Toxicities in Immune Checkpoint Inhibitor therapy

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Objectives

- Recognize the spectrum of autoimmune toxicities, the so-called “immune-related adverse events” (irAEs) that occur as a consequence of ICI therapy
- Review strategies for managing immune-related adverse events (irAE) in the corticosteroid-refractory setting
- Appreciate challenges & unknowns in management of various irAEs

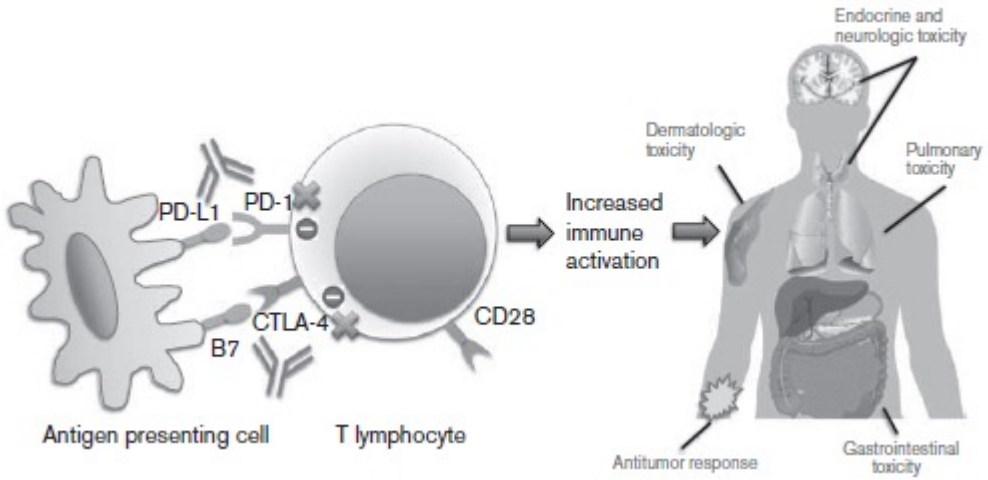
Immune Checkpoint Inhibitor (ICI) therapy

- Cancer treatment strategies directed at improving the host immune response to cancer and which target immune checkpoint molecules

Anti-PD-1	Anti-PD-L1	Anti-CTLA4
Pembrolizumab	Atezolizumab	Ipilimumab
Nivolumab	Avelumab	
Cemiplimab	Durvalumab	
Dostarlimab		

Immune-related adverse events (irAE)

- Definition: Adverse events that occur via the activation of a patient's immune system that can occur in any tissue, organ or system
  - Can be SEVERE and sometimes FATAL



Mayo Clinic Image

Kottschade, L., et al. (2016). "A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy." Melanoma Res **26**(5): 469-480.

Assess irAE Risk And Special Populations

- History of Autoimmune conditions/prior irAE
- Transplant population (e.g. Hodgkin lymphoma)
- Use of concurrent steroids or other immunosuppressants
- Prior endocrinopathy or other conditions
- Poor liver, renal, lung or cardiac function
- Chronic viral infections, e.g. HIV, hepatitis B / C
- Live vaccines / Allergies, etc.

Pre-existing Autoimmune Conditions

- Traditionally excluded from ICI clinical trials
- Patients not on chronic immunosuppresion are generally considered for ICI therapy
- Based on retrospective series, response rates may be lower

Kennedy et al.(2019)

Transplant Patients

- Often on high doses of immunosuppression-? Response rates
- Concern of loss of transplanted organ
- Need to have frank conversations regarding risk/benefit ratio
- Minimal data in this population, limited 1° case reports

Vaccines And ICI Therapy

- Early clinical trials disallowed vaccination while on study
- Small study from Switzerland described unexpectedly high rate of irAE's.
- Recent retrospective review from MSKCC-Chong et al. (2019)
  - 370 patients on ICI vaccinated for influenza
  - No increase in irAE's over previously published irAE rates
- Inactivated influenza generally considered safe
- Currently no data on other vaccines
- Generally recommended not to administer live-attenuated vaccines immediately before, during or immediately after ICI therapy.
- Recommendation from ASCO and SITC ok to give COVID-19 vaccine

Clinical Pearls in the Management of irAE's

Chemotherapy

Immune
Suppression

≠

Immunotherapy

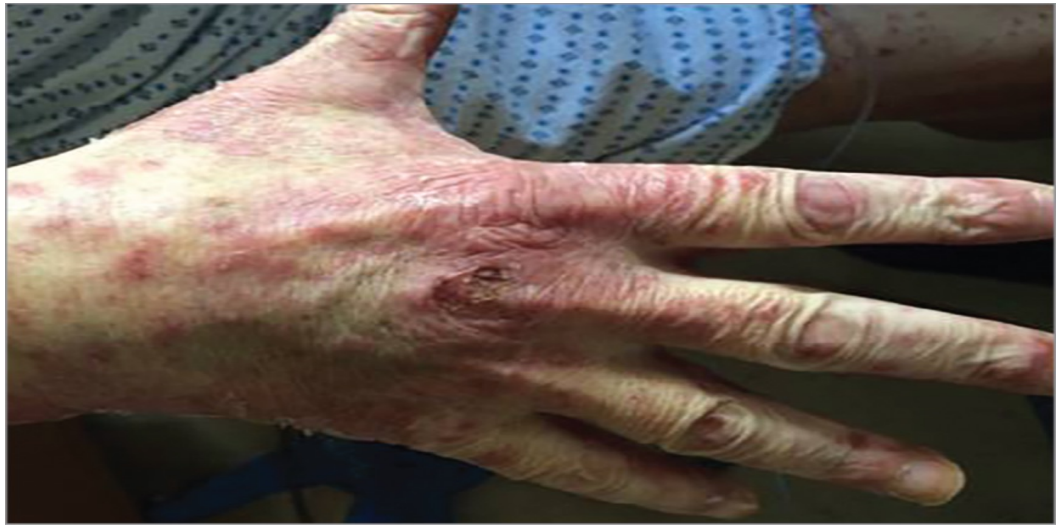
Immune
Activation

Case Study

- 65 yo female with breast cancer
- Received Paclitaxel and cemiplimab on I-SPY trial
- Diagnosed with taxane induced peripheral neuropathy
- When she walks she feels like she is “walking on balled up socks”
- Started on gabapentin at 300 mg QHS

Most Common irAEs

- Dermatologic
- Gastrointestinal
- Hepatic
- Endocrine



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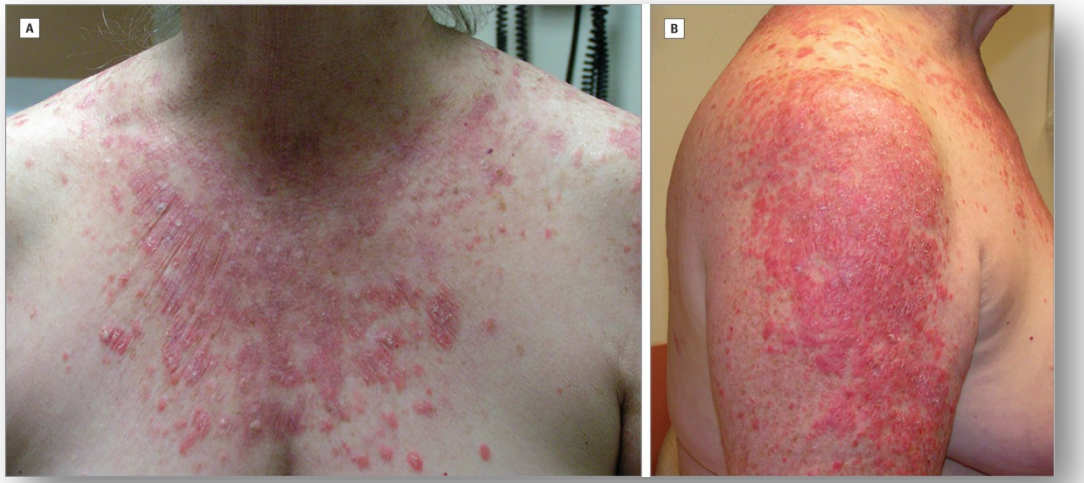

