Immune Checkpoint Inhibitors

Toxicity and Management

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- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

Discuss	Discuss the mechanism of action of Immune checkpoint inhibitors (ICI) and their role in cancer treatment.
Recognize	Recognize the most common immune-related adverse events (irAEs) that occur from immune checkpoint inhibitors
Review	Review strategies for managing immune-related adverse events

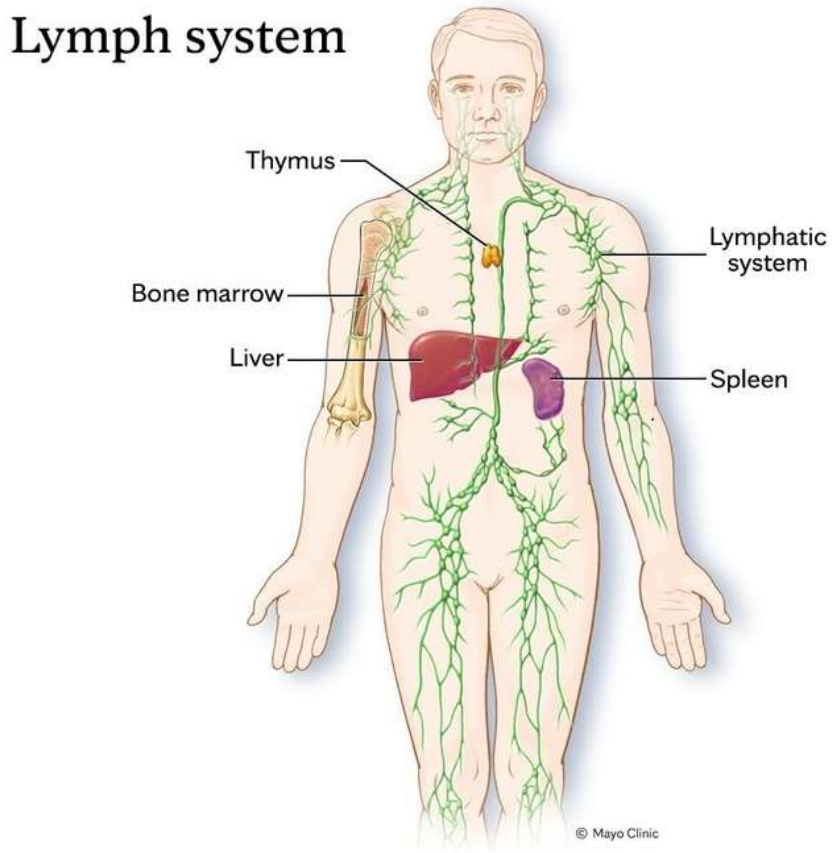
Cancer Immunotherapy

Goal:

Stimulate the immune system to kill cancer!

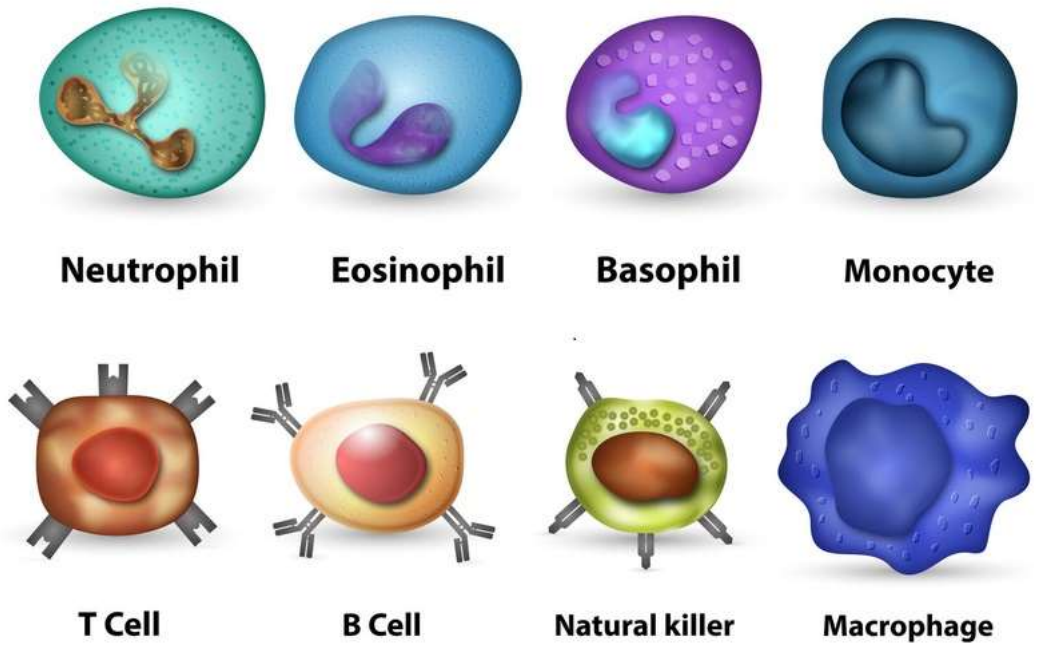
Healthy Immune System

- Complex network of organs, tissues and cells
- Cells in our immune system move throughout the body
- Their main job is to rid the body of bacteria and abnormal cells.



