Endocrine complications of cancer treatments

MANCHESTER 1824

The University of Manchester

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28.2.2019

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The Christie Hospital
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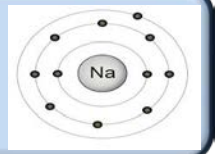
Manchester Academic Health Science Centre

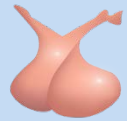
Living With ..... And Beyond

Electrolyte Disorders

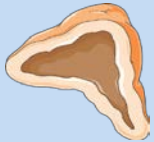


Onco-Endocrinology

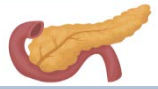
Pituitary hormone dysfunction



Acute Hormone Dysfunction

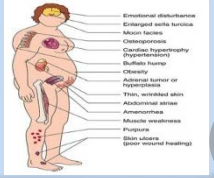


Diabetes

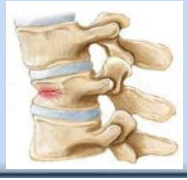


Hypogonadism POF Infertility

Paraneoplastic Syndrome



Bone Health



Obesity and Metabolic Risk

Cancer

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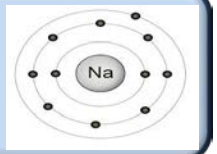
Living With ..... And Beyond

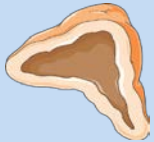
Electrolyte Disorders



Onco-Endocrinology

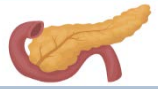
Pituitary hormone dysfunction

Acute Hormone Dysfunction

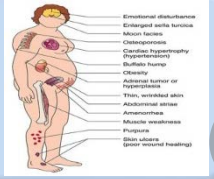


Hypogonadism
POF
Infertility

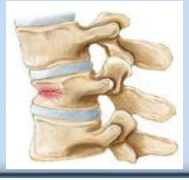
Diabetes



Paraneoplastic Syndrome



Bone Health



Obesity and Metabolic Risk

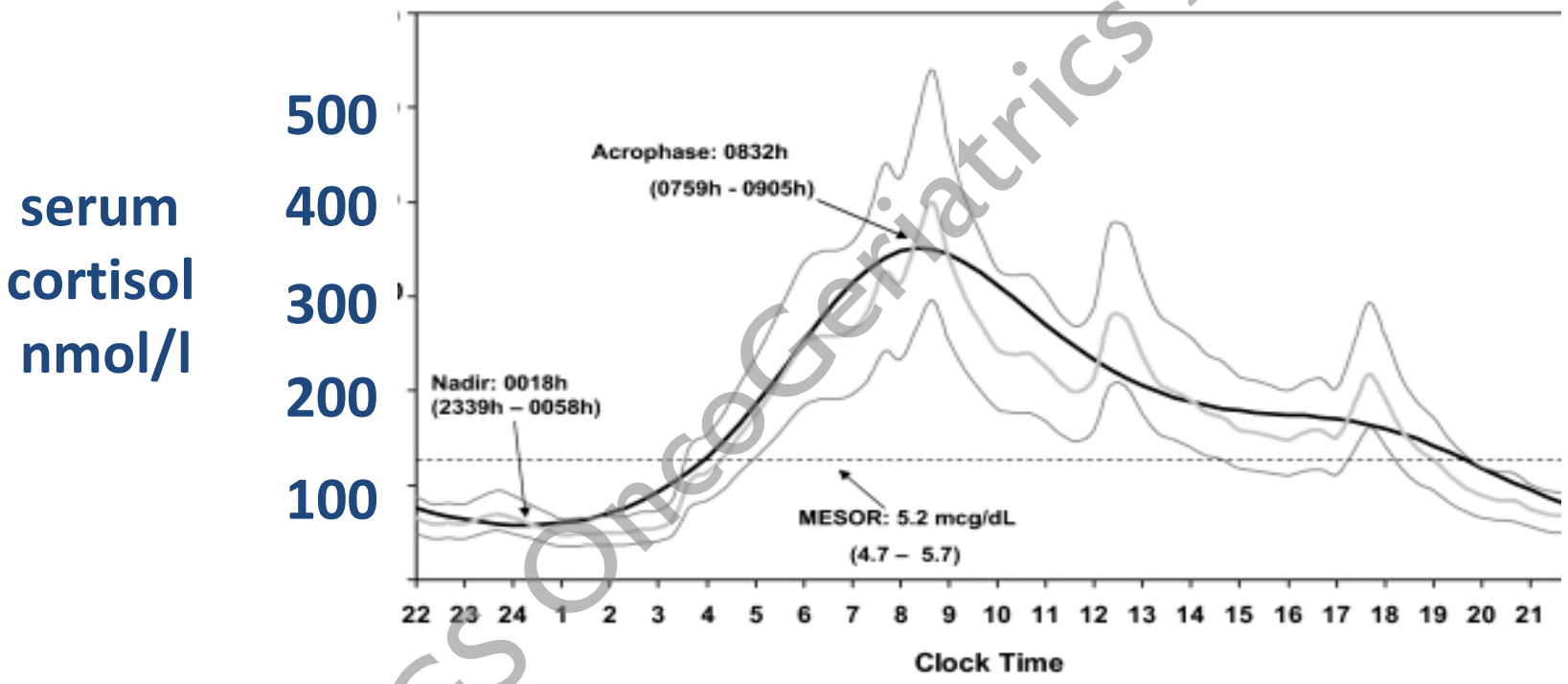
Cancer

Telephone call from Phil, Clinical Scientist

Mrs B 85 yr old lady

"serum cortisol is 85 nmol/l" (200-600)

Is Mrs B's cortisol normal?: circadian rhythm of cortisol



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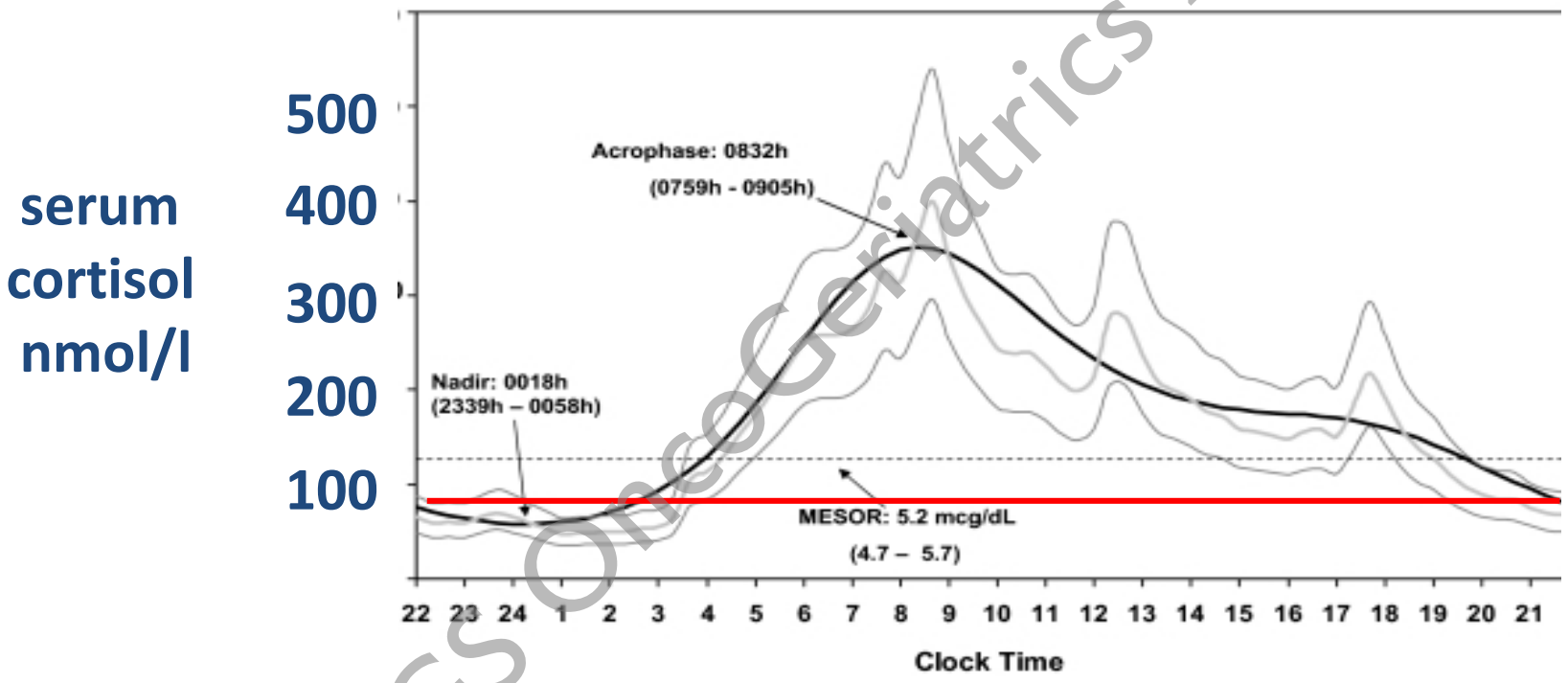
Debono et al, JCEM 2009 94: 1548-1554

