Now We've Got Problems: Immunotherapy-Related Adverse Events

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Disclosures

- I have no financial relationship with any pharmaceutical companies, biomedical device manufacturers or distributors, or others whose products or services may be considered related to the content of my presentation.

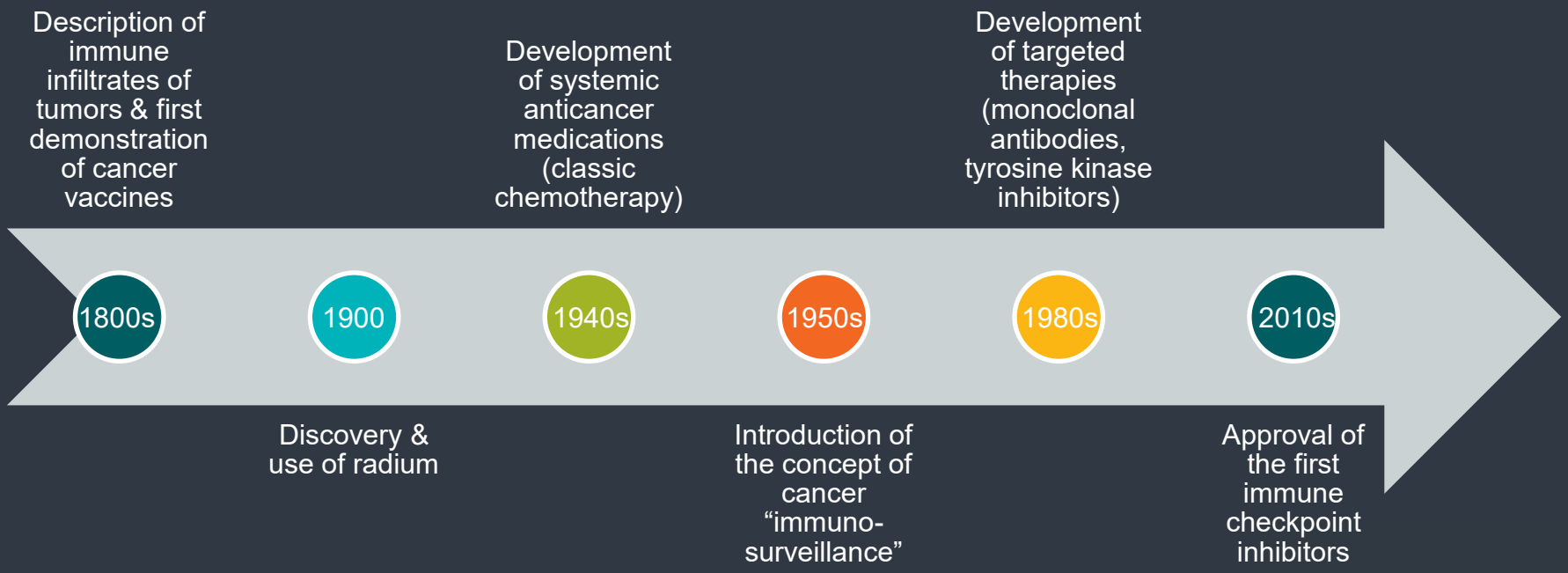
- Off-label medication uses, in the context of guideline-directed treatment recommendations, will be reviewed and discussed in this presentation.

Objectives

- Identify common and life-threatening adverse events related to immune checkpoint inhibitors.

- Interpret current guidelines for the management of immune-related adverse events.

