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Immune Checkpoint Inhibitor Toxicities: What the Intensivist Needs to Know

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No conflict of interests

Objectives

- Review toxicities and workup of toxicities associated with novel immunotherapies
- Discuss available treatment options for neurologic, cardiac, an pulmonary complications related to immunotherapy

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Background

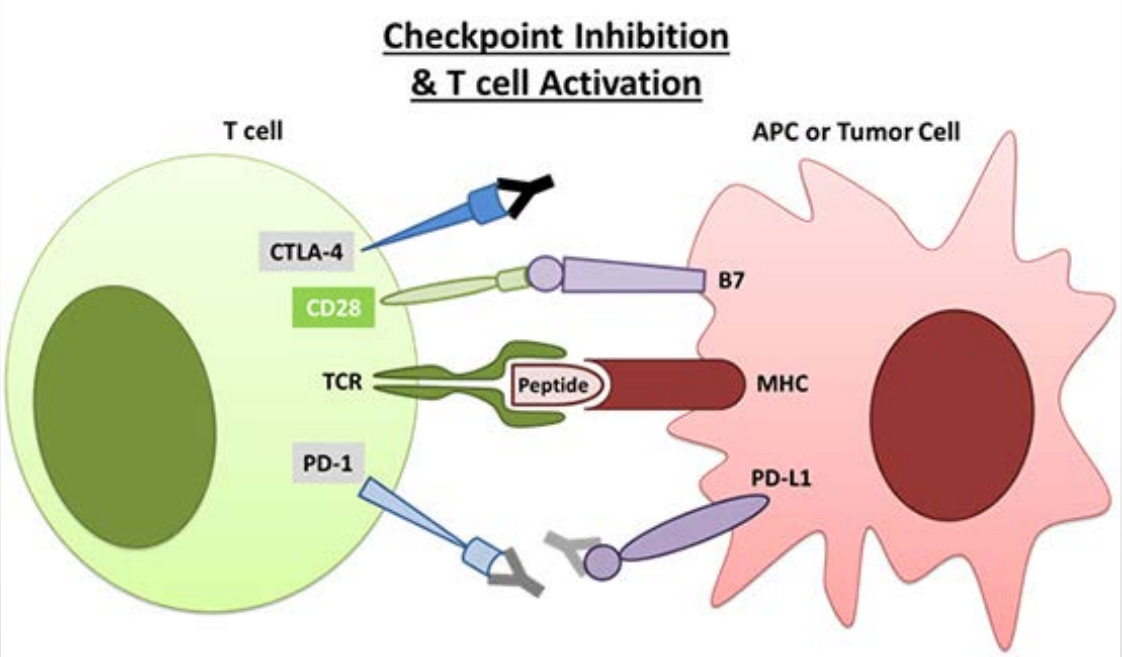
- Significant improvements in cancer therapy- using the immune system to suppress tumoral activity
- Immunotherapy: Cell therapy (CARs and TCRs), monoclonal antibodies, vaccines and **Immune checkpoint inhibitors** (ICIs)
- First FDA approved was Ipilimumab (anti-CTLA4) for melanoma in 2011
- 7 have now FDA approval as single or combination therapy for multiple malignancies.

Agent	Target receptor	FDA-approved indications [b]
Ipilimumab	CTLA-4	Melanoma, MSI-H/dMMR CRC, intermediate- or poor-risk RCC (in combination with nivolumab)
Tremelimumab	CTLA-4	Not yet approved; under investigation
Nivolumab	PD-1	MSI-H or dMMR CRC, HNSCC, HCC, melanoma, cHL, NSCLC, RCC, urothelial cancer, SCLC
Pembrolizumab	PD-1	Cervical cancer, gastric cancer, HNSCC, HCC, cHL, melanoma, MCC, MSI-H/dMMR cancers, NSCLC, primary mediastinal DLBCL, urothelial cancer
Cemiplimab	PD-1	Cutaneous SCC
Atezolizumab	PD-L1	NSCLC, urothelial cancer
Avelumab	PD-L1	MCC, urothelial cancer
Durvalumab	PD-L1	NSCLC, urothelial carcinoma

Marin-Acevedo JA, et.al. Mayo Clinic 2019

Why does toxicity occur?

