednisone or methylprednisolone.
  - 86% of patients will respond to this within a few days.9
  - Pneumonitis may recur following rapid steroid taper, so a minimum treatment duration of 4-6 weeks may be beneficial.2
  - 14% of patients respond poorly to steroid.
    - Ideal treatment for these patients is unknown. Historically they tend to do poorly.9
    - Recommended steroid doses vary between articles. In the absence of any solid data, it's possible that higher steroid doses (e.g. 4 mg/kg/day) could be attempted in patients refractory to lower doses (30189190).
    - Other options include infliximab 5-10 mg/kg, IV immunoglobulin, mycophenolate mofetil, or tocilizumab

**sarcoidosis-mimic**

https://emcrit.org/ibcc/checkpoint/
Less common than pneumonitis, checkpoint inhibitor pneumonitis may mimic sarcoidosis. Beyond pulmonary involvement, this may involve other organs (ocular, myocardial, neurologic, hypercalcemia).

more information

ASC0 2018 guidelines, page 15 pneumonitis

presentation

Diarrhea is generally the first symptom. While often mild, this may progress to colitis with pain, fever, and mucus in stool. Upper gastrointestinal tract involvement can occur, with nausea and vomiting. Toxic megacolon and perforation occur in ~1% of patients.

evaluation

Stool testing for bacterial pathogens, clostridioides difficile, and norovirus. May also consider testing for shiga toxin (considering E. coli O157:H7), listeria, aeromonas, yersinia, and vibrio. CT scan of the abdomen to evaluate distribution and exclude perforation. Checkpoint inhibitor colitis tends to have one of three patterns: pancolitis, segmental colitis with diverticulosis, or isolated rectosigmoid colitis without diverticulosis. Colonoscopy with biopsies may be used to exclude alternative diagnoses (e.g. CMV or ischemic colitis) and guide therapy (if ulceration is seen, this predicts steroid-refractory disease requiring infliximab). In cases of diarrhea without CT findings of colitis, upper endoscopy with biopsies may also be considered to evaluate for gastric or duodenal involvement.

treatment

Fluid resuscitation as needed for volume depletion. Avoid agents that reduce gut motility (e.g. opioids, loperamide). Steroid

- Indicated if >6 stools per day, hospitalization required due to colitis, or more serious complications.
- Dose equivalent to 1-2 mg/kg/day prednisone, depending on severity. Remember to taper slowly over 5-6 weeks.
- Surgical consultation for perforation or toxic megacolon.
- For severe disease that doesn’t respond to steroid within ~3 days, infliximab 5-10 mg/kg may be added. Mycophenolate mofetil can be considered, and occasionally surgery is necessary.

more information

ASC0 2018 guidelines, page 10: colitis

hepatitis

clinical findings

Usually asymptomatic, but there may be fever and jaundice. Mostly elevated AST/ALT, but bilirubin can be increased. Rarely can lead to fulminant hepatic failure and death.

differential diagnosis includes:

- Hepatitis due to other medications
- Alcoholic hepatitis
- Viral hepatitis
- Reactivation of chronic hepatitis (e.g. autoimmune hepatitis)
- Budd-Chiari syndrome
- Liver metastases
- Shock liver due to myocarditis
- Biliary obstruction

**evaluation**

- Obtain alcohol history.
- Review drug history for potential hepatotoxins (including over-the-counter drugs containing acetaminophen, supplements, and chemotherapeutic agents).
- Review other medications and supplements for potential hepatotoxins.
- Evaluate perfusion & vital signs, echocardiogram if needed (exclude shock liver).
- Labs for viral hepatitis (including HAV, HBV, HCV, and HSV), autoimmune hepatitis (ANA, anti-smooth muscle antibodies, liver-kidney microsomal antibody).
- Hepatic ultrasound, including doppler (to exclude Budd-Chiari syndrome, biliary obstruction)