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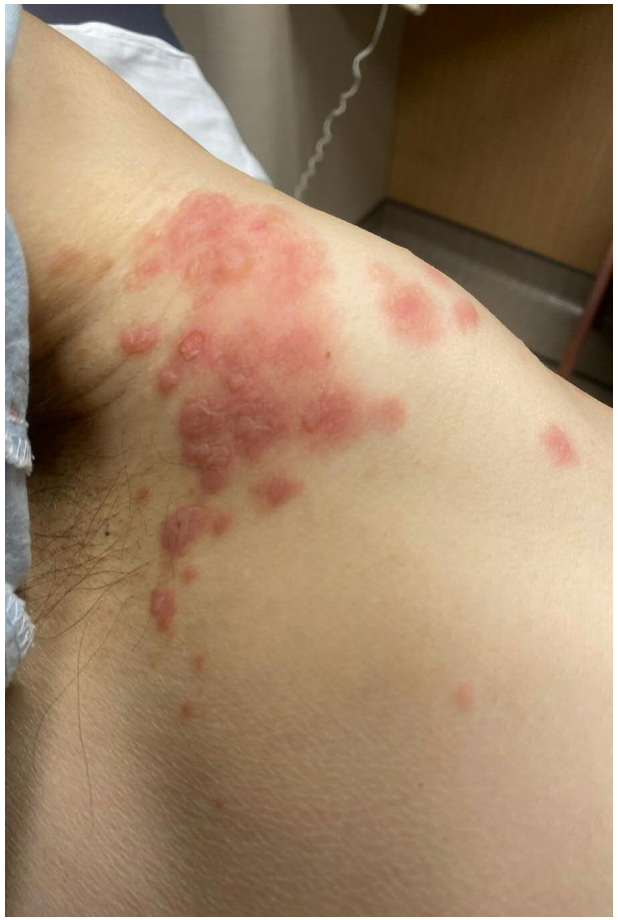
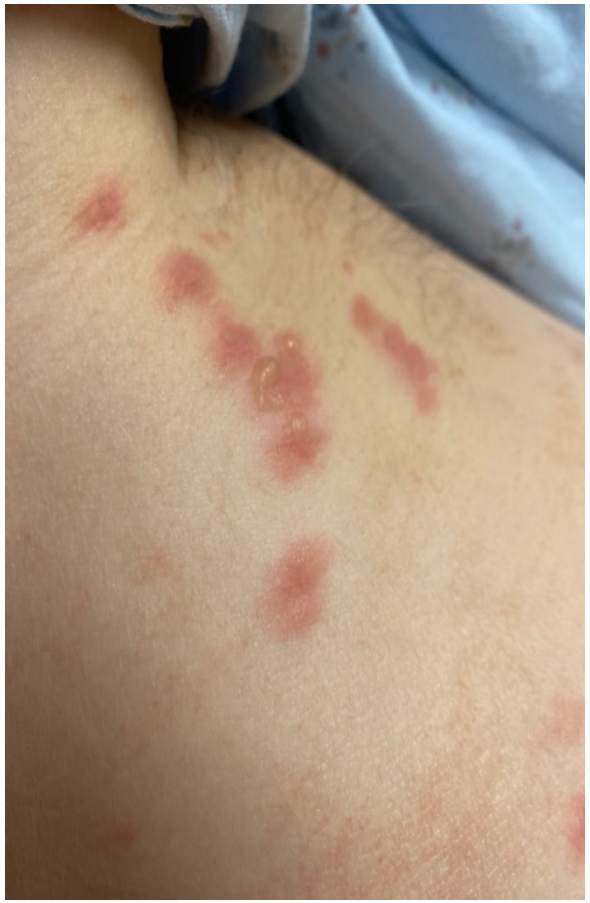
Dermatologic irAEs

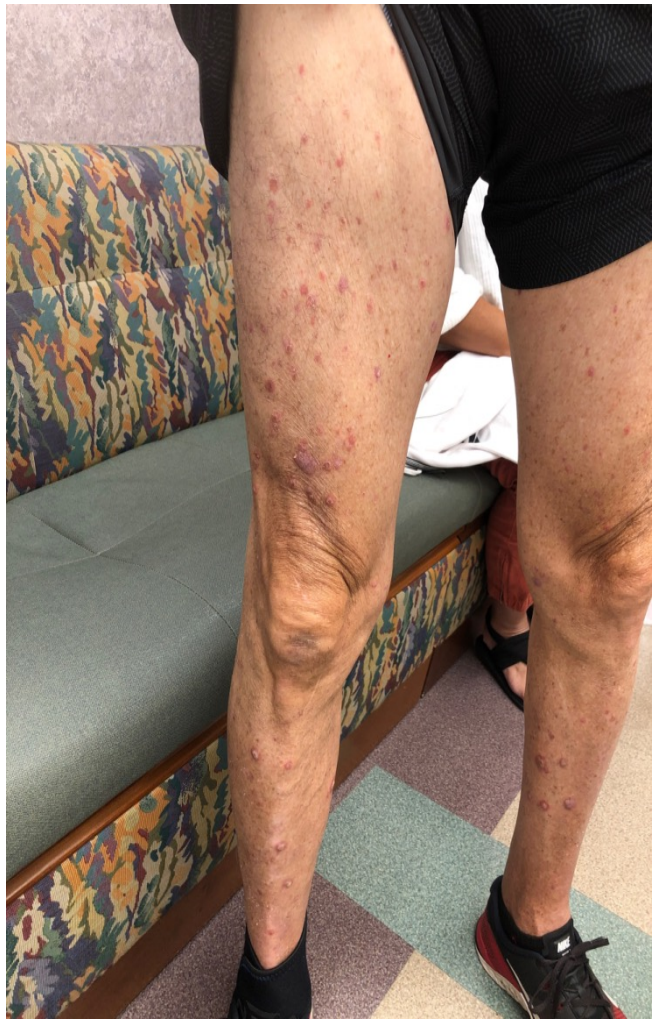
- Most frequent for both anti-CTLA-4 and anti-PD-1 blockade (40% single agent-60% combo therapy)
  - Diffuse maculopapular rash and/or pruritus
  - Vitiligo
- Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported
- Many patients will have pruritus in the absence of rash (10-30%)
- Can be just, if not more bothersome than physical rash