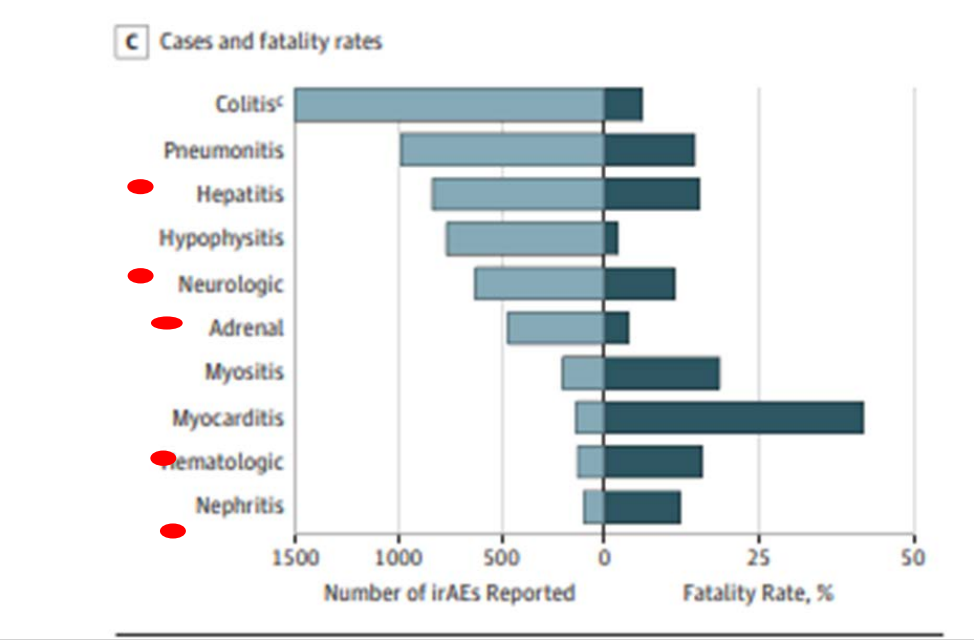
- Cytotoxic T-cell have anti-tumoral effects
- Check and balances on T-cell activation and inhibition
- ICIs block T-cell suppression of CTLA4/PD-1/PDL-1 pathway and enhance immune mediated anti-tumoral activity
- Enhanced T-cell activity ⟶ high immunogenic response ⟶ Immune related adverse events (IRAEs)

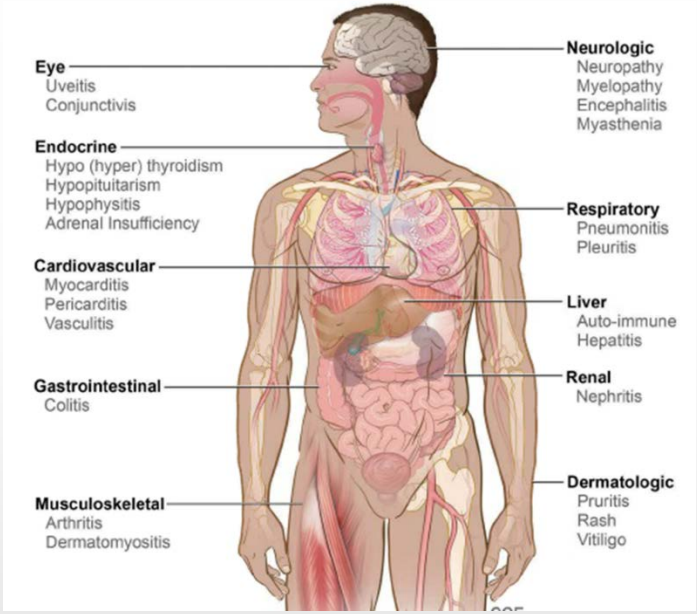


Kershaw et. al. Nature Reviews Cancer. 2013.
www.genscrypt.com
Das R, et.al. J of Immun. Feb 2015.

