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Adrenal Insufficiency: Patient Safety First

Dr Helen Simpson

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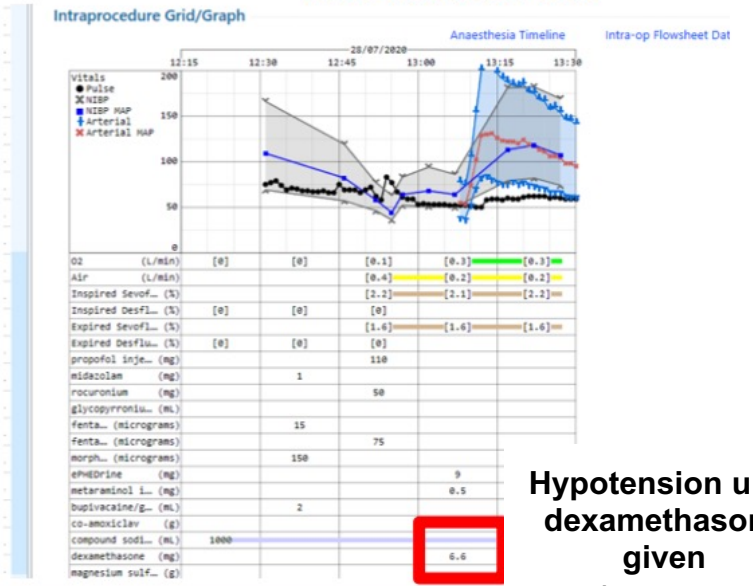
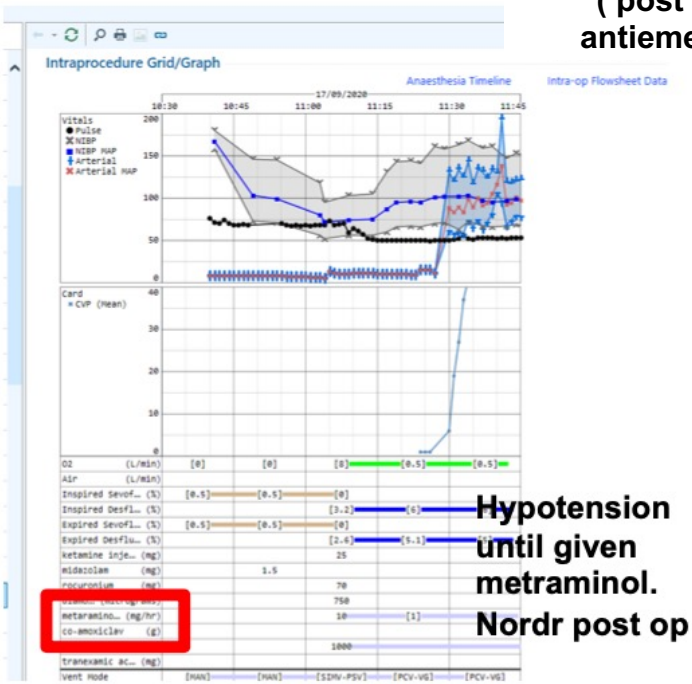
- 76yo lady
- Intra-articular steroids 2-4 times a year
- Last one 12m ago
- High dose inhaled steroids
- Adrenal crises peri-operatively twice
- 1st op dexamethasone as antiemetic and BP came up, not noticed cortisol 21nmol/L



Hypotension until dexamethasone given (post op antiemetic)

- 2nd op BP trace opposite- required noradrenaline infusion
- Cortisol 99nmol/L
- Started hydrocortisone



Hypotension until given metraminol. Nordr post op

- 49yo female
- Seen in Covid follow up clinic: Fatigue and cortisol 20
- Covid April 2020
- Inhaled steroids for ENT issues:
  - Beclomethasone 200mcg daily
  - Mometasone nasal spray 100-200mcg daily
  - Prednisolone 30mg reducing course for 6 days
- Stopped 7/5/21
- HC 5mg bd- stopped after normal SST
- Advice given: at risk of AI again if on higher doses of steroids across any route.

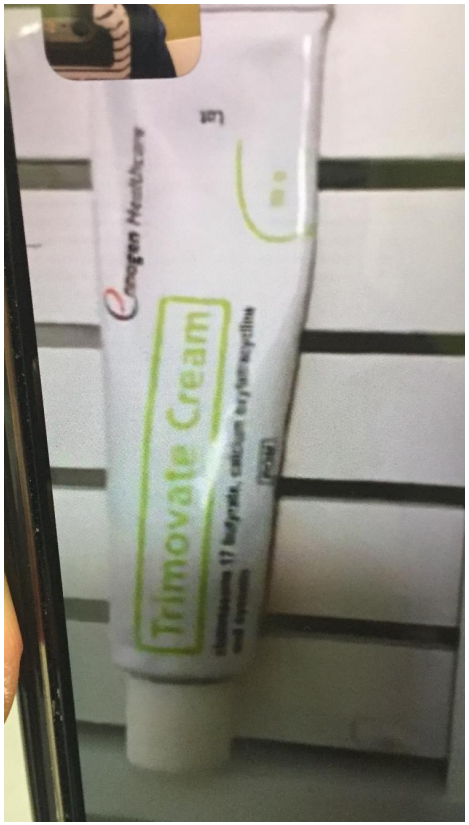
		11/5	12/5	13/5	21/5	21/5
Cortisol	nmol/l	20	57	184	550	635 (SST 30 min)
ACTH	pmol/L			31.6	59.6	