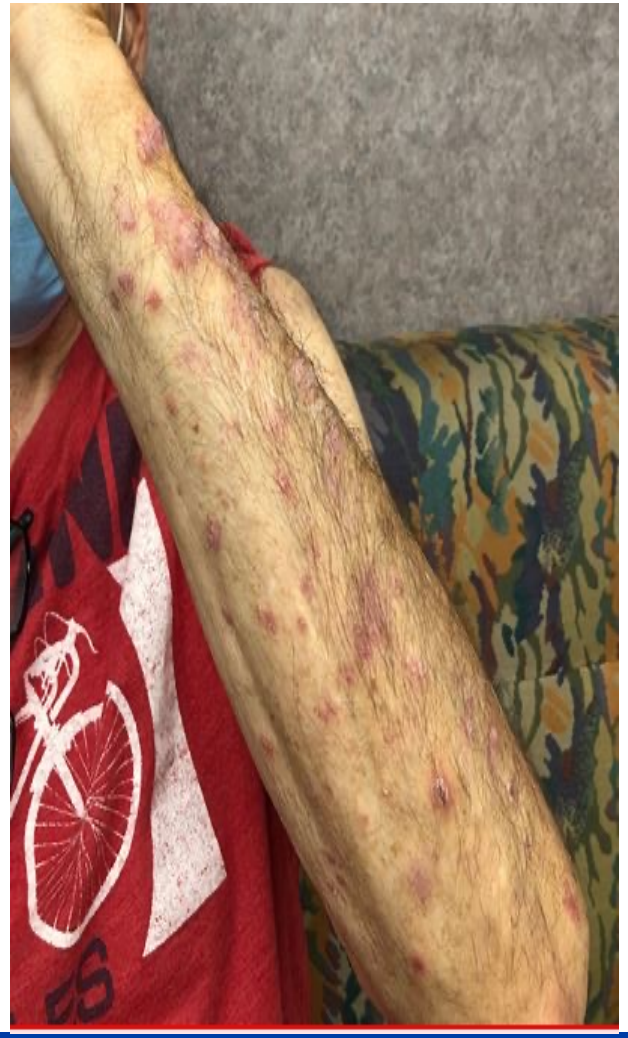
Bullous Pemphigoid



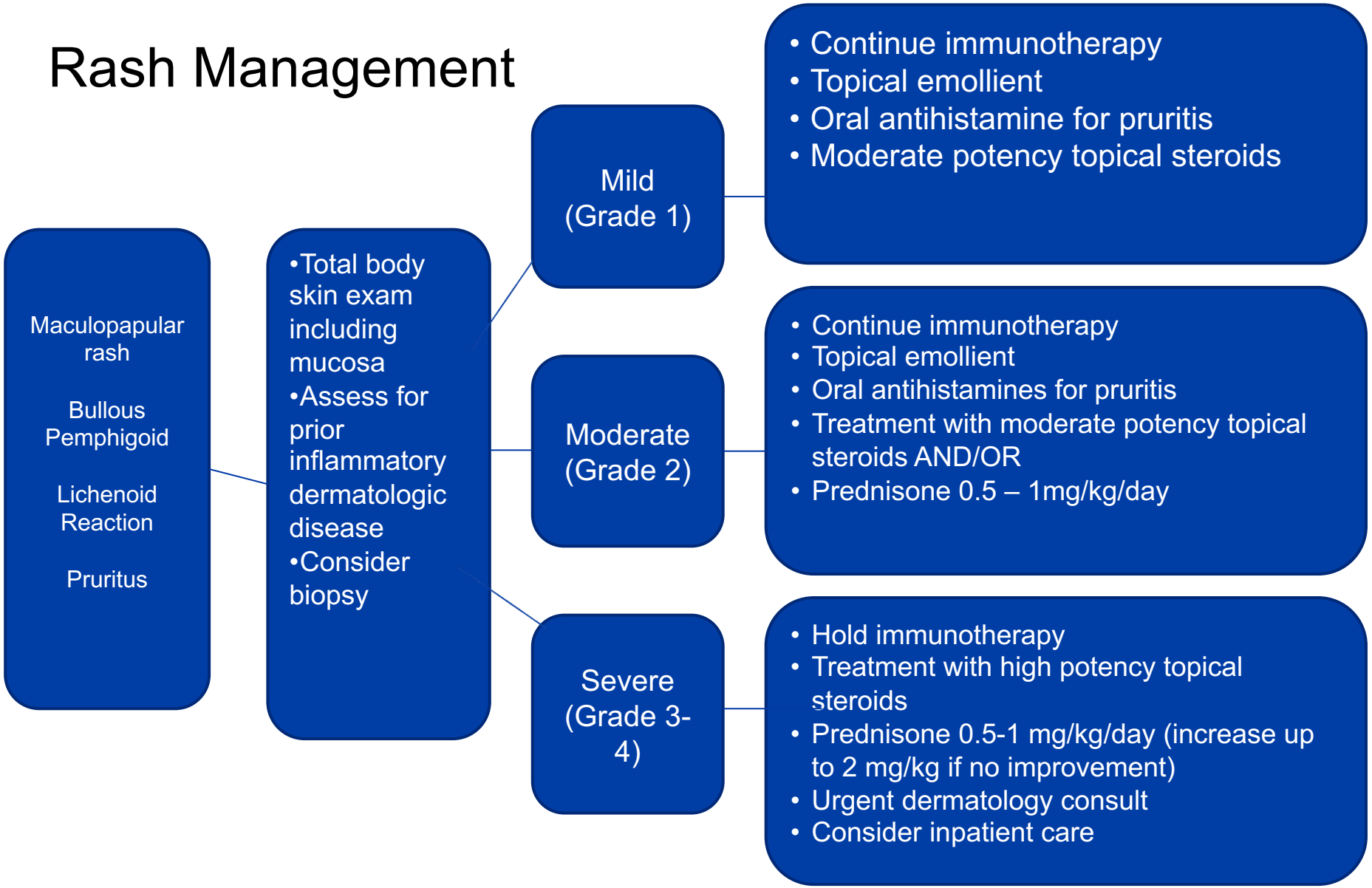


Lichenoid Reaction



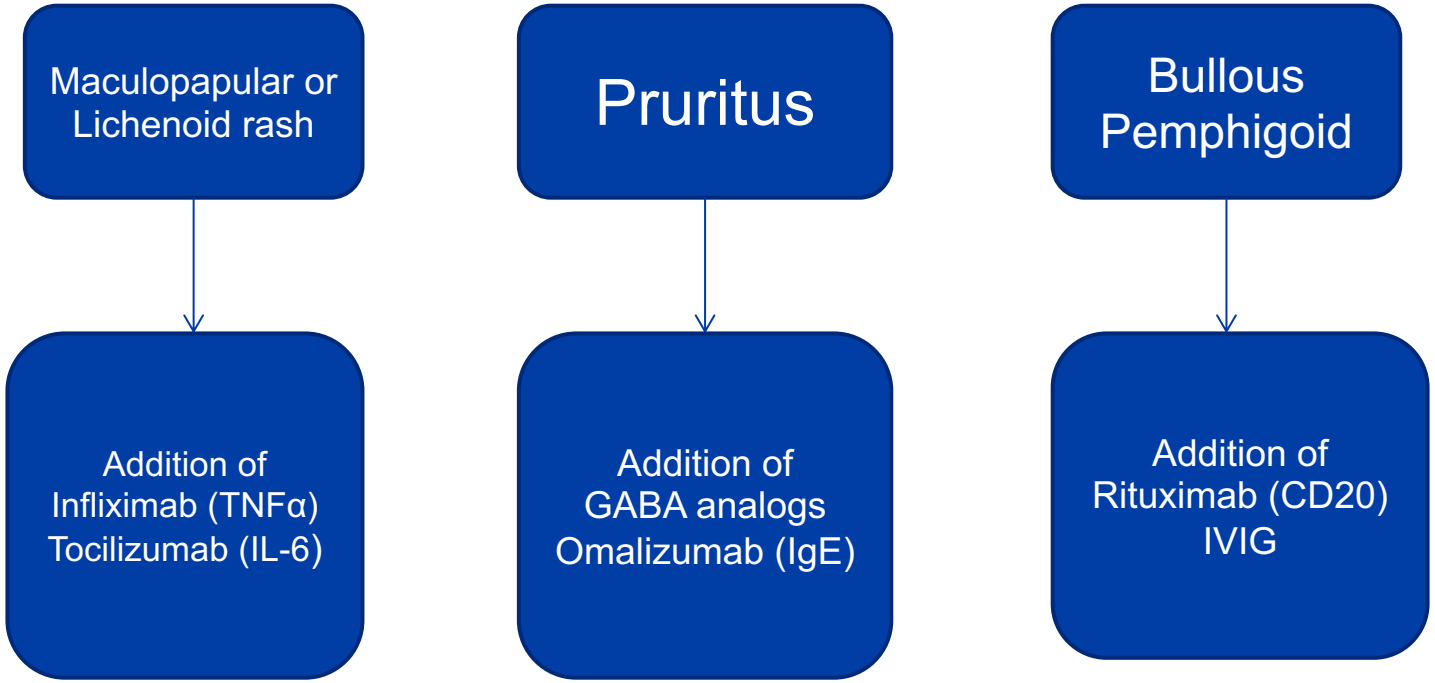


Rash Management



NCCN. Management of Immunotherapy-Related Toxicities. V.1.2020. (Accessed 01/04/2020)
Phillips et. al (2019)

Rash Management (steroid refractory)



