

Identification and Management of Immune-Related Adverse Events in the Emergency Setting

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Disclosures

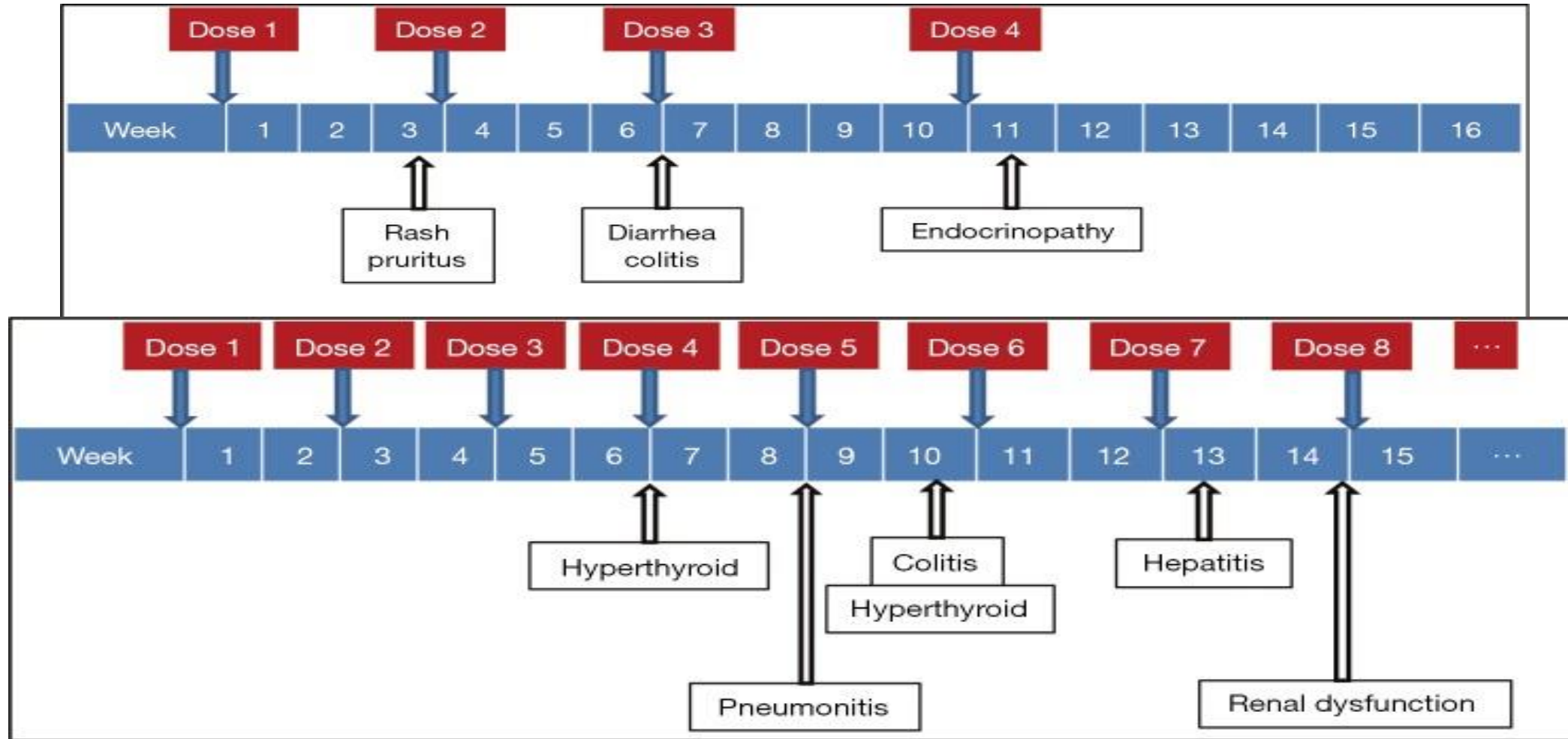
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Mechanism CTLA-4 & PD-1

