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Society for Immunotherapy of Cancer

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Pharmacological Management of Immune-Related Adverse Events (irAEs)

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

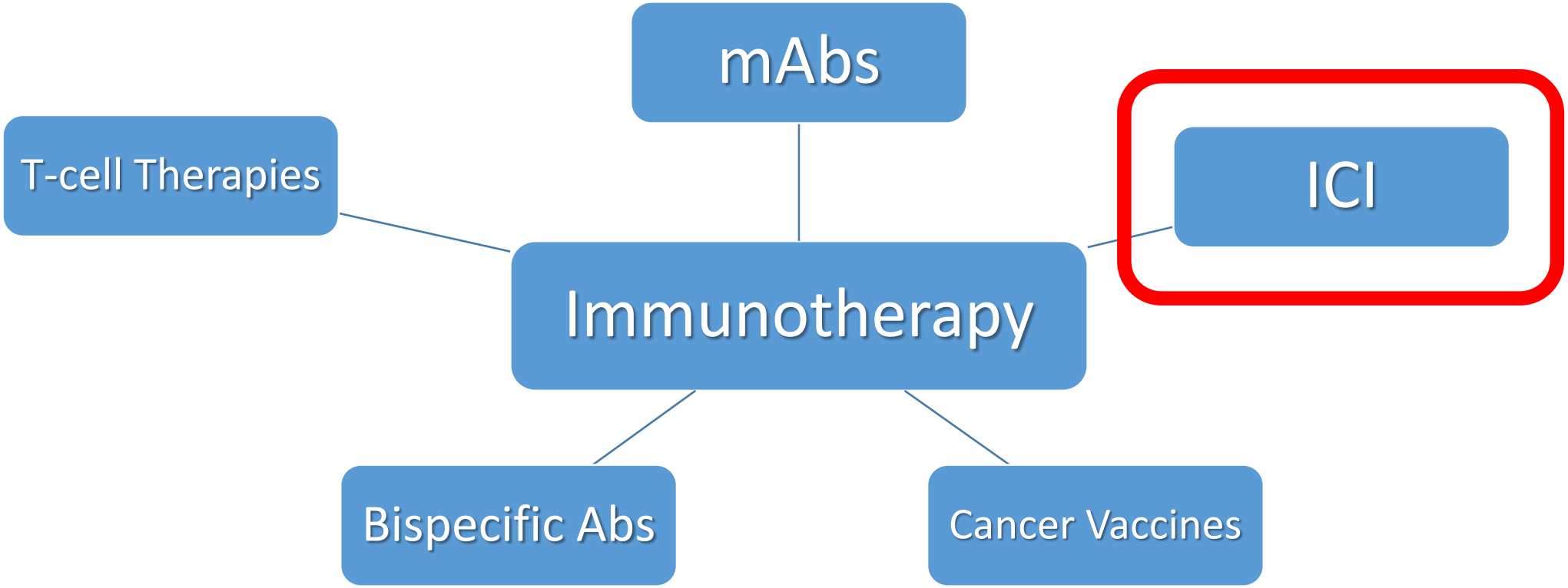
Clovis Oncology, Employee (effective 11/6/2017)

There will be discussion about the use of products for non-FDA approved indications in this presentation as there are currently no products approved by the FDA for the treatment and/or management of irAEs.

