



Adrenal insufficiency (AI) is a potential immune-related adverse event (irAE) of immunotherapy (e.g., checkpoint inhibitor). If not identified and treated promptly, AI can be life-threatening. Unlike other irAEs, AI may be irreversible, requiring long-term glucocorticoid and mineralocorticoid replacement. Provider and patient education are essential in the management of immune checkpoint inhibitor-induced AI.

#### AT A GLANCE

- Treatment with immunotherapy may lead to irAEs, such as AI.
- Glucocorticoid and mineralocorticoid replacement may be required in patients with AI.
- To manage AI over time, advanced practice RNs must be aware of its signs and symptoms.

#### KEYWORDS

adrenal insufficiency; immune checkpoint inhibitor; immune-related adverse event

#### DIGITAL OBJECT IDENTIFIER

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# Adrenal Insufficiency

## Immune checkpoint inhibitors and immune-related adverse event management

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Immune checkpoint inhibitor (ICI) therapy is rapidly evolving as an effective treatment option for many cancers. This class of immuno-oncology has revolutionized treatment and improved progression-free and overall survival, particularly for patients with advanced melanoma (Larkin et al., 2019). ICIs target specific T-cell inhibition mechanisms of cancer cells, releasing the T cells from inhibition and allowing their attack on cancer cells (Barroso-Sousa et al., 2018). Checkpoint inhibition mechanisms are also responsible for physiologic immune self-tolerance and homeostasis (Chang et al., 2019); the release of inhibition may result in a spectrum of autoimmune-like toxicities classified as immune-related adverse events (irAEs) (Barroso-Sousa et al., 2018; Wood, 2019). The exact mechanism triggering irAEs is not fully understood, but nearly every organ can be affected (Chang et al., 2019; Cukier et al., 2017). The most commonly affected organs are the skin, gastrointestinal tract, lungs, liver, and endocrine system (Gordon et al., 2017).

Endocrine irAEs are increasing in incidence with expanded use of ICIs (Barroso-Sousa et al., 2018). ICI-induced endocrinopathies can present as hyperthyroidism, hypothyroidism, hypophysitis, diabetes mellitus, primary adrenal insufficiency (PAI), or a combination of these in the same patient. The combination of cytotoxic T lymphocyte-associated antigen 4 (CTLA4)

and programmed cell death protein 1 (PD-1) or programmed cell death protein ligand 1 (PD-L1) immunotherapy may result in enhanced antitumor response but also can increase the risk of irAEs (Barroso-Sousa et al., 2018; Guo et al., 2017), including the risk of AI from autoimmune adrenalitis.

#### Adrenal Function

The adrenal glands consist of two distinct zones: an interior medulla and an outer cortex. Autoimmune adrenalitis is a disorder of the adrenal cortex, the portion of the gland responsible for secretion of steroid hormones, including the glucocorticoid cortisol and the mineralocorticoid aldosterone (Barroso-Sousa et al., 2018; Chang et al., 2019; Cole, 2018). Cortisol levels have a normal diurnal pattern, with peak levels in the early morning and lowest levels around midnight (Bancos et al., 2015; Debono et al., 2009). In response to new physiologic or emotional stress, additional cortisol is released, resulting in widespread effects on carbohydrate and protein metabolism (Cole, 2018). Cortisol is essential to the stress response.

Aldosterone is responsible for sodium reabsorption and potassium excretion by the kidneys, the maintenance of a homeostatic extracellular fluid volume, and, ultimately, regulation of arterial blood pressure (Cole, 2018). Aldosterone release from the adrenal cortex is controlled by the renin-angiotensin system in response to decreased blood pressure,