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity
- Autoimmune type response
 - Thinking “Chemo” will lead down wrong path
 - **Think Graft versus Host disease**

Timing

- Most occur within first 3 months
- May occur after final dose
- Some dose dependent
- Grade 3-4 toxicity - 10% overall



Dermatologic Toxicity

Dermatologic Toxicity

- Presents three weeks into therapy
- **Mild**
 - Maculopapular rash
 - With or without symptoms
 - Pruritus, burning, tightness
 - 10%-30% TBSA
 - Limiting ADL's
 - Topical steroids, hydroxyzine, diphenhydramine
- **Moderate**
 - Diffuse, non-localizing rash
 - 30-50% TBSA
 - Topical corticosteroids, hydroxyzine, diphenhydramine
 - Consider systemic corticosteroids if no improvement in one week (0.5-1mg/kg/day)

Dermatologic Toxicity

- **Severe**

- Blisters, dermal ulceration, necrotic, bullous or hemorrhagic
- Systemic corticosteroids 1-2 mg/kg/day prednisone equivalent
- Taper over one month following improvement

Stevens Johnsons Syndrome (SJS) TEN (Toxic Epidermal Necrolysis)



Dermatologic Toxicity

- **Vitiligo**
 - Most cases permanent
 - No treatment
 - Intra-oral lesions – consider candidiasis



Vitiligo



Patient 1

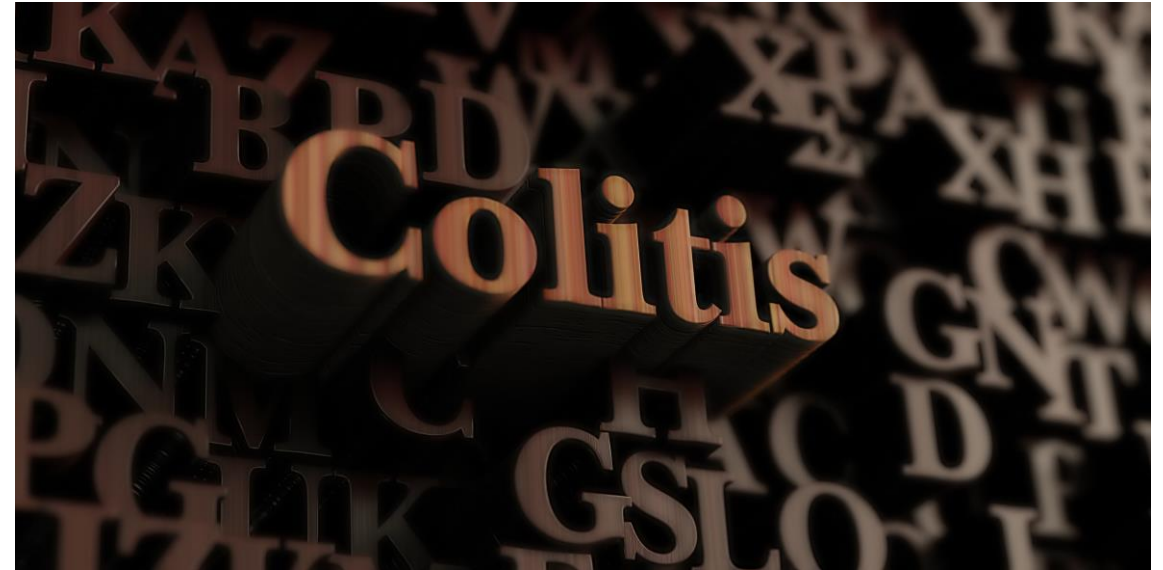




- PMH:
 - Small cell lung cancer
 - Hypertension
 - Diabetes
- Meds:
 - Nivolumab

Management

- Evaluation
 - Stool studies
 - CT imaging
- Treatment
 - Hydration
 - Analgesia, anti-emetics
 - Antibiotics
 - Steroids