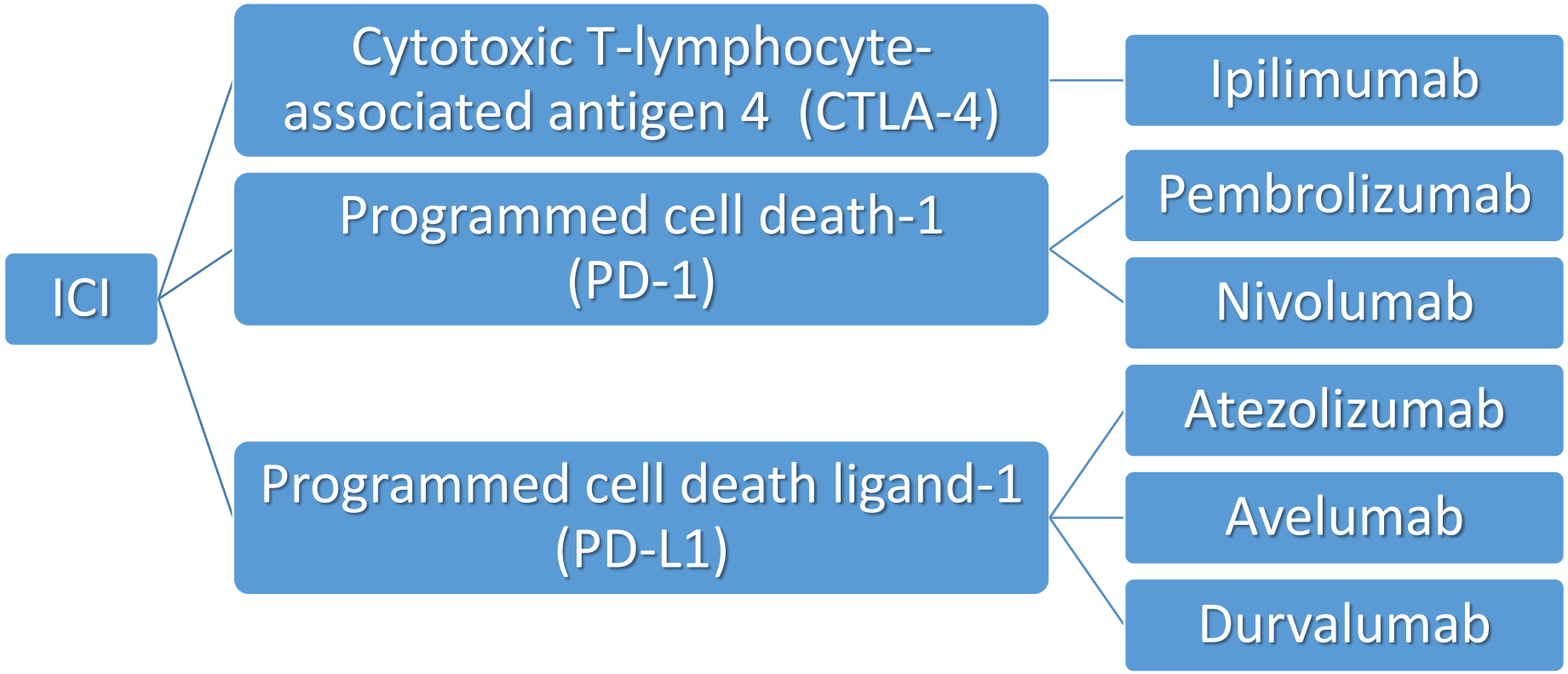
Objectives

- Identify immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI) therapy
- Outline practical guidance on the appropriate management of common irAEs

Why is this topic important?



Why is this topic important?[1-7]