Advancements in Anti-Cancer Treatments & Immunotherapy

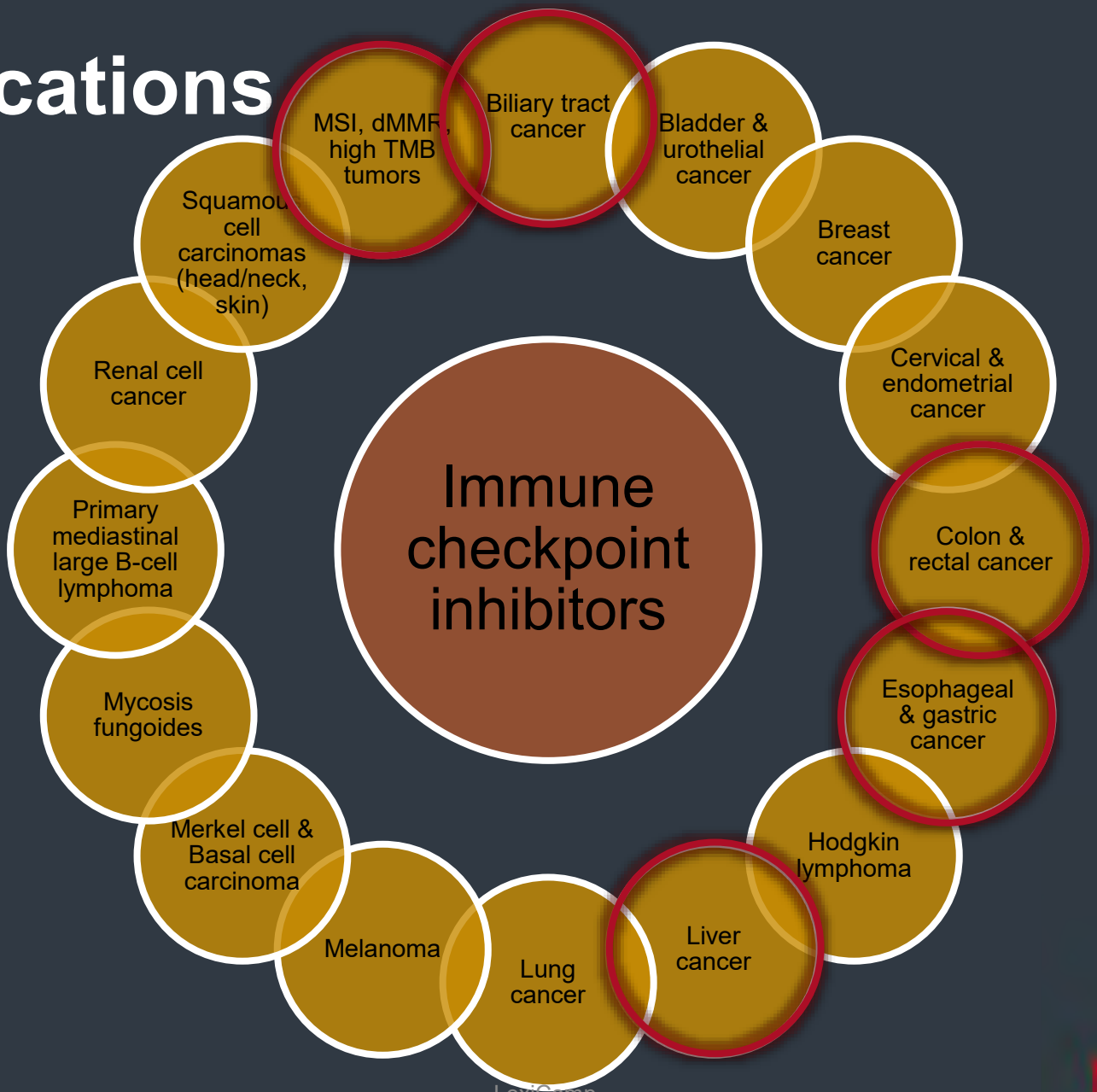


Front Pharmacol 2018;9:1300. //
Discov Med 2016;21:125-33. // Front Immunol 2023;14:1167975.

Immune Checkpoint Inhibitors (ICIs)

CTLA-4 Inhibitor	PD-1 Inhibitors	PD-L1 Inhibitors	LAG-3 Inhibitor
• Ipilimumab (*Yervoy*®) • Tremelimumab (*Imjudo*®)	• Nivolumab (*Opdivo*®) • Pembrolizumab (*Keytruda*®) • Cemiplimab (*Libtayo*®) • Dostarlimab (*Jemperli*®) • Retifanlimab (*Zynyz*®)	• Atezolizumab (*Tecentriq*®) • Avelumab (*Bavencio*®) • Durvalumab (*Imfinzi*®)	• Relatlimab (*only available in combination with Nivolumab as Opdualag*®)

Indications

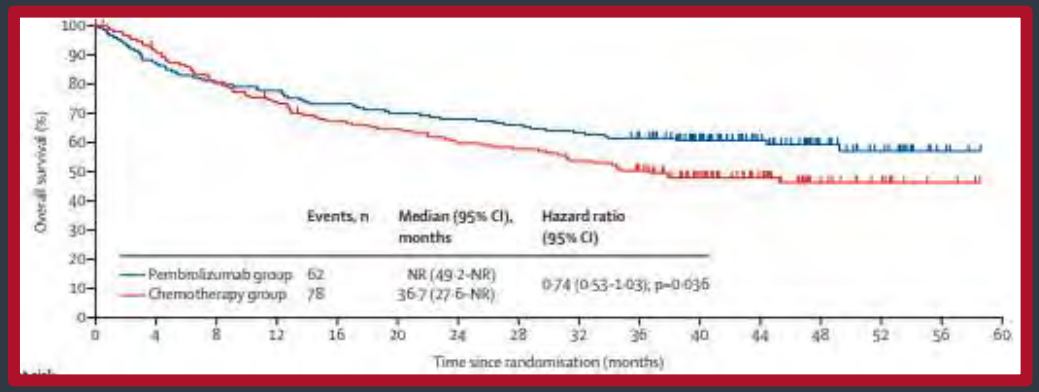


LexiComp.

Immunotherapy in Metastatic Colon & Rectal Cancer

KEYNOTE-177

- First-line immunotherapy vs Fluorouracil-based chemotherapy
  - dMMR or MSI-H pathology only
- Improved progression free survival rates & durable response to treatment



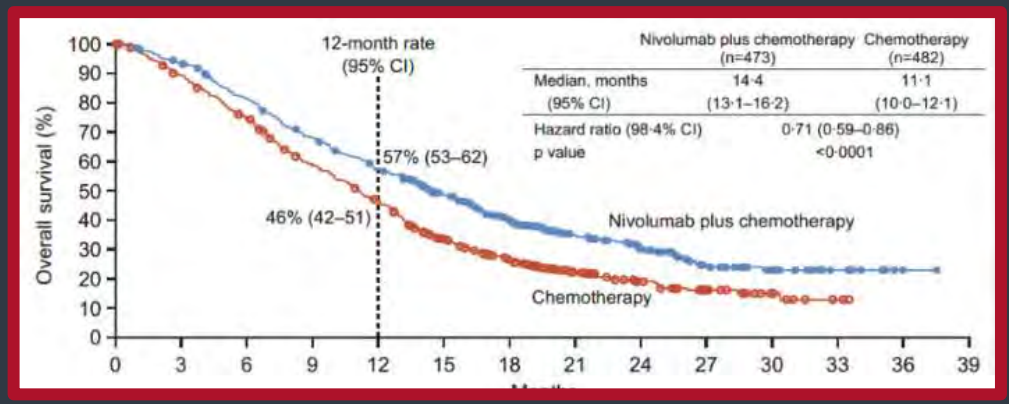
Immunotherapy is guideline-recommended as first-line treatment, regardless of performance status, for patients with colorectal cancer with dMMR, MSI-H pathology only.