Diarrhea / Colitis

Diarrhea / Colitis

- **Mild**
 - ≤ 4 stools above baseline/day
 - Testing
 - C-diff, lactoferrin, O&P, stool cultures
 - Treatment
 - Symptomatic: oral hydration & bland diet
 - No corticosteroids
 - Avoid antidiarrheal medications

Diarrhea / Colitis

- **Moderate**
 - 4-6 stools above daily baseline
 - Symptoms
 - Abdominal pain, blood or mucus in stool
 - Testing
 - C-diff, lactoferrin, O&P, stool cultures
 - Systemic corticosteroids
 - 0.5mg/kg/day prednisone equivalent if symptoms > one week

Diarrhea / Colitis

- **Severe**
 - ≥ 7 stools above daily baseline
 - Symptoms
 - Peritoneal abdomen
 - Ileus
 - Fever
 - Testing
 - Stool studies
 - Rule out perforation
 - Admission

Diarrhea / Colitis

- **Severe**
 - Consider empiric antibiotics for fever or leukocytosis
 - Systemic corticosteroids - 1-2mg/kg/day equivalent, if no perforation
 - Hold if clinically stable until stool studies available (24hrs)
 - Unstable – high dose corticosteroids: methylprednisolone 125 mg IV daily x 3 days to evaluate responsiveness
- **Other**
 - Infliximab 5 mg/kg if no response to corticosteroids
 - Consider mycophenolate mofetil for select patients

Hepatotoxicity

Hepatotoxicity

- 8-12 weeks after therapy initiation
- Avoid alcohol and acetaminophen



Hepatotoxicity

Grade 2 toxicity

- $2.5 < \text{AST/ALT} < 5$ times normal
- $1.5 < \text{Bilirubin} < 3$ times normal
- Corticosteroids 0.5-1 mg/kg/day,
1 month taper

Grade ≥ 3 toxicity

- Admission
- Methylprednisolone IV 125mg/day
- Consider mycophenolate mofetil
500mg PO Q12hrs

Endocrinopathies

Endocrinopathies

- 6 weeks after the initiation of therapy
- Rare
 - <10%
- Both CTLA & PD-1 inhibitors
- Dose dependent



Endocrinopathies

- **Hypothyroidism**
 - 1 wk to 19 months after onset of therapy
 - Appropriate levothyroxine replacement
- **Hyperthyroidism**
 - Acute thyroiditis secondary to immune activation
 - Corticosteroids 1 mg/kg for symptomatic patients
- **Adrenal Insufficiency**
 - Admission
 - Corticosteroids 60-80 mg prednisone or equivalent

Endocrinopathies

- **Hypophysitis**
 - 1-2 months after initiation of therapy
 - Fatigue, headaches, visual field defects
 - ACTH, TSH, FSH, LH, GH, prolactin
 - Imaging – enlarge pituitary gland
 - Steroids
 - Corticosteroids 1 mg/kg/day
 - Dexamethasone 6 mg IV Q6hr x 3 days
 - Methylprednisolone 125 mg IV daily

Pneumonitis

Pneumonitis

- 5 months after treatment initiation
- Occur with CTLA-4 & PD1 inhibitors
- New cough or dyspnea
- Multiple grades

Pneumonitis

- Grade 2
 - Admission
 - Prednisone/prednisolone
 - Taper over one month after improvement seen
- Grade 3-4
 - Admission
 - Prednisone/prednisolone
 - Six week taper



Pancreatitis

Pancreatitis

- Elevation amylase & lipase
 - With both CTLA-4 & PD1 inhibitors
 - Without overt pancreatitis
 - Monitor
 - Grade 3-4 with symptoms
 - Hold immunotherapy
- New onset diabetes with DKA
 - Aggressive treatment of DKA
 - With severe disease, consider steroids for adrenal insufficiency