How do toxicities present?

- Any organ can be affected
- Within days to months (3m) from last administration of the ICI
- Mild toxicities are more common, and usually respond to treatment
- Grade 3 and 4 toxicities: Incidence and mortality seems now to be higher than what was reported on initial studies





- Meta-analysis from 2009-2018: 613 fatal toxic events

Wang DY, et.al. JAMA Oncol. 2018.

Can we predict these toxicities?

- No specific patient characteristics have been associated to toxicities
- Severe toxicities are more common with combination therapy (anti-CTLA4: 27%, anti-PD-1/PDL-1: 16%, combination: 55%)
- Anti-CTLA4: colitis, hepatitis, skin, hypophisitis

  Anti-PDL1/PD-1: thyroiditis, pneumonitis, myocarditis
- Different distribution within malignancies?
- De-novo vs reactivation of underlying disease?
- In-vivo changes of T-cell, B-cell and NK activity (gene upregulation, cytokine profile and molecular expression) → Can this be used not only for ICI response but toxicity?

Das, R et.al. JCI. Jan 2018.
Hopkins AM. Br J Cancer. 2017

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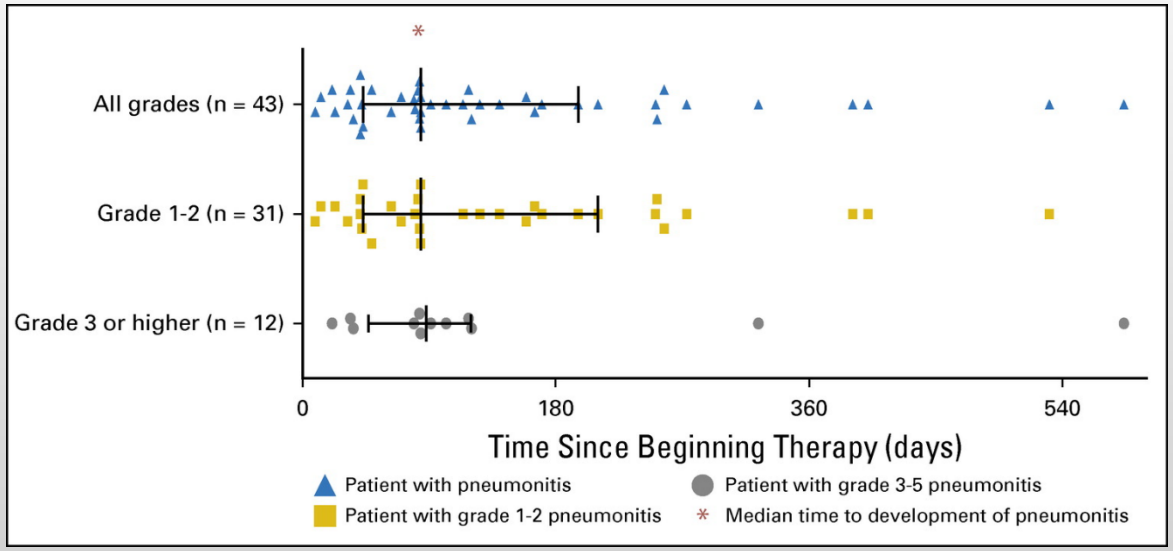
What are the Main Toxicities Observed in the ICU?