2016-17 FDA New Approvals & Label expansions

17

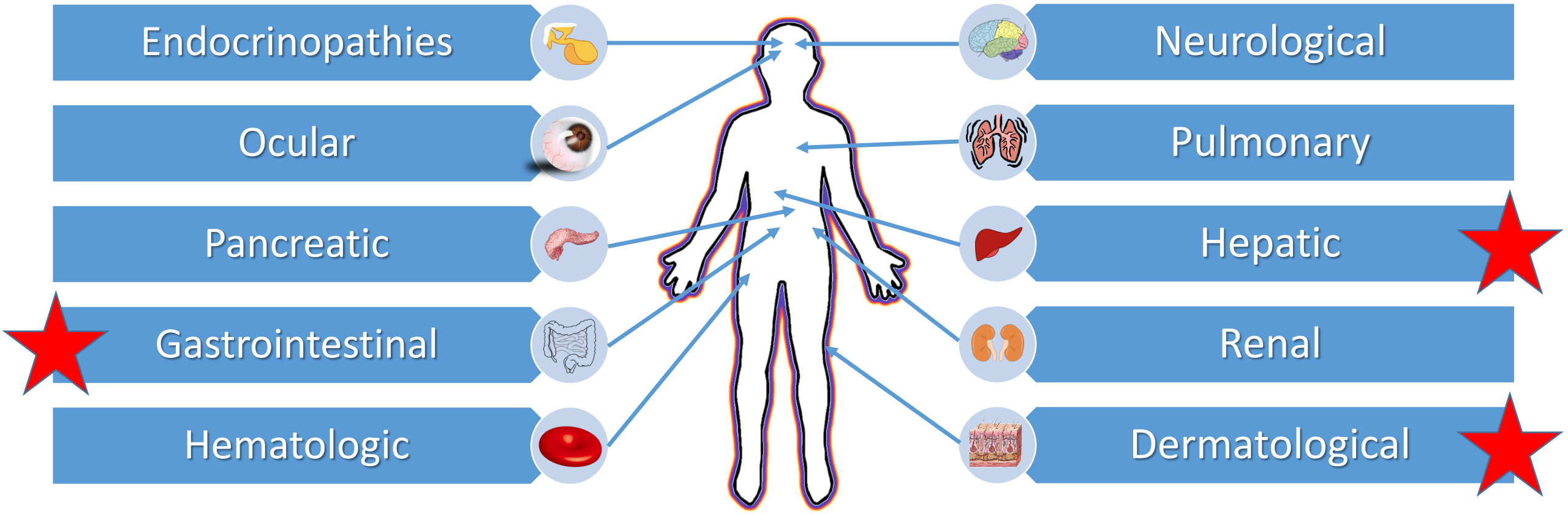
Why do irAEs occur?[8]