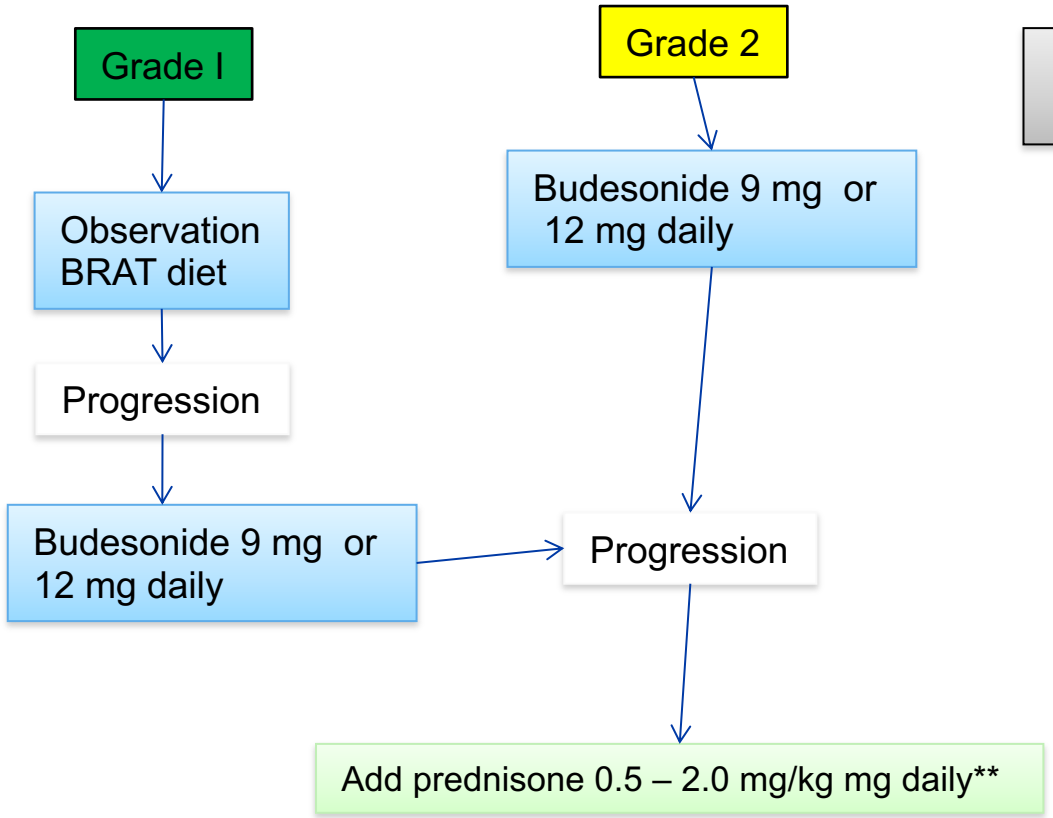
Phillips et. al (2019) Treatment of Outcomes of Immune-Related Cutaneous Adverse Events. *JCO*

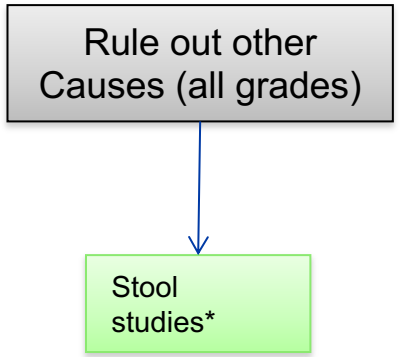
Gastrointestinal

- Both diarrhea (increase in stool frequency) and colitis (diarrhea &abdominal pain with imaging/endoscopic evidence of colonic inflammation)
  - more common with anti-CTLA-4 (30%)-vs PD-1/PD-L1 (15%)
  - combo therapy (50%)

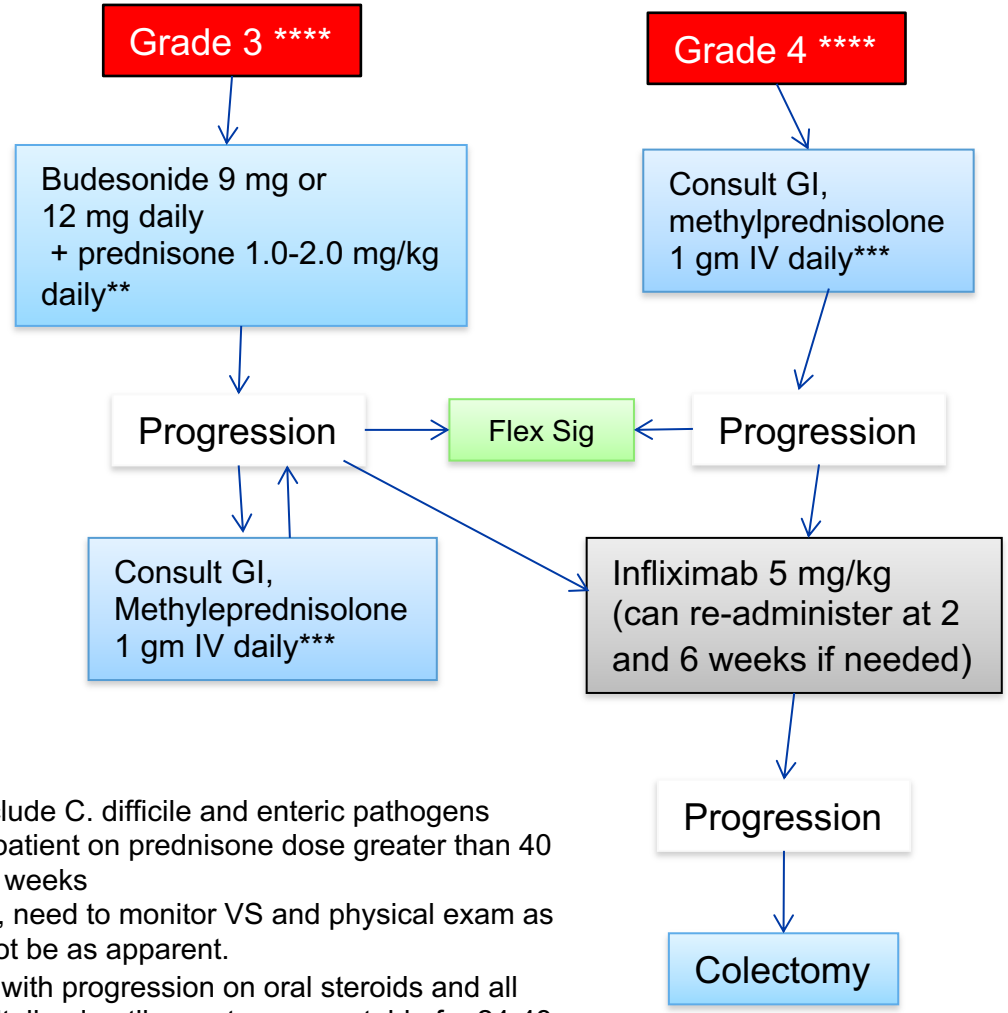
- Colitis – shares histologic features of Crohn's disease
  - Fatal bowel perforation reported in 1% of patients treated with ipilimumab

Algorithm for management of diarrhea/colitis from immune checkpoint inhibitors



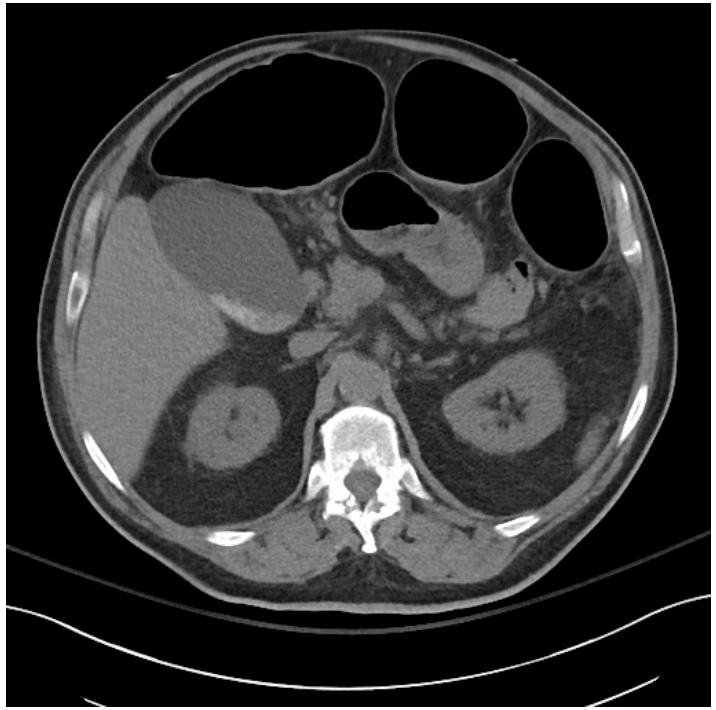


Vedolizumab 300 mg IV week 0, 2, 6 and then q 8 weeks as needed



*Stool studies should include C. difficile and enteric pathogens
**Consider GI consult if patient on prednisone dose greater than 40 mg daily for more than 4 weeks
***Consult w/in 48 hours, need to monitor VS and physical exam as bowel perforation may not be as apparent.
**** Patient with grade 3 with progression on oral steroids and all grade 4 should be hospitalized until symptoms are stable for 24-48 hours on oral steroids