NCCN Guidelines – Colon Cancer / Rectal Cancer.
N Engl J Med 2020;383:2207-18. // Lancet Oncol 2022;23:659-70.

Immunotherapy in Metastatic Gastric & Esophageal Cancer

CheckMate-649

- First-line immunotherapy + chemotherapy vs chemotherapy alone
- Improved progression free survival & overall survival rates
    - Especially if CPS ≥5



Combination of immunotherapy* & chemotherapy is guideline-recommended as first-line treatment for patients with advanced/metastatic gastric/esophageal cancer.

**pending CPS score, HER2 testing*

NCCN Guidelines – Gastric Cancer / Esophageal Cancer.
Lancet 2021;398:27-40.

Clinical Trial Toxicity Profiles

Study	Tumor Type	Treatment	All Toxicities	≥Grade 3 Toxicities
TOPAZ-1	Biliary tract	Durvalumab + chemotherapy	93%	63%
KEYNOTE-177	Colorectal	Pembrolizumab	80%	22%
CheckMate-649	Gastro-esophageal	Nivolumab + chemotherapy	94%	59%
KEYNOTE-811	Gastro-esophageal	Pembrolizumab + Trastuzumab + chemotherapy	97%	57%
HIMALAYA	Hepatocellular	Durvalumab + Tremelimumab	76%	26%
KEYNOTE-158	dMMR/MSI-H tumors	Pembrolizumab	65%	12%

NEJM Evid 2022;1(8). // N Engl J Med 2020;383:2207-18. // Lancet 2021;398:27-40. // Nature 2021;600:727-30. // Annals Oncol 2022;33:929-38.

Chemotherapy vs Immune-Related Adverse Events

Chemotherapy

- Acute onset adverse events
- Cyclical
- Targeting rapidly dividing cells (nausea/vomiting, diarrhea or constipation, myelosuppression)

Immunotherapy

- Onset can be acute OR delayed
- Inflammatory or autoimmune effects

NCCN Guidelines – Management of Immunotherapy-Related Toxicities.

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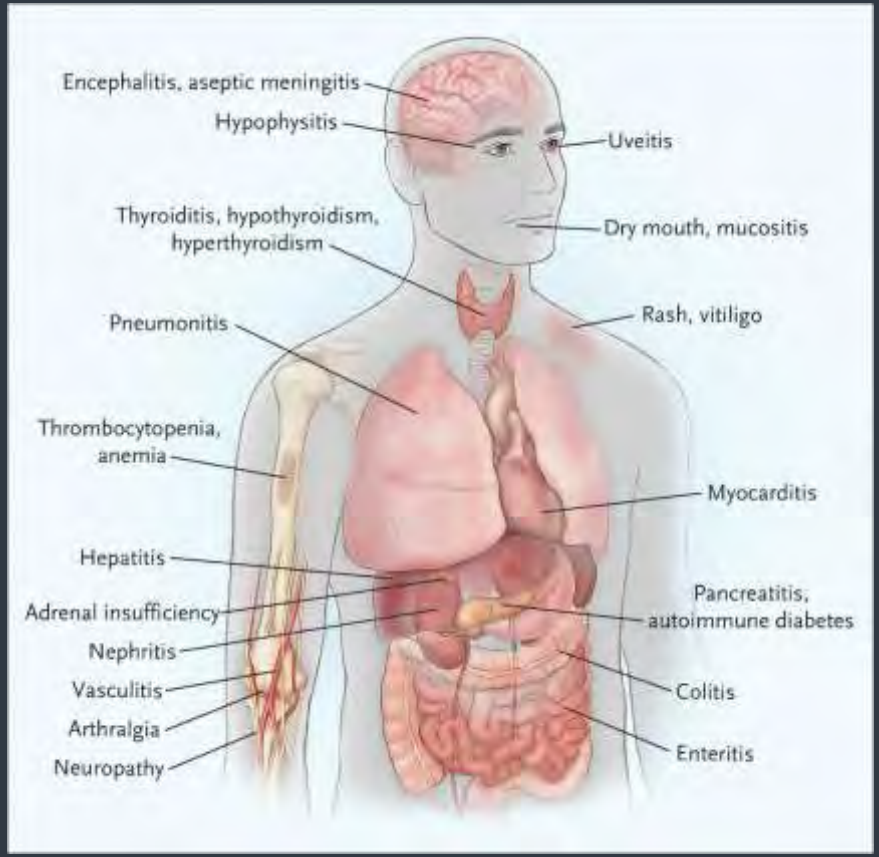
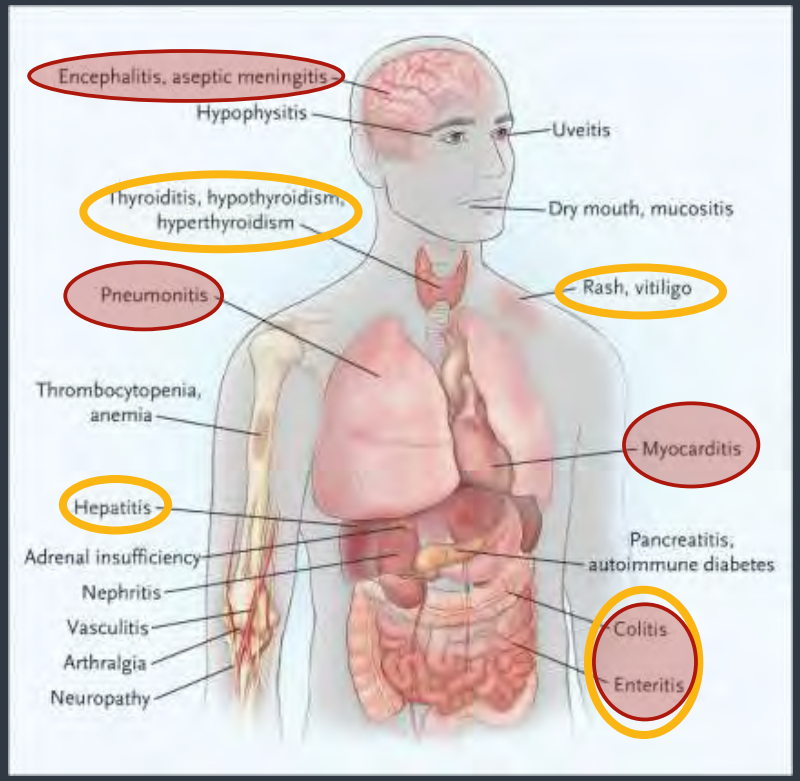
Immune-Related Adverse Events (irAEs)