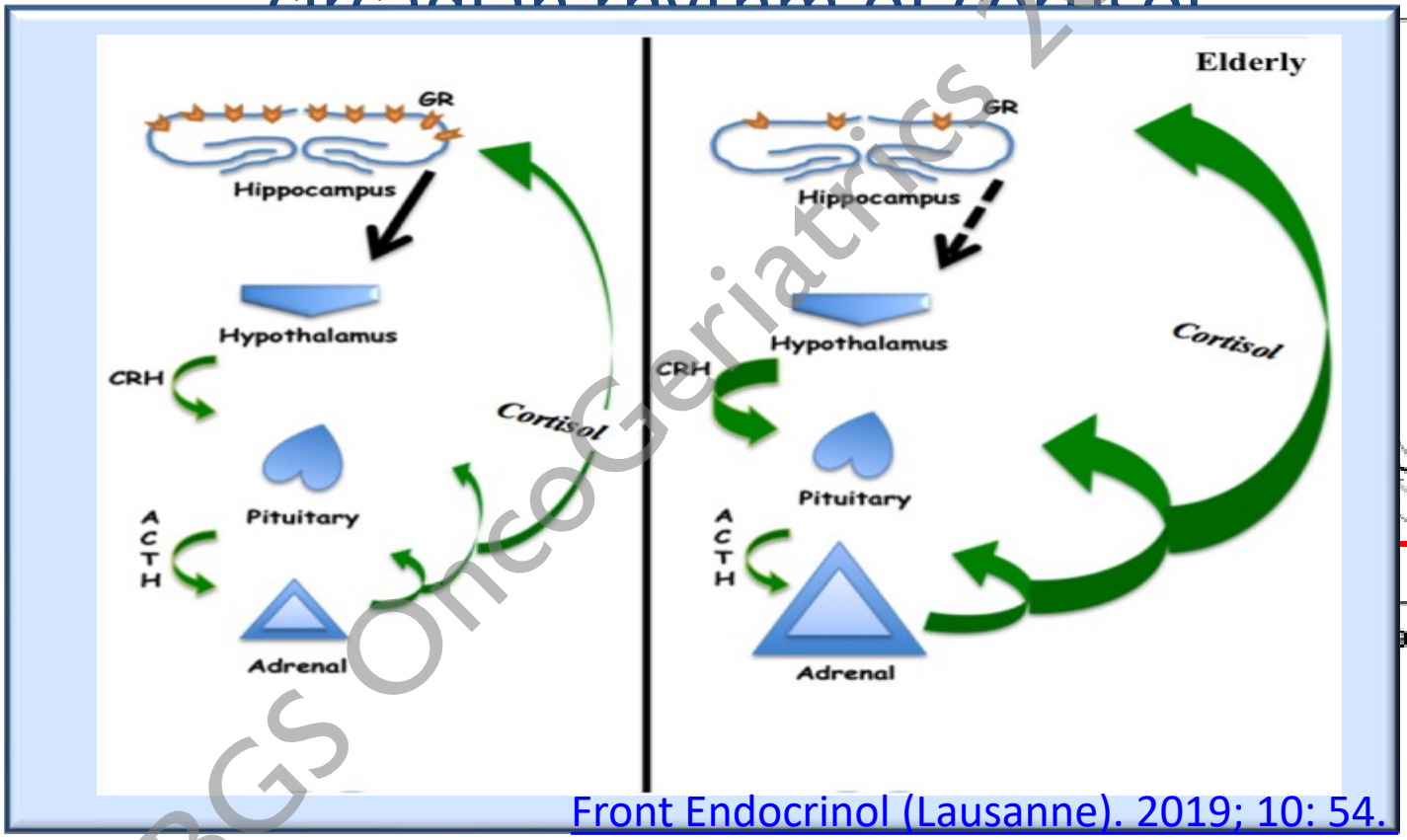
Is Mrs B's cortisol normal?: circadian rhythm of cortisol



Debono et al, JCEM 2009 94: 1548-1554

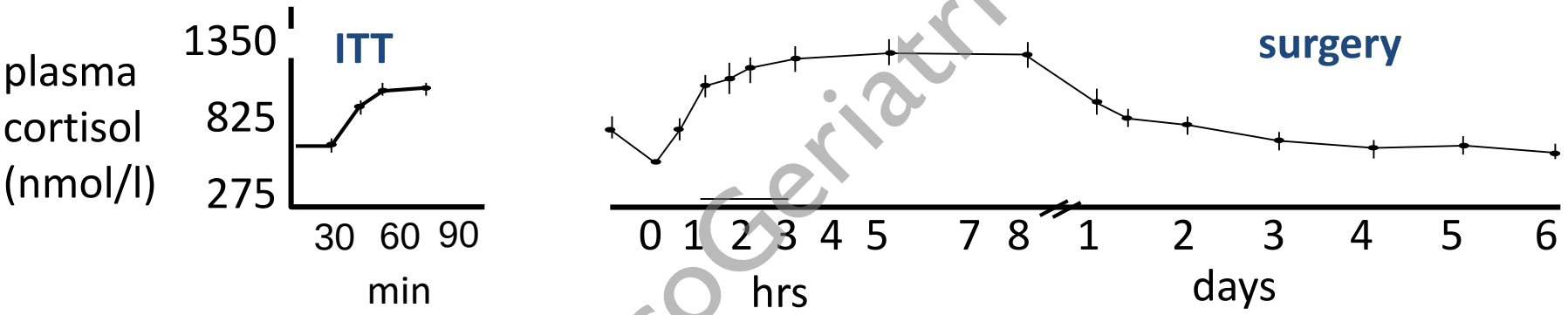
Is Mrs B's cortisol normal?: circadian rhythm of cortisol

serum cortisol nmol/l



Front Endocrinol (Lausanne). 2019; 10: 54.

