# Clinical Pharmacology & Toxicology Pearl of the Week

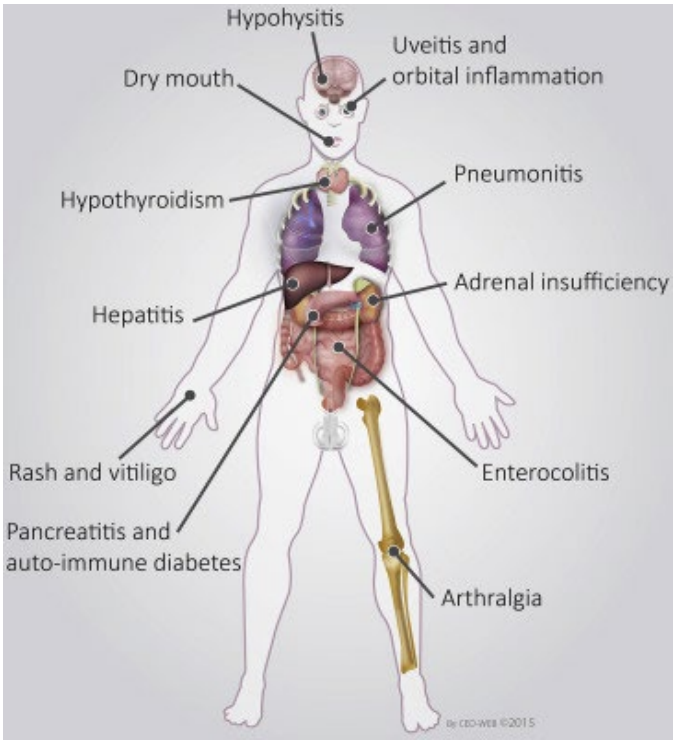
## ~Immune Checkpoint Inhibitors Part 2: Toxicity~

Case

- ✓ A 64 y/o male presents to the ED with increasing headaches, decreased libido, and erectile dysfunction.
  - PMHx: HTN, dyslipidemia, and Stage III melanoma on the back of his neck treated 6 months prior with nivolumab (anti-PD-1) and ipilimumab (anit-CTLA-4)
  - Physical exam is unremarkable aside from bitemporal hemianopsia and orthostatic hypotension
  - Laboratory work demonstrates hyponatremia (125), hyperkalemia (5.7). A non-contrast head CT is unremarkable.
  - Internal medicine is consulted for concerns of adrenal insufficiency and neurology is consulted.
- ✓ How do we proceed to manage this patient?

Toxicity

- ✓ Toxicity can occur within **ANY organ system**, and can often present as any immune-related disease
  - Dermatologic is most common, followed by colitis, then hepatitis, pneumonitis and other endocrinopathies
  - Dermatologic toxicity generally, presents as erythematous maculopapular rash, though can also involve isolated pruritus, vitiligo, or Steven-Johnson Syndrome
  - Myasthenia Gravis, Guillain-Barré and IDDM are possible autoimmune effects
- ✓ Incidence of toxicity is high. 90% for CTLA-4 inhibitors and 70% for the rest
  - Fortunately, **toxicity is generally associated with a good outcome for cancer treatment**
- ✓ Toxicity is not dose dependent and is unpredictable
- ✓ Patients on combination immune checkpoint inhibitor therapy are at higher risk of more severe toxicity




Source: Michot et al, Eur J Cancer 2016,

Grading of toxicity:

