Endocrinopathy Immune-Related Adverse Event Management Algorithm: Pituitary dysfunction

Grading of pituitary toxicity	Action	Follow-up
Vague symptoms Of tiredness/reduced appetite with no headache etc or asymptomatic and low cortisol **Usual context:** PD1/PDL1 inhibitors alone, or CTLA4 +/- PD1 inhibitors, or withdrawal from LT exogenous gluco-corticoid. Typically later in ICI treatment	**Investigations** • Ideally 9am cortisol and ACTH, U&Es, glucose, prolactin, free T4 + TSH • Urgent MRI Pituitary	See Management of Possible Cortisol Insufficiency in 'Adrenal Dysfunction' section (9 am cortisol <350 nmol/l)
Acute Hypophysitis Moderate symptoms (headache, no visual disturbance or symptoms of acute adrenal crisis/cortisol deficiency) **Usual context:** CTLA4 +/- PD1 inhibitors (often within 12w of commencing ICI)	**Investigations** • Bloods: cortisol, ACTH, U&Es, glucose, prolactin, fT4, TSH, LH/FSH and testosterone or oestradiol (T or E2) • Urgent MRI Pituitary **Emergency Rx:** • 100mg hydrocortisone IV / IM (after blood drawn but do not wait for the results). Followed by 50mg hydrocortisone and fluid resuscitation as required. • Once stable, oral hydrocortisone replacement (double dosing for 3 days then standard replacement).	Steroid advice, steroid card and emergency pack (including IM hydrocortisone). Contact endocrinology on-call for advice: Consult Endocrinology (IP) **Subsequent pituitary assessment:** - Reassess LH / FSH and T/E2 (if pre-menopausal) when recovered from acute phase. - If persistent deficiency, consider sex-hormone replacement if not in context of acute illness (via Endocrinology).
Acute Hypophysitis Severe mass effect symptoms (Severe headache, nausea and vomiting, visual symptoms/visual field defects, mass on MRI pituitary) **Usual context:** CTLA4 +/- PD1 inhibitors (often within 12w of commencing ICI)	**Investigations** • As above **Emergency Rx:** • As above	- Contact endocrinology on-call for advice: Consult Endocrinology (IP) - Consider IV Methylprednisolone 1mcg/kg if optic chiasm compression - Oral prednisolone e.g. 20mg/day if severe headache with no resolution **Subsequent pituitary assessment:** As above
Acute ACTH deficiency causing adrenal crisis/acute cortisol deficiency **Usual context:** CTLA4 +/- PD1 inhibitors or PD1/PD1L-1 inhibitors alone, or withdrawal from LT exogenous glucocorticoid Typically, later in ICI treatment	**Investigations** • As above **Emergency Rx:** • 100 mg hydrocortisone IV/IM (after blood drawn but do not wait for results). Followed by hydrocortisone replacement (consider double dosing for a few days) then standard replacement. • Steroid advice, steroid card and emergency pack.	Contact endocrinology on-call for advice: Consult Endocrinology (IP) **Subsequent pituitary assessment if CTLA4 inhibitor:** Reassess LH/FSH and T/E2 (if pre-menopausal) when recovered from acute phase. If persistent deficiency; consider sex hormone replacement if not in context of acute illness (via Endocrinology)

Endocrinopathy Immune-Related Adverse Event Management Algorithm: Adrenal dysfunction

Cortisol insufficiency	Action	Follow up
9 am Cortisol: **<100 nmol/l** Cortisol insufficiency likely: manage as in 'Pituitary Dysfunction above: Acute ACTH deficiency' ACTH low; pituitary ACTH deficiency or exogenous glucocorticoid ACTH ≥ 2xULN primary adrenal insufficiency (rare, see section on RARE endocrine Abnormalities)	**Investigations:** • Urgent ACTH, U&Es, glucose, prolactin, free T4, TSH, LH/FSH, testosterone or oestradiol (T or E2) **Emergency Rx:** • 100mg hydrocortisone IV / IM (after blood drawn but do not wait for the results).	• Hydrocortisone replacement (consider double dosing for a few days): hydrocortisone 20mg/10mg/10mg for 3 days and reduce to 10mg/5mg/5mg. • Steroid advice, steroid card and emergency pack (including IM hydrocortisone). • Contact endocrinology on-call for advice.
9 am Cortisol: **>100 nmol/l and ≤350 nmol/l** **Context:** anti-CTLA4 (possible acute ACTH deficiency)	Possible acute pituitary failure; review symptoms. If unwell, assess pituitary profile and start hydrocortisone replacement as above.	If asymptomatic; repeat 9 am cortisol in 1 week and warn patient of symptoms of concern. Contact endocrinology on-call for advice.
9am Cortisol: **>100 nmol/l and ≤350 nmol/l** **Context**: anti-PD1/PDL1 and/or exogenous glucocorticoid	Possible cortisol insufficiency, non-diagnostic. Consider patient symptoms, timing of ICI and exogenous glucocorticoids.	Repeat 9 am cortisol. Consider commencement hydrocortisone 10/5/5 mg replacement and repeat 9 am cortisol pre-hydrocortisone in 6w, consider short synacthen test. If in doubt, contact endocrinology on-call for advice.
9am Cortisol: > 350 nmol/l	Cortisol insufficiency unlikely; monitor and review symptoms.	