Patient 2



Renal Insufficiency

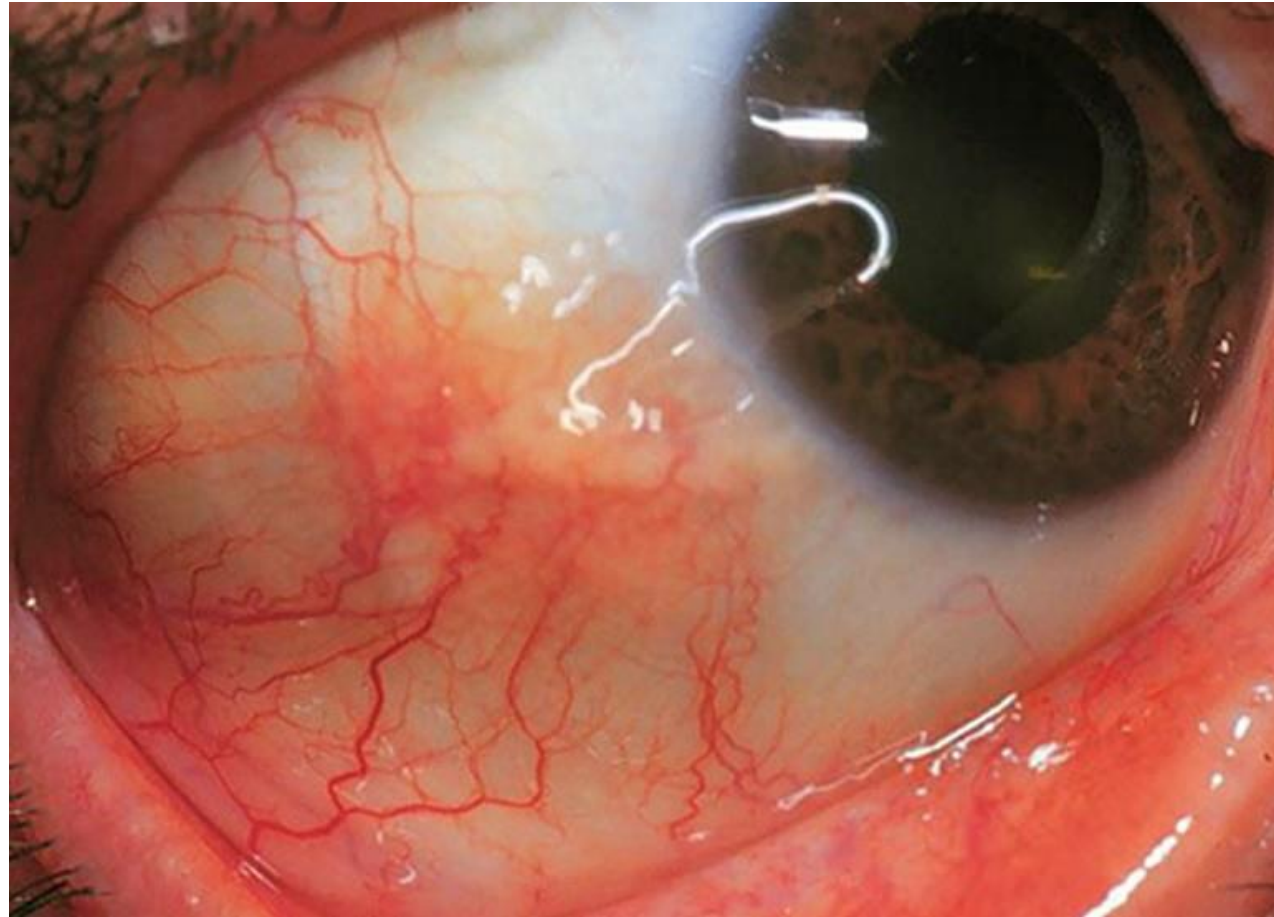
Renal Insufficiency

- 10-12 months after initiation of treatment
- Rare, < 1%
- Grade 1: up to 1.5 times above baseline
- Grade 2 to 3: 1.5-6 times baseline
 - Full recovery with high dose corticosteroids (>40 mg/day)