**treatment**

- Discontinue all potentially hepatotoxic medications.
- Immunosuppressive therapies are shown in the table below. Resolution usually takes about two months.  

```
<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade I: Asymptomatic liver abnormality, AST/ALT elevated up to 3x upper limit, OR Bilirubin elevated up to 1.5x upper limit | - May continue immune checkpoint inhibitor 
- Observe lab monitoring |
| Grade II: Asymptomatic liver abnormality, AST/ALT 3-5x upper limit, OR Bilirubin 1.5-3x upper limit | - Stop immune checkpoint inhibitor 
- May use 0.5-1 mg/kg prednisone for symptoms and laboratory abnormalities that don't abate after 3-5 days |
| Grade III: Symptomatic liver dysfunction, OR AST/ALT > 5x upper limit, OR Bilirubin > 3x upper limit | - Stop immune checkpoint inhibitor 
- Methotrexate 1-2 mg/kg/day (or equivalent) 
- If no improvement after 3 days, consider mycophenolate mofetil or cyclosporine |
| Grade IV: Severe symptoms (e.g. jaundice, encephalopathy), OR AST/ALT > 10x upper limit, OR Bilirubin > 5x upper limit | - Stop immune checkpoint inhibitor 
- Methotrexate 2 mg/kg/day (or equivalent) 
- If no improvement after 2 days, consider mycophenolate mofetil 500-1000 mg BID |
```

more information


**nephritis**

The most common form of renal toxicity is acute tubulointerstitial nephritis (ATIN), which is what the remainder of this section explores. However, some cases of glomerulonephritis have also been reported. Additionally, checkpoint inhibitor-induced microangiopathic hemolytic anemia can cause renal failure (more on this in the hematology section below).

**presentation**

- Usually asymptomatic laboratory abnormality.
- Can present with manifestations of renal failure, for example:
  - Accumulation of renally cleared medications.
  - Uremic encephalopathy, poor appetite
  - Volume overload, electrolyte abnormalities

**evaluation**

- Nephritis is one of the less common toxicities of immune checkpoint inhibitors, so these patients require a thorough evaluation to exclude other causes of renal failure (e.g. obstruction, other nephrotoxic medications, volume depletion).
- CBC and blood smear should be performed to exclude microangiopathic hemolytic anemia (checkpoint inhibitors can cause thrombotic thrombocytopenic purpura or hemolytic uremic syndrome).
Creatinine kinase should be measured to exclude checkpoint inhibitor-induced myositis causing rhabdomyolysis. Urinalysis may be entirely normal. Abnormalities that may be seen include mild proteinuria (<1 gram/day), sterile leukocyturia, microscopic hematuria, and granular casts. Renal biopsy isn't needed if there is no alternative cause of kidney injury.

**treatment**

- Prompt steroid initiation may prevent further kidney injury.
- Initial treatment is shown below. If this treatment fails, then additional immunosuppression may be considered (e.g. mycophenolate mofetil).

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Creatinine increase of &gt;0.5 mg/dl</td>
</tr>
<tr>
<td>Grade II</td>
<td>Creatinine 1.5-3x baseline level</td>
</tr>
<tr>
<td>Grade III</td>
<td>Creatinine 3-5x baseline level</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Creatinine &gt;5x baseline, OR</td>
</tr>
<tr>
<td>Grade V</td>
<td>Life-threatening electrolyte abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Consider temporarily holding immune checkpoint inhibitor</td>
</tr>
<tr>
<td>Grade II</td>
<td>Hold immune checkpoint inhibitor</td>
</tr>
<tr>
<td>Grade III</td>
<td>Evaluate for other causes, if excluded then start 0.5-1 mg/kg/day prednisone</td>
</tr>
<tr>
<td>Grade IV</td>
<td>If worsening or no improvement, then increase to 1-2 mg/kg/day prednisone</td>
</tr>
<tr>
<td>Grade V</td>
<td>Same as for Grade II, but permanently discontinue immune checkpoint inhibitor</td>
</tr>
</tbody>
</table>