Endocrinopathy Immune-Related Adverse Event Management Algorithm: Thyroid dysfunction

Thyroid toxicity	Action	Follow up
Hyperthyroidism TSH suppression +/- elevation fT4/fT3 **Likely diagnosis:** Thyroiditis leading to transient thyrotoxic phase	**Investigations** • Complete endocrine panel including TSHRAb. • If persistent >4 weeks and / or eye symptoms, then consider thyroid uptake scan if TSHRAb negative or palpable nodule. • Discuss with endocrinology. **Management** • Consider propranolol 10-40mg TDS if symptomatic • Monitor closely for subsequent primary hypothyroidism	• Recheck TFTs within 3 weeks and then 3-6 weekly thereafter (majority of cases will turn hypothyroid) • Continue immunotherapy (unless patient acutely unwell with thyrotoxicosis)
Primary Hypothyroidism TSH > 10mIU/L and reduced fT4/fT3 May/not follow hyperthyroidism	**Investigations** • Bloods: TPO • Ensure normal cortisol reserve prior to treatment. **Management** • Levothyroxine 1mcg/kg OD (round to nearest 25mcg) – except if comorbidities (e.g. AF / IHD) or age >65. In this case then start at 25-50mcg OD	• Monitor TFTs at least every 6 weeks for dose adjustment – increase in 25mcg increments. • Advice to be given regarding levothyroxine: take on empty stomach and wait at least 30 minutes before eating/drinking, avoid calcium, iron, cholestyramine and multivitamins for 4 hours. • Referral to endocrine team if unable to stabilize thyroid function. • Continue immunotherapy.
Low TSH and low/normal fT4 **DDx:** 1. Secondary hypothyroidism if anti-CTLA4 2. Chronic illness (sick euthyroid)	**Investigations** • Bloods: TPO **Management** • Levothyroxine replacement if secondary hypothyroidism (ensure normal cortisol reserve first)	• Discuss with Endocrinology • Advice to be given regarding levothyroxine: take on empty stomach and wait at least 30 minutes before eating/drinking, avoid calcium, iron, cholestyramine and multivitamins for 4 hours.

Rare Possible Endocrine Abnormalities (contact endocrinology to discuss)

Primary Adrenal Failure	Cortisol deficiency with ↑ACTH (2xULN) +/- ↑Renin ↓Na and ↑K and postural hypotension (NB ↓Na seen in acute ACTH deficiency too)
Parathyroid Hormone deficiency causing hypocalcaemia	Ca < 2.1 mmol/l Check PTH, Mg and Vitamin D Emergency management if acute
Diabetes Insipidus	New polyuria and polydipsia; check 24h urine volume and paired osmolality and urine with U and E

Monitoring All Patients Receiving ICI

Exogenous Glucocorticoids for other indication	**Temporary/Permanent discontinuation of ICI**	**Bone Health**
Consider pituitary/adrenal suppression; In particular: ≥5mg prednisolone ≥4w Dexamethasone ≥4 mg/d or prednisolone ≥40 mg/d for ≥1w Potent topical steroid e.g. clobetasol, betamethasone, mometasone	*Continue to monitor fT4/TSH* Continue to monitor fT4/TSH 3m/6m and 12 monthly, or if clinically indicated Monitor cortisol at 4w, 8w and 12w then 3, 6 months if CTLA4 blockers	*Consider in every patient;* Consider vitamin D +/- calcium In particular, consider bone protection in any patient treated with oral glucocorticoids particularly aged >50y and receiving 7.5 mg (equivalent) prednisolone (except if replacement hydrocortisone) Advice; metabolic bone clinic and NOGG[8] Bone protection should be considered for all patients who have an annual average steroid threshold of 2.5mg prednisolone (or equivalent) or more a day

Please see [INSERT LINK HERE] for endocrine department guideline on endocrinopathy IO toxicity.

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