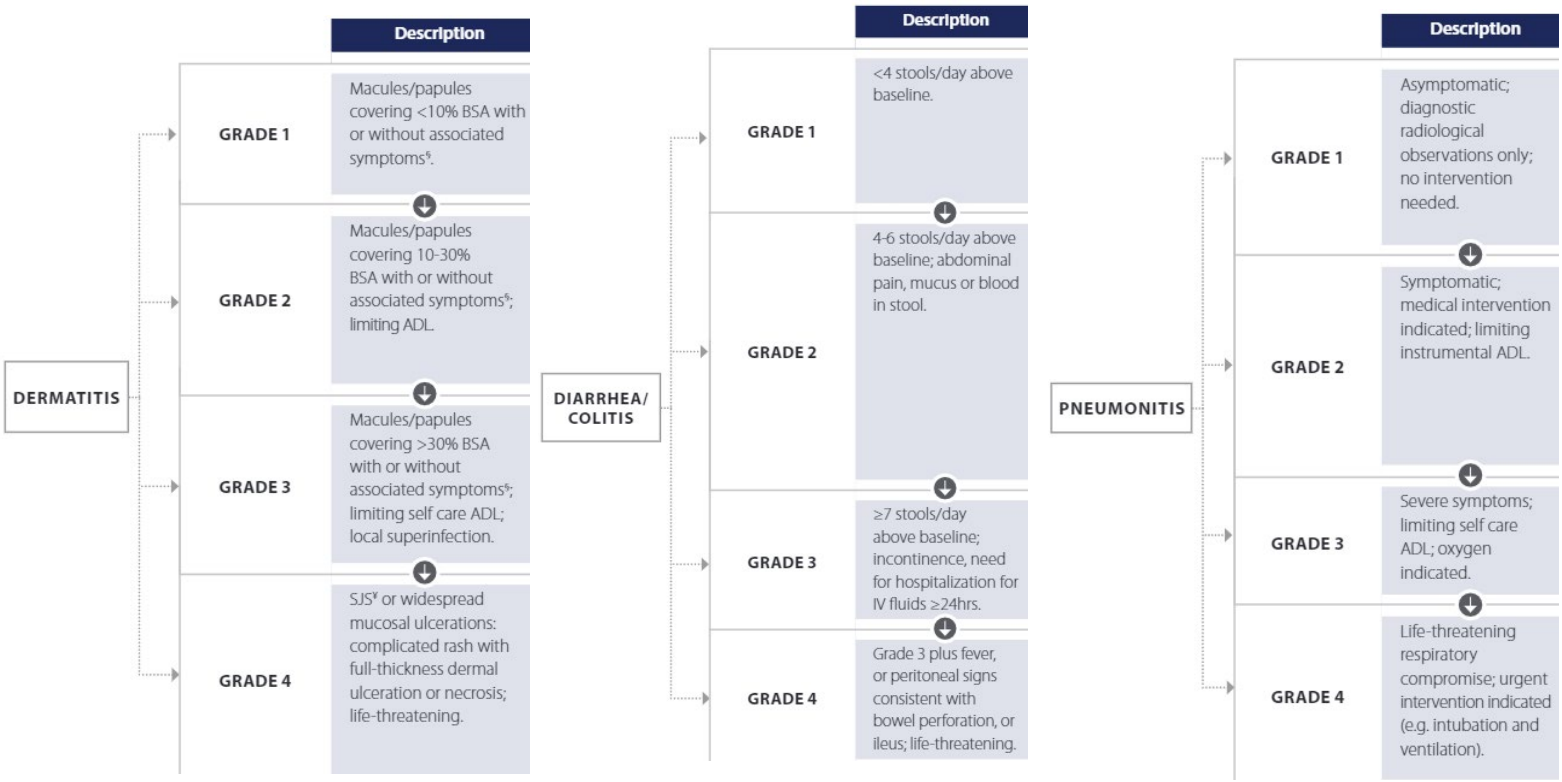
- ✓ Grading of immune checkpoint inhibitor toxicity is organ specific, though are based on degree of symptoms, degree of end organ damage, and effect of activities of daily living
- ✓ Consensus guidelines are available from the Society for Immunotherapy of Cancer (SITC) Toxicity Management working group (Puzanov et al, J Immunother Cancer 2017 Nov 21, 5(1):95) and Cancer Care Ontario (Cancer Care Ontario Clinical Practice Guideline)