N Engl J Med 2018;378:158-68.

Immune-Related Adverse Events (irAEs)

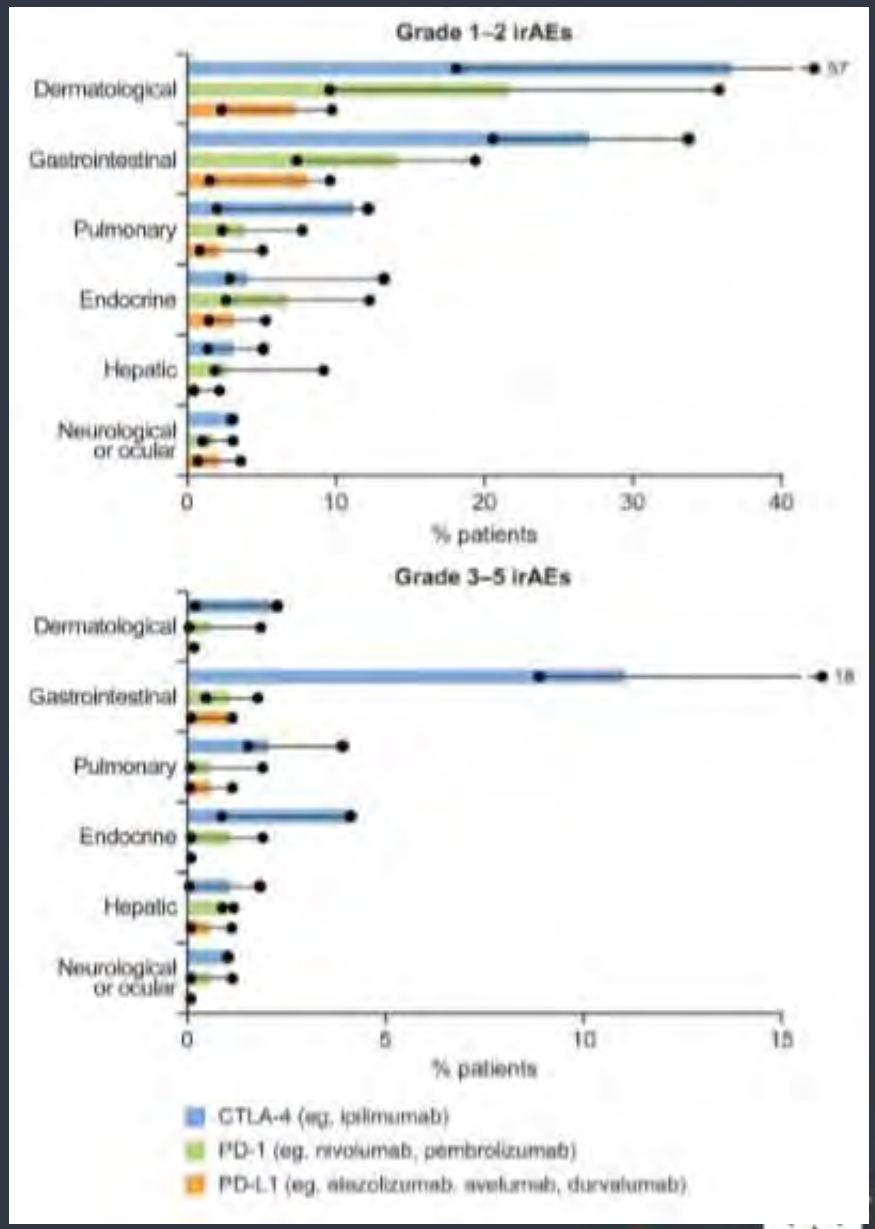


Most common irAEs	Life-threatening irAEs
Colitis	Cardiac toxicity
Dermatitis	Colitis
Endocrine toxicities	Neurologic events
Hepatitis	Pneumonitis

N Engl J Med 2018;378:158-68. // Front Immunol 2023;14:1167975.