- 26yo
- Sickle cell anaemia
- Weight loss, fatigue

- MST 60mg bd
- Sevredol
- Budesonide/formoterol (SYMBICORT) 100micrograms/6micrograms turbohaler 2 puffs BD

Cortisol	nmol/l	40	46	301	60	11

- 65yo gentleman
- 3cm adrenal nodule, Referred to endocrinology
- Bloods as part of investigations cortisol 29
  - Came to ED
  - Started HC 10/5/5mg
- SPR asked family to look to see what meds were at home



Hypothalamo-pituitary-adrenal axis

Physiological Stress
Vasopressin
Oxytocin
Adrenaline

Sleep

CRH

Proopiomelanocortin

Negative feedback

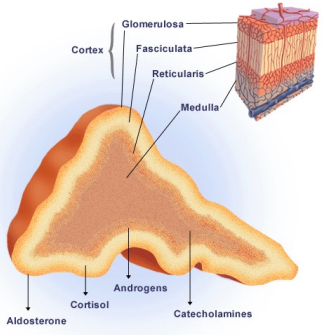
ACTH

αMSH (PAI-pigmentation)

Exogenous steroids

(intact RAAS)

Cortisol



Renin/angiotensin System ➡ **Zona glomerulosa** ➡ **aldosterone**

ACTH ➡ **Zona fasciculata** ➡ **cortisol**

ACTH ➡ **Zona reticularis** ➡ **DHEA/testosterone**

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Hypothalamo-pituitary-adrenal axis

Oral

Inhaled

Intra articular

Topical

IV/IM

Physiological Stress
Vasopressin
Oxytocin
Adrenaline

Sleep

Negative feedback

Exogenous steroids

(intact RAAS)

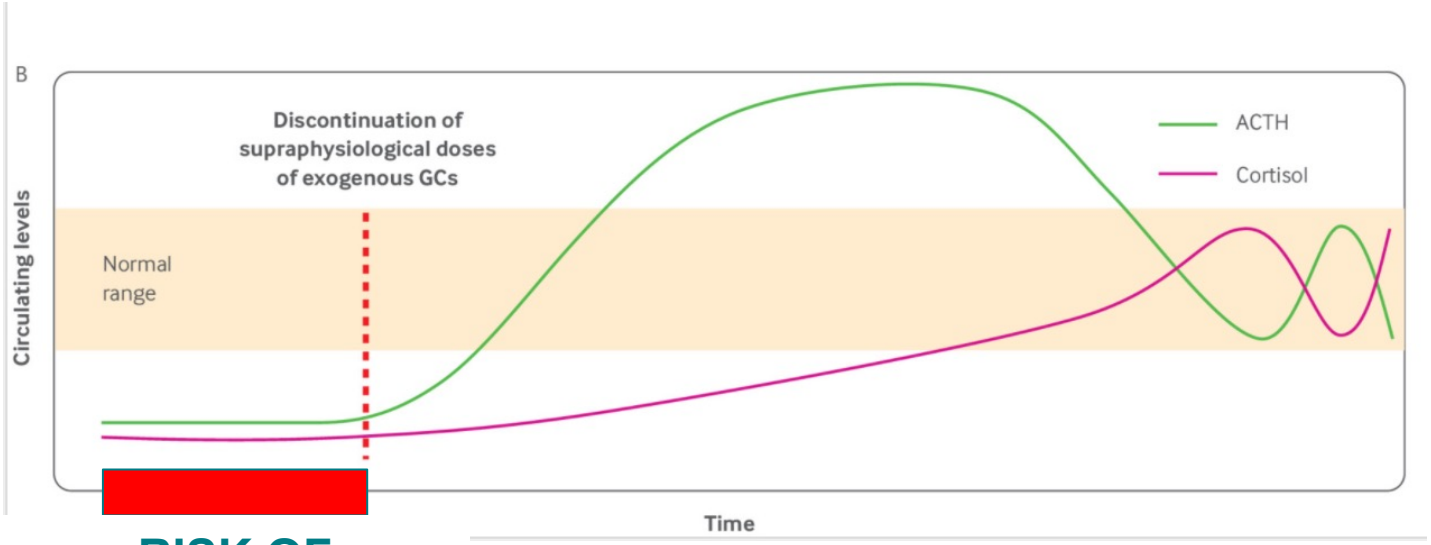
CRH

Proopiomelanocortin

ACTH

αMSH (PAI-pigmentation)