Kottschade, L et. al- (2016) *Melanoma Research*



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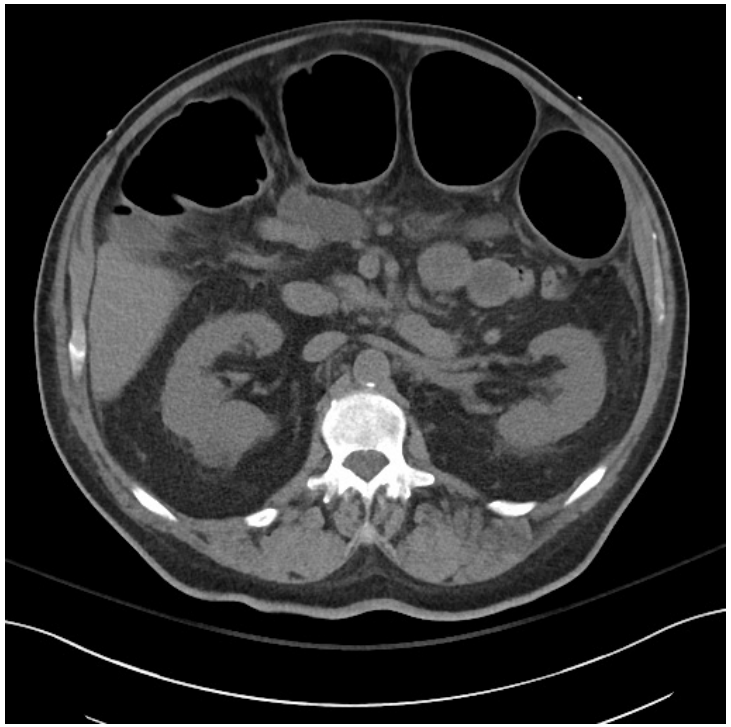

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Patient with grade 4 colitis from Ipi/Nivo. Self-medicated with loperamide. Presented to the ED with sepsis and hypotension, diagnosed with toxic megacolon. Required ICU admission and pressor support. Responded well to high dose methylprednisolone and decompression.

Management Of Diarrhea/Colitis

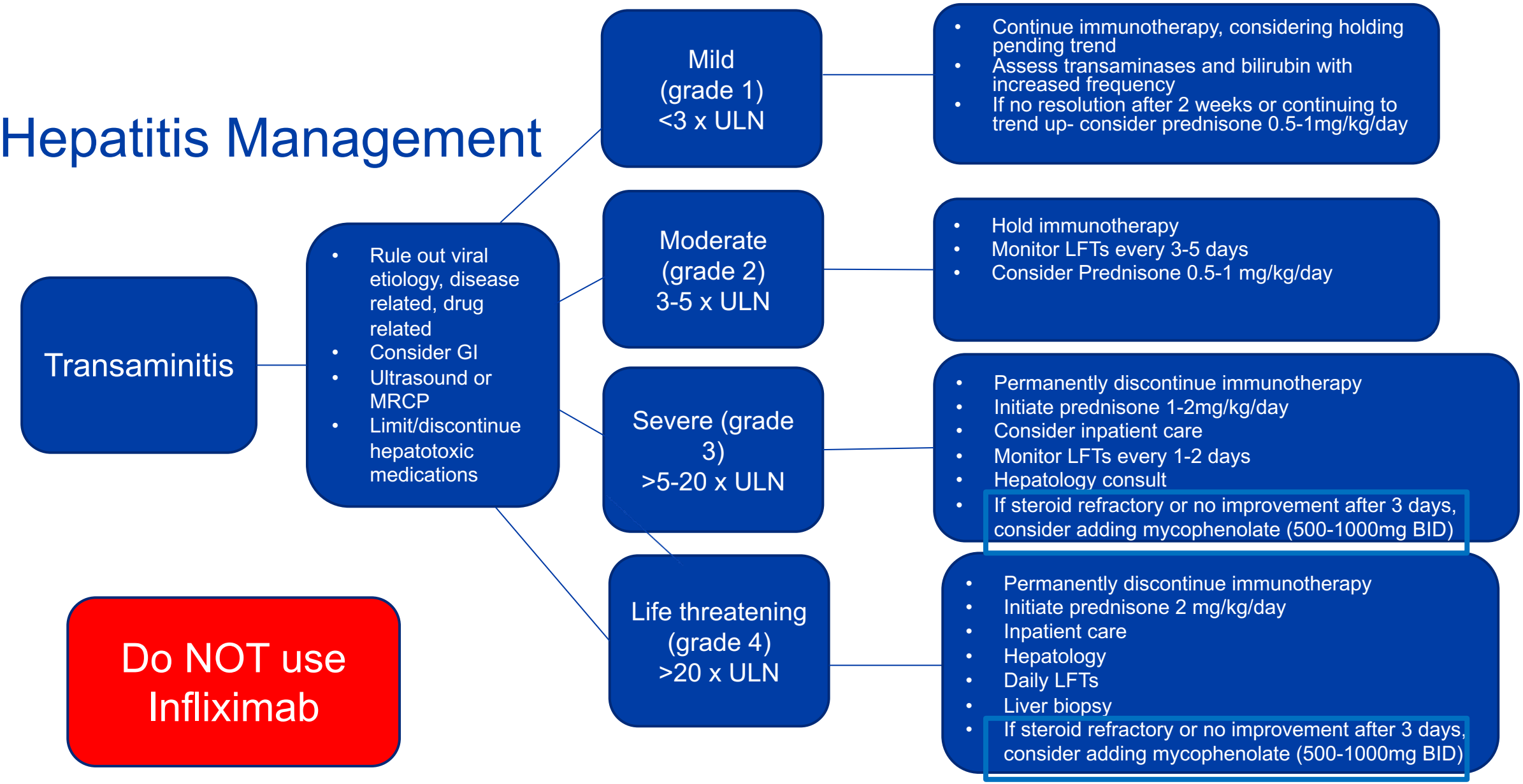
- Once symptoms are grade 0 or 1
  - Taper of steroids should occur over at least 1 month
  - **Beware of rebound diarrhea!**
- If patients on budesonide in addition to systemic steroids, taper the prednisone FIRST.
- Do NOT administer antidiarrheals in patients with ≥ Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.

Hepatic irAEs

- Hepatotoxicity – asymptomatic transaminitis and/or hyperbilirubinemia
  - 30% in combination therapy (15% grade 3-4)
  - <10% in monotherapy
  - 0.2% hepatic failure

Rule out new or progressive hepatic involvement by malignancy

Hepatitis Management



NCCN. Management of Immunotherapy-Related Toxicities. V.1.2020. (Accessed 01/04/2020)

Endocrinopathies

Two main classifications

- Thyroid (most common with PD-1/PD-L1 inhibitors)
- Pituitary (most common with anti-CTLA-4)

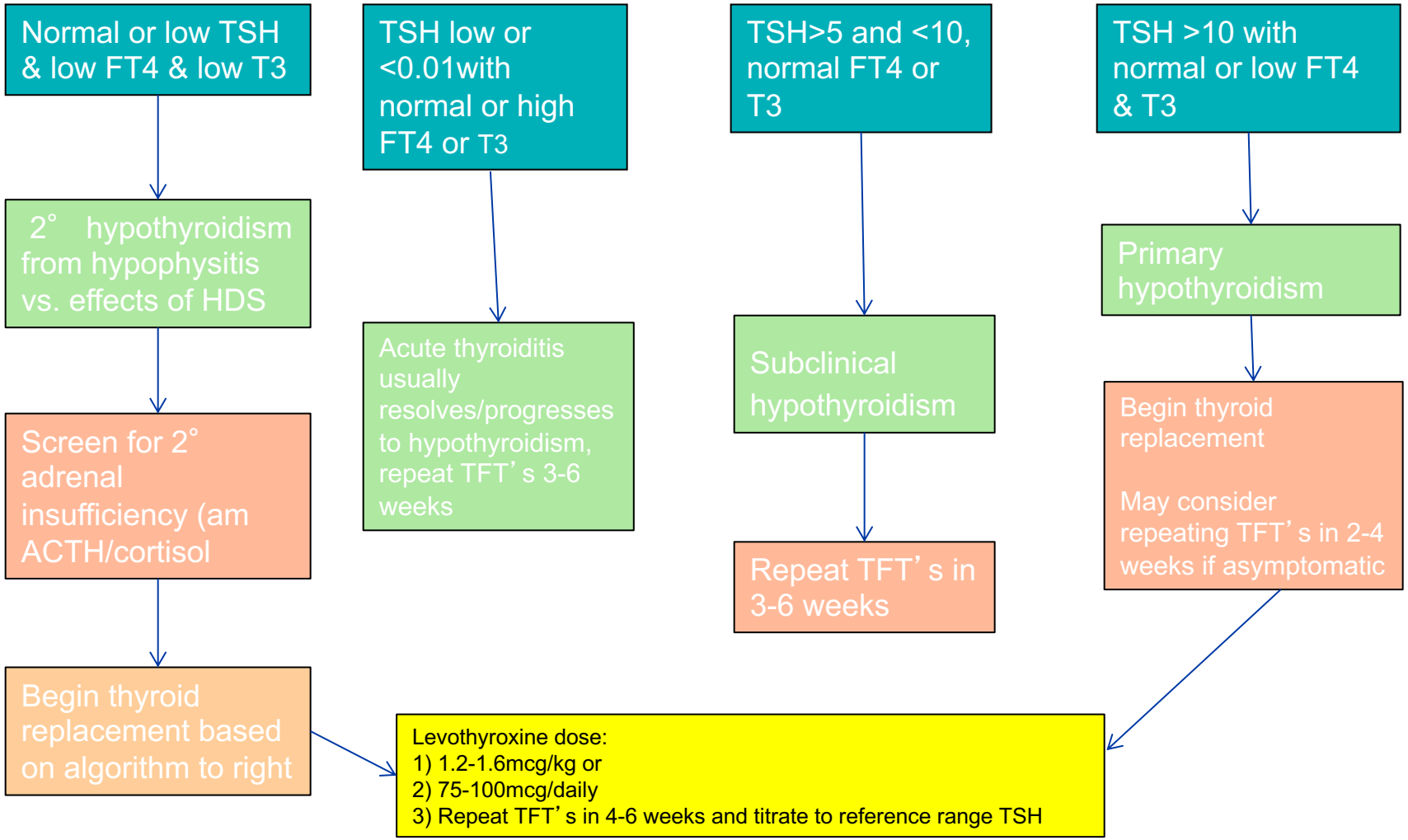
- Additional rare incidences of autoimmune (insulin dependent) diabetes