The Immune System Army

- Dendritic Cells
- Macrophages
- Monocytes
- Neutrophils
- B-Cells
- Natural Killer Cell
- T-Cells



Adaptive Immune Response

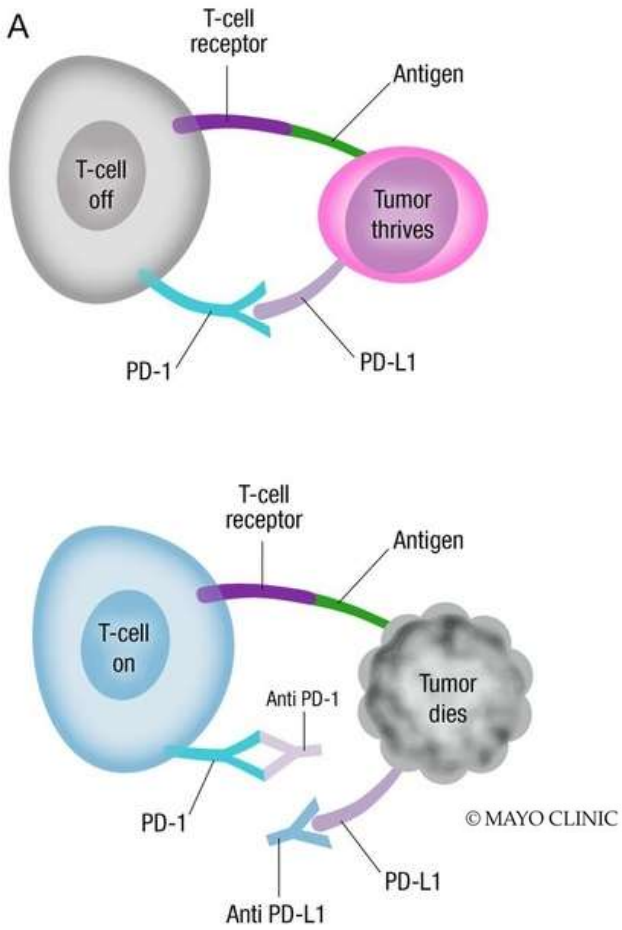
- Antigen-Presenting Cells (APC) = Dendritic Cells
  - Patrol the body, when it finds something suspicious, it alerts the T-Cells to multiply and attack the suspicious cells
- As cancer cells break down, the fragments of these cells are called antigens
  - Immune system can attach to the cells and bring to the lymph nodes – MHC complex
- Tumor target is presented to the T-Cell
  - T-Cell is activated and turns to a “killer” T-Cell

Checkpoints

- When you get sick, your immune system activates
- Something must tell the immune system when it's done
- Checkpoints are normally present to help prevent immune system from damaging normal structures
- Cancers can upregulate these molecules to turn the immune system off
- Checkpoints include: PD-1/PDL-1/CTLA-4/LAG-3*

PD-1 and PDL-1

- Expression of the **programmed death-1 (PD-1) ligand 1 (PD-L1)** is used to select patients and analyze responses to anti–PD-1/L1 antibodies.
- Tumor learns to expresses PD-1/PDL-1
  - Works to disguise the tumor
- PDL-1 deactivates T-Cells by binding to PD-1
- If you BLOCK the PDL-1 and PD-1connection, you can turn the T-Cell back on
    - “Anti-PD-1” or “Anti-PDL-1”


A
T-cell receptor
Antigen
T-cell off
Tumor thrives
PD-1
PD-L1
T-cell receptor
Antigen
T-cell on
Anti PD-1
Tumor dies
PD-1
PD-L1
Anti PD-L1
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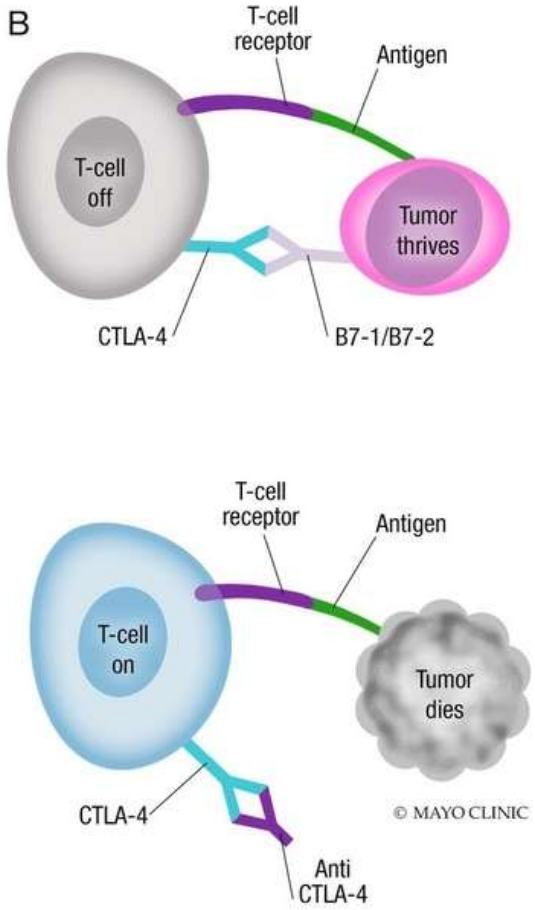
CTLA-4

- **Cytotoxic T lymphocyte-associated antigen (CTLA-4)**, also known as CD152, is a co-inhibitory molecule that functions to regulate T cell activation.
- Antibodies that block the interaction of CTLA-4 with its ligands B7. 1 and B7. 2 can enhance immune responses, including anti-tumor immunity.
- When CTLA-4 is bound to another protein called B7, it helps keep T cells from killing other cells, including cancer cells.
- When this protein is blocked, the “brakes” on the immune system are released and the ability of T cells to kill cancer cells is increased


