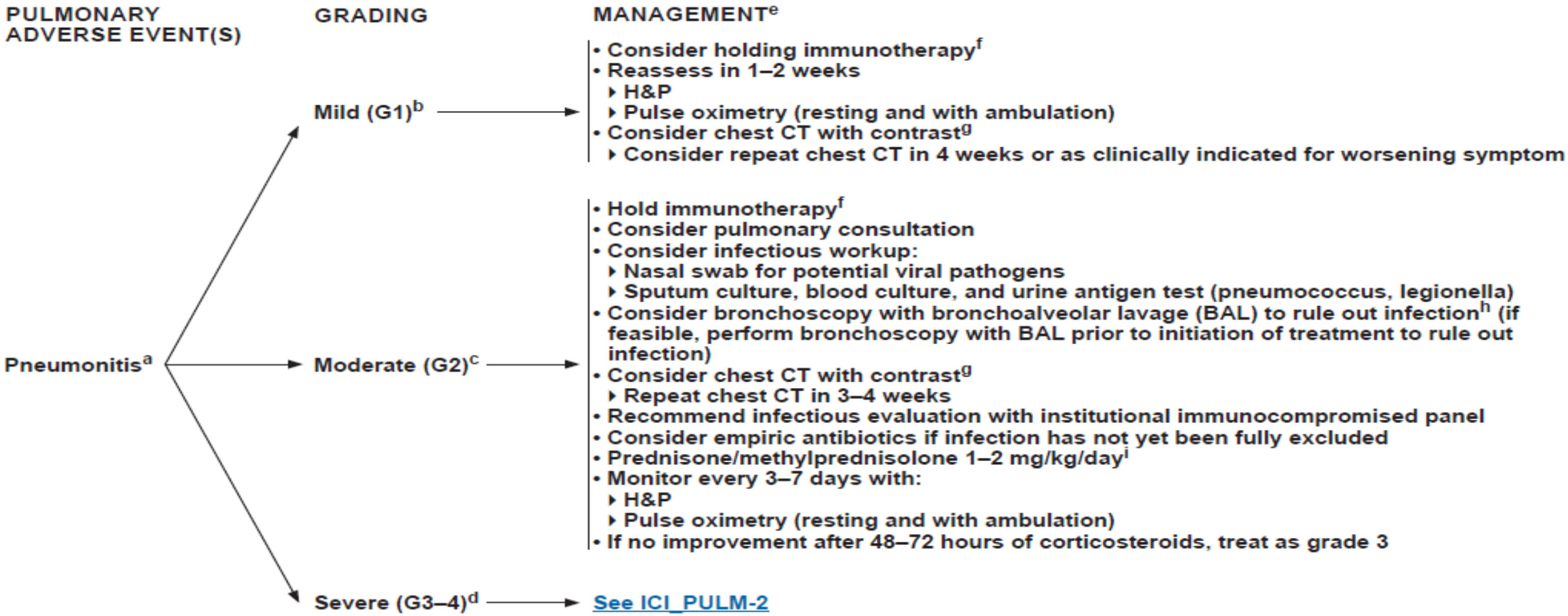
PNEUMONITIS

- **Start with 1-2 mg/kg steroids**
- **Encourage hospitalization**
- **Can be difficult to treat, especially at higher grade**
- **Consider infliximab/ mycophenylate**
- **Protect against opportunistic infections**
- **Re challenge is-more data on re challenge are needed but can be considered**



[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities) with or without dry cough. Consider infectious etiologies.
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[c] Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] CT with contrast to rule out other etiologies if not contraindicated.
[h] If concern for lymphangitic spread of tumor, biopsy is indicated.
[i] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

ASSESSMENT/ GRADING	MANAGEMENT[e]
Severe (G3–4)[d] pneumonitis[a]	• Permanently discontinue immunotherapy[f] • Inpatient care • Infectious workup: ▸ Consider that patient may be immunocompromised ▸ Nasal swab for potential viral pathogens ▸ Sputum culture, blood culture, and urine culture • Pulmonary and infectious disease consultation • Bronchoscopy with BAL to rule out infection and malignant lung infiltration • Consider empiric antibiotics if infection has not yet been fully excluded • Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks • Consider adding any of the following if no improvement after 48 hours:[j] ▸ Infliximab[k] 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider ▸ Intravenous immunoglobulin (IVIG)[l] ▸ Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities) with or without dry cough. Consider infectious etiologies.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] Options are listed in alphabetical order. There are no data to support the use of one over another.
[k] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[l] Total dosing should be 2 g/kg, administered in divided doses over 2 to 5 days as per package insert.