Severity of irAEs

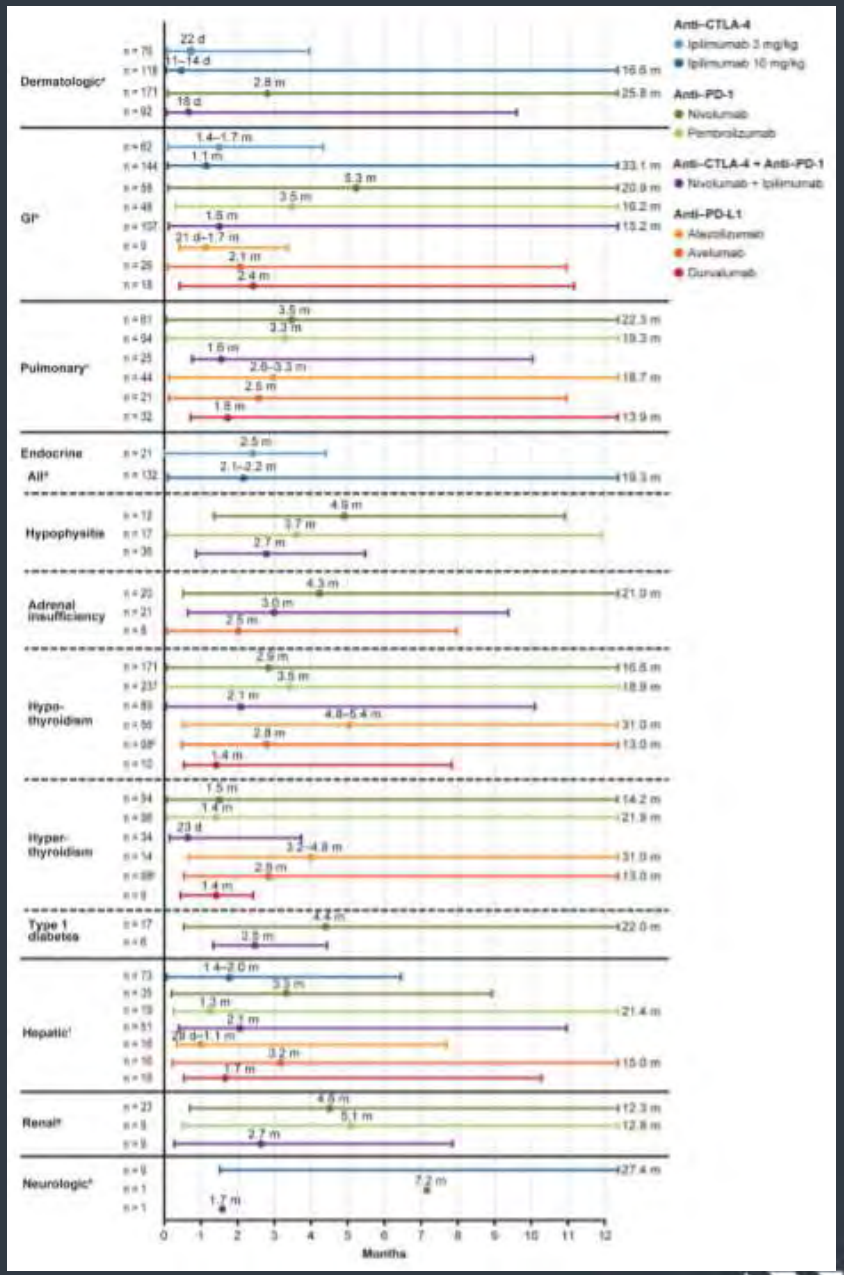
- ANY organ system
- ALL grades of severity
- Presentation & severity may wax and wane over the treatment course



J Oncol Pharm Pract 2020;33:338-49. // Engl J Med 2018;378:158-68. //
NCCN – Management of Immunotherapy-Related Toxicities.

Timing of irAEs

- Onset varies by type of ICI
- Can occur at ANY point during therapy
- May present after STOPPING therapy



J Oncol Pharm Pract 2020;33:338-49. // Engl J Med 2018;378:158-68. // NCCN – Management of Immunotherapy-Related Toxicities.

Monitoring During ICI Therapy

Toxicity	NCCN	ASCO
Diarrhea & Rash	Assess at each visit	
Pneumonitis	SpO2 at baseline; repeat based on symptoms	----
Hepatitis	CMP at baseline; repeat prior to each treatment or every 4 weeks during treatment	AST, ALT, total bilirubin prior to each infusion
Endocrine • Thyroid • Glucose	• TSH and FT4 at baseline; repeat every 4-6 weeks during treatment • CMP as above; HbA1c if glucose elevated	• TSH and FT4 every 4-6 weeks • CMP prior to each infusion
Cardiac	Consider periodic testing for abnormal baseline or symptoms	Baseline ECG and troponins; repeat if symptomatic

+ additional AS NEEDED tests based on clinical presentation

NCCN Guidelines – Management of Immunotherapy-Related Toxicities.
J Clin Oncol 2018;36:1714-68.