B
T-cell receptor
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Tumor thrives
CTLA-4
B7-1/B7-2
T-cell receptor
Antigen
T-cell on
Tumor dies
CTLA-4
Anti CTLA-4
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LAG-3

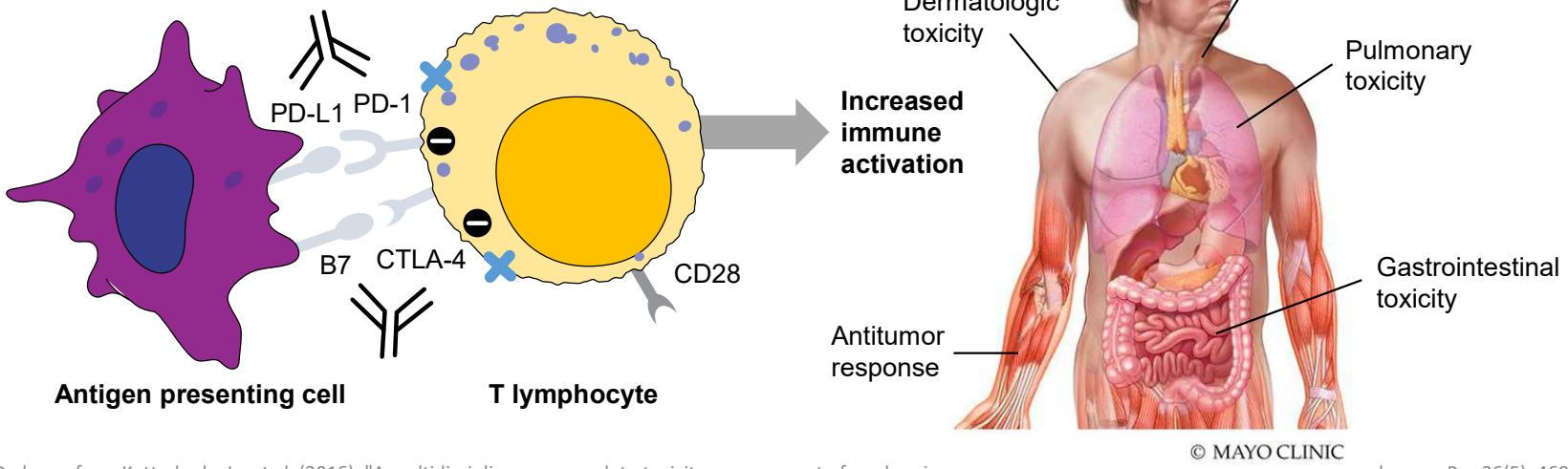
- Lymphocyte activation gene-3
  - Co-inhibitory receptor expressed on the cell surface
  - Stimulation = suppression of T-Cell
- LAG-3 binds to the antigen MHC complex on APCs
- This limits T-cell activation and proliferation – leading to their exhaustion
- Synergy with PD-1 in multiple settings

Immune checkpoint inhibitors

Anti-PD-1	Anti-PD-L1	Anti-CTLA4	LAG-3
Pembrolizumab	Atezolizumab	Ipilimumab	Relatlimab
Nivolumab	Avelumab		
Cemiplimab	Durvalumab		

Immune-Related adverse events

- **Definition:** Adverse events that occur via the activation of a patient's immune system that can occur in any tissue, organ or system
- Can range from mild/moderate to severe and sometimes fatal
- Combination therapies increase risk of immune-related adverse events



Redrawn from 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

Special populations at increased risk of toxicity

- 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.

Principles of routine monitoring

- Physical Exam at each visit with symptom assessment
- Imaging periodically as indicated
- General bloodwork prior to immunotherapy treatment
  - CBC/CMP/TSH

Things to Remember

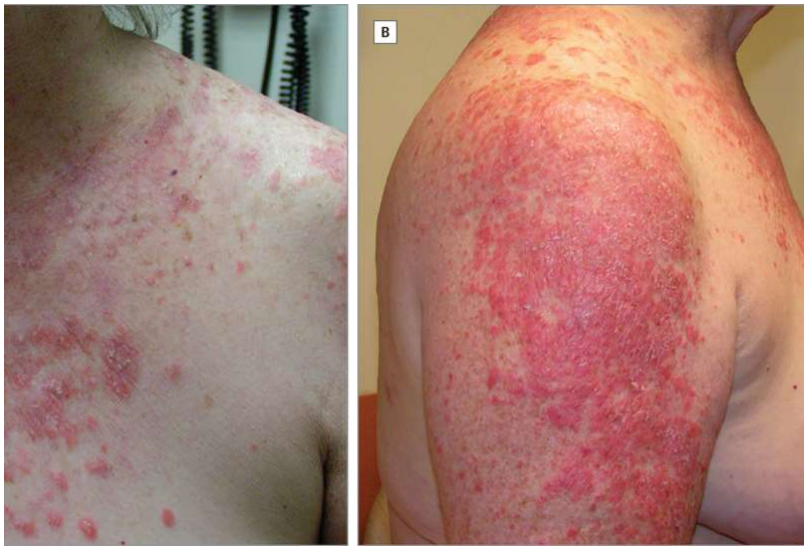
- Everyone is different
- Early detection is crucial
- Starting steroids early at the correct dose can save lives

common immune-related adverse events

Dermatalgic	Gastrointestinal	Hepatic	Endocrine
• Rash • Pruritis	• Colitis	• Hepatitis	• Thyroiditis • Pituitary/Adrenal dysfunction • Pancreatitis • Diabetes