ICI enhances immune system function

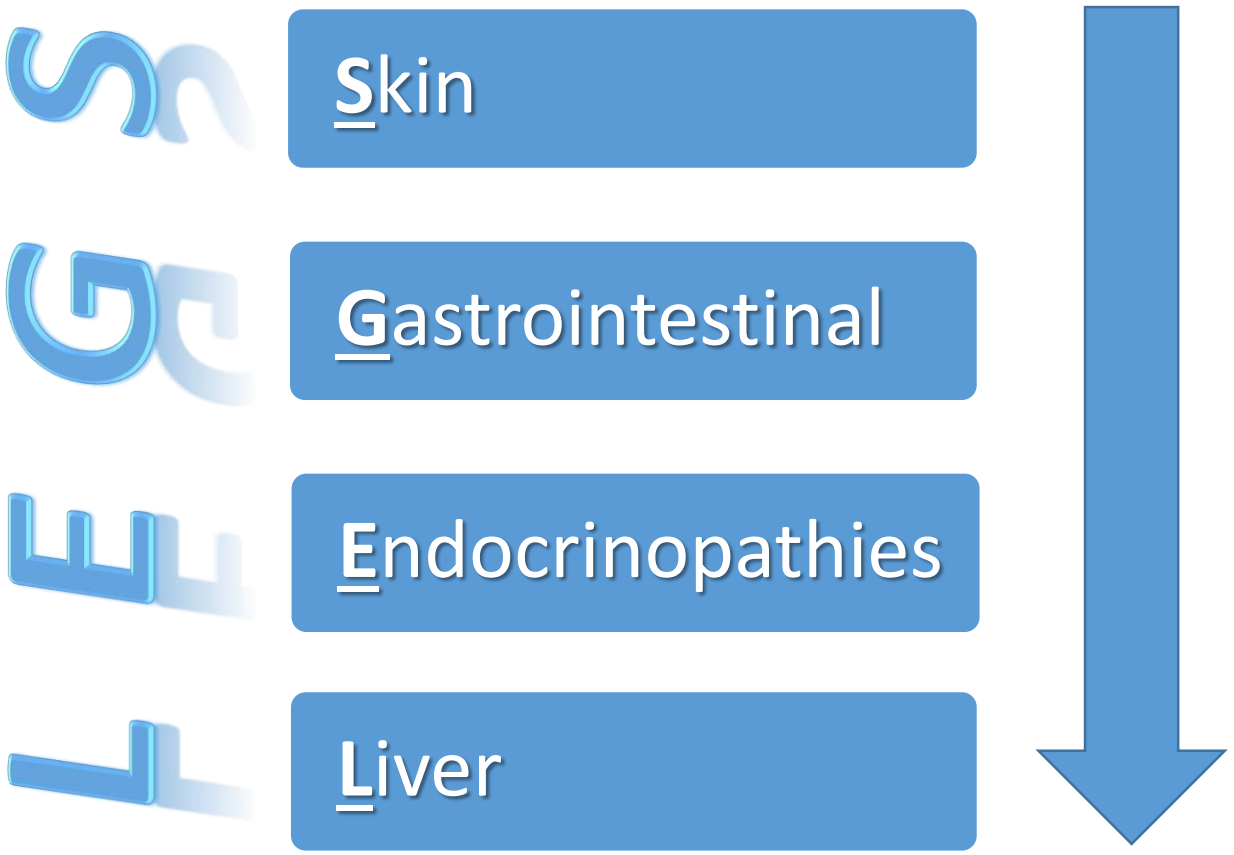
Autoinflammatory reactions occur

irAEs

Types of irAEs[9]



Time to Onset of irAEs[10]



- Timing
  - Occur as early as day 1
  - Late in treatment
  - Following discontinuation
- May be reversible if treated promptly and appropriately

Approach to Treatment[11-12]

- Early recognition
- Common Terminology Criteria for Adverse Events
  - Pros vs Cons
- Rule out all other causes
- Judicious use of immunosuppression

Pharmacological Treatment Options & Considerations [11,13]

- Close monitoring
- Ambulatory vs Inpatient
- Symptom management
- Immunotherapy suspension or termination
- Immunosuppression
- Prophylaxis

- Corticosteroids
- TNFα antagonists
  - Infliximab
- Mycophenolate mofetil
- Cyclosporine
- Tacrolimus
- Azathioprine
- Vedolizumab

Dermatologic[14-16]

Onset	3-4 weeks	
Adverse Events	Common	Rash, pruritus, vitiligo
	Rare	Alopecia areata, stomatitis, xerosis cutis, photosensitivity, lichenoid skin reaction
Exclude	Infection, drug or disease induced cause	

Dermatologic[14-16]

CTCAE Grade	Level of Involvement	Treatment	Immunotherapy
1	< 10% BSA	Topical steroids (mild) PO antihistamines	Continue
2	10-30% BSA	Topical steroids (moderate/high) PO antihistamines	May continue with reevaluation in 1 week Hold if no improvement to grade 1
3	> 30% BSA	Topical steroids (high) PO antihistamines Consider 0.5-1 mg/kg/day PO Prednisone	Hold until improvement to grade 1
4	> 30% BSA Severe symptoms	Grade 3 Support + 1-2 mg/kg/day IV methylprednisolone	Permanently Discontinue

Gastrointestinal[14-16]

Onset	6-8 weeks	
Adverse Events	Frequent	Diarrhea, increase in stool frequency
	Severe	Abdominal pain, cramping, bloody stool, nausea, vomiting, colitis, perforation
Exclude	Infection, antibiotic use, tumor progression	

Gastrointestinal[14-16]