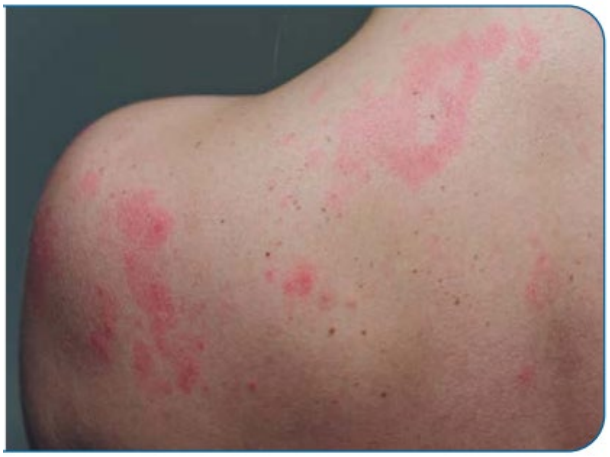
**Table 4.** General treatment recommendations of immune related adverse events per the ASCO guidelines [17].

| Grade | Definition* | Treatment | Disposition |
|---|---|---|---|
| 1 | Mild; asymptomatic or mild symptoms;<br>Clinical or diagnostic observations only<br>Intervention not indicated. | Symptomatic treatment | Discharge, if possible after discussion with oncologist<br>Ensure outpatient follow |
| 2 | Moderate; minimal, local or noninvasive intervention indicated<br>Limiting age appropriate instrumental ADL | Glucocorticoids (initial dose of 0.5–1 mg/kg/d of prednisone or equivalent) | Consider hospitalization versus discharge<br>May consider observation status if short stay is anticipated<br>Discuss disposition with oncologist |
| 3 | Severe or medically significant but not immediately life-threatening<br>Hospitalization indicated<br>Disabling; limiting self-care ADL | High-dose glucocorticoids (prednisone 1–2 mg/kg/d or equivalent)<br>Glucocorticoids should be tapered over 4–6 weeks | Admission to the hospital |
| 4 | Life-threatening consequences with urgent intervention indicated | Same as Grade 3 | Admission with ICU level care if indicated |

ASCO: American Society of Clinical Oncology; ICU: intensive care unit. *Definitions follow the Common Terminology Criteria for Adverse Events (Version 5).

- ✓ Examples of grading for three specific adverse effects (Source: Cancer Care Ontario)

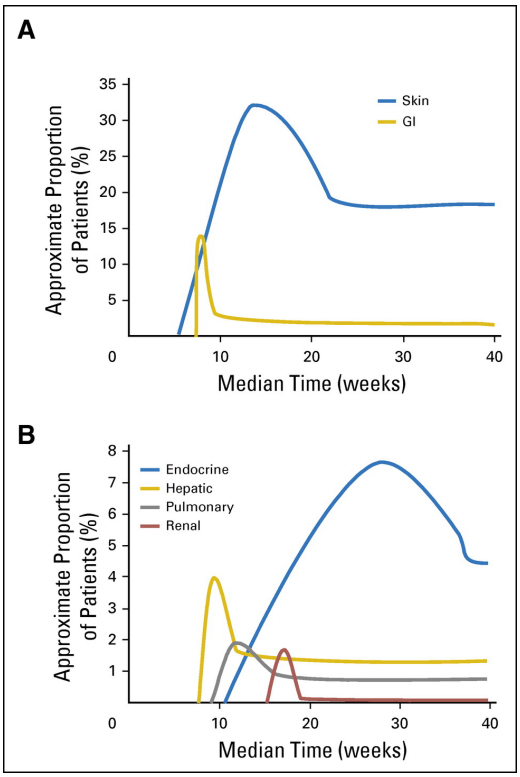




Example Rash. Source: NCCN Immunotherapy Side Effects

Timing of Toxicity

- ✓ Toxicity can occur **months to years after exposure**, making a detailed history of all chemotherapeutics taken during treatment paramount in identifying potential immune checkpoint inhibitor toxicity
- ✓ Generally, dermatologic, hepatic, and intestinal toxicity occurs earlier following treatment compared to pulmonary, renal, neurologic, and endocrine toxicity
- ✓ However, **toxicity can occur at any time**




Source: Weber et al, J Clin Onc 2017, 35(7):785-792

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**The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.**

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