Cortisol



RISK OF ADRENAL CRISIS

Glucocorticoid induced adrenal insufficiency Prete et al 2021 BMJ

Causes of adrenal insufficiency

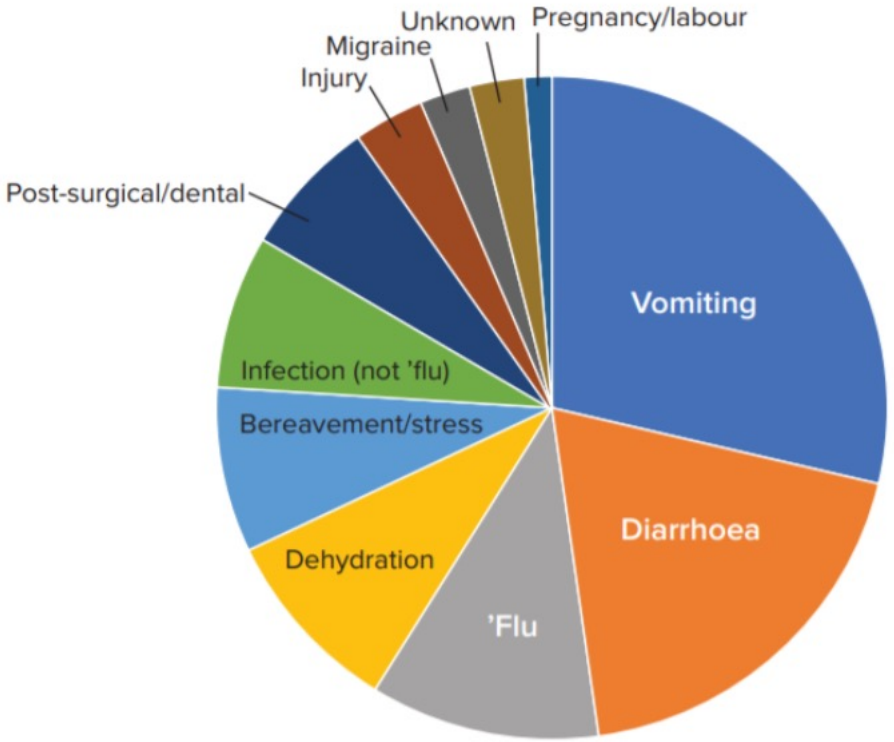
Primary adrenal insufficiency:

- Addison's disease, congenital adrenal hyperplasia, infections,
- bilateral adrenal haemorrhage, adrenal metastases, lymphoma, TB, bilateral adrenalectomy

Secondary/Tertiary Adrenal insufficiency:

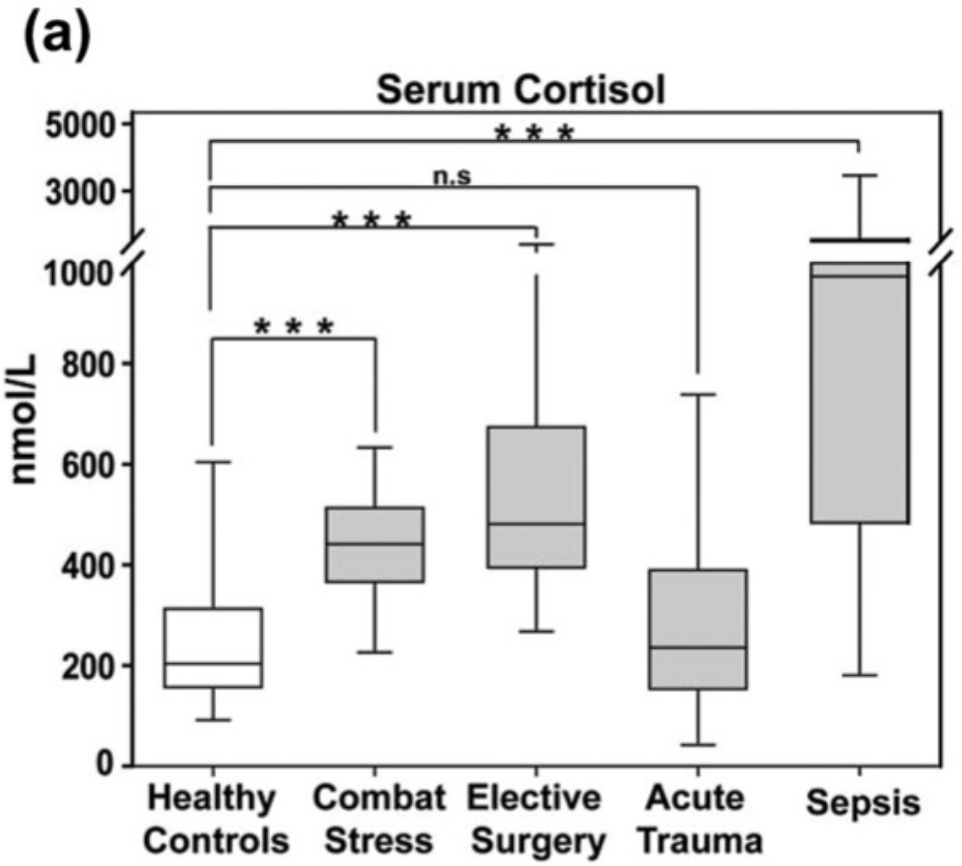
- Pituitary tumours, surgery, irradiation
- Hypothalamic tumours, surgery, irradiation
- Pituitary apoplexy
- Sheehan's syndrome
- Exogenous steroids for any reason, all routes (eg.oral, inhaled, topical, intra-articular)
- Drugs: inhibiting cortisol clearance- anti fungals, antiretrovirals, checkpoint inhibitors, opiates
- Infections/infiltration