Pneumonitis

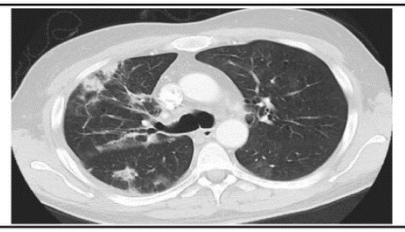
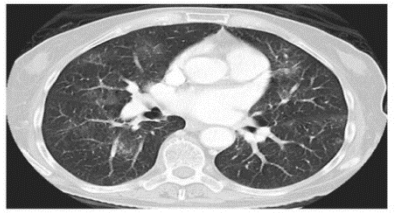
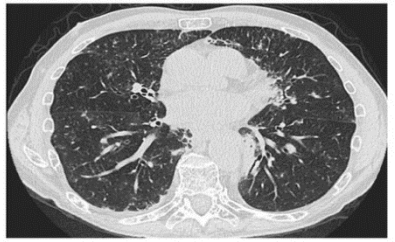
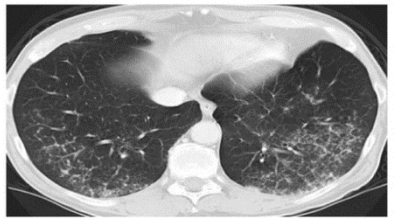
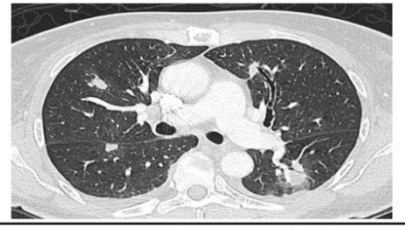
- 1-10% and is more common with anti-PD-1/PD-L1 agents and with combination therapy (15%)
- Most are mild presentations and resolve but can have 14% mortality
- Typically 3 months after last treatment but can be earlier if dual therapy



Naidoo J, et.al. JCO 2017

Pneumonitis

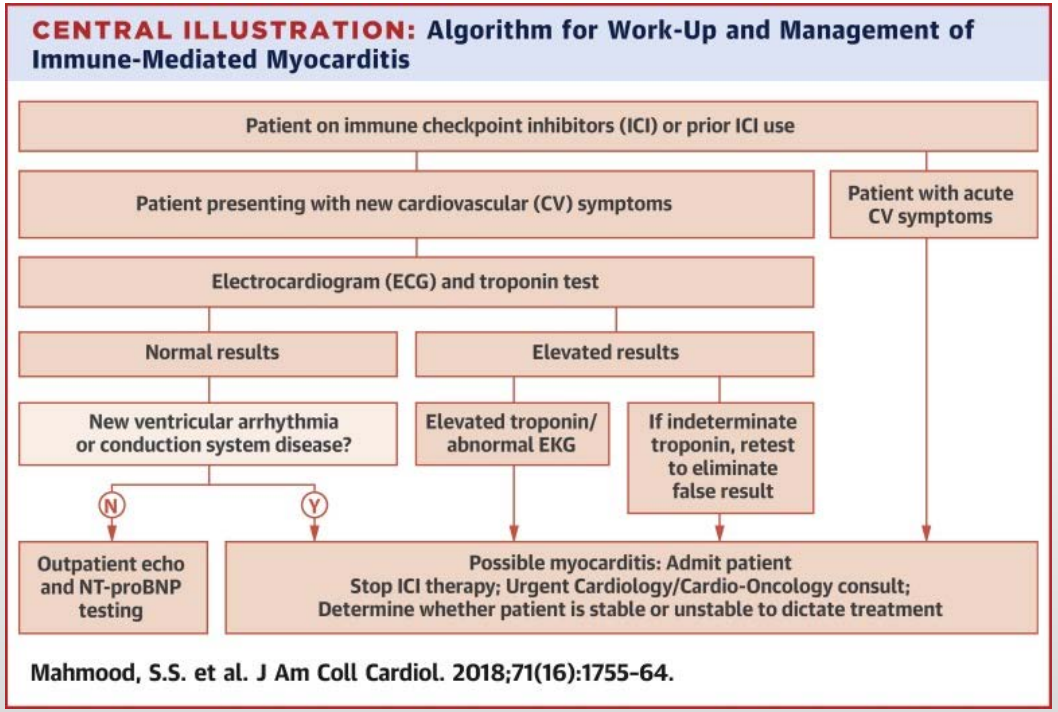
- Grading of symptoms as per CTCAE (Grade 3- >50% lungs and Grade 4-life threatening)
- Imaging and bronchoscopy but usually to help rule other underlying causes of respiratory failure.
- “Sarcoid-like” reactions have been described