Dermatologic Toxicity

- Routine Monitoring: Examination of skin and mucosa
- Most frequent with CTLA-4 and anti-PD1
  - 40% single agent-60% combo therapy
- Many patients will have pruritus in the absence of rash (10-30%)
- Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported



Rash Management

Maculopapular Rash Bullous Pemphigoid Lichenoid Reaction SJS/TEN	Grade 1	<10% BSA with or without symptoms	Continue immunotherapy Oral antihistamine Moderate potency topical steroids
	Grade 2	10-30% BSA with or without symptoms	Continue immunotherapy Oral antihistamine High potency topical steroids Prednisone 0.5-1mg/kg/day
	Grade 3-4	10-30% BSA with or without symptoms	Hold immunotherapy High potency topical steroids Prednisone 0.5-1mg/kg/day (increase up to 2mg/kg/day if needed) Dermatology consult

Pruritus management

Grade 1	Mild or localized	Continue immunotherapy Oral antihistamine Topical steroids
Grade 2	Intense or widespread Intermittent Skin changes from scratching	Continue immunotherapy Oral antihistamine High potency topical steroids Dermatology consultation
Grade 3	Intense or widespread Constant Limiting ADLs or sleep	Hold immunotherapy Oral antihistamines Prednisone 0.5-1mg/kg/day Urgent Dermatology consultation

Rash Management (Steroid Refractory)

Maculopapular or Lichenoid Rash

- Addition of Infliximab (TNFα)
- Tocilizumab (IL-6)

Bullous Pemphigoid

- Addition of Rituximab (CD20)

Pruritus

- Addition of GABA analogs
- Omalizumab (IgE)

Gastrointestinal Toxicity

- Diarrhea: Increase in stool frequency
- Colitis: Diarrhea &abdominal pain with imaging/endoscopic evidence of colonic inflammation
  - Shares histologic features of Crohn's disease
  - Fatal bowel perforation reported in 1% of patients treated with ipilimumab
- Stool studies should ALWAYS be done – do not use Imodium!
  - C. difficile and enteric pathogens
- 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

Diarrhea/Colitis Management

Grade 1	Fewer than 4 BM above baseline/day No colitis symptoms	Consider holding immunotherapy BRAT diet Hydration Consider Loperamide
Grade 2	4-6 BM above baseline/day Colitis symptoms	Hold immunotherapy Budesonide 9-12mg daily
Grade 3	More than 6 BM above baseline/day Colitis symptoms Interfering with ADLs	Discontinue immunotherapy Budesonide 9-12mg daily + prednisone 1.0-2.0 mg/kg daily Consider Flex Sig
Grade 4	Serious complications such as ischemic bowel, perforation, toxic mega-colon	Discontinue immunotherapy Consult GI IV Methylprednisolone 1-2mg/kg daily Infliximab 5 mg/kg

Always do stool testing!

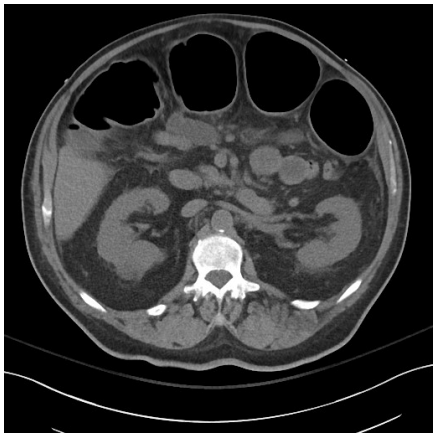
Colitis

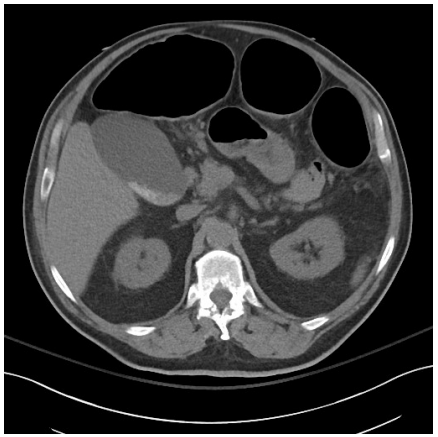
Patient with grade 4 colitis from Ipi/Nivo.

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 solumedrol and decompression.





Hepatotoxicity

- 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
- Rule out viral etiology, disease related, drug related Consider GI, Ultrasound or MRCP, Limit/discontinue hepatotoxic medications
- **Labs to check:** AST, ALT, Bilirubin (total and direct), Alk Phos, Acute Hepatitis Profile (HBs Antigen, Hep B IgM, Hep A IgM, HCV w/ reflex), CMV, HSV, EBV

Hepatitis Management

Grade 1	<3x ULN	Continue immunotherapy Assess LFTs with increased frequency If no resolution after 2 weeks or continuing to trend up- consider prednisone 0.5-1mg/kg/day
Grade 2	3-5x ULN	Hold Immunotherapy Monitor LFTs every 3-5 days Prednisone 0.5-1mg/kg/day
Grade 3	>5-20x ULN	Permanently discontinue immunotherapy Prednisone 1-2mg/kg/day Monitor LFTs every 1-2 days If steroid refractory or no improvement after 3 days, consider adding mycophenolate (500-1000mg BID)
Grade 4	>20x ULN	Permanently discontinue immunotherapy Prednisone 2mg/kg/day Inpatient/Liver Biopsy If steroid refractory or no improvement after 3 days, consider adding mycophenolate (500-1000mg BID)

