Immune-Related Adverse Events

Checkpoint inhibitor toxicity · Almost any organ, and steroids are the answer — usually

GRADE 3 → 1–2 mg/kg
taper over 4–6 weeks

THINK OF IT FIRST *any new symptom in a patient on immunotherapy is an irAE until excluded*

ASK THE DRUG HISTORY

Anti-PD-1 (pembrolizumab, nivolumab), **anti-PD-L1** (atezolizumab, durvalumab), **anti-CTLA-4** (ipilimumab). **Combination therapy has substantially higher toxicity** than single agent. Effects can appear **weeks to many months after starting, and even after stopping**.

THE COMMON ONES

Skin — rash and pruritus, usually earliest. **Colitis** — diarrhea. **Hepatitis** — transaminitis. **Thyroid** — thyroiditis then hypothyroidism. **Pneumonitis** — cough and breathlessness.

THE LETHAL ONES

Myocarditis — rare but high mortality. **Hypophysitis and adrenal insufficiency**. **Myasthenia-like syndrome and myositis**, which can overlap with myocarditis. **Severe colitis with perforation**. **Neurological** disease including encephalitis and Guillain-Barré-like syndrome.

MANAGE BY GRADE *ASCO framework, graded on CTCAE v5.0*

Grade	Checkpoint inhibitor	Immunosuppression
Grade 1 mild	**Generally continue** with close monitoring	Supportive care and symptomatic treatment. No steroids for most.
Grade 2 moderate	**Consider holding**, and **resume when symptoms return to grade 1 or less**	**Prednisone 0.5–1 mg/kg/day** or equivalent for most grade 2 toxicities.
Grade 3 severe	**Hold**, and discuss whether rechallenge is appropriate	**High-dose corticosteroids, prednisone 1–2 mg/kg/day** or equivalent, **tapered over at least 4–6 weeks**. A short taper causes rebound.
Grade 4 life-threatening	**Permanently discontinue — with the exception of endocrinopathies**, which are managed with hormone replacement and do not require stopping the drug	High-dose intravenous steroids and admission, with early specialist involvement.

If there is no improvement within 48–72 hours of high-dose steroids, escalate — **infliximab**, **vedolizumab** (particularly colitis), **rituximab**, mycophenolate or cyclophosphamide, depending on the organ involved. **Do not simply continue waiting on steroids alone.**

THE ORGAN-SPECIFIC TRAPS *where the general rule does not apply*

Toxicity	What is different
Myocarditis	**Treat aggressively and immediately** — high mortality. **Stop the drug permanently**, give high-dose steroids without waiting for confirmation, and involve cardiology. Check **troponin and ECG**; look for coexisting myositis and myasthenic weakness.
Endocrinopathies	**The exception to permanent discontinuation.** Hypophysitis, thyroiditis, adrenal insufficiency and type 1 diabetes are managed with **hormone replacement**, and immunotherapy can usually continue. **Give steroid replacement before thyroxine** if both axes are affected.
Colitis	**Exclude infection, especially *C. difficile*, before escalating immunosuppression.** Severe cases need flexible sigmoidoscopy. Escalate early to **infliximab or vedolizumab** if steroid-refractory — perforation risk is real.
Pneumonitis	**Distinguish from infection and progression** — get a CT and consider bronchoscopy. Withhold the drug even at grade 2, since deterioration can be rapid.
Adrenal crisis	Can present as **fatigue, hypotension and hyponatremia** and be mistaken for progression or sepsis. **Give hydrocortisone on suspicion** — do not wait for a cortisol result.

WHILE ON STEROIDS *the complications of the treatment*

PROTECT THE PATIENT

Pneumocystis prophylaxis for prolonged high-dose steroid exposure · **gastroprotection** · **glucose monitoring** · bone protection · screen for **hepatitis B and latent TB** before infliximab. **Infliximab is contraindicated in hepatitis**, where mycophenolate is used instead.

DOCUMENT AND COMMUNICATE

Record the toxicity, its grade and the outcome clearly, and give the patient **written information and an alert card** — they may present to a clinician who does not know they are on immunotherapy. **Discuss rechallenge with oncology**, never unilaterally, and note that irAEs may correlate with tumor response, so stopping is not a neutral decision.

WHEN THEY APPEAR *timing helps, but nothing is off the table at any point*

TYPICAL SEQUENCE

Skin is usually earliest, often within the first weeks. **Colitis and hepatitis** follow at around 6–12 weeks. **Endocrinopathies** tend to appear later, from around 9 weeks onward and often insidiously. **Pneumonitis** is variable and can be very late. **Myocarditis is typically early, within the first 6–8 weeks**, which is when vigilance should be highest.

BUT DO NOT RELY ON IT

Any irAE can occur at any time, including months after the last dose — checkpoint inhibitors have durable immunological effects long after the drug has cleared. A patient who stopped treatment six months ago and presents with diarrhea, breathlessness or fatigue **still warrants an irAE workup**. **Ask about immunotherapy in the past year**, not just current medications.

PEARLS & PITFALLS

- **Any new symptom on a checkpoint inhibitor is an irAE until excluded.** These patients present to every specialty, often to clinicians unaware of the drug.
- **Grade 4 means permanent discontinuation — except endocrinopathies**, which are replaced and the drug continued.
- **Taper steroids over at least 4–6 weeks.** Fast tapers cause rebound and a second, worse presentation.
- **Myocarditis kills.** Treat on suspicion with high-dose steroids and stop the drug permanently.
- **Exclude *C. difficile* before treating "immune colitis"**, and exclude infection before treating "pneumonitis".
- **Escalate at 48–72 hours** if steroids are not working, rather than waiting longer on the same dose.

References: Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update (J Clin Oncol, 2021) · NCCN guidelines on the management of immunotherapy-related toxicities · CTCAE v5.0.

Educational aid; verify against local oncology protocol and patient factors.

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