Causes of adrenal crisis in PAI



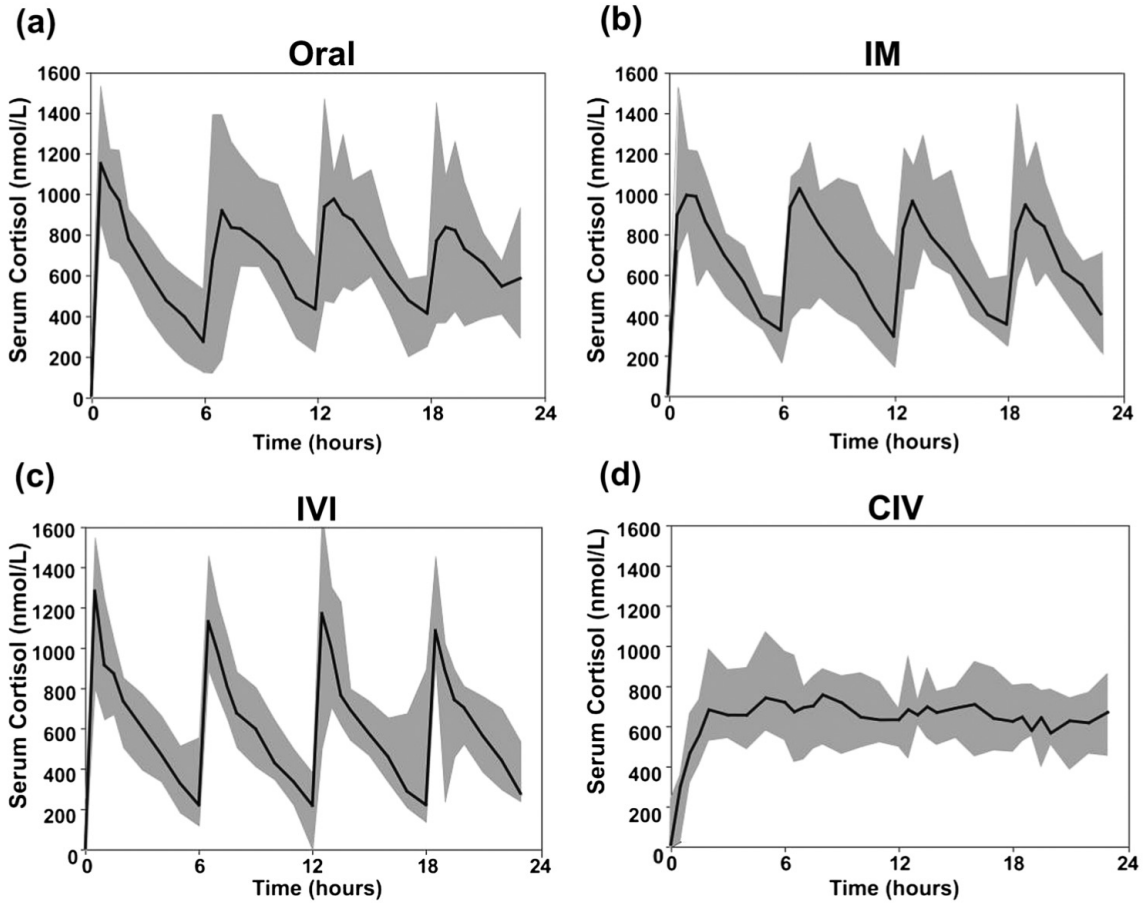
White, Arlt Eur J Endocrinol. 2010

Cortisol levels in Adrenal Crisis



Prete et al JCEM 2020

Hydrocortisone 50mg 6 hourly (PO/IM/IV) vs 200mg/24 hours IV infusion



Prete et al JCEM 2020

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Management of adrenal crisis

100 mg Hydrocortisone per i.v. or i.m. injection, followed by 200mg Hydrocortisone/24h continuous iv infusion in Glucose 5%/24h , or 50mg every 6 hours* i.m. or i.v.
Close monitoring environment

↓

Resuscitation with 500ml fluid bolus of sodium chloride 0.9% over 15 minutes and then replacement of any fluid and/or electrolytes deficits.

↓

Rehydration (3-4 litres of sodium chloride 0.9% solution in 24 hours (initially 1litre/h), drinking ad libitum)

↓

‼ don't delay treatment

‼ Watch for severe hyponatraemia and treat accordingly

Presentation of Addison's Disease

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Simpson et al Clin Medicine 2020

- **Conversion to oral steroids**
  - **When eating and drinking, or recovering**
  - **Hydrocortisone 20mg 6am, 12-1pm, 5-6pm (pred 5mg bd)**
- **Wean to standard replacement dose**
  - **Hydrocortisone 10/5/5mg**
  - **Prednisone 3-5mg/day**

- **Consider fludrocortisone prior to discharge**
- **Refer to endocrinology for further advice on diagnosis, starting regular oral steroids or tapering steroids, education regarding Sick Day Rules**
- **More detailed information can be found at http://www.endocrinology.org/adrenal-crisis**

Sick Day Rule 1
Moderate intercurrent illness:
Fever, infection requiring antibiotics, surgical procedure under local anaesthesia
HC 20mg then 10mg 6 hourly
Prednisolone 5mg 12 hourly

Sick Day Rule 2
Severe intercurrent illness, persistent vomiting (eg GI viral illnesses), during preparation for colonoscopy, acute trauma or surgery

Hydrocortisone 100 mg i.m. or i.v, followed by initiation of a continuous infusion of hydrocortisone 200 mg.24 h-1
Or 50mg every 6 hours* i.m. or i.v.

Conversion to oral steroids
When eating and drinking, or recovered
20mg 6am, 12-1pm, 5-6pm (pred 5mg bd)
Wean to usual dose when recovered

Simpson et al Clin Medicine 2020

Steroid dose increases and Covid-19

- Covid-19 causes a stress response
- Deterioration day 10 (7-14)
- Patient with Addisons Disease have gone into crisis on usual ‘sick day ‘ doses of hydrocortisone
- Higher increases in steroids needed for patients with Covid-19
  - Hydrocortisone 20mg p.o. 6 hrly
  - Prednisolone 10mg p.o. 12 hrly
  - If in hospital and on 200mg/24 hours i.v.infusion or 50mg i.m./i.v. 6hly and can withhold fludrocortisone.