Is Mrs B unwell?: cortisol response to hypoglycaemia and major abdominal surgery



- **Peak cortisol of 20 mcg/dl = 551 nmol/l predicts an adequate response to surgery**
- **Gold Standard for comparing tests of adrenal function – the Short Synacthen Test (Abdu et al 600 nmo/l)**

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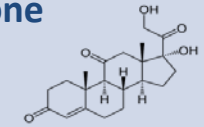
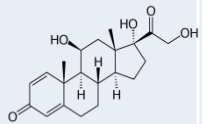
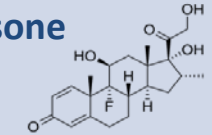
Plumpton Brit J Surg 1969 56 216 Abdu et al JCEM 1998 84: 838

Is Mrs B on glucocorticoid therapy ?

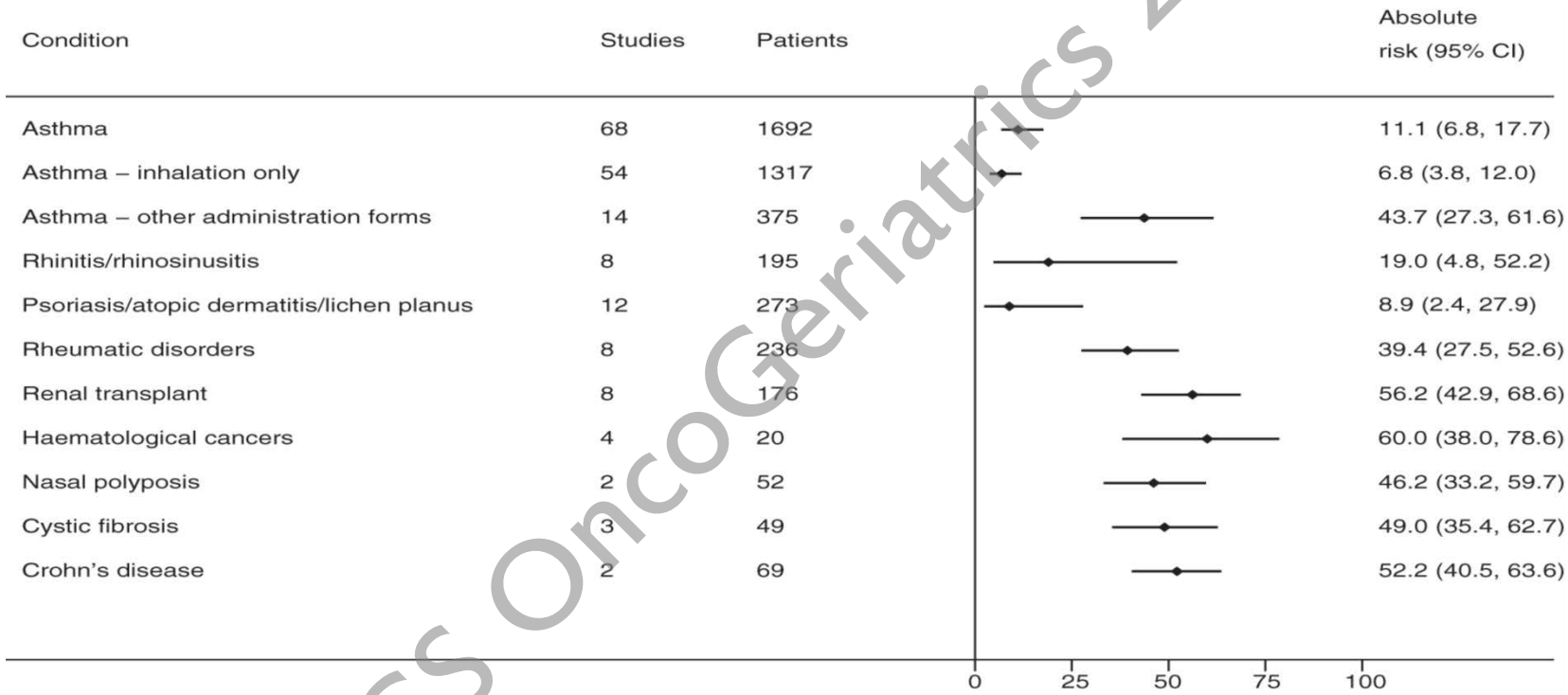
	Immunoassay	Result (nmol/l)	Mass spectrometry	Result
Hydrocortisone 	same as endogenous cortisol	300 nmol/l	same as endogenous cortisol	300 nmol/l
Prednisolone 	cross reactivity dependent on assay	240 nmol/l	cortisol distinguishable from prednisolone	<50 nmol/l
Dexamethasone 	no cross reactivity	< 50 nmol/l	no cross reactivity	< 50 nmol/l
Inhaled GCs (fluticasone/ beclamethasone/ budesonide/ ciclesonide)	cross reactivity dependent on assay (usually minimal)		no cross reactivity	

Dose equivalence (physiological)
A reminder !

oral prednisolone	3.75-6.25 mg per day
oral hydrocortisone	12.5-15 mg per day
oral dexamethasone	0.75 mg per day

Has Mrs B recently been on any glucocorticoid therapy?

Condition	Studies	Patients	Absolute risk (95% CI)
Asthma	68	1692	11.1 (6.8, 17.7)
Asthma – inhalation only	54	1317	6.8 (3.8, 12.0)
Asthma – other administration forms	14	375	43.7 (27.3, 61.6)
Rhinitis/rhinosinusitis	8	195	19.0 (4.8, 52.2)
Psoriasis/atopic dermatitis/lichen planus	12	273	8.9 (2.4, 27.9)
Rheumatic disorders	8	236	39.4 (27.5, 52.6)
Renal transplant	8	176	56.2 (42.9, 68.6)
Haematological cancers	4	20	60.0 (38.0, 78.6)
Nasal polyposis	2	52	46.2 (33.2, 59.7)
Cystic fibrosis	3	49	49.0 (35.4, 62.7)
Crohn's disease	2	69	52.2 (40.5, 63.6)



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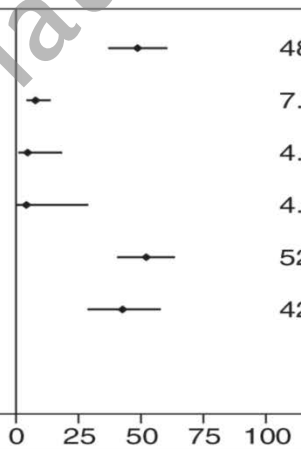
The Journal of Clinical Endocrinology & Metabolism, Volume 100, Issue 6, 01 June 2015, Pages 2171–2180, https://doi.org/10.1210/jc.2015-1218

Has Mrs B recently been on any glucocorticoid therapy – what about inhalers/creams/injections?

Administration	Studies	Patients	Absolute risk (95% CI
Oral	38	1419	48.7 (36.9, 60.6)
Inhalation	60	1418	7.8 (4.2, 13.9)
Topical	15	320	4.7 (1.1, 18.5)
Nasal	8	173	4.2 (0.5, 28.9)
Intra–articular	4	69	52.2 (40.5, 63.6)
Multiple forms	11	354	42.7 (28.6, 58.0)



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The Journal of Clinical Endocrinology & Metabolism, Volume 100, Issue 6, 01 June 2015, Pages 2171–2180
https://doi.org/10.1210/jc.2015-1218

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Has Mrs B recently been on any glucocorticoid therapy – what about inhalers/creams/injections?