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

Naidoo J, et.al. JCO 2017

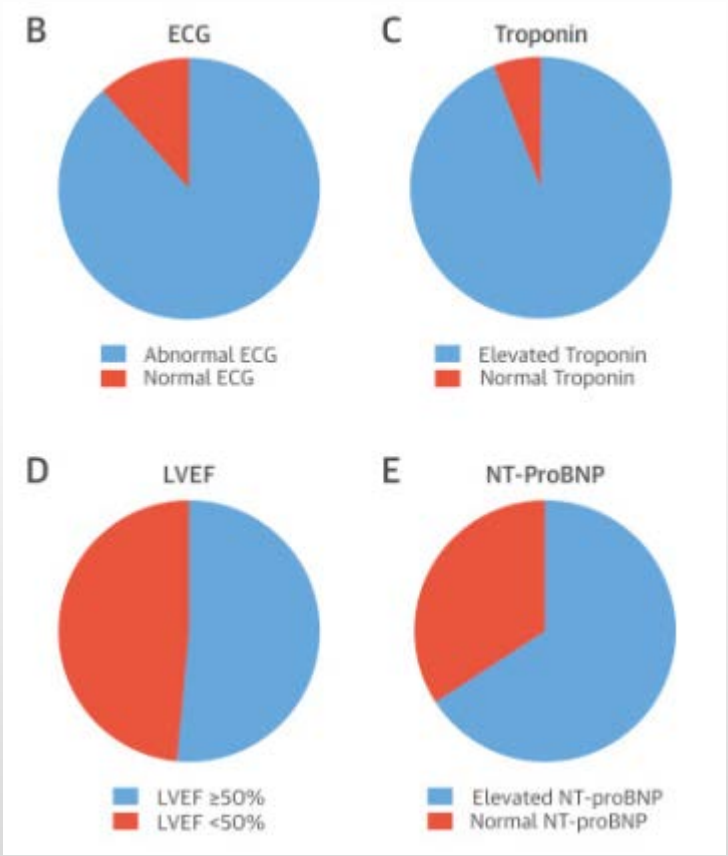
Cardiac toxicities

- Clinical presentations: Myocarditis, pericarditis, heart failure and arrhythmias
- More common with PD-1/PDl-1
- Uncommon (incidence varies on reporting system) but mortality as high as 50%
- Median incidence at 10 weeks (2w-8m)



Cardiac toxicities-Myocarditis

- Usually fulminant if left untreated and severe cardiovascular events occur even with a normal EF
- Diagnosis: Cardiac MRI and biopsy
- Multicenter registry of 8 centers of 4 years:
  - Incidence approximately 1.2% (n=35) and more common with PD-1, (2.5% with combined therapy)
  - 50% had major events (higher than general population with other causes of myocarditis)
  - No risk factors we identified (malignancy, prior treatments, EKG changes or cardiovascular risk factors)
  - Biopsy: T-cell–predominant lymphocytic infiltrate within the myocardium
  - Major CV events were associated to higher peak troponin levels