Do NOT use Infliximab

Endocrinopathies

- **Thyroid dysfunction-Most common with PD-1/PD-L1 (0-15%)**
  - Acute/inflammatory/painless thyroiditis associated thyrotoxicosis (↓TSH, ↑FT4 and/or T3)
  - Incidence in combination therapy (40%)
  - Resolution to euthyroid or progress to overt hypothyroidism (TSH >10); minority regain function

Thyroiditis Management

Normal or low TSH Low FT4 Low T3	Low TSH or <0.01 normal or high FT4 or T3	TSH >5 and <10 Normal FT4 or T3	TSH >10 Normal or low FT4 and T3

• **2° hypothyroidism from hypophysitis vs. effects of HDS**
  • Screen for 2° adrenal insufficiency (am ACTH/cortisol
  • Begin thyroid replacement
	• **Acute thyroiditis**
	  • Usually resolves/progresses to hypothyroidism
	  • Repeat TFT's 3-6 weeks
		• **Subclinical Hypothyroidism**
		  • Repeat TFT in 3-6 weeks
			• **Primary Hypothyroidism**
			  • Begin Thyroid Replacement
			  • May consider repeating TFT in 2-4 weeks if asymptomatic

Levothyroxine Dosing

1.2-1.6 mcg/kg

75-100mcg daily

Repeat TFT's in 4-6 weeks and titrate to reference range TSH

Endocrinopathies

- **Pituitary/Adrenal-most common with anti-CTLA-4**
  - **Primary Adrenal Insufficiency (AI)=medical emergency**
    - Diagnosed by presence of volume depletion and electrolyte abnormalities
    - **Low or undetectable AM cortisol and high ACTH**
    - Hospitalize with fluid replacement, correct electrolytes and high dose steroids (1-2mg/kg)
  - **Secondary AI**
    - **Low or undetectable AM cortisol and low ACTH**
    - Can be from hypophysitis or long-term steroid use

Primary Adrenal Insufficiency Management

Primary Adrenal Insufficiency	Volume depletion Electrolyte abnormalities Low AM Cortisol <5 High ACTH	Endocrine Consult Hospitalized with fluid replacement Correct electrolytes High dose steroids	Patients need to be instructed in stress dose steroids and sick day dosing. * Patients who remain asymptomatic and are on maintenance dosing only can be rechallenged*.
Secondary Adrenal Insufficiency	Low AM Cortisol <5 Low ACTH	<u>Symptomatic:</u> Begin high dose steroids (1-2 mg/kg) x 1-2 weeks or until asymptomatic, then rapid taper to physiologic dose	<u>Asymptomatic:</u> Begin physiologic steroid replacement 15-20 mg in am and 5-10 mg in early afternoon

Refer to endocrinologist for further management and education on hormone replacement therapy

Endocrinopathies

- **Hypophysitis**
  - 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%)

Must consider CNS involvement by malignancy or other neurological toxicity

Hypophysitis Management

Tests:	Low AM Cortisol Low ACTH FSH, LH, TSH, T4	MRI Brain w+w/o contrast with pituitary cuts
Treatment:	Hold immunotherapy until symptoms resolve	If symptomatic: Prednisone 1-2mg/kg/day

Pancreatitis

Generally presents with classic symptoms:

- Severe belly pain that may spread to your back or chest (it may feel worse after you eat)
- Nausea
- Vomiting
- Rapid heart rate
- Fever

May have isolated radiologic findings/lab elevations only

Workup:

- Amylase, Lipase
- IgG4
- CT Abdomen

Pancreatitis Management

Grade 1	<u>One of the following:</u> Elevation of amylase/lipase >3x ULN radiologic findings on CT Clinical findings	Continue immunotherapy Clinical assessment Consider imaging
Grade 2	<u>Two of the following:</u> Elevation of amylase/lipase >3x ULN radiologic findings on CT Clinical findings	Hold Immunotherapy Prednisone 0.5-1mg/kg/day
Grade 3	<u>All of the following:</u> Elevation of amylase/lipase >3x ULN radiologic findings on CT Severe abdominal pain/vomiting	Discontinue immunotherapy Prednisone 1-2mg/kg/day

Diabetes

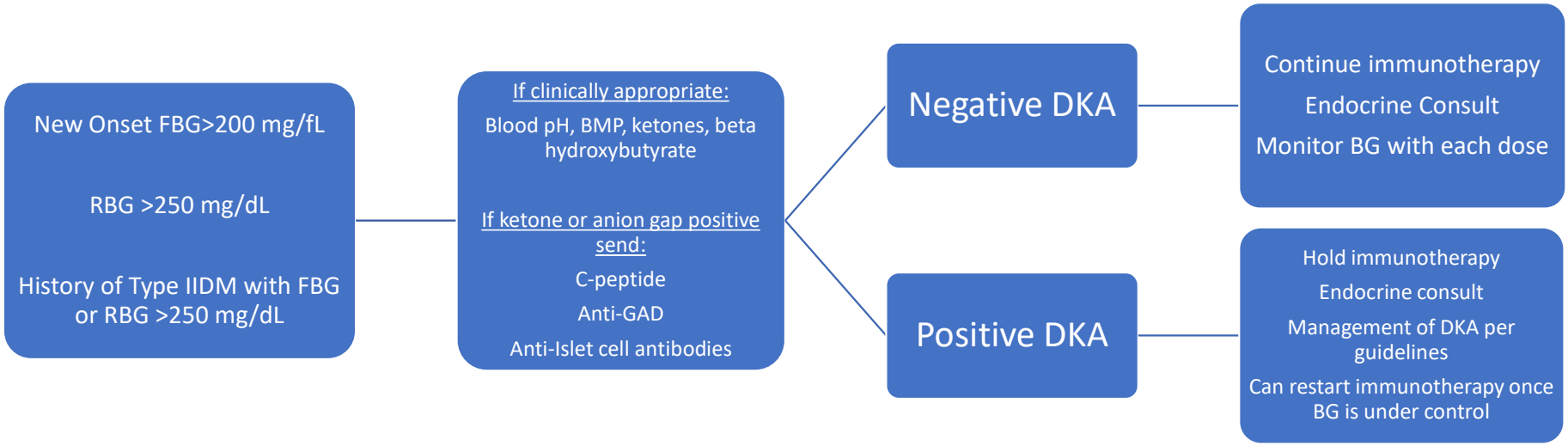
Both new onset Type I –complete islet cell failure or severe worsening of Type II