- Fluid balance: lots of insensible losses so may become dry. Ensure plenty of fluid – high sodium and acute kidney injury

Arlt et al EJE 2020

HPA Axis suppression

Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis

Leonie H. A. Broersen, Alberto M. Pereira, Jens Otto L. Jørgensen, and Olaf M. Dekkers

J Clin Endocrinol Metab **100: 2171–2180, 2015**

Conclusions: 1) Adrenal insufficiency after discontinuation of glucocorticoid occurs frequently; 2) there is no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded with certainty, although higher dose and longer use give the highest risk; 3) the threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for those patients with nonspecific symptoms after cessation. (***J Clin Endocrinol Metab*** **100: 2171–2180, 2015)**

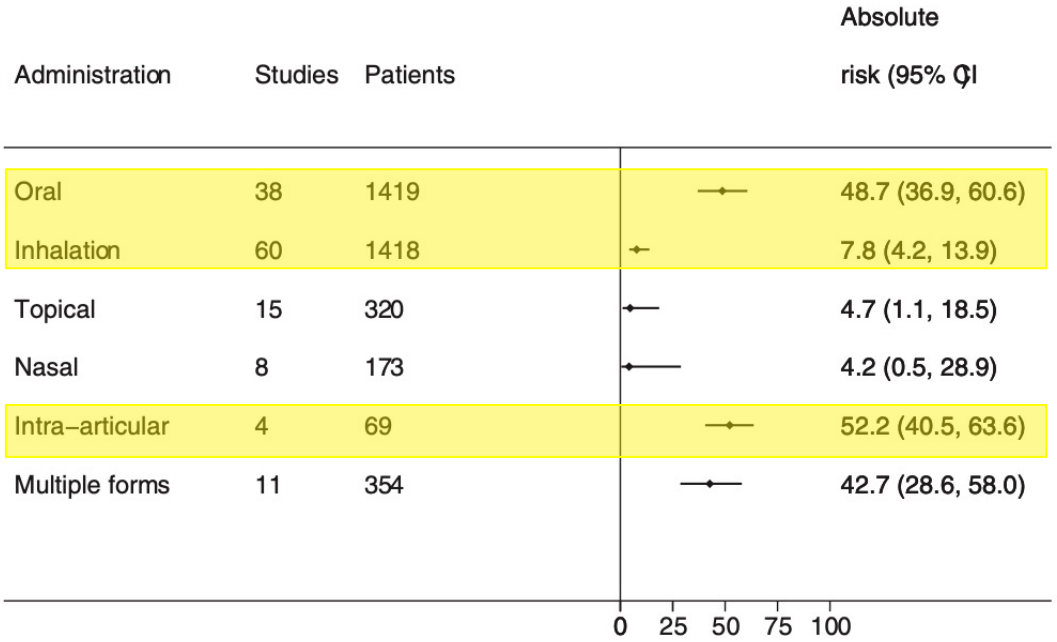


Figure 1. Meta-analysis, adrenal insufficiency after corticosteroids use by administration form.

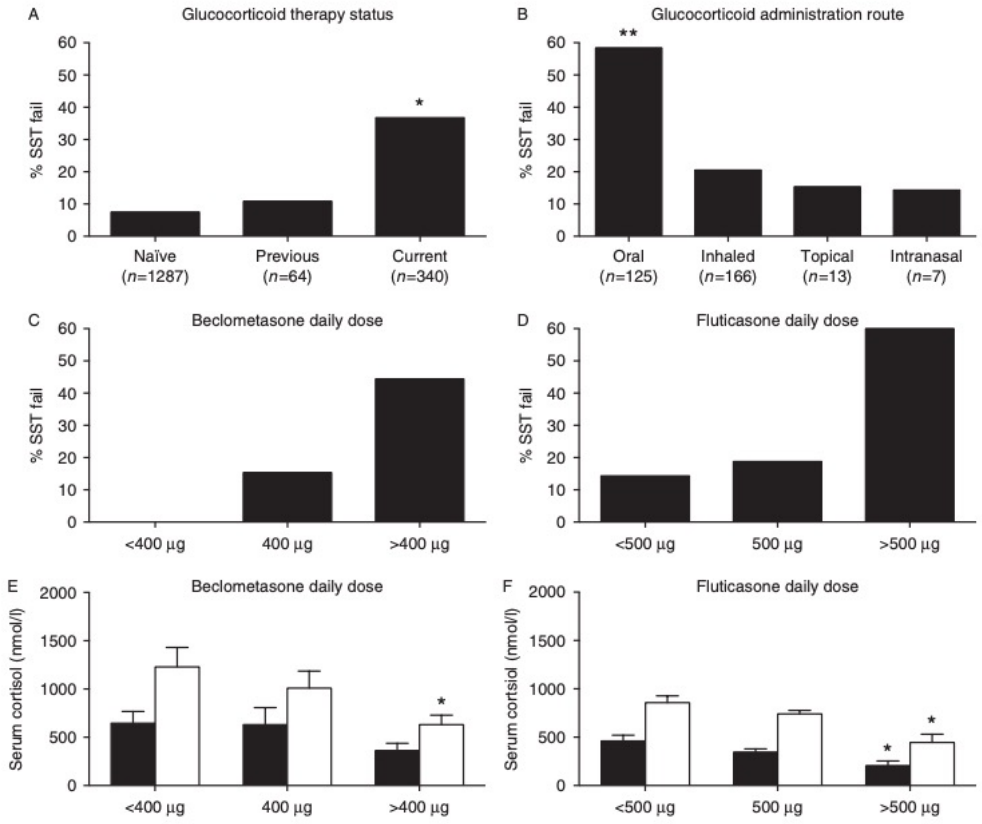
- Asthma
  - Inhaled steroid 11%
  - Oral prednisolone 43-91%
  - On retesting 6m later 25% still had AI
- Intraarticular injections 52%
- Multiple routes 42.7%