*Based on ASCO 2018 guidelines, PRO 20442340*

Endocrinopathies occur in ~10% of patients on checkpoint inhibitors. The possibility of either central (pituitary) failure or peripheral (thyroid/adrenal) failure makes this especially complex. Endocrine toxicity is distinct from most other organ toxicities for two reasons:

1. Treatment with steroids usually isn’t used. Treatment focuses on managing the patient clinically (e.g. with hormone replacement), rather than trying to save the endocrine gland.
2. Organ dysfunction is often persistent, requiring chronic hormone replacement.

**primary hypothyroidism**

- Symptoms are those of hypothyroidism (e.g. fatigue, weight gain, cold intolerance, constipation, depression).
- Diagnosed on the basis of elevated TSH and low free T4.
- Treatment: Thyroid hormone replacement as clinically indicated.

**hyperthyroidism**

- **Two forms**
  - 1) *Thyroiditis* is more common – causes milder hyperthyroidism. Over several weeks this destroys the gland, leading to permanent hypothyroidism.
  - 2) *Graves’ disease* is much less common – antibodies stimulate thyroid activity, leading to more persistent and severe hyperthyroidism.
- **Symptoms**
  - Hyperthyroidism (e.g. weight loss, heat intolerance, dyspnea, diarrhea, tremor, palpitations).
  - Graves disease may cause additional symptoms: opthalmopathy and digital clubbing.
- **Diagnosis**
  - Hyperthyroidism is diagnosed on basis of reduced TSH and elevated free T4.
  - Thyroiditis may be differentiated from Graves disease based on serologies (e.g. thyroid stimulating hormone receptor antibody) and radioactive iodine uptake by the thyroid
- **Treatment**

---

Mild-moderate symptoms: consult endocrinology, may consider thionamide (steroid not usually needed).
Severe symptoms: prednisone 1-2 mg/kg/day plus additional therapies as needed to treat thyroid storm.

**primary adrenal insufficiency**

- **Symptoms** range from chronic adrenal insufficiency (e.g. fatigue, weight loss) to adrenal crisis (distributive shock).
- **Evaluation**:
  - Basic labs
  - AM cortisol & ACTH levels (should see low cortisol and elevated ACTH level).
  - If urgent situation or persistent diagnostic confusion: ACTH stimulation test
  - CT scan to evaluate for adrenal metastases/hemorrhage.
- **Differential diagnosis**: Must sort this out from pituitary dysfunction based on ACTH level (see below).
- **Treatment**:
  - Mild symptoms: Start hydrocortisone replacement at usual dose (e.g. 10-20 mg in the morning and 5-10 mg in the afternoon).
  - Moderate symptoms: Start hydrocortisone at twice normal dose (e.g. 20-30 mg in the morning and 10-20 mg in the afternoon).
  - Severe symptoms: Start steroid without delay (either hydrocortisone 100 mg IV q8hr, or 4 mg dexamethasone if the diagnosis is uncertain). Additional aspects of treating adrenal crisis are discussed [here](https://emcrit.org/ibcc/adrenal-crisis/).

**pituitary dysfunction (hypophysitis)**

- **Symptoms**
  - Usually present with adrenal insufficiency, but can also present with elements of hypothyroidism, diabetes insipidus, and hypogonadism.
  - Headache (85%).
- **Evaluation** (pituitary dysfunction causes all hormone levels to be decreased)
  - Electrolytes
  - AM cortisol and ACTH levels
  - TSH and free T4
  - Lutenizing hormone, follicle-stimulating hormone, and either testosterone/estrogen level.
  - Brain MRI to evaluate pituitary, exclude other abnormalities.
- **Treatment**
  - Glucocorticoid replacement if needed (same as for primary adrenal insufficiency above). For severe symptoms, consider prednisone 1-2 mg/kg daily to decrease pituitary inflammation.
  - Thyroid replacement if needed (same as for primary hypothyroidism above).
  - Make sure to start glucocorticoid replacement before thyroid replacement, to avoid precipitating adrenal crisis.
  - Endocrinology consultation, sex hormone replacement PRN.