- Often asymptomatic hyperglycemia (400-500's)
- Can present as DKA

Workup/Treatment

- Evaluate for presence of DKA

DKA


New Onset FBG>200 mg/fL
RBG >250 mg/dL
History of Type IIDM with FBG or RBG >250 mg/dL
If clinically appropriate:
Blood pH, BMP, ketones, beta hydroxybutyrate
If ketone or anion gap positive send:
C-peptide
Anti-GAD
Anti-Islet cell antibodies
Negative DKA
Continue immunotherapy
Endocrine Consult
Monitor BG with each dose
Positive DKA
Hold immunotherapy
Endocrine consult
Management of DKA per guidelines
Can restart immunotherapy once BG is under control

Less Common Immune Related Adverse Events

Renal	Cardiac	Pulmonary	Musculoskeletal
• Nephritis	• Myocarditis • Pericarditis	• Pneumonitis	• Myositis • Arthritis

Nephritis

Acute Interstitial Nephritis

- Incidence rate around 2-5% (based on kidney bx registries)
- Presentation: Asymptomatic crt elevation
- Triad of fever, rash, eosinophilia with crt elevation

Glomerular Nephritis

- Case reports –exact incidence unknown

Workup

- CRP, RBP
- Random Urine, UA/Microscopic,
- Bilateral Kidney Ultrasound
- Protein/CR Ratio
- Retinol Binding Protein

Nephritis Management

Grade 1	Cr 1.5-2x above baseline	Consider holding immunotherapy Follow Cr and urine protein every 3-7 days
Grade 2	Cr 2-3x above baseline	Hold Immunotherapy Follow Cr and urine protein every 3-7 days Prednisone 0.5-1mg/kg/day
Grade 3	Cr >3x baseline	Discontinue immunotherapy Consider inpatient care Prednisone 1-2mg/kg/day
Grade 4	Cr >6x baseline	Discontinue immunotherapy Start high dose prednisone 500-1000mg Consider renal biopsy Consider adding infliximab or mycophenolate

*Do not use Bactrim for PJP prophylaxis

Cardiovascular Toxicity

Myocarditis/Pericarditis/Cardiomyopathy

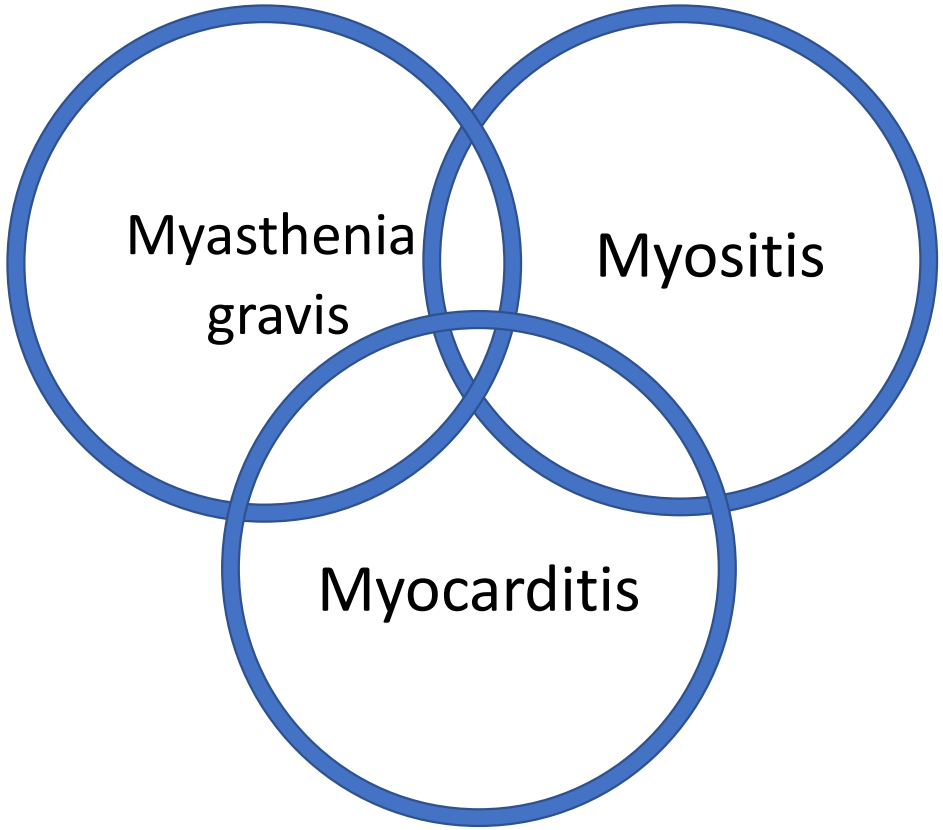
Myocarditis is a rare but serious condition in which the heart muscle becomes thick and inflamed. It often affects people who also have myositis or myasthenia gravis