GI TOXICITY

- **Consider colonoscopy for evaluation of right-sided disease**
- **Lactoferrin + in the absence of infection may be a good marker of colitis**
- **Can start with steroids, but encourage early use of infliximab or vedolizumab**
- **Fecal transplant may be an effective alternative therapy**
- **Steroids have little efficacy in acute immune-related pancreatitis**

GASTROINTESTINAL ADVERSE EVENT(S)

- Diarrhea
- Colitis[a]

ASSESSMENT/GRADING

- Stool evaluation to rule out infectious etiology[b]
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - *C. difficile*
  - Ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; consider microsporidia, *Cyclospora/isospora* spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin[c]
- Consider abdominal/pelvic CT with contrast if G2–G4 colitis[a]
- Consider GI consultation if G2–G4
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy[c]

MANAGEMENT[g]

Mild (G1)[d]
- Consider holding immunotherapy[h]
- Loperamide or diphenoxylate/atropine for 2–3 days
  - If no improvement and not already done, obtain labs for infectious workup
- Hydration
- Close monitoring[i]
- If persistent or progressive symptoms, check lactoferrin
  - If positive, treat as G2 (below)
  - If negative and no infection, continue G1 management and add mesalamine, cholestyramine

Moderate (G2)[e]
- Hold immunotherapy[h]
- Prednisone/methylprednisolone[j] (1–2 mg/kg/day)[k]
- No response in 2–3 days, continue steroids, consider adding infliximab[l,m,n] or vedolizumab[n] within 2 weeks

Severe (G3–4)[f] → See ICI_GI-2

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
[b] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).
[c] If positive lactoferrin, strongly recommend early endoscopy or flexible sigmoidoscopy with biopsy within first 2 weeks of the onset of symptoms.
[d] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[e] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[f] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] If progressive, consider stool evaluation to rule out infectious etiology.
[j] Convert to prednisone when appropriate.
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 weeks should be made to minimize the complication of infection.
[l] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.

GRADING	MANAGEMENT[g]
Severe (G3–4)[f] diarrhea or colitis	• G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity[h] • G4: Permanently discontinue immunotherapy agent responsible for toxicity[h] • Consider inpatient care for provision of supportive care • Intravenous (IV) methylprednisolone[j] (1–2 mg/kg/day)[k] ▸ No response in 2 days, continue steroids, strongly consider adding infliximab[l,m,n] or vedolizumab[n] within 2 weeks[o]