Endocrine irAE

- Thyroid dysfunction (0-15%)[1,2]
  - Acute/inflammatory/painless thyroiditis associated thyrotoxicosis (↓TSH, ↑FT4 and/or T3)
    - Higher incidence in combination therapy (40%)
    - Resolution to euthyroid or progress to overt hypothyroidism (TSH >10); minority regain function

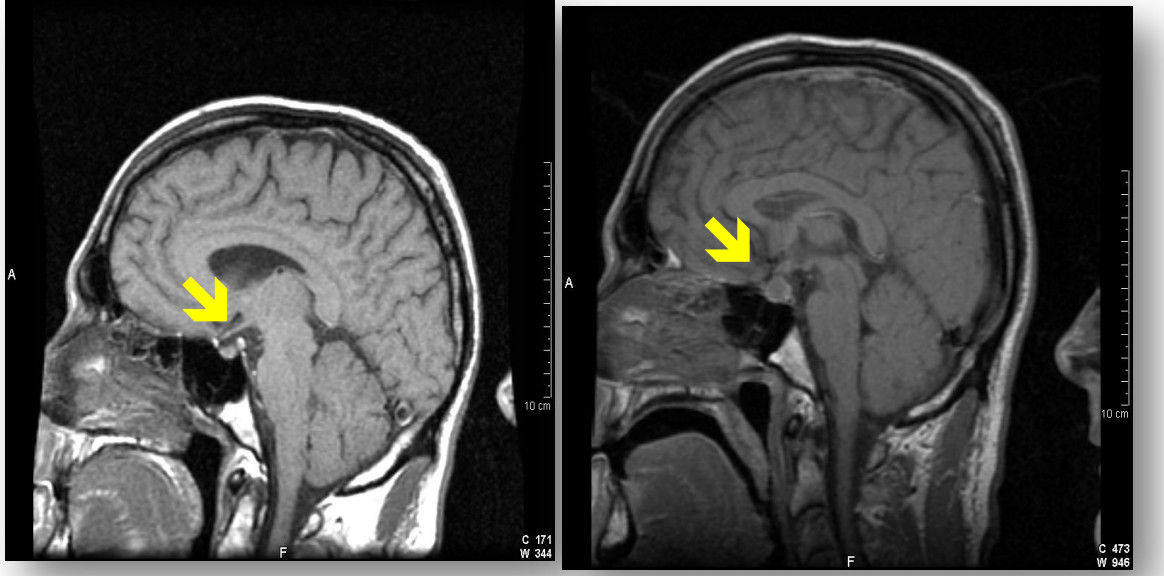
[1]Corsello, S. M., et al. (2013). "Endocrine side effects induced by immune checkpoint inhibitors." J Clin Endocrinol Metab **98**(4): 1361-1375.
[2]Delivanis, D. A., et al. (2017). "Pembrolizumab-Induced Thyroiditis: Comprehensive Clinical Review and Insights Into Underlying Involved Mechanisms." J Clin Endocrinol Metab **102**(8):

Evaluation of thyroid function



Kottschade, L et. al- *Melanoma Research 2016*

Endocrine irAE- (continued)



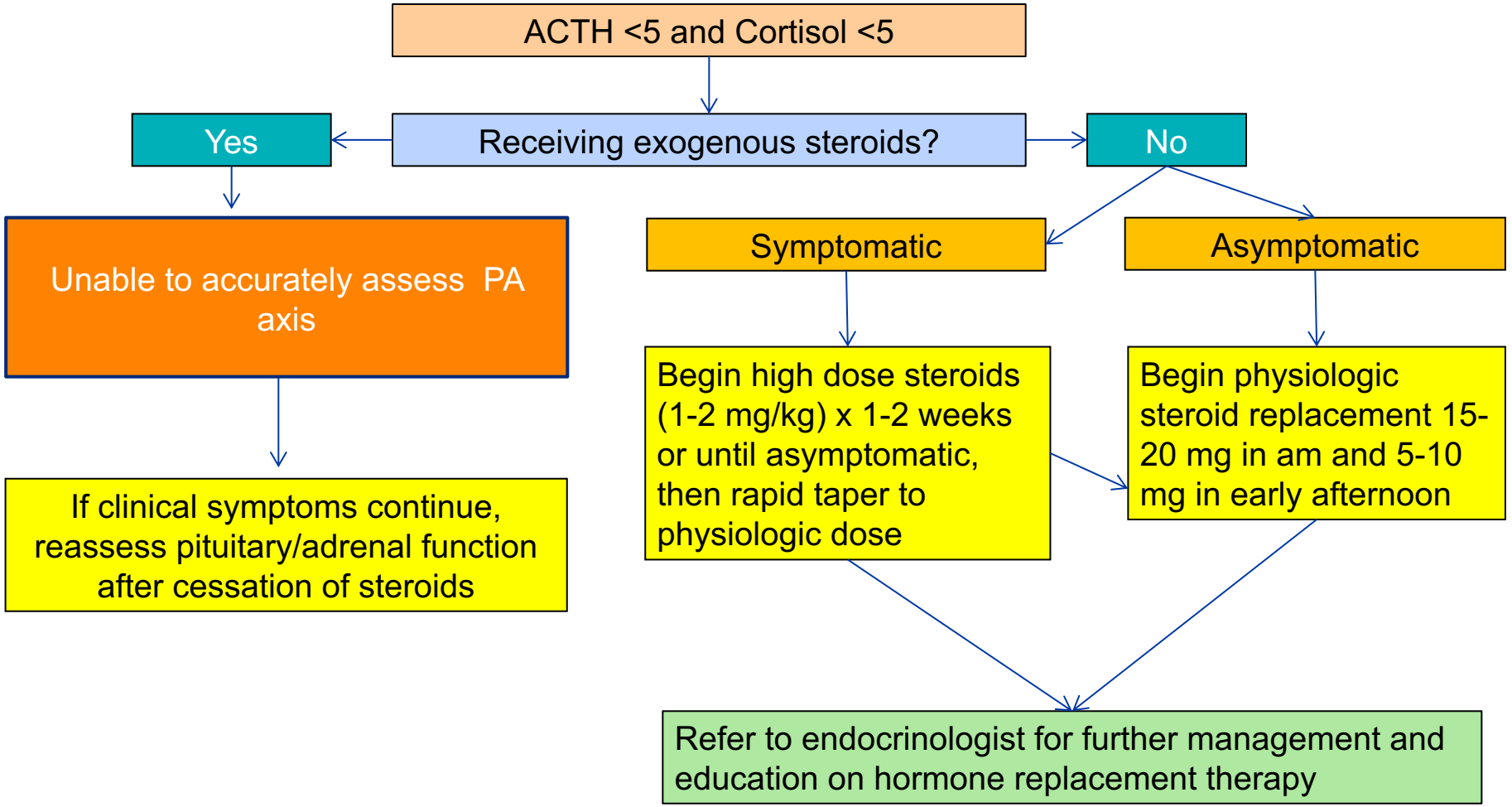
Pre-ipilimumab **Post-ipilimumab**

- **Hypophysitis**[1]
  - Clinically present with fatigue (the "run over by the truck" phenomenon) abrupt onset headache, possible visual changes/nausea/vomiting
  - Low or undetectable ACTH & AM cortisol levels
  - Enlarged pituitary on MRI (75%)

  Differential- must consider CNS involvement by malignancy or other neurological toxicity

[1]Ryder, M., et al. (2014). "Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution." Endocr Relat Cancer **21**(2): 371-381.