- high dose/long term glucocorticoids highest risk – consider routine testing
- can occur even after low dose, topical Rx
  - low threshold for testing if symptomatic
- warn patients of potential risk

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The Journal of Clinical Endocrinology & Metabolism, Volume 100, Issue 6, 01 June 2015, Pages 2171–2180
https://doi.org/10.1210/jc.2015-1218

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Key Points

- What was the time of the serum cortisol sample ?
- Is the patient unwell?
- Is the patient currently taking glucocorticoids?
  - oral/intra-articular/inhaled/topical
- How is serum cortisol measured in my hospital?
- Has the patient had previous glucocorticoids?
  - oral/intra-articular/inhaled/topical
  - exclude HPA axis suppression

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81 yr old gentleman

Performance Status 1

Medical History

endovascular repair for AAA aged 70

BP 183/74

Medications

Doxazosin 2mg od, Aspirin 75mg od, Allopurinol 300mg od Finasteride 5mg, Digoxin 125mcg od, Pravastatin 40mg od Indapamide 2.5mg od, Carvedilol 12.5mg od, Ramipril 10mg od

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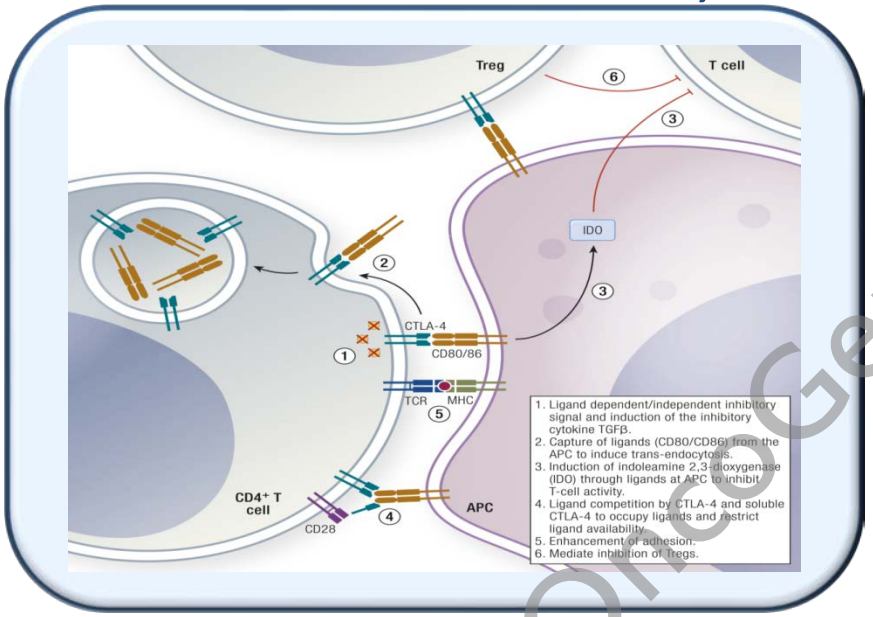
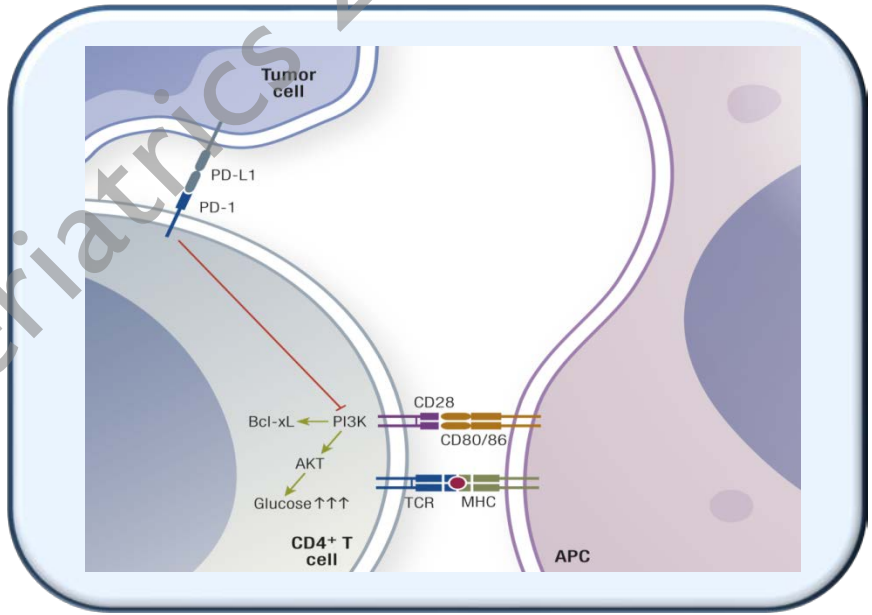
81 yr old gentleman

metastatic melanoma
stage IV M1c

Pembrolizumab mono

Monoclonal antibodies targeting CTLA- 4 , PD-1 and PDL-1





CTLA-4 inhibits conventional T-cell activity

some tumour cells express PDL-1 to avoid immune detection

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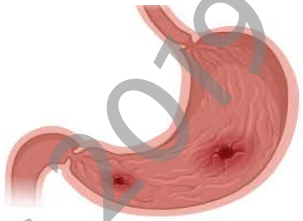
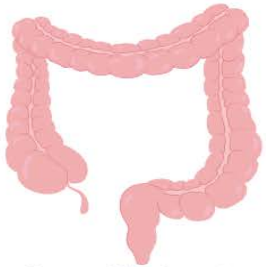
Chang et al Immune Checkpoint Inhibitor-Related Endocrinopathy Endocrine Reviews, February 2019, 40(1):17–65

melanoma

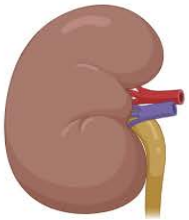
hepatocellular carcinoma



gastric cancer

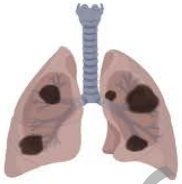


microsatellite insufficient or instability high colorectal cancer

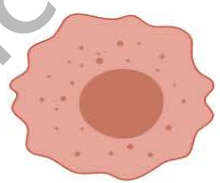


renal call carcinoma

FDA approved indications (May 2018)

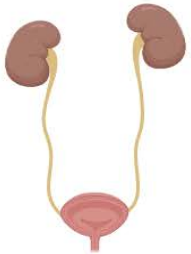


non small cell lung cancer



Hodgkin Lymphoma

head and neck squamous cell cancer



urothelial cancer

Adapted from: Chang et al Immune Checkpoint Inhibitor-Related Endocrinopathy Endocrine Reviews, February 2019, 40(1):17–65

81 yr old gentleman

metastatic melanoma
stage IV M1c

Pembrolizumab mono

81 yr old gentleman

- 5 months into treatment
- falls, confusion and tiredness
- admitted to Acute Oncology Unit

81 yr old gentleman

- 5 months into treatment
- falls, confusion and tiredness
- admitted to Acute Oncology Unit

- Serum sodium 125 mmol/l (135-145 mmol/l)
- BP 90/40

Management of a life-threateningly unwell (CTCAE grade 3–4) patient

Assess for the following signs/symptoms:

- hypotension (systolic BP <90 mmHg)
- postural hypotension (>20mmHg drop in BP from standing to sitting)
- dizziness / collapse
- hypovolemic shock
- abdominal pain, tenderness and guarding
- nausea and vomiting
- tachycardia +/- cardiac arrythmias
- fever
- confusion/delirium
- coma
- hyponatraemia/hyperkalemia/hypoglycemia
- pre-renal/renal failure

Severe, potentially life threatening and possibility of hypoadrenalism: needs urgent management

Measure (alongside other acute assessment measures as indicated e.g. blood cultures):

- random serum cortisol and plasma ACTH (footnote 1)
- U+Es/LFTs/CRP/FBC/TSH/fT4/glucose (footnote 2)
- Prolactin, testosterone/oestradiol, LH/FSH (footnote 3)

Treat as adrenal insufficiency as per Society for Endocrinology Emergency Endocrine Guidance: (footnote 4)

Hydrocortisone (immediate bolus injection of 100 mg hydrocortisone i.v. or i.m. followed by continuous intravenous infusion of 200 mg hydrocortisone per 24 h (alternatively 50 mg hydrocortisone per i.v.or i.m. injection every 6 h)

Rehydration with rapid intravenous infusion of 1000 mL of isotonic saline infusion within the first hour, followed by further intravenous rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients)

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SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Acute management of the endocrine complications of checkpoint inhibitor therapy.