[f] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complicatic (eg, ischemic bowel, perforation, toxic mega-colon).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 week should be made to minimize the complication of infection.
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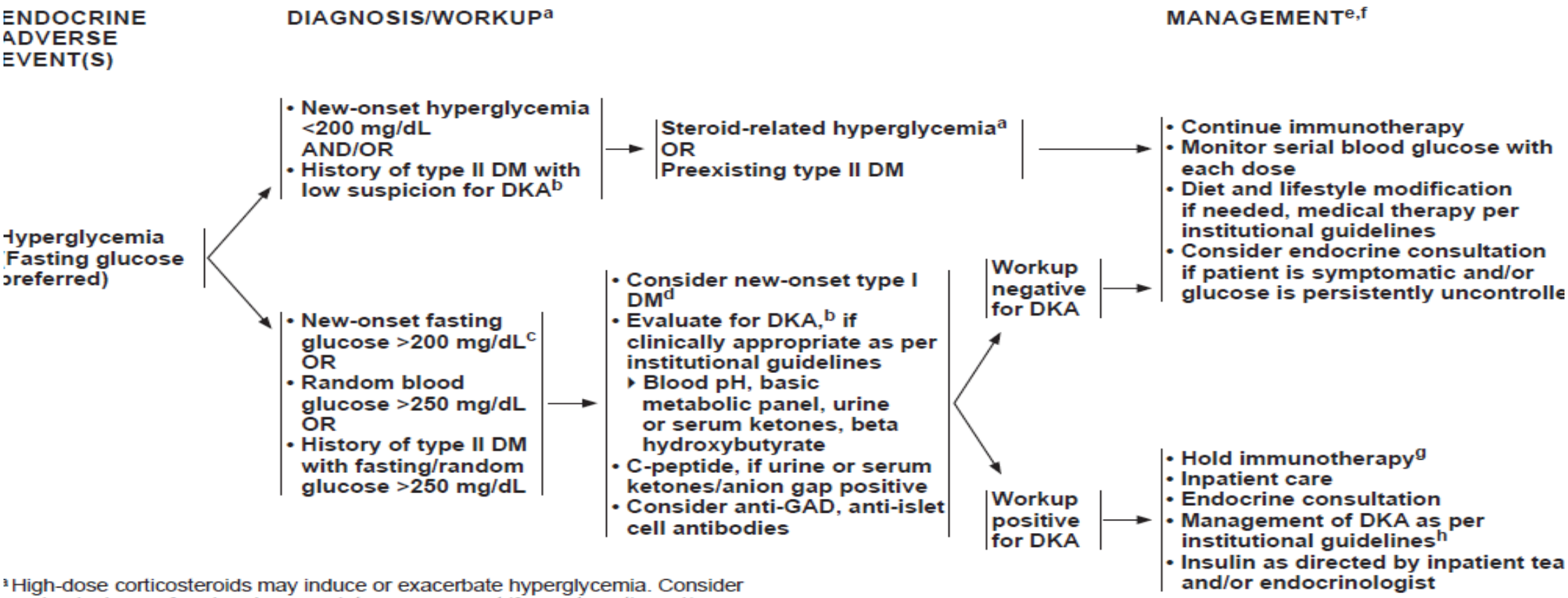
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.
[o] Fecal transplantation may be considered for immunosuppressant refractory colitis based on institutional availability and expertise.



[a] High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.

[b] Symptoms of diabetic ketoacidosis (DKA) may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.

[c] In patients who are critically ill/ill-appearing with sugars >200 mg/dL (typically 300–500 mg/dL), urgent/emergent evaluation for DKA is indicated.

[d] The development of type I DM is rare but can be life-threatening if insulin therapy is not provided. Once new type I DM is diagnosed, management and monitoring should be directed by endocrinology team.