Principles & Management of irAEs

- **Patient & caregiver education** extremely important
- **Early recognition and treatment** needed to prevent morbidity and treatment discontinuation
  - Referral to disease-specific subspecialty
  - Additional testing as indicated
- May need to hold and/or discontinue ICI
- **Treatment of choice for higher grade events = HIGH-DOSE STEROIDS**
  - 1-2 mg/kg/day
  - May require admission for IV administration ± supportive care
  - Steroids are slowly tapered over several weeks

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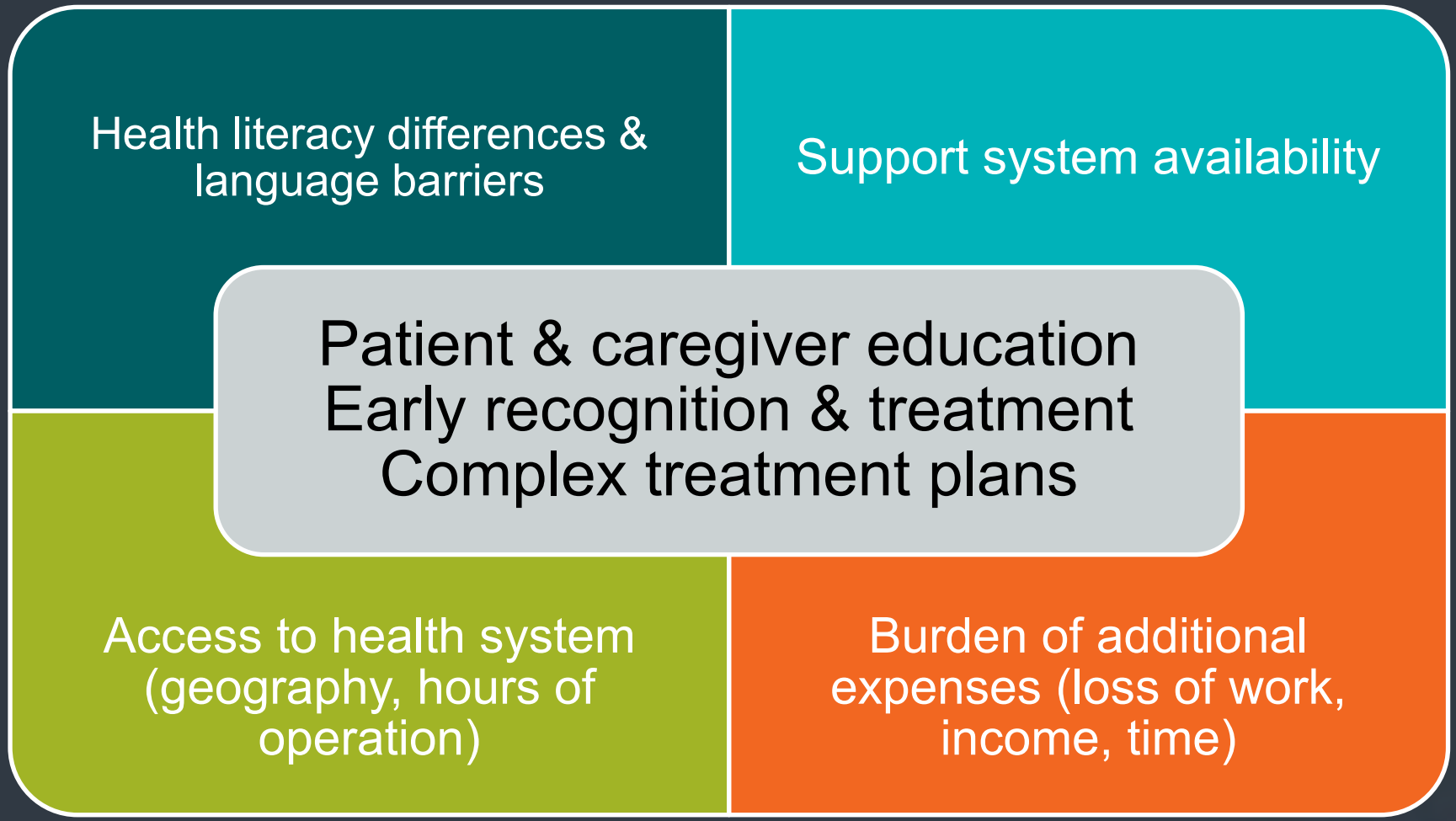
Disparities in the Management of irAEs