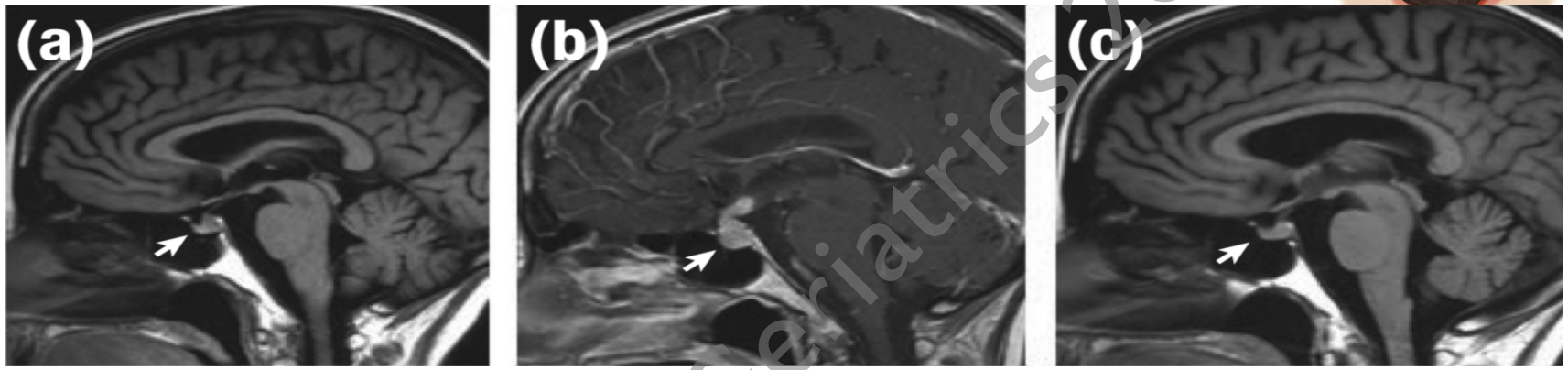
Higham CE et al Endocr Connect. 2018 Jul;7(7):G1-G7. doi: 10.1530/EC-18-0068

81 yr old gentleman

- 5 months into treatment
- falls, confusion and tiredness
- admitted to Acute Oncology Unit

- Serum sodium 125 mmol/l (135-145 mmol/l)
- Serum cortisol 97 nmol/l

CPI induced hypophysitis



- admitted to Acute Oncology Unit
- serum sodium 125 mmol/l (135-145 mmol/l)
- serum cortisol 97 nmol/l
- ACTH < 5ng/ml
- SST at 18/12 serum cortisol 60 mins: 189 nmol/l

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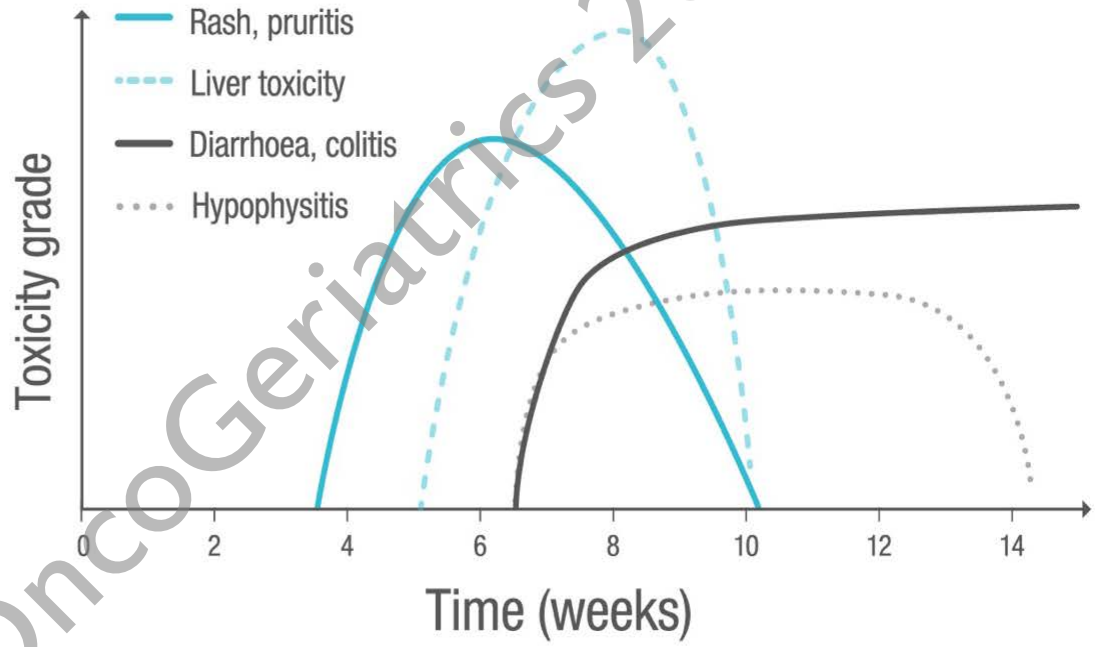
Endocrine Reviews, Volume 40, Issue 1, 03 September 2018, Pages 17–65, https://doi.org/10.1210/er.2018-00006

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



Weber JS et al. J Clin Oncol 2012;30:2691–2697. Reprinted with permission. ©2012 American Society of Clinical Oncology. All rights reserved.

Watch out for adrenalitis !

- serum sodium 125 mmol/l (135-145 mmol/l)
- serum cortisol 97 nmol/l

- treated with high dose hydrocortisone for 3/7
- hyponatremia resolved
- reducing regimen of H/C 10,5,5 mg
- serum sodium 125 mmol/l

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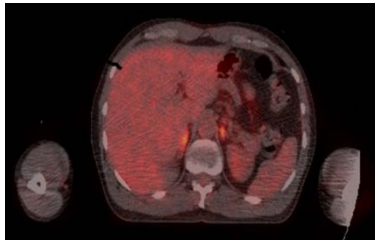
Hyponatraemia secondary to nivolumab-induced primary adrenal failure.
Trainer H, Hulse P, Higham CE, Trainer P, Lorigan P. Endocrinol Diabetes Metab Case Rep. 2016;2016. pii: 16-0108.

Watch out for adrenalitis !