CTCAE Grade	Presentation	Treatment	Immunotherapy
1	< 4 stools per day over baseline Mild abdominal symptoms	Symptomatic Management: bowel rest, diet changes, antidiarrheal agents (if needed)	Continue
2	4-6 stools per day over baseline Moderate new symptoms	Symptomatic Treatment including antidiarrheal agents PO steroids if persists > 3 days	Hold until improvement to grade 1
3	> 7 stools per day over baseline Severe new symptoms	Symptomatic Treatment including antidiarrheal agents PO/IV steroids, Infliximab or alternative if refractory	Hold until improvement to grade 1
4	Perforation or ileus	Gastroenterology Consultation	Permanently Discontinue

Hepatic[14-16]

Onset	8-12 weeks	
Adverse Events	Common	Asymptomatic ↑ AST/ALT
	Less Common	Elevations in AlkPhos, bilirubin Hepatomegaly
Exclude	Disease-related causes, concomitant drugs, infection	

Hepatic[14-16]

CTCAE Grade	Presentation	Treatment	Immunotherapy
1	AST/ALT: ULN – 3x ULN Total Bilirubin: 1.5x ULN	No intervention needed Repeat labs in 1 week	Continue
2	AST/ALT: 3-5x ULN Total Bilirubin: 1.5-3x ULN	Repeat labs in 3 days 1 mg/kg/day PO Prednisone	Hold until improvement to grade 1
3	AST/ALT: 5-20x ULN Total Bilirubin: 3x ULN	Daily labs PO/IV steroids, alternative if refractory (no infliximab)	Discontinue
4	AST/ALT: > 20x ULN Total Bilirubin: 3x ULN	1-2 mg/kg/day IV methylprednisolone Mycophenolate mofetil if refractory	Permanently Discontinue

Question 1

- Which of the following is an acceptable first line pharmacologic treatment option for the management of many common moderate to severe irAEs associated with ICIs?

A. Mycophenolate mofetil
B. Infliximab
C. Prednisone
D. Tacrolimus

Pearls for Steroid Use[14-16]

- Typically require a long taper
  - Short tapers run the risk of recurrence of symptoms and toxicity
- Risk for opportunistic infections
  - Antimicrobial prophylaxis
- Gastric acid suppression
  - Proton pump inhibitor
- Bone health
  - Calcium and Vitamin D supplementation

Immunotherapy Suspension vs Termination[14-16]

Temporary Suspension	Permanent Discontinuation
irAE stabilized ≤ Grade 1	Life-threatening (Grade 4)
≤ 10mg/day Prednisone	Severe (Grade 3) & recurring
No other immunosuppression	Moderate (Grade 2) & no resolution in 3 months

General Management Approach for irAEs[8-9]

CTCAE Grade	Ambulatory vs Inpatient	Corticosteroids	Alternative Immunosuppresion	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical or systemic oral steroids 0.5-1 mg/kg/day		Suspend temporarily*
3	Hospitalization	Systemic oral or IV steroids 1-2 mg/kg/day x 3 days the ↓ 1 mg/kg/day	Consider if symptoms unresolved after 3-5 days of steroids Organ specialist referral advised	Suspend & discuss resumption with patient based on risk/benefit ratio
4	Hospitalization (consider ICU)	Systemic IV methylprednisolone 1-2 mg/kg/day x 3 days the ↓ 1 mg/kg/day		Discontinue permanently

Lessons and Take Home Messages[9]

- Occurrence or worsening of new symptom should be promptly reported

Digestive	Endocrine	Skin	Respiratory	Neurological
Diarrhea	Fatigue	Extensive rash	Shortness of breath	Headache
Blood or mucus in the stool	Weight loss	Pruritis	Coughing	Confusion
Severe abdominal pain	Nausea/vomiting			Muscle weakness
	Thirst of appetite increase			Numbness

Lessons and Take Home Messages[9]

- Patients should avoid self management of symptoms
- Timing of irAE may occur at the start, during, or after treatment discontinuation
- Early identification and treatment of irAEs is essential to limiting the duration and severity of irAEs

Questions

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