Workup

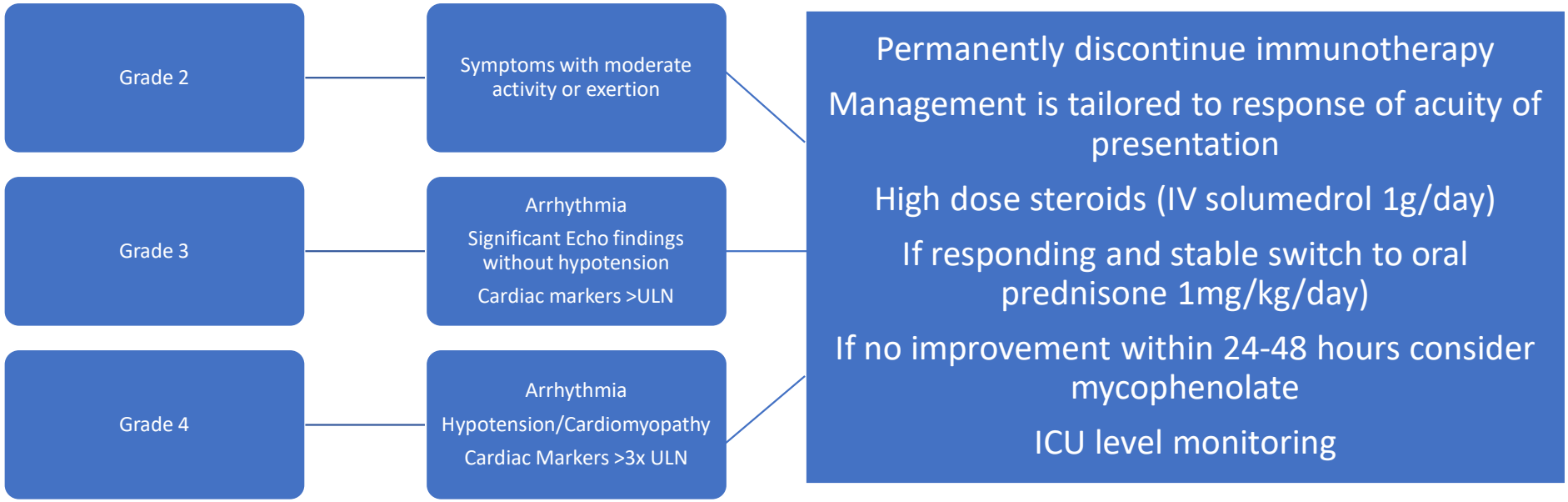
- Standard cardiac workup to r/o ischemia
- Troponins, CK, BNP, ESR, CRP
- ECG
  - See ST-T wave abnormalities, new arrhythmias (i.e heart block or ectopy)
- Echocardiogram
  - See diffuse LV systolic dysfunction, RWMA, increased wall thickness, pericardial effusion and strain abnormalities
- If Echocardiogram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

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

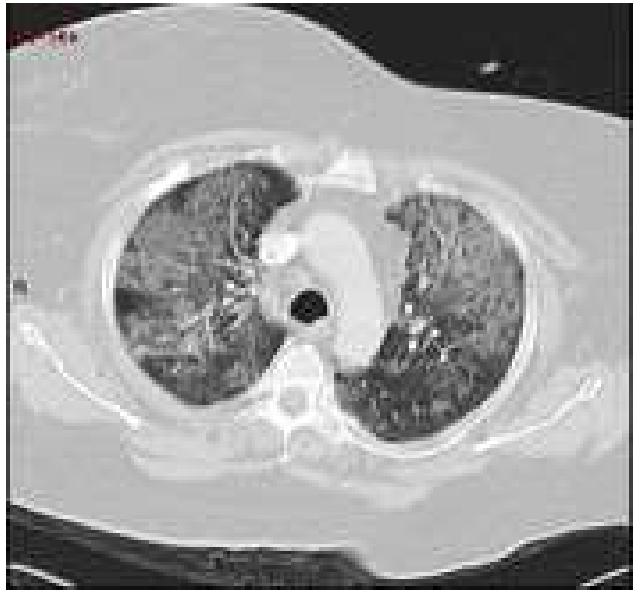


Myocarditis/Pericarditis Management



Pulmonary Toxicity

- Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)
  - Usually seen as GGO
- May present asymptomatically (only seen radiographically)
- Symptoms
  - DOE, SOB at rest, orthopnea
  - Dry nagging cough (deep in chest)
  - Chest pain
  - Afebrile
- Workup:
  - CT Chest
  - Pulse Oximetry (rest and walking)
  - Pulmonary function testing
- Differential: Pulmonary embolism, progression of disease, infection



Pneumonitis Management

Grade 1	Asymptomatic Radiologic findings only	Consider holding immunotherapy Monitor with pulse oximetry Repeat CT in 3-4 weeks
Grade 2	Symptomatic: SOB, DOE, Cough, Fever, Increased O2 requirements	Hold Immunotherapy Consult Pulmonary Infectious workup (consider bronch) Prednisone 1-2mg/kg/day Repeat CT in 3-4 weeks *IF no improvement in 2-3 days, treat as grade 3
Grade 3/4	Severe Symptoms: SOB, DOE, Cough, Fever, Increased O2 requirements Involving >50% lung fields Limiting self ADL	Permanently discontinue immunotherapy Consider inpatient care with infectious workup High dose steroids (1g Solumedrol) *IF no improvement in 2 days or worsening symptoms consider mycophenolate 1000 mg BID or Infliximab 5 mg/kg IV or IVIG 0.4 g/kg/day