Ophthalmologic

Ophthalmologic

- Rare, <1%
- Episcleritis



Ophthalmologic

- Rare, <1%
- Episcleritis
- Scleritis



Ophthalmologic

- Rare, <1%
- Episcleritis
- Scleritis
- Conjunctivitis



Rare irAEs

- <1%
 - Red cell aplasia
 - Thrombocytopenia
 - Hemophilia A
 - Guillain-Barre syndrome
 - Myasthenia gravis
 - Posterior reversible encephalopathy syndrome
 - Aseptic meningitis
 - Transverse myelitis
 - ??

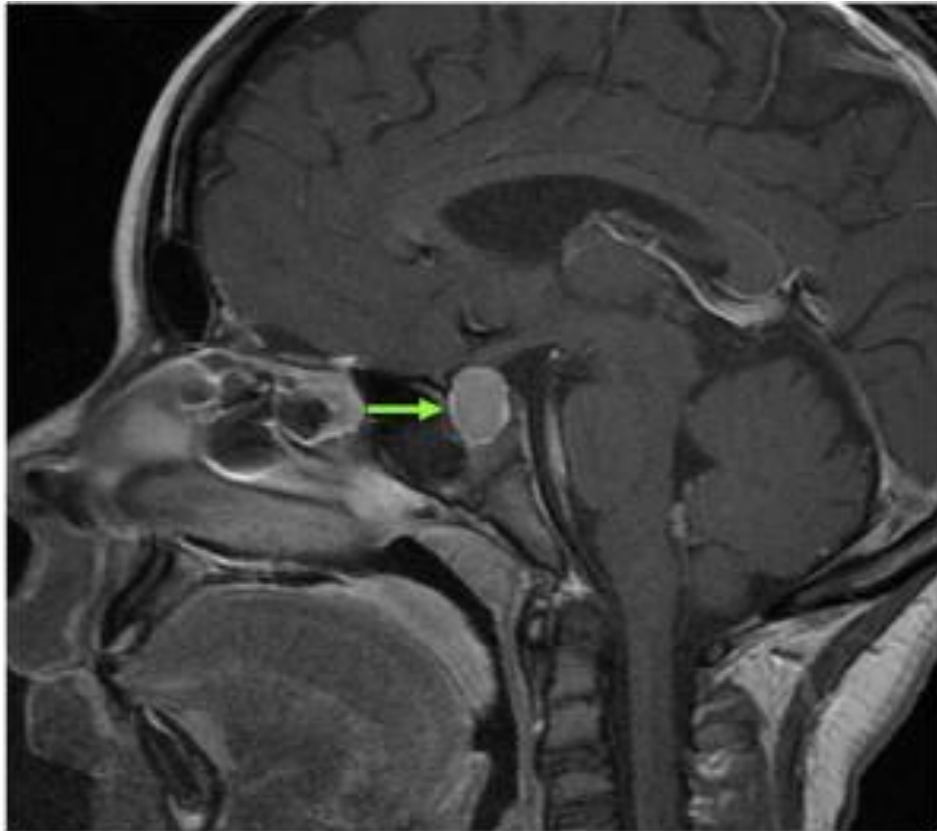
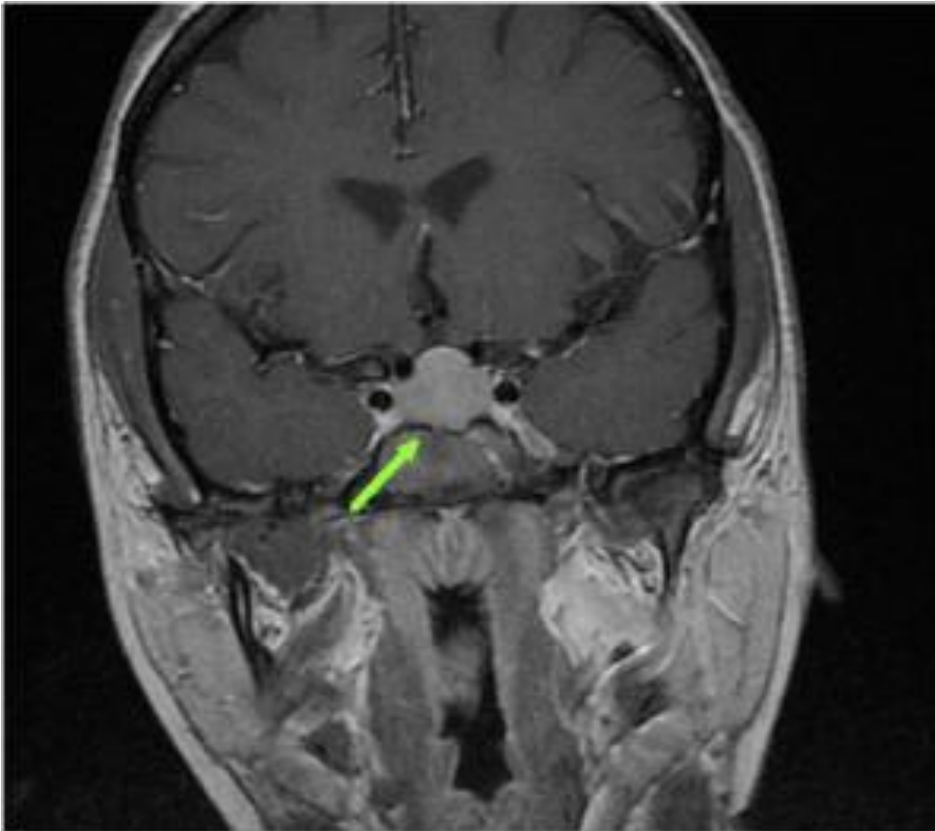
Patient 3