- serum sodium 125 mmol/l
- serum cortisol 97 nmol/l
- ACTH 200 ng/ml (0-46)
- plasma renin activity activity 19.8 nmol/l/hr (0.3-2.2)
- aldosterone < 100 pmol/l

hydrocortisone 10, 5 mg
fludrocortisone 100 mg

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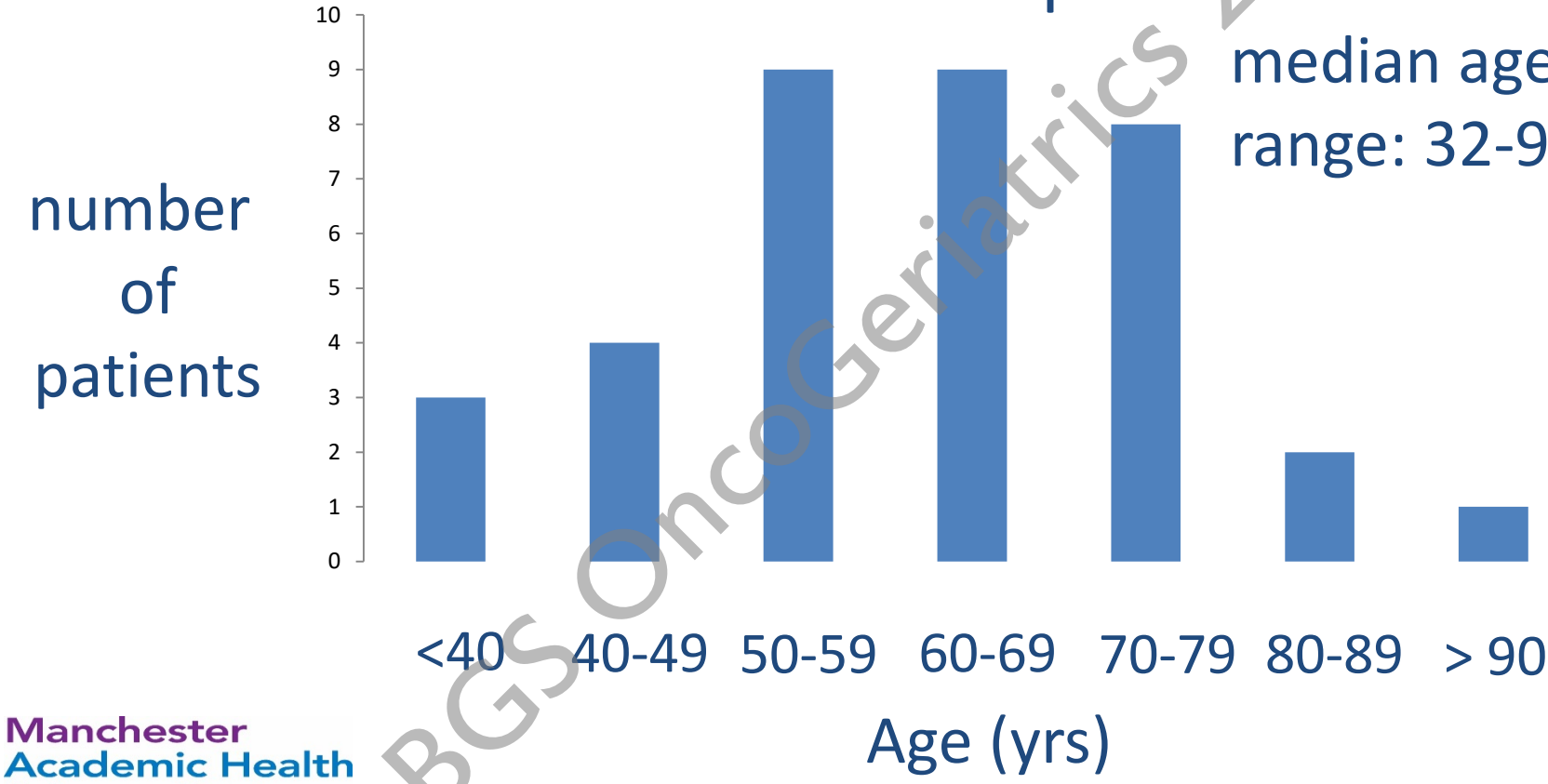
Hyponatraemia secondary to nivolumab-induced primary adrenal failure.
Trainer H, Hulse P, Higham CE, Trainer P, Lorigan P. Endocrinol Diabetes Metab Case Rep. 2016;2016. pii: 16-0108.

Age distribution in CPI induced HPA damage Christie Hospital



median age: 61 yrs
range: 32-92 yrs

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Available Clinical Guidance

- **American Society of Clinical Oncology**

  Brahmer JR et al J Clin Oncol. 2018;36(17):1714–1768.

- **European Society for Medical Oncology**

  Haanen J et al Ann Oncol. 2017;28(suppl_4):iv119–iv142.

- **UKONs Initial Management Guidelines**

  Version 3 in draft

- **UK Society for Endocrinology Emergency Guidance**

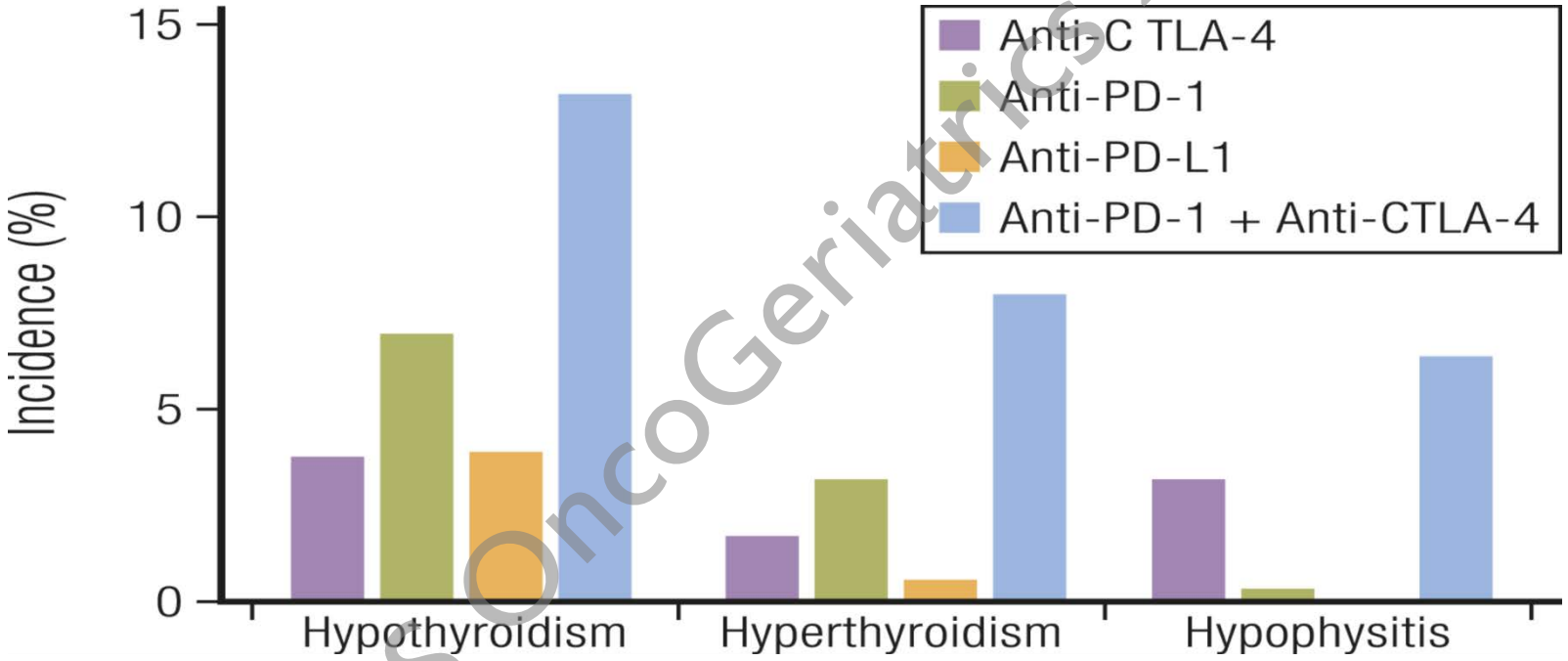
  Higham CE et al, Endocr Connect. 2018 Jul;7(7):G1-G7

Areas of Uncertainty

- the use of high dose IV methylprednisolone in hypophysitis/adrenalitis
  - minimal evidence of recovery of ACTH axis
  - possible excess mortality with high dose IVMP
  - possible role if visual compromise/intractable headache ? severe hypoadrenalism
- can immunotherapy be safely continued following endocrinopathy?
- does the development of toxicity relate to better clinical outcomes?
- are toxicities age dependent?