**diabetes**

- May cause new-onset, autoimmune type-I diabetes, including diabetic ketoacidosis (DKA).
- The differential diagnosis here often centers around type-II diabetes vs. type-I diabetes. Serologies may help sort this out (anti-glutamic acid decarboxylase, anti-islet cell, or anti-insulin autoantibodies). For immediate clinical management, however, this doesn't matter.
- Diagnosis and treatment of diabetic ketoacidosis is explored [here](https://emcrit.org/ibcc/dka/).

**neurologic**

**myasthenia gravis**

- **Symptoms**: Fatigable and fluctuating weakness, especially involving ocular and bulbar muscles.
- **Differential diagnosis includes**

more information

• Myositis (including oculobulbar myositis) or Miller-Fisher variant of Guillain-Barre syndrome may present with prominent ocular/bulbar symptoms.
• Patients presenting with dyspnea: Pneumonitis, myocarditis

**Evaluation**
• Creatinine kinase, aldolase (to evaluate for myositis)
• Acetylcholine receptor and anti-striated muscle antibodies
• MRI of brain and/or spine may be useful, depending on anatomic distribution of weakness
• Electrodiagnostic studies

**Treatment**
• Pyridostigmine starting 30 mg TID and up-titrating to a maximum of 120 mg QID as tolerated.
• Prednisone 1-1.5 mg/kg/day.
• IVIG (0.4 grams/kg/day for five days) or plasmapheresis for severe symptoms (including any dyspnea, facial weakness, or dysphagia)
• Avoid medications that can worsen myasthenia (beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides, macrolides)

**Guillain-Barre syndrome**

• **Symptoms**: Progressive, ascending, symmetric muscle weakness which may eventually involve respiratory and bulbar muscles. Often starts with sensory symptoms or neuropathic pain in legs. May cause dysautonomia.

• **Differential diagnosis includes**
  - Myositis
  - Spinal cord pathology

**Evaluation**
• Creatinine kinase, aldolase (to evaluate for myositis)
• MRI of the spine
• Lumbar puncture: typically, elevated protein and often elevated WBCs (unlike classic Guillain-Barre syndrome).
• Serum antiganglioside antibody tests for Guillain-Barre syndrome
• Electrodiagnostic studies

**Treatment**
• IVIG (0.4 grams/kg/day for five days) or plasmapheresis
• Methylprednisolone 2-4 mg/kg/day

**Transverse myelitis**

• **Symptoms**: Acute or subacute weakness or sensory changes bilaterally, often with increased deep tendon reflexes (unlike Guillain-Barre syndrome, which causes reduced reflexes).

• **Differential diagnosis includes**: Guillain-Barre syndrome, myasthenia gravis, myositis, abscess, malignancy

• **Evaluation**: MRI spine, lumbar puncture.

• **Treatment**:
  - Methylprednisolone (either 2 mg/kg/day or strongly consider a pulse dose of 1 gram/day for 3-5 days)
  - Strongly consider IVIG

**Encephalitis**

• **Symptoms**: Confusion, altered behavior, headache, seizures, memory loss, focal weakness, speech abnormality, reduced level of consciousness.

• **Differential diagnosis includes**: Infection, paraneoplastic encephalitis, brain metastases, thyroid disease

**Evaluation**
• Brain MRI (may be normal, might see T2 FLAIR signals similar to autoimmune encephalopathies or limbic encephalitis)
• Lumbar puncture (may see lymphocytic pleocytosis, elevated protein). In addition to usual studies, check oligoclonal bands and [autoimmune encephalopathy panel](https://uvmlabs.testcatalog.org/show/ENC1).
• TSH and free T4

**Treatment**
• Antibiotics and acyclovir until CSF results return.
- Methylprednisolone 1-2 mg/kg. However, if severe symptoms or oligoclonal bands are present, consider pulse steroid (methylprednisolone 1 gram IV daily for 3-5 days) plus IVIG 0.4 grams/kg/day for five days.
- If positive for autoimmune encephalopathy antibody and there is limited improvement, consider rituximab or plasmapheresis.