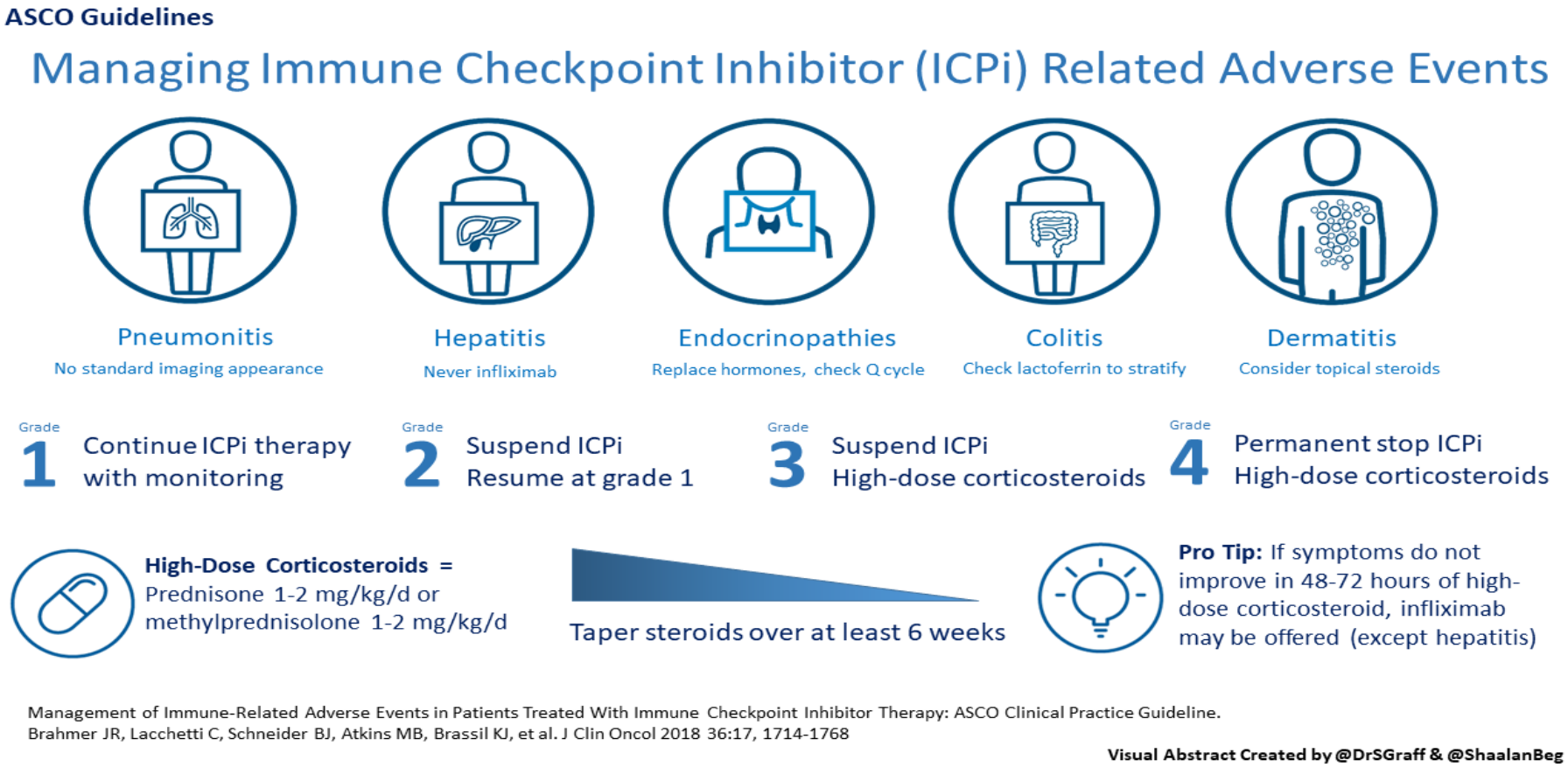
[e] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplemе if needed.

[f] Insufficient evidence to suggest corticosteroids may reverse type I DM induced l immunotherapy, and may complicate glycemic control.

[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

[h] Institutional guidelines may include but are not limited to: IV fluids +/– potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anio gap.

Some General Principles:



Some General Principles:

- **Have a high index of suspicion that new symptoms are treatment related**

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Grade 1:

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  (except some neurologic, hematologic, and cardiac tox)