Mahmood SS, et.al. J Am Coll Cardiol. 2018

Neurotoxicity

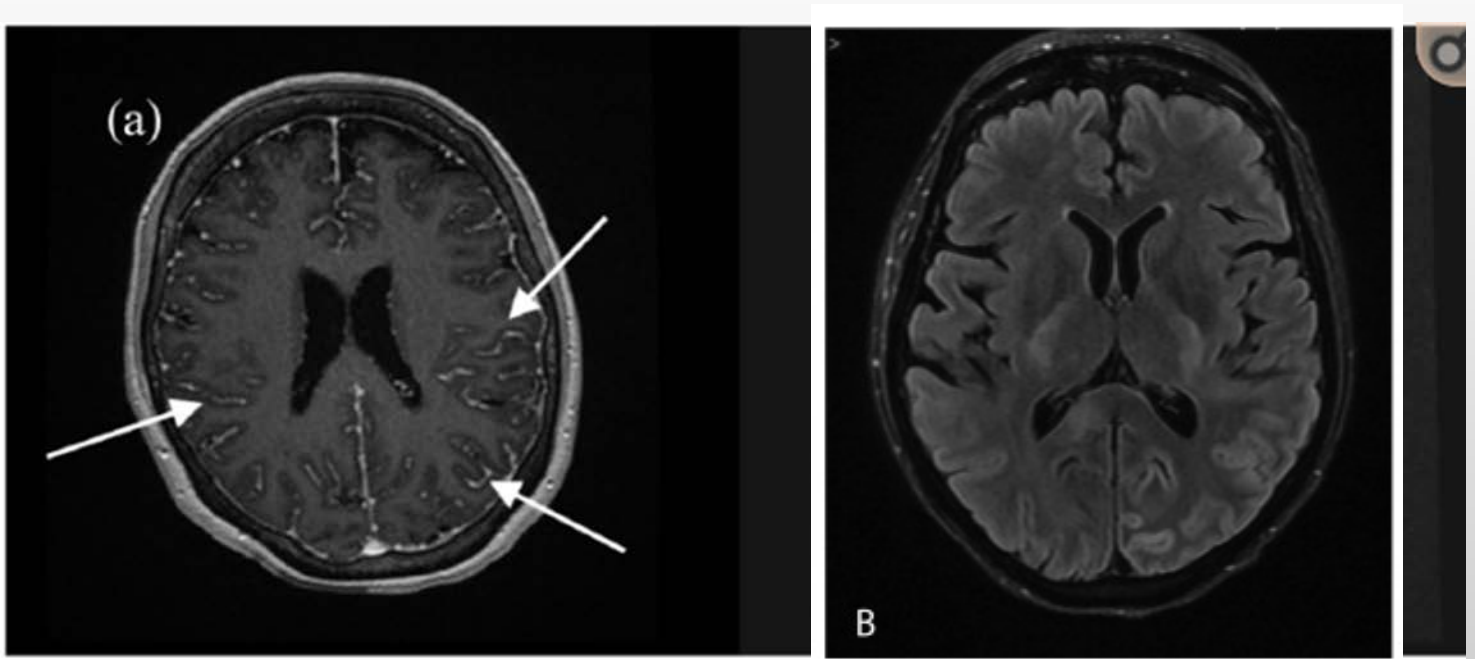
- Until recently were considered to be rare (<1% incidence) but higher incidences now being reported (1%-12% of patients receiving therapy)

- Neuro iAEs compromise 6-15% of all immune checkpoint inhibitor AE related mortality. Unclear data on morbidity

- Clinical Presentations:
  - Neuromuscular disorders: Guillain-Barre Syndrome and Myasthenia Gravis
  - Seizures
  - Posterior Reversible Encephalopathy Syndrome (PRES)
  - Encephalitis, aseptic meningitis
  - Transverse myelitis
  - Cerebral edema
  - Encephalopathy

Neurotoxicity

- Routine diagnostic workup (antibodies for MG, paraneoplastic titers, EEG, EMG)
- Findings on MRI have significant variability
- Lumbar puncture with lymphocytosis can be suggestive, but there is variability in findings- useful to rule out infectious process