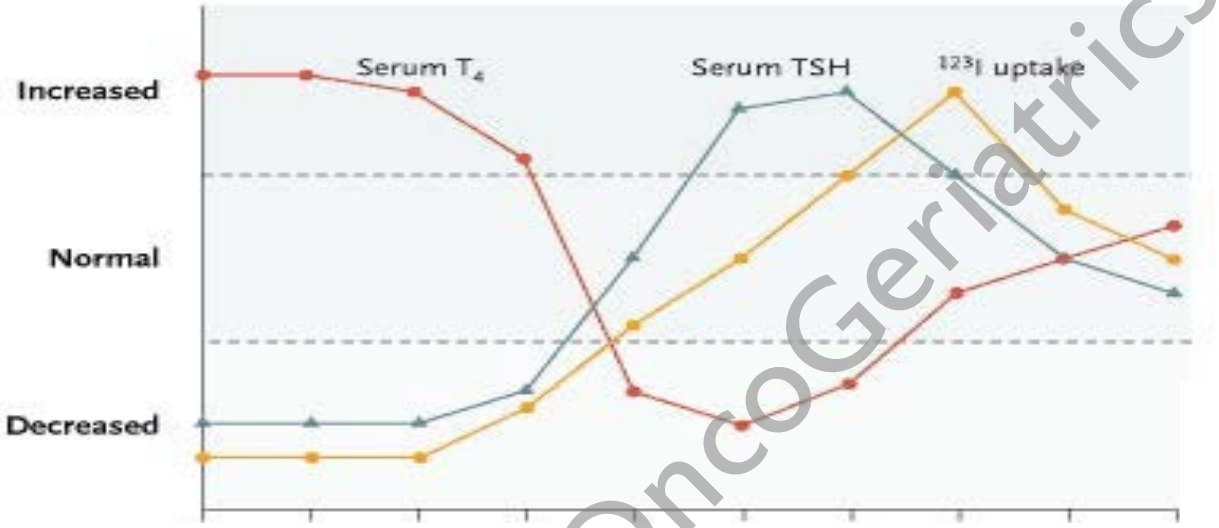
Emergency management of immune-related hypophysitis: Collaboration between specialists is essential to achieve optimal outcomes. Cooksley T, ***Higham C***, Lorigan P, Trainer P. Cancer. 2018 Dec 15;124(24):4731. doi: 10.1002/cncr.31789. Epub 2018 Oct 23

Spectrum of endocrinopathies

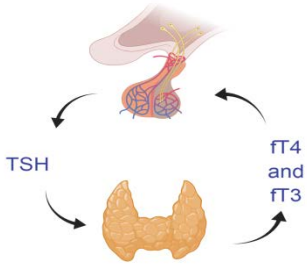


Endocrine Reviews, Volume 40, Issue 1, 03 September 2018, Pages 17–65, https://doi.org/10.1210/er.2018-00006

Usual Course of Destructive Thyroiditis

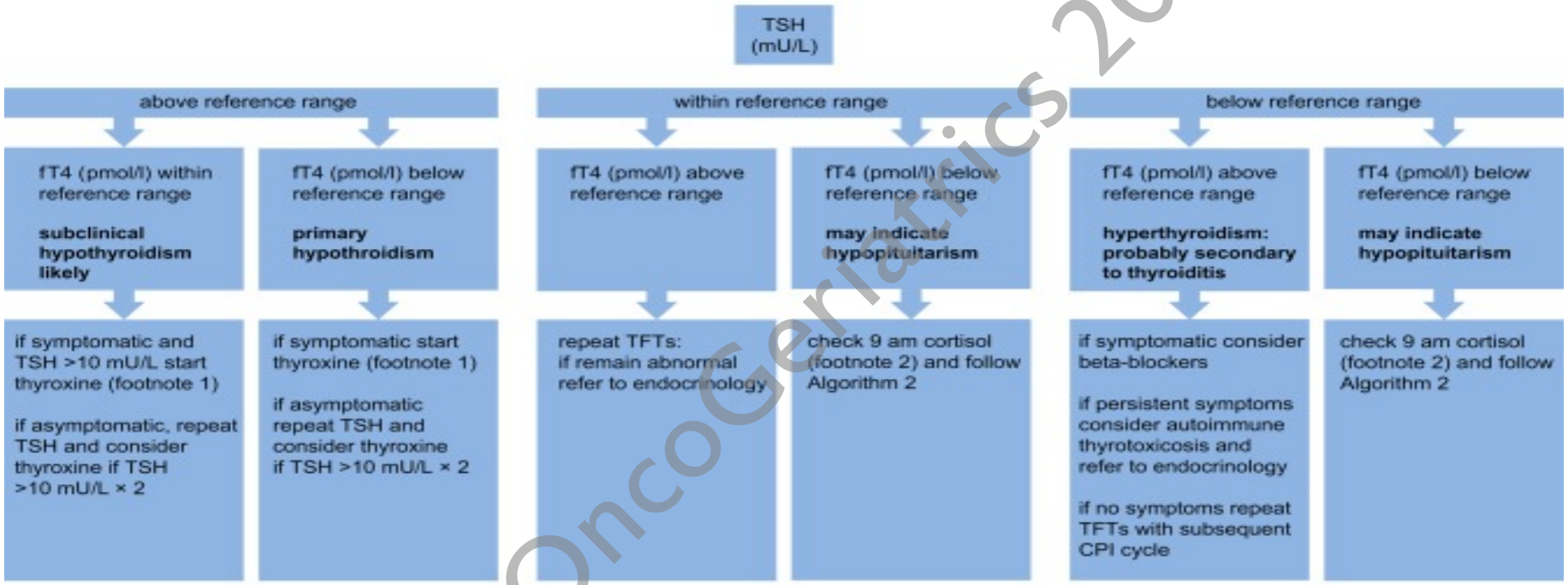


- mainly asymptomatic
- TPO and TSHR Ab variable



Adapted from Pearce EN et al. N Engl J Med 2003;348:2646-2655.

Management of patient with mild/moderate symptoms (CTCAE grade 1–2) compatible with thyroid dysfunction



Footnotes:
Footnote 1 Start levothyroxine 75 mcg od unless history of AF/IHD (start with 25 mcg).
Footnote 2 If hypopituitarism suspected check cortisol and commence hydrocortisone if necessary prior to starting levothyroxine management.