**other neurologic complications:**
- Peripheral neuropathy
- Autonomic neuropathy
- Aseptic meningitis
- Posterior reversible encephalopathy syndrome (PRES)
- Optic neuritis, flare of underlying multiple sclerosis

more information

- ASCO 2018 guidelines, page 30: nervous system toxicities

---

**autoimmune hemolytic anemia**

- **Symptoms:** Weakness, pallor, jaundice, dark urine.
- **Differential diagnosis includes:** Hemorrhage, marrow-toxic medication, aplastic anemia
- **Evaluation**
  - CBC
  - Reticulocyte count
  - Hemolysis labs (LDH, haptoglobin)
  - DIC panel (INR, PTT, fibrinogen)
  - Direct agglutinin test
- **Treatment**
  - Prednisone 1-2 mg/kg/day
  - Conservative transfusion strategy (target 7 mg/dL)
  - Folic acid supplementation.
  - If steroid-refractory, start other immunosuppressives (e.g. rituximab, IVIG, cyclosporin A, mycophenolate mofetil)

**immune thrombocytopenia**

- **Symptoms:** Petechiae, bleeding.
- **Differential diagnosis includes:** Drug-induced marrow toxicity; post-viral; disseminated intravascular coagulation; aplastic anemia; thrombotic thrombocytopenic purpura; atypical hemolytic uremic syndrome
- **Evaluation**
  - CBC with differential, blood smear.
  - Testing for HIV, HCV, HBV.
  - Reticulocyte count, direct agglutinin test to exclude Evan's syndrome (concurrent autoimmune hemolytic anemia and thrombocytopenia)
  - Bone marrow aspiration (if other cell lines decreased and there is concern for aplastic anemia).
- **Treatment**
  - Prednisone 1-2 mg/kg/day.
  - IVIG 1 gram/kg one-time dose, if a more rapid increase in platelet count is required.

**lymphopenia**

- **Symptoms**
  - May lead to opportunistic infections similar to those seen in AIDS (e.g. pneumocystis jirovecii pneumonia). Note that CD4+ T-cells are a subset of lymphocytes, so the CD4 count must always be lower than the lymphocyte count.
Differential diagnosis includes: Lymphocyte-depleting therapy (e.g. anti-thymocyte globulin, cytotoxic chemotherapy, radiation exposure).

Evaluation
- CBC with differential, peripheral smear (lymphopenia defined as <1,500 lymphocytes/mm3).
- Chest x-ray for evaluation of thymoma.
- Tests for HIV, CMV
- CD4+ T-cell count

Treatment
- If lymphocyte count <250/mm3, start prophylaxis for pneumocystis jirovecii and mycobacterium avium complex.

aplastic anemia

Symptoms: May cause failure of all cell lines (anemia, thrombocytopenia, neutropenia)

Differential diagnosis includes: Marrow failure due to medications, radiation, toxin, or recent viral infection.