Laserna, A. SAGE Open Med Case Rep. 2018
Zafar R. Clin Med Res. 2019

Neurotoxicity: Guillain-Barre and Myasthenia Gravis

- Data available is from case series, however in general poor response to treatment and morbidity is significant
- Can be typical presentations or variants (ie: bulbar symptoms alone are common)
- Highly associated to myositis (complicating clinical picture) and myocarditis
- Close monitoring in the ICU
- Treatment is similar to non ICI related: Piridostigmine, corticosteroids, IVIg, plasmapheresis

Other organ toxicities:

- Endocrine:
  - Different to all other IRAEs they don't reverse after discontinuation of therapy
  - Hypophysitis (6.4% incidence with combination therapy, 8-9 weeks after therapy)
  - Hypo/hyperthyroidism and adrenal crisis can occur therefore monitoring of serial cortisol, ACTH levels and thyroid function
  - Diabetes insipidus
  - De-novo DM <1% (presenting as either DKA or HHS)

- Nephrotoxicity
  - 2% to 5% (when combination therapy)
  - Acute interstitial nephritis or minimal change disease
  - Increased risk when underlying auto-immune disease? Or "2nd hit" ?

- Gastrointestinal:
  - Colitis, pancreatitis and hepatitis

Diagnosis

- Differential diagnosis should be kept and treated concomitantly when necessary (ie: antibiotics for possible infectious causes while ruling out pneumonitis)

- Biopsy -can be considered (colitis, myocarditis, pneumonitis, nephrotoxicity)

  -helpful to rule out other conditions

  -does it play a role in “customizing therapy”?

Treatment

- Guidelines by ASCO, ESMO, SITC and others

	1st line	2nd line
ASCO		
Pulmonary	corticosteroids (1-2 mg/kg methylpred)	mycophenolate, IVIg, infliximab or cyclophosphamide
Neurological	corticosteroids (1-2 mg/kg or 1gr methylpred)	IVIg or plasmapheresis. Rituximab
Cardiac	corticosteroids (1-2 mg/kg or 1gr methylpred)	mycophenolate, infliximab or ATG
ESMO		
Pulmonary	corticosteroids (1-2 mg/kg methylpred)	infliximab, mycophenolate, cyclophosphamide
Neurological	corticosteroids (1-2 mg/kg methylpred)	plasmapheresis or IVIg, azathioprine, cyclosporine, mycophenolate
Cardiac	corticosteroids ("high dose")	mycophenolate, infliximab or ATG

Others: methylprednisolone 4 mg/kg/day

Firedman CG, et.al. JAMA Oncol. 2016
Puzanov I. J imm Cancer. 2017
Schmidt L. J Clin Oncol. 2019
Haanen, JBAG. Annals Oncol. 2017

Treatment: General Approach

- Discontinuation of the agent (can they be restarted?)
- Corticosteroids:
  - start with prednisone 0.5 mg/kg daily and increase to 1-2mg/kg methylprednisolone up to pulse dose.
  - Prolonged taper of 4 to 6 weeks
- For steroid refractory:
  - Cyclophosphamide, tacrolimus, mycophenolate, ATG
  - Plasmapheresis and IVIg

Treatment: Directed Therapy

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- More than 10% of patients require additional immunosuppressant
- Consider using early in certain severe AEs such as myocarditis
- Biopsy driven?
  - T-cell -IL-6, IL-1R, IL-12 and IL-23 blockade
  - B-cell: anti-CD20
  - Monocytes: anti-TNFα