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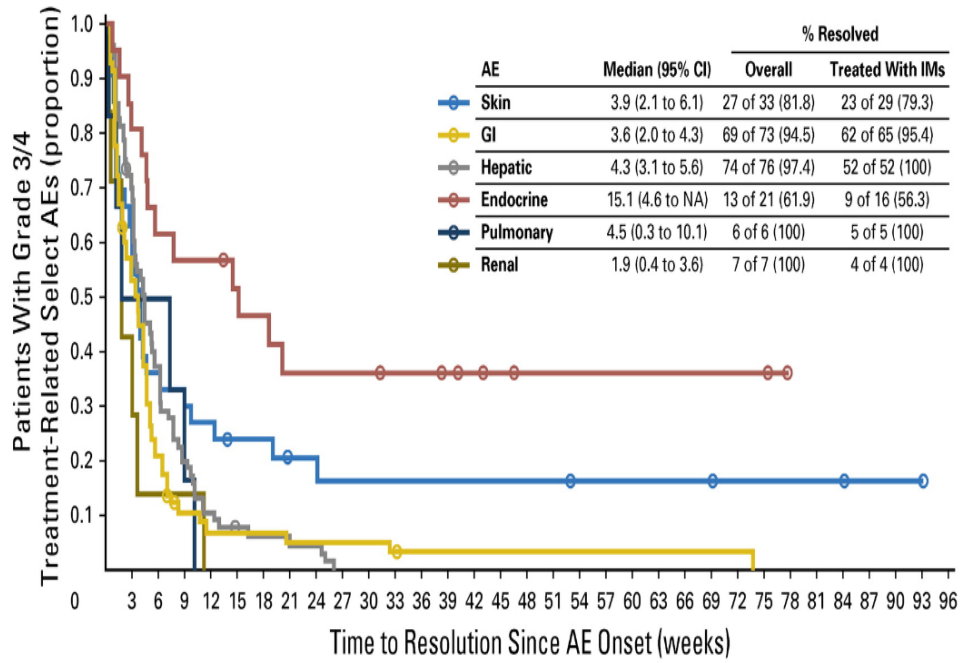
Grade 1:
- CONTINUE ICI with close monitoring
  (except some neurologic, hematologic, and cardiac tox)

Grade 2:
- HOLD ICI
- Consider resuming when symptoms and/or labs revert to ≤Grade 1
- Corticosteroids (initial dose 0.5-1 mg/kg/d prednisone or equivalent) MAY be administered

- **Grade 3:**
- HOLD ICI
- START HIGH-DOSE CORTICOSTEROIDS (prednisone 1-2 mg/kg/day or methylprednisolone IV 1-2 mg/kg/day)
- If symptoms do not improve in 24-48 hours, infliximab may be offered for some toxicities
- Taper steroids over 4-6 weeks

Grade 4:
- All of the above +
- Permanent discontinuation of ICI (except endocrinopathies controlled by hormone replacement)

With Appropriate Treatment, Most irAEs Resolve



AE	Median (95% CI)	% Resolved	
		Overall	Treated With IMs
Skin	3.9 (2.1 to 6.1)	27 of 33 (81.8)	23 of 29 (79.3)
GI	3.6 (2.0 to 4.3)	69 of 73 (94.5)	62 of 65 (95.4)
Hepatic	4.3 (3.1 to 5.6)	74 of 76 (97.4)	52 of 52 (100)
Endocrine	15.1 (4.6 to NA)	13 of 21 (61.9)	9 of 16 (56.3)
Pulmonary	4.5 (0.3 to 10.1)	6 of 6 (100)	5 of 5 (100)
Renal	1.9 (0.4 to 3.6)	7 of 7 (100)	4 of 4 (100)

No. at risk:

Endocrine	21	17	13	12	12	10	9	7	7	7	7	6	6	5	4	3	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0
GI	73	38	14	6	4	4	4	3	3	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
Hepatic	76	51	28	15	8	5	4	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pulmonary	6	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal	7	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin	33	19	12	10	9	7	7	5	5	4	4	4	4	4	4	4	4	3	3	3	3	3	2	2	2	2	2	1	1	1	0

When symptoms and/or laboratory values revert to ≤ grade 1, rechallenging with ICI MAY be offered

However, CAUTION is advised, especially with early-onset irAEs

Dose adjustments are NOT recommended

Take Home Points:

- ✓ **Recognition is key**
- ✓ **irAEs are relatively common with ICI but also treatable**
- ✓ **Guidelines are available for management**
- ✓ **Treating irAEs with immunosuppression DOES NOT seem to compromise anti-tumor efficacy**

- Thank you

Acknowledgement /References

- NCI website
- Postow et al NEJM 2018
- 2018 palliative and supportive care in Oncology Symposium
- Best of ASCO
- Allison Betof Warner,MD PhD
- Annals of Oncolgy2018
- Brahmer et al Journal Clinical Oncology 2018
- Boutros et al . Nature Reviews Clinical Oncology 2016