Evaluation And Management Of Pituitary/Adrenal Function



Kottschade, L et. al- *Melanoma Research 2016*

Adrenal Insufficiency (Primary Vs Secondary)

- Primary Adrenal Insufficiency (AI)=**medical emergency**
  - Volume depletion, electrolyte abnormalities, and low or undetectable am cortisol and **high ACTH**
  - Hospitalize with fluid replacement, correct electrolytes and high dose steroids (1-2mg/kg)
- Secondary AI
  - Diagnosed by low or undetectable am cortisol and low ACTH
  - Can be from hypophysitis or long term steroid use

Less commonly reported irAEs

Endocrine
- Diabetic ketoacidosis
- Primary adrenal insufficiency
- Grave's like disease
- Hypercalcemia

Renal
- Nephritis

Ocular
- Uveitis
- Episcleritis

Cardiac
- Myocarditis
- Pericarditis
- Vasculitis

Neurologic
- Peripheral neuropathy
- Encephalitis
- Myasthenia Gravis
- Guillain Barre
- Aseptic Meningitis

Rheumatologic

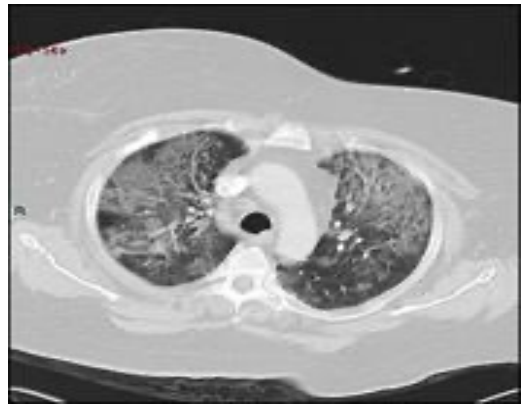
Pulmonary
- Pneumonitis
- ARDS/AIP
- Pleuritis
- Sarcoid-like reaction

Hematologic
- Thrombocytopenia
- Hemolytic anemia
- Aplastic anemia

Musculoskelatal
- Myositis
- Arthritis

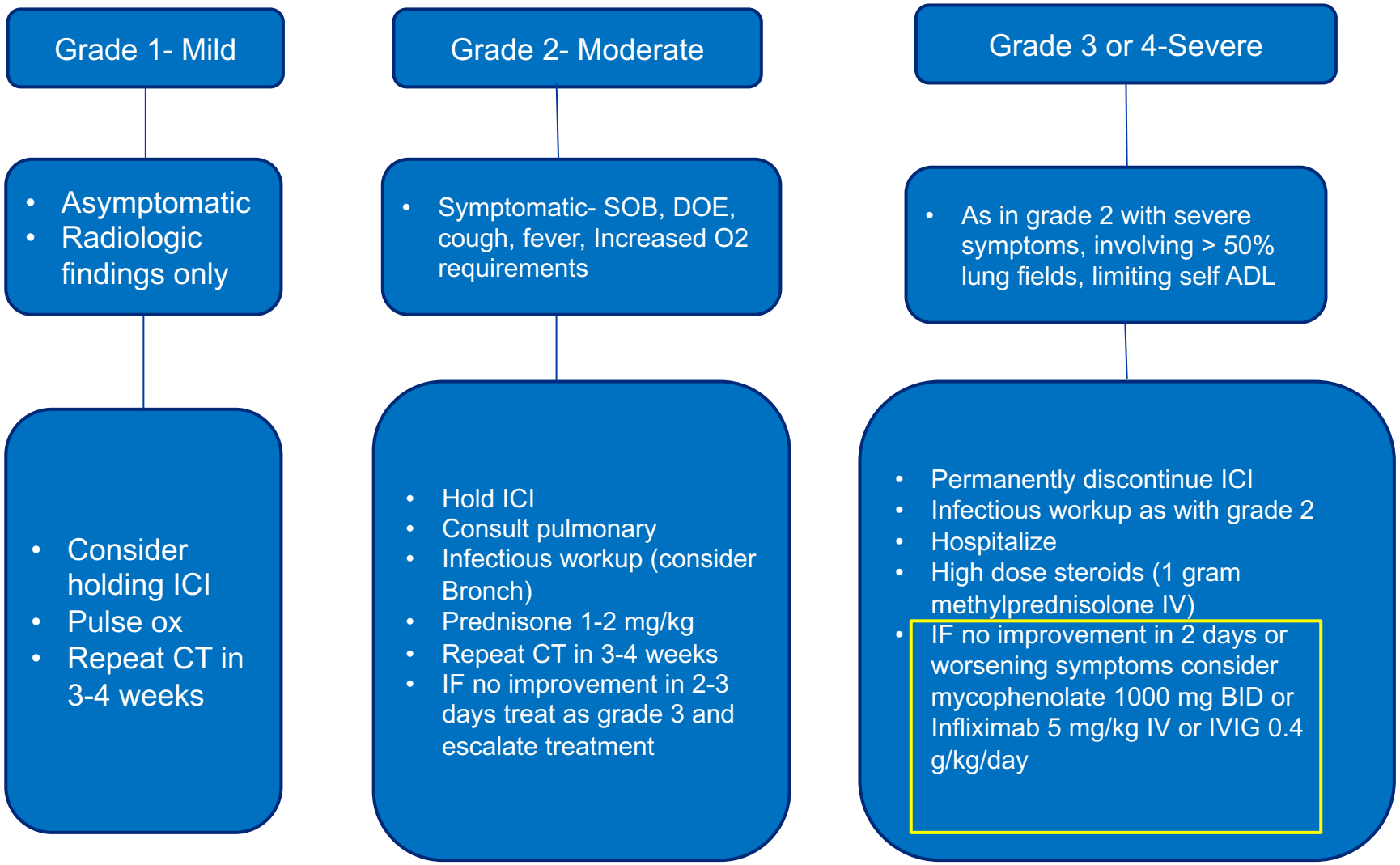
Life-Threatening irAE's

Pneumonitis



- Differential- pulmonary embolism, progression of disease, infection
- **CT chest**
  - New lung infiltrates after immune check point inhibitor
- Pulse oximetry (rest and walking)
- If grade 2 or greater, infectious work up to include:
  - Nasal swab, sputum culture and sensitivity, blood culture and sensitivity,
  - Consult pulmonology for consideration of bronchoscopy

Pneumonitis Treatment



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Kottschade, L., et al. (2016). "A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy." Melanoma Res **26**(5): 469-480.

Neurotoxicity

- Incidence was 3.8% for CTLA-4 inhibitors, 6% with PD-1 inhibitors, 12% with combination therapy
- Variable presentation, nonspecific symptoms, wide range of differentials
- Time to onset ranges from 3 days to 17 months, median time is about 6 weeks
- Broad spectrum of conditions
  - Guillain Barre syndrome
  - Myasthenia gravis
  - Central or peripheral neuropathy
  - Encephalitis
  - Aseptic meningitis
  - Transverse myelitis

Santomasso, B. et al. Journal of Clinical Oncology. 2018.
Johnson, D. et al. Journal for Immunotherapy of Cancer. 2019.
NCCN. Management of Immunotherapy-Related Toxicities. V.1.2020. (Accessed 01/04/2020)

Neurologic Management

- Workup
  - MRI of brain/spine, lumbar puncture, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA), paraneoplastic panel, infectious workup, AchR antibodies, possible EMG.
  - Consult Neuro immediately
- Treatment (for severe grade 3 or 4)
  - Hospitalization
  - High dose steroids 1-2 mg/kg
  - IVIG
  - If unresponsive consider plasmapheresis or rituximab

MAYO CLINIC

NCCN. Management of Immunotherapy-Related Toxicities. V.1.2020. (Accessed 01/04/2020)