	irAE indications	Protocols
Anti-IL-1 blockade	Severe irAE during acute phase; severe or refractory arthritis; chronic inflammatory; demyelinating polyradiculoneuritis; psoriasis-like reactions; psoriasis exacerbation; severe and anti-TNFα refractory colitis; myasthenia gravis; encephalitis; aseptic meningitis; myocarditis; pneumonitis	Anakinra 100 mg once per day, or canakinumab 300–600 mg once every 8 weeks
Anti-IL-6 blockade	Severe irAE during acute phase; severe or refractory arthritis; large vessel vasculitis; uveitis; myocarditis; pneumonitis; myasthenia gravis	Tocilizumab 8 mg/kg intravenously once per month or subcutaneous 162 mg once per week
Intravenous immunoglobulins	Guillain-Barrè syndrome; subacute and chronic inflammatory demyelinating polyradiculoneuritis; subacute and chronic inflammatory neuropathies; immune neutropenia; immune thrombocytopenia; facial nerve palsy; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis	Intravenous immunoglobulins 400 mg/kg per day for 5 days, or once per month for a total of 3–4 courses
Anti-CD20 depletion	Systemic lupus erythematosus; severe Sjögren's syndrome; ANCA-associated vasculitis; cutaneous vasculitis; autoimmune autonomic ganglionopathy; sensory ganglionopathy; nephritis; myasthenia gravis; transverse myelitis; enteric neuropathy; encephalitis; aseptic meningitis; hepatitis	Rituximab 1 g every 2 weeks for 2 courses or 375 mg/m² once per week for 4 courses; ofatumumab 300 mg on the first day and 1000 mg on the second day; obinutuzumab 1000 mg on the first day; ocrelizumab 300 mg on the first and fourth day
Anti-IL-17 blockade	Severe colitis and anti-TNFα refractory colitis; severe or refractory arthritis; anti-IL-6 refractory irAEs	Ixekizumab 80 mg subcutaneous once every 2 weeks; brodalumab 210 mg subcutaneous once every 2 weeks; secukinumab 150 mg subcutaneous once every 2 weeks
Anti-TNFα blockade	Severe colitis; hepatitis; severe or refractory arthritis; nephritis; uveitis; pneumonitis; myocarditis	Infliximab 5 mg/kg once every 2 weeks; adalimumab 40 mg once every 2 weeks; golimumab 50 mg once per month; etanercept 50 mg once a week; certolizumab 400 mg once a month
Anti-integrin 4 blockade	Limbic encephalitis	Natalizumab 300 mg once per month
Anti-IL-23 and anti-IL-12 blockade	Acute phase, severe, or anti-TNFα refractory colitis; severe or anti-TNFα refractory psoriasis; severe or refractory arthritis	Ustekinumab initial dose 40 mg then 45 mg after 4 weeks and then 45 mg every 12 weeks
Janus kinase inhibitor	Severe or refractory arthritis	Tofacatinib 5 mg twice per day

irAE=immune-related adverse event; IL=interleukin type; ANCA=antineutrophil cytoplasmic antibody.

***Table*: New therapeutic perspectives for the management of immune-related adverse events**

Martins, F, et.al. Lancet Oncol. 2019.

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Conclusion

- Wide variety in clinical presentation therefore intensivists should consider IRAEs from Immune checkpoint inhibitors as part of the differential.
- No clear risk factors prior to treatment identified yet.
- Low incidence, but high mortality once admitted to the ICU therefore quick and aggressive treatment with collaboration of subspecialties and oncologists is of great importance.
- Important to work up the patient for non-ICI related causes of organ failure (ie: infections, myocardial infarction, etc…)
- Treatment is mainly corticosteroids, with guidelines varying on recommendations of refractory cases. Therefore experienced physicians should be called to help with management.

Learning Assessment Question #1

- What are the two types of targets of checkpoint inhibitors?
  a) Anti-PD-1
  b) Anti-PDL-1
  c) Anti-CTLA4
  d) All of the above

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Learning Assessment Question #2

- Which is NOT a toxicity associated to checkpoint inhibitors?
  a) Myocarditis
  b) Pneumonitis
  c) Myasthenia Gravis
  d) Hypophysitis
  e) Acute myocardial infarction

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QUESTIONS?