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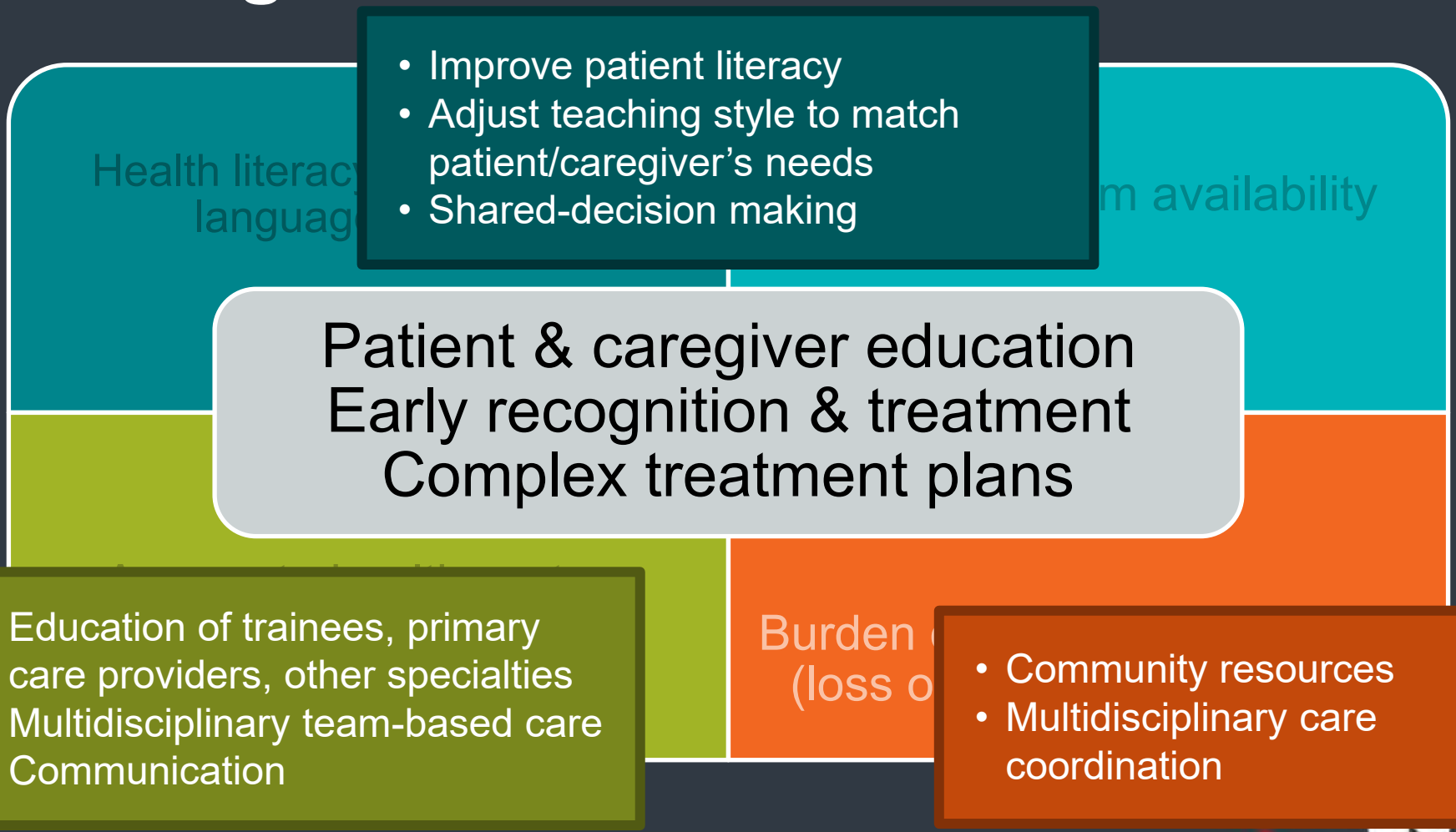
ASCO Education Book 41 (April 8, 2021) 66-78.

Overcoming Disparities in the Management of irAEs



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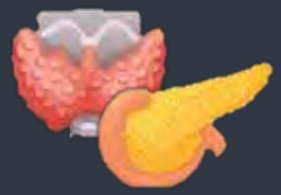
Dermatitis

Exact management depends on presentation & extent of dermatologic involvement. Refer to guidelines & literature.

Mild Grade 1	Moderate Grade 2	Severe Grade 3-4	Refractory
• Continue ICI • Moderate potency topical steroids	• Continue ICI • Moderate-high potency topical steroids	• HOLD ICI • High potency topical steroids • Steroids 0.5-1 mg/kg/day (escalate if indicated)	• Dupilumab • Omalizumab • UVB phototherapy • Rituximab ± IVIG

NCCN – Management of Immunotherapy-Related Toxicities.

Endocrinopathies



Thyroid dysfunction

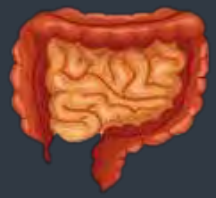
- May present as hypo- or hyperthyroidism
- Okay to continue ICI, especially if asymptomatic
- Treat with hormone replacement as indicated

ICI-related diabetes

- Endocrine consult & management of insulin
- If DKA present: HOLD ICI until DKA resolves, then okay to resume

NCCN – Management of Immunotherapy-Related Toxicities.

Colitis



Grade 1
<4 stools above baseline; no symptoms

May continue or consider holding ICI

Rule out infection

Symptom management
- Antidiarrheals
- Hydration
- Dietary changes

Grade 2
4-6 stools above baseline; blood/mucus

HOLD ICI

If confirmed by biopsy, Budesonide 9 mg po daily prior to systemic steroids

High-dose oral steroids

Refractory therapies

Grade 3-4
≥7 stools over baseline; peritoneal signs or life-threatening consequences

Permanently DISCONTINUE ICI

High-dose IV steroids

Refractory:
- Infliximab
- Vedolizumab
- Tofacitinib
- Ustekinumab

If no response to steroids after 3 days (Grade 2) or 1-2 days (Grade 3-4), considered steroid refractory

NCCN – Management of Immunotherapy-Related Toxicities.