Cardiac

- Myocarditis/pericarditis/cardiomyopathy
- Exact incidence rates vary
- Once symptomatic 50% fatality rate

Rapid Increase in Reporting of Fatal ICI-Associated Myocarditis

Table: Characteristics of patients with immune checkpoint inhibitor associated myocarditis (n=101)	
Characteristic	**Percent (%)**
Male gender	66
Cancer	
Melanoma	40
NSCLC	30
Renal	7
Other*	23
Concomitant medications	
Aspirin	11
Statin	11
Beta blocker	7
ACE/ARB	12
Diabetes medication	9
No CV/Diabetes medications	75
Regimen	
Anti-PD-1 monotherapy	
- Nivolumab	43
- Pembrolizumab	15
Anti-PD-L1 monotherapy#	3
Anti-CTLA-4 (Ipilimumab) monotherapy	5
Combination anti-PD-1/PD-L1 + anti-CTLA-4	27
Combination anti-PD-1/PD-L1 + other agents**	8
Timing (median, range)	25 days (5-120)
Concurrent irAEs	
Myositis/rhabdomyolysis	25
Myasthenia gravis	10
Colitis	4
Severe cutaneous events†	4
Other†	5
Fatal outcome	52
Reporting year	
2010 – 2014	3
2015	6
2016	15
2017 (through Dec. 6)	76

- Fatality rates:
- Anti-PD-1/PD-L1 plus anti-CTLA-4: 78%
- Anti-PD-1/PD-L1 monotherapy: 42%
  - p=0.004

Moslehi, Salem…Johnson. *Lancet*. 2018.

Clinical Myocarditis Presentations: N=35

Subjective Complaints

- Chest pain 37%
- SOB 58%
- Orthopnea 16%
- Paroxysmal nocturnal dyspnea 16%
- Fatigue 21%

Clinical Findings

- Troponin elevation 94%
- Abnormal ECG 89%
- LVEF decreased 49%
- BNP or NT-BNP elevated 66%

Mahmood, S.S. (2018). Myocarditis in Patients Treated with Immune Checkpoint Inhibitors . *JACC, 71* (16); 1755-1765.

Cardiac

Workup

- Standard cardiac workup to r/o ischemia
- Troponins, CK, BNP, ESR, CRP
- ECG
  - See ST-T wave abnormalities, new arrhythmias (i.e heart block or ectopy)
- Echocardiogram
  - See diffuse LV systolic dysfunction, RWMA, increased wall thickness, pericardial effusion and strain abnormalities
- If Echocardiogram inconclusive consider:
  - Cardiac MRI
  - Cardiac Biopsy

NCCN. Management of Immunotherapy-Related Toxicities. V.1.2020. (Accessed 01/04/2020)

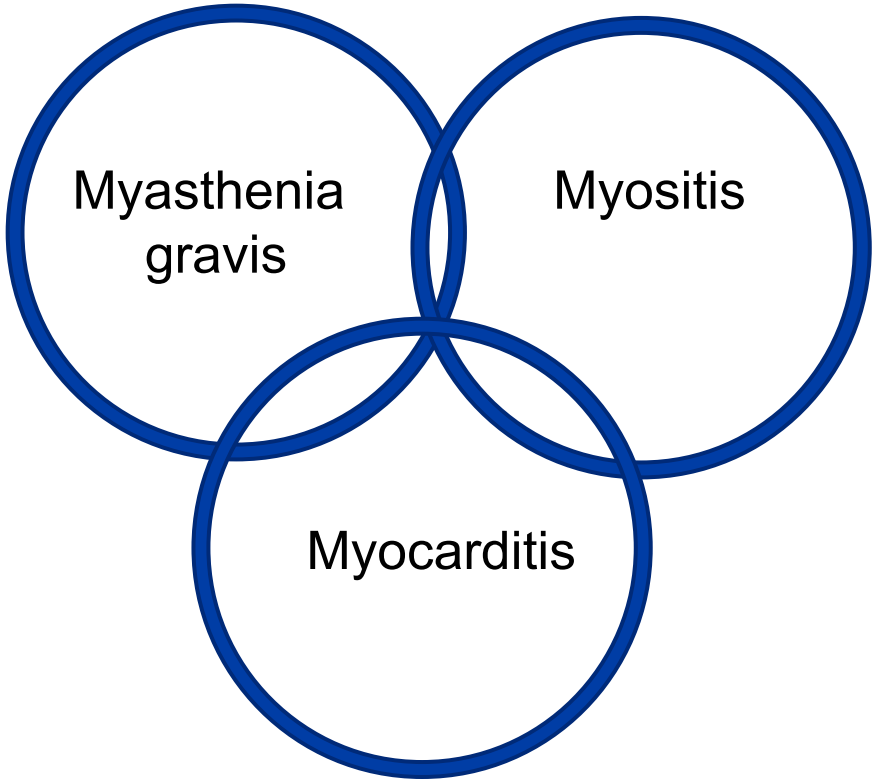
Cardiac

Treatment

- Permanently discontinue ICI agent
- If ACS ruled out, high dose steroids (1 gram methylprednisolone x 3-5 days) then 2 mg/kg/day
- Admit for further diagnostic workup (i.e CMR, possible cardiac biopsy)
- For patients who are unresponsive to steroids, consider antithymocyte globulin (ATG) or infliximab

Triple “M” Syndrome

- Fatigue, weakness, frequently with ocular or bulbar symptoms
- May have respiratory symptoms
- May have chest pain
- Muscle pain/weakness
- Early detection is key



Johnson, D.B et al. Journal for Immunotherapy of Cancer,. 2019.
Brahmer, J. et al. Journal of Clinical Oncology. 2018.

Back to our case study….

- Patient presents for follow up and discussion of adjuvant therapy
- Peripheral neuropathy getting worse, presents to appointment in wheelchair, due to balance issues
- She is tired and has lost about 8 pounds
- Gabapentin is increased

Fast Forward about one week….

- Patient now has lightheadedness, dizzy, and word finding difficulties
- Describes “ I just feel weak”- states this got worse with increase in gabapentin
- Presents to ED after syncopal episode
- What would be in your differential?

Diagnostics

- Vital signs WLN
- CMP normal except for sodium of 133
- Troponin T elevated at 69
- Mild ST elevation in anterior leads 1st degree AV block
- CT head is normal
- Neuro exam normal except for evidence of CIPN.

Next steps

- Recommended random cortisol, ACTH, CK, and thyroid studies

Results

- Cortisol <1.0
- ACTH <5.0
- TSH 17.4
- FT4 0.8
- CK- normal

Case study conclusion

- Patient diagnosed with secondary AI
- MRI confirmed resolving hypophysitis
- Patient was stress dosed with IV hydrocortisone
- Cardiac workup for myocarditis
- After 3 days, patient completely recovered
- Peripheral neuropathy completely resolved within the week, and gabapentin discontinued.

Principles Of Steroid Management

- DO NOT use methylprednisolone dosepak(s)
- Once irAE is resolved to grade 1 or baseline, taper steroids over at least one month-many need longer.
- Beware of emerging irAE's during steroid tapers.
- Closely monitor diabetics (or those at risk) for changes in glucose levels.
- PJP prophylaxis in those on high dose prolonged course (> 20 mg prednisone daily for >2 weeks).
- Determining "steroid-refractory" should be individualized and based on organ system involved.

Summary

- ICIs are effective cancer therapies that target the host immune system
- irAEs manifest as organ-specific and systemic autoimmunity and are a common consequence of ICI
  - Broad clinical spectrum; lab abnormalities → life-threatening
  - Rare and/or chronic irAEs are being increasingly reported
  - Can appear months after ICI discontinuation
- Management of irAEs is organ-specific
  - Published algorithms available from NCCN/ASCO and SITC
- Have low threshold for suspicion of irAEs – delays can intensify toxicity
- Care should be coordinated by treating oncologist/hematologist and relevant subspecialty providers

Initiatives At Mayo Clinic

- Institutional multidisciplinary ICI toxicity working group
    - Includes providers across disciplines and subspecialties
- ICI responsible person of the day
    - Pager carried by ICI experts to be resource to both Oncology and Non-Oncology providers (eg ED/Hospital Based Medicine)
- Inpatient ICI consulting service
    - Alert sent through EMR to admitting service that patient is on ICI and requires further consultation/management
- Outpatient ICI clinic
    - Run by APP's to evaluate and manage acute symptoms, provide hospital follow up, and provide ongoing care to patients with ICI toxicity.

Thank you!

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