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SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Acute management of the endocrine complications of checkpoint inhibitor therapy.
Higham CE, Olsson-Brown A, Carroll P, Cooksley T, Larkin J, Lorigan P, Morganstein D, Trainer PJ; Society for Endocrinology Clinical Committee. Endocr Connect. 2018 Jul;7(7):G1-G7

Key Points

- Spectrum of endocrinopathy is treatment specific

- Onset can be insidious -low threshold for measurement
  - 9am cortisol and ACTH
  - TSH and fT4 / fT3

- HPA axis insufficiency can be rapidly fatal
  - thyroxine replacement can trigger adrenal crisis
  - all patients on adrenal replacement need
    - sick day rules
    - hydrocortisone emergency pack
    - Endocrinology review

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82 yr old gentleman

referred with

- fatigue
- weight gain and reduced concentration
- loss of libido and erectile dysfunction

9am testosterone 3.5 nmol/l (8.4-31)

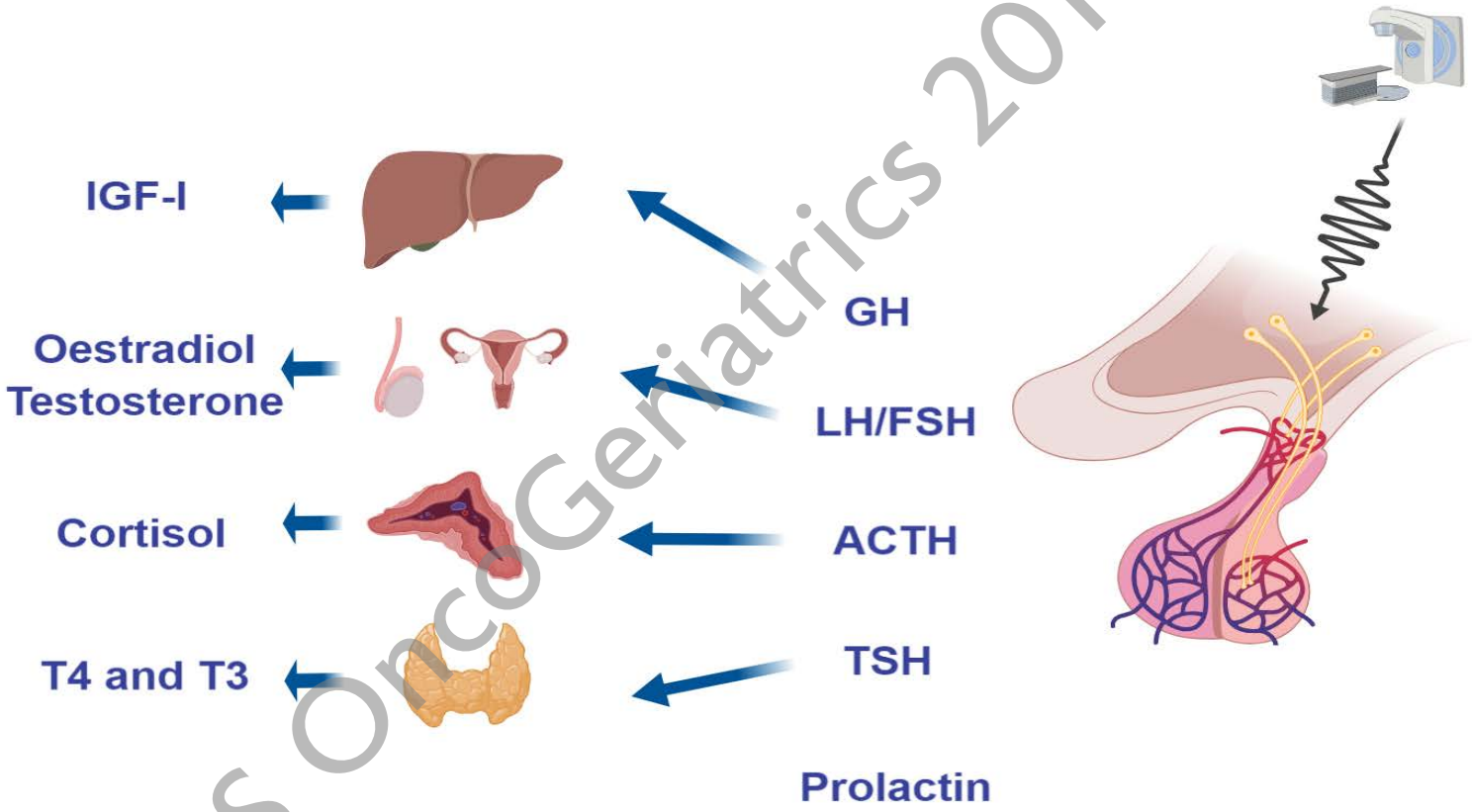
TFTs: fT4 14.5 pmol/l (9-22), TSH 0.06 mU/L (0.55-4.78

on 75mcg of thyroxine

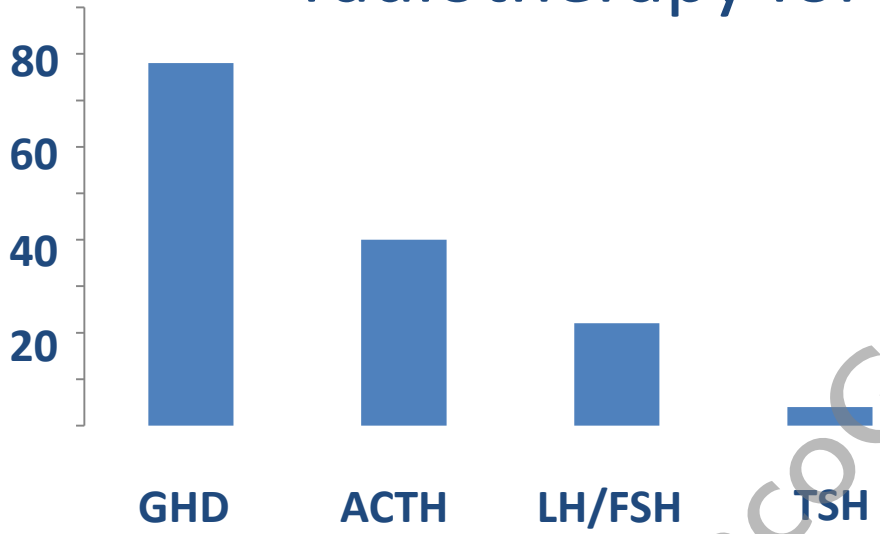
12 years earlier ……

- squamous cell carcinoma of nasopharynx
- 5,742cGy radical radiotherapy

- Lost to follow-up after 5 yrs (tumour free)



Pituitary axis dysfunction following radiotherapy for nasopharyngeal cancer



- dynamic axis testing
- mean radiation dose 66 Gy
- mean of 7 yrs post treatment

Ratnasingam J et al, Pituitary 2014

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Key Points

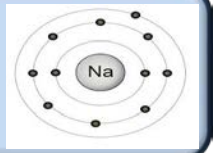
- Radiotherapy dose to adult pituitary gland > 30Gy
  - head and neck/nasopharyngeal cancer
  - brain tumours (childhood and adult)
  - lymphoma/plasmacytoma/sarcoma

- High chance of hypopituitarism up to 20yrs after Rx

- Under - diagnosed and under-screened

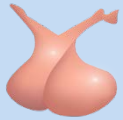
Living With ..... And Beyond

Electrolyte Disorders

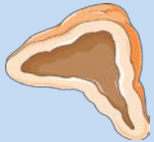


Onco-Endocrinology

Pituitary hormone dysfunction

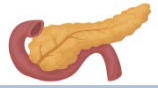


Acute Hormone Dysfunction

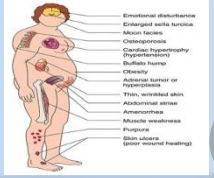


Hypogonadism POF Infertility

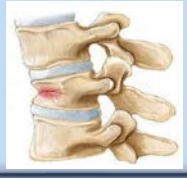
Diabetes



Paraneoplastic Syndrome



Bone Health



Obesity and Metabolic Risk

Cancer

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