Clinical Study
Open Access
C P Woods, N Argese and others
Adrenal reserve and inhaled glucocorticoids
173:5
633–642

Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol

Table 1 The results of SSTs in 2773 patients divided according to indication.

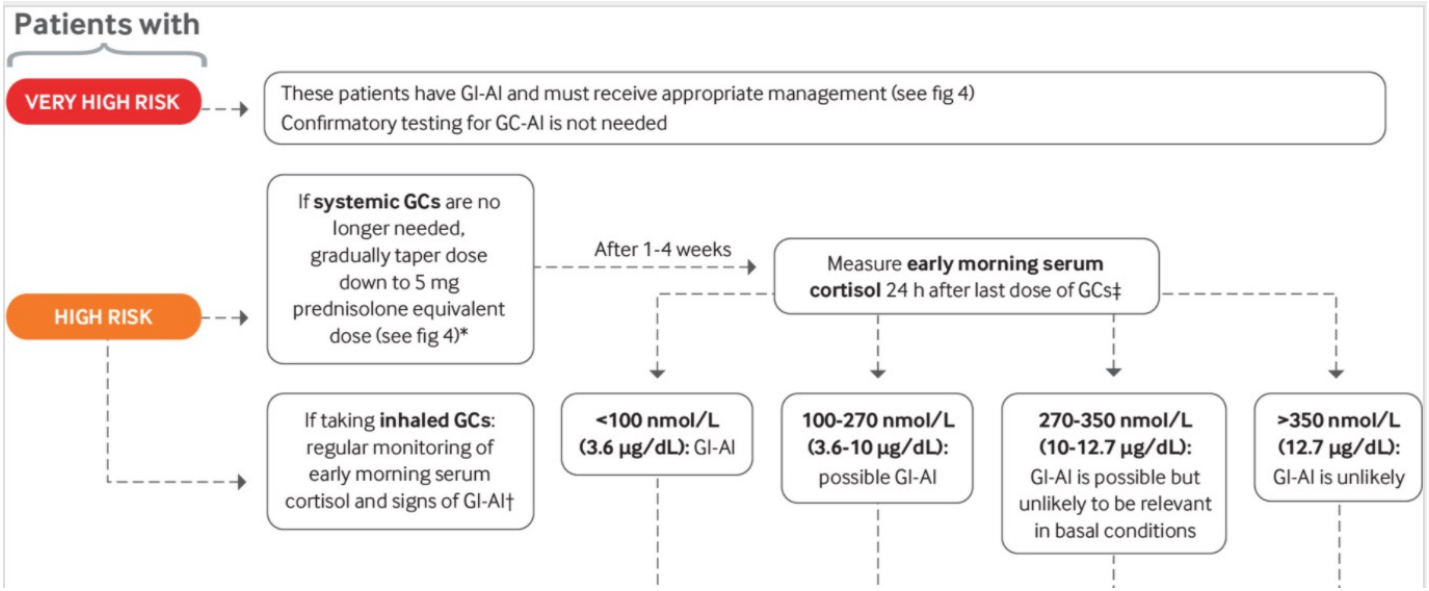
	Description of indication	Total (*n*)	% Pass (*n*)	% Fail (*n*)
1	Treatment with inhaled, intra-nasal or topical glucocorticoids	228	75.4 (172)	24.6 (56)
2	Treatment with oral or i.v. glucocorticoids	176	55.7 (98)	44.3 (78)
3	Post-operative assessment after pituitary surgery (without radiotherapy)	195	70.3 (137)	29.7 (58)
4	Post-operative assessment after pituitary surgery (with radiotherapy)	59	71.2 (42)	28.8 (17)
5	Pituitary adenoma (without surgery or radiotherapy)	264	89.8 (237)	10.2 (27)
6	Other conditions affecting the pituitary	175	77.1 (135)	22.9 (40)
7	Other tumours of the CNS	315	74.9 (236)	25.1 (79)
8	Adrenal disease (CAH, Addison's disease, adenoma, carcinoma)	74	39.2 (29)	60.8 (45)
9	Co-existent autoimmune disease (thyroid disease, type 1 diabetes mellitus, premature ovarian failure, vitiligo)	113	92.0 (104)	8.0 (9)
10	Hyponatraemia or hyperkalaemia	68	91.2 (62)	8.8 (6)
11	Hypoglycaemia	32	100 (32)	0 (0)
12	Hypotension, syncope, collapse	173	96.0 (166)	4.0 (7)
13	Fatigue, weight loss, malaise	178	92.7 (165)	7.3 (13)
14	Other indications, including critical care admission or not specified	723	91.6 (662)	8.4 (61)
		2773	82.1% (2277)	17.9% (496)



All passed SST
9am cortisol
348nmol/l

All failed SST
9am cortisol
<34nmol/L

Suggestion of how to assess for adrenal insufficiency



Glucocorticoid induced adrenal insufficiency Prete et al 2021 BMJ

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Why does this matter?