Evaluation
- CBC, reticulocyte count
- Viral studies including CMV, HHV6, EBV, parvovirus
- B12 level
- Bone marrow aspiration

Treatment
- Erythrocyte transfusion as needed (should be irradiated and filtered)
- Platelet transfusion as indicated
- If severe: Anti-thymocyte globulin and cyclosporine

acquired thrombotic thrombocytopenic purpura (TTP) -OR- atypical hemolytic uremic syndrome (aHUS)

Symptoms
- Both TTP and aHUS: non-palpable purpura, renal failure, fever, abdominal pain and vomiting
- More suggestive of TTP: neurologic abnormalities (e.g., seizure, hemiplegia, visual disturbances)

Differential diagnosis includes
- Disseminated intravascular coagulation
- Intracranial hemorrhage
- Renal failure due to acute tubulointerstitial nephritis
- Microangiopathic hemolytic anemia due to other drugs (e.g. chemotherapy, cyclosporine, tacrolimus)

Evaluation
- CBC with differential and peripheral blood smear
- Hemolysis labs (LDH, haptoglobin)
- DIC panel (INR, PTT, fibrinogen)
- ADAMTS13 activity level and inhibitor titer
- Complement testing: C3, C4, CH50
- Urinalysis
- If diarrhea: test for bacterial pathogens (shigella, E. coli 0157:H7)

Treatment
- Steroid: Either prednisone 1 mg/kg/day or pulse dose steroid (methylprednisolone 1 gram IV for 3 days) depending on severity.
- TTP: Plasma exchange
- aHUS: Eculizumab 900 mg weekly

acquired hemophilia A

Symptom: Bleeding, due to antibody which inhibits Factor VIII.

Evaluation: CBC, Coagulation studies (INR, PTT, thrombin time, fibrinogen), Mixing study, Quantification of inhibitor level

Treatment
- Prednisone 1-2 mg/kg/day +/- rituximab.
- Factor replacement and transfusion support
Presentations are numerous, may include:

- Maculopapular rash
- Maculopustular rash, bullae
- Vitiligo
- Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis
- Drug reaction with eosinophilia and systemic symptoms (DRESS)

Investigation

- Review medication list to evaluate for any other potential causes (e.g. drugs linked to Steven Johnson Syndrome / Toxic Epidermal Necrolysis).
- Consult dermatology, consider skin biopsy if nature of rash is unclear.

Treatment

- Mild rashes may be managed with antihistamines and topical steroid.
- Steroid is indicated for more severe involvement, with a dose roughly proportional to the severity of the rash. For example:
  - Blistering involves 10-30% body surface area: Prednisone 1 mg/kg/day
  - Signs of Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis: Prednisone 2 mg/kg/day.
- Consider antibiotics if signs of secondary cellulitis.

Algorithm

One approach to probable checkpoint-inhibitor pneumonitis

- **Empiric therapy**
  - Azithromycin, beta-lactam
  - Prednisone 1-2 mg/kg/d
  - High flow nasal cannula
- **Stable enough for bronch?**
  - Either Imubered or relatively low oxygen requirement
  - **Yes**
    - Bronchoscopy, then start prednisone & antibiotics therapy. De-escalate based on bronchoscopy result
  - **No**
    - Narrow treatment as results return. For example, if procalcitonin is negative, stop beta lactam. Broenchscopy if no improvement
- **Empiric therapy**
  - Azithromycin, beta-lactam
  - Prednisone 1-2 mg/kg/d
  - TMP/SMX if concern for PIP
  - Itraconazole if concern for fungal pneumonia
  - High flow nasal cannula
- **Follow up noninvasive workup**
  - Consider bronchoscopy after 24-48 hours of therapy (patients may improve rapidly, allowing safe bronchoscopy & de-escalation)

Remember that checkpoint inhibitor reactions can occur months after initiation of treatment (or even after stopping the checkpoint inhibitor entirely).

- Maintain a broad differential diagnosis, including disorders related to the checkpoint inhibitor, complications of the malignancy itself, toxicity related to other interventions (e.g. chemotherapy, radiotherapy), as well as the possibility of entirely unrelated new diseases.

- Diagnosis of an immune-related adverse reaction from a checkpoint inhibitor may be difficult to make with 100% certainty. In many situations, empiric steroid may be required while continuing to sort out the situation (and sometimes while providing concomitant antibiotic therapy).

**Going further:**


6. Horvat T, Adel N, Dang T, et al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time...