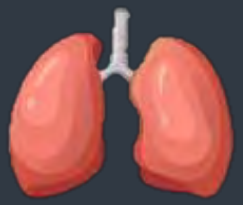
Hepatitis

Grade 1 <3 x ULN	Grade 2 3-5 x ULN	Grade 3 >5-20 x ULN	Grade 4 >20 x ULN
• Consider holding ICI • Increase frequency of lab monitoring	• HOLD ICI • Monitor labs every 3-5 days • If worsening or not improving in 3-7 days, treat as Grade 3	• HOLD ICI	• DISCONTINUE ICI

- Liver biopsy if feasible
- Steroids 1 mg/kg/day
- If no improvement after 1-2 days of steroids, refractory options:
  - Mycophenolate
  - ATG
  - Azathioprine
  - Tacrolimus

NCCN – Management of Immunotherapy-Related Toxicities.

Pneumonitis



Grade 1 asymptomatic

Supportive care

May continue or consider holding ICI

Grade 2 symptomatic

HOLD ICI

Empiric antibiotics if infection not excluded

High-dose steroids

Grade 3-4 severe symptoms // life-threatening

Grade 2 management + permanently DISCONTINUE ICI

Refractory (*after 2-3 days of steroids*):
- Infliximab
- IVIG
- Mycophenolate

NCCN – Management of Immunotherapy-Related Toxicities.

Myocarditis

DISCONTINUE ICI

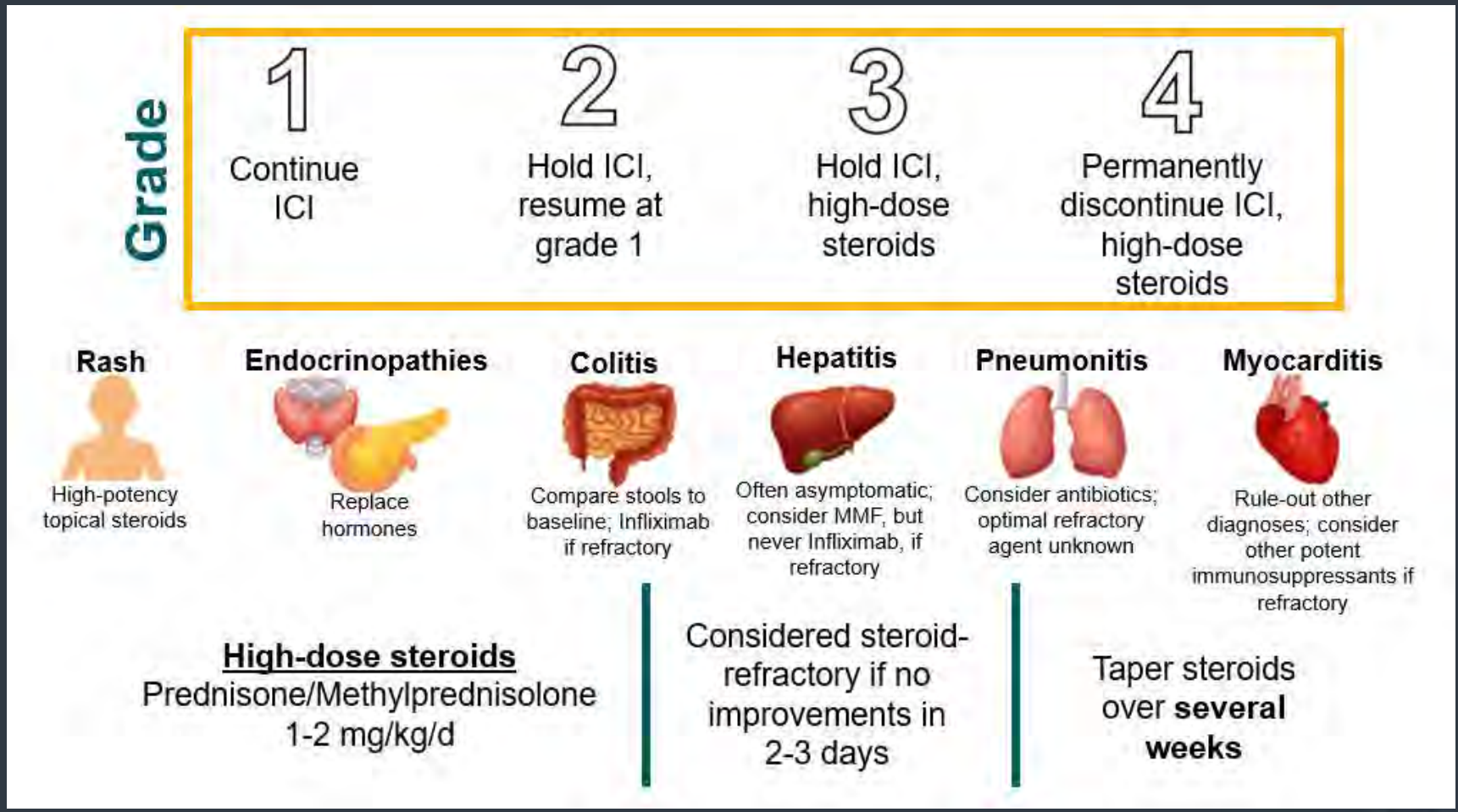
Management depends on acuity of symptoms

High-dose steroids

Refractory (*after 1-2 days of steroids*):
Abatacept
Mycophenolate
IVIG
Infliximab
ATG

NCCN – Management of Immunotherapy-Related Toxicities.

Summary of irAE Management



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