Frequency of adrenal crisis and death in chronic adrenal insufficiency

- Every 6 -12th patient with adrenal insufficiency will have an adrenal crisis within the next 12 months
- Every 200th patient will die from adrenal crisis within the next 12 months

Allolio EJE 2014

- National Learning Reporting System 2020

  In 2 years there were 4 deaths, 4 patients admitted to ITU and 320 incidents of harm from omission of glucocorticoids

  Pituitary disease
  Transplant patient
  Exogenous steroids

3 pieces of work

- Joint working between Society for Endocrinology, RCP Patient Safety Committee, NHSE/I Patient Safety group
  - National Patient Safety Alert: organisational level
  - Clinical Guidance: health care professional level
  - NHS Steroid Emergency card: patient level

National Patient Safety Alert | Royal College of General Practitioners | Royal College of Physicians | Society for Endocrinology | NHS

Steroid Emergency Card to support early recognition and treatment of adrenal crisis in adults

Date of issue:	13 August 2020	Reference no:	NatPSA/2020/005/NHSPS
This alert is for action by: Acute trusts, private providers/independent treatment centres providing NHS care, ambulance trusts, mental health trusts, community trusts, general practice and community pharmacists.			
This is a safety critical and complex National Patient Safety Alert. Implementation should be co-ordinated by an executive lead (or equivalent role in organisations without executive boards).			

A search of the National Reporting and Learning System (NRLS) for a recent two-year period identified four deaths, four patients admitted to critical care, and around 320 other incidents describing issues with steroid replacement therapy for patients with adrenal insufficiency or emergency treatment for adrenal crisis. While substantial resources[4-7] exist, specialist clinicians and patients have told us that some clinical staff are not aware of the risk of adrenal crisis or the correct clinical response should one occur.

Actions required ⚠

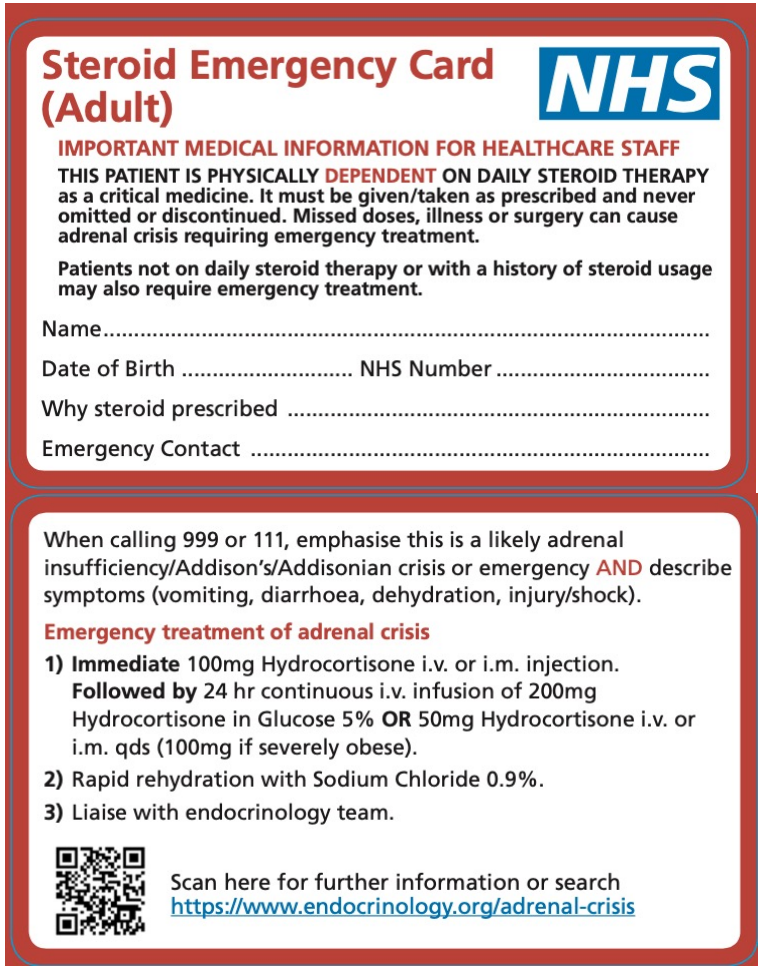
All actions to be completed by 12 months

All organisations where steroid prescriptions are initiated should review their processes/policies/electronic prompts etc to ensure that prescribers issue all eligible patients with a Steroid Emergency Card, as outlined in new guidance[1].
[Action by: 6 months]

As a one-off exercise, prescribers undertaking reviews (e.g. in clinics or when authorising repeat prescriptions) should ensure systems are in place to check that all eligible patients, previously prescribed steroids, are supplied a Steroid Emergency Card.
[Action by: 12 months]

Providers that treat patients with acute physical illness, trauma, or who may require emergency or elective surgical, or other invasive procedures, including day patients, should review their admission/assessment/ examination/clerking documentation to ensure it includes prompts to check for risk of adrenal crisis and to establish if the patient has a Steroid Emergency Card[1,2].
[Action by: 6 months]

Community and hospital pharmacies should ensure they are able to source and supply replacement Steroid Emergency Cards[a,b,c] when required.
[Action by: 12 months]



Steroid Emergency Card (Adult)

NHS

IMPORTANT MEDICAL INFORMATION FOR HEALTHCARE STAFF

THIS PATIENT IS PHYSICALLY DEPENDENT ON DAILY STEROID THERAPY as a critical medicine. It must be given/taken as prescribed and never omitted or discontinued. Missed doses, illness or surgery can cause adrenal crisis requiring emergency treatment.