54-year-old male with NSCLC

- New immunotherapy 8 weeks ago for lung cancer
- Painless blurry vision
- Mild HA
- Exam
 - 20/25 right eye (OD), 20/125 left eye (OS)
 - IOP: 10 mmHg OD, 12 mmHg OS
 - Pupils: 5 → 3 mm in both eyes (OU)
 - Confrontation visual fields: temporal loss OD, central scotoma OS

Plan

- Imaging?
 - CT/MRI
- Labs?
 - ACTH, TSH, FSH, LH, GH prolactin



Treatment

- Steroids
 - Corticosteroids 1 mg/kg/day
 - Dexamethasone 6mg IV Q6hr x 3 days
 - Methylprednisolone 125mg daily
 - Switch to oral prednisone after improvement
1-2 mg/kg qd
- Contact Oncology ASAP

Summary

- Address the A, B, Cs
- Consider irAEs when patients develop organ dysfunction
- Don't forget to rule out opportunistic infections and surgical emergencies
- Consider steroids for symptomatic patients, high grade reactions

Bibliography

- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Translational Lung Cancer Research*. 2015;4(5):560-575. doi:10.3978/j.issn.2218-6751.2015.06.06.
- Abdel-Wahab N, Shah M, Suarez-Almazor M. Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. *PLOS*. 2016.07.29.
- Jeffrey S. Weber, Katharina C. Kähler, and Axel Hauschild. [Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab](#). *Journal of Clinical Oncology* 2012 30:21, 2691-2697
- Horvat T, Adel N, et al. Immune-Related Adverse Events, Need for systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients with Melanoma Treated with Ipilimumab at MSKCC. *Journal of Clinical Oncology* 33, no. 28 (October 2015) 3193-3198.
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