Musculoskeletal Toxicity

- Arthritis: A disorder characterized by inflammation involving a joint.
  - Labs to check: ANA, Anti-CCP, CRP, ESR, RF
- Myositis: A disorder characterized by inflammation involving the skeletal muscles.
  - Labs to check: CMP, ESR, CRP, anti-CCP, aldolase, troponin

Arthritis Management

Grade 1 (Mild)	Mild pain with inflammation, erythema, or joint swelling	Continue immunotherapy NSAIDS Consider intra-articular steroids in affected joints
Grade 2 (Moderate)	Moderate pain associated with signs of inflammation, erythema, or joint swelling. Limiting instrumental ADs	Consider holding immunotherapy Prednisone 0.5mg/kg/day
Grade 3 Severe	Severe pain associated with signs of inflammation, erythema, or joint swelling. Irreversible joint damage. Limiting self-care ADL	Hold or Discontinue immunotherapy Prednisone 1mg/kg/day If worsening consider: infliximab

Myositis Management

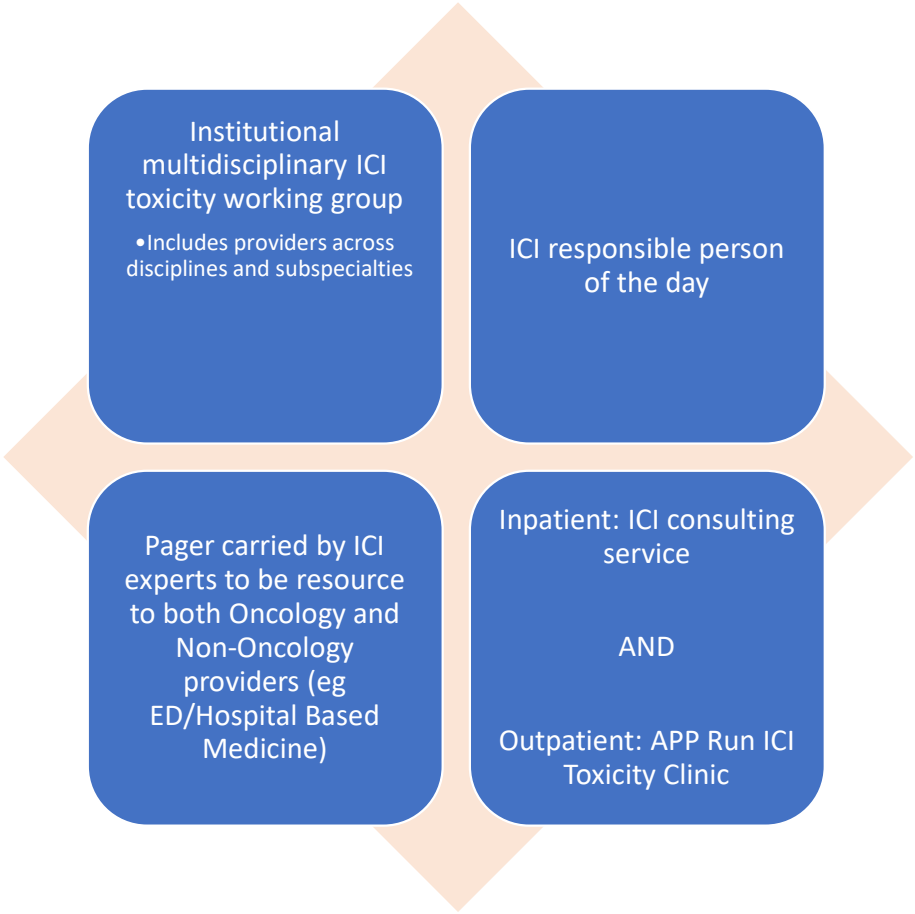
Grade 1	Mild Pain	Continue immunotherapy Monitor labs Pain treatment PRN
Grade 2	Moderate pain associated with weakness Pain limiting ADL	Hold immunotherapy Prednisone 1-2mg/kg/day Muscle MRI and EMG Consider muscle biopsy
Grade 3	Pain associated with severe weakness Limiting self care ADL	Hold immunotherapy Prednisone 1-2mg/kg/day Muscle MRI and EMG Consider muscle biopsy Consider IVIG Consider Infliximab

Principles of Steroid management

- Not a “one size fits all” approach
- DO NOT use Medrol 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)
- GI protection: Famotidine (Pepcid) 20mg daily
- Determining “steroid-refractory” should be individualized and based on organ system involved.

Principles of Rechallenging

- Proceed with caution – GO SLOW!
- PERMANENT DISCONTINUATION in the setting of severe/life-threatening
- Immunotherapy may resume with patient still on 10-20mg prednisone daily.



Mayo Clinic Initiatives

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

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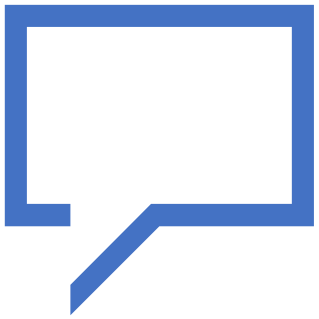
Thank you!

QUESTIONS
& DISCUSSION



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