Patients not on daily steroid therapy or with a history of steroid usage may also require emergency treatment.

Name.....

Date of Birth ..... NHS Number .....

Why steroid prescribed .....

Emergency Contact .....

When calling 999 or 111, emphasise this is a likely adrenal insufficiency/Addison's/Addisonian crisis or emergency AND describe symptoms (vomiting, diarrhoea, dehydration, injury/shock).

Emergency treatment of adrenal crisis

1) **Immediate** 100mg Hydrocortisone i.v. or i.m. injection. **Followed by** 24 hr continuous i.v. infusion of 200mg Hydrocortisone in Glucose 5% **OR** 50mg Hydrocortisone i.v. or i.m. qds (100mg if severely obese).
2) Rapid rehydration with Sodium Chloride 0.9%.
3) Liaise with endocrinology team.

Scan here for further information or search https://www.endocrinology.org/adrenal-crisis

- Royal College of Physicians
- NHSE/I Patient Safety
- Society for Endocrinology
- Royal College of GPs
- Royal Pharmaceutical Society
- Patient Support Groups
- BNF team

- NHS Digital and NHSX
  - Looking to find a way to search who needs a Steroid emergency card in the GP records, and send to patients as a pdf.

- Plan to merge red and blue steroid cards

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Society for Endocrinology 75 YEARS 1946-2021

Scan here for further information or search
https://www.endocrinology.org/adrenal-crisis

Adrenal Crisis Information

Diagnostic measures should never delay treatment and if adrenal crisis is suspected, treatment should be initiated WITHOUT DELAY. Short-term administration of high doses of glucocorticoids is never harmful but failure to treat adrenal crisis can result in the death of the patient.

↓ Management of adrenal crisis summary

- If you suspect established or developing adrenal crisis in a patient
- Published guidance on adrenal insufficiency
- NHS Steroid Emergency card
- BSPED Paediatric Steroid Treatment Card
- Queries about the blue steroid card and London Respiratory Network Card
- Patient Information Sheet
- Steroid Emergency Card Working Group members
- Resources developed to implement the NHS Steroid Emergency Card

↓ Download sick day rules

↓ Download sick day rules figure


Steroid Emergency Card (Adult) NHS
IMPORTANT MEDICAL INFORMATION FOR HEALTHCARE STAFF
THIS PATIENT IS PHYSICALLY DEPENDENT ON DAILY STEROID THERAPY as a critical medicine. It must be given/taken as prescribed and never omitted or discontinued. Missed doses, illness or surgery can cause adrenal crisis requiring emergency treatment.
Patients not on daily steroid therapy or with a history of steroid usage may also require emergency treatment.
Name.....
Date of Birth ..... NHS Number .....
Why steroid prescribed .....
Emergency Contact .....

→ Download NHS Steroid Emergency Card

→ Download Paediatric Steroid Treatment Card

Related Content

- COVID-19 adrenal crisis information
- COVID-19 resources for managing endocrine conditions
- Clinical guidance

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Clinical Medicine 2020 Vol 20, No 4: 371–8 CONCISE GUIDANCE

Guidance for the prevention and emergency management of adult patients with adrenal insufficiency

Authors: Helen Simpson,[A] Jeremy Tomlinson,[B] John Wass,[C] John Dean[D] and Wiebke Arlt[E]

Guidelines

Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency

Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK

T. Woodcock,[1] **P. Barker,**[2] **S. Daniel,**[3] **S. Fletcher,**[4] **J. A. H. Wass,**[5] **J. W. Tomlinson,**[6] **U. Misra,**[7] **M. Dattani,**[8,9] **W. Arlt**[10] and **A. Vercueil**[11]

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Exogenous steroids treatment in adults.

Adrenal insufficiency and adrenal crisis-who is at risk and how should they be managed safely.

David Erskine- Specialist Pharmacy Services (SPS)
Helen Simpson on behalf of Society for Endocrinology Steroid Emergency Card working group

Endorsed by the Society for Endocrinology and the British Association of Dermatologists

Who should be issued with a Steroid Emergency Card?

- **Steroid cover if admitted to hospital unwell**
- **Steroid cover when undergoing a surgical or invasive procedure**

- Patients who have received a long-term course of glucocorticoids at a dose equivalent or higher than prednisolone 5mg
- 3 or more short courses of high-dose oral glucocorticoids within the last 12 months, and for 12 months after stopping
- 3 or more intra-articular/intramuscular glucocorticoid injections within the last 12 months, and for 12 months after stopping
- Inhaled steroids >1000mcg/day beclomethasone or >500mcg/day fluticasone (or equivalent dose of another glucocorticoid), and for 12 months after stopping

- Repeated courses of dexamethasone as an antiemetic in oncology regimens, and for 12 months after stopping (the Steroid Emergency Card should be given on first cycle of dexamethasone) when future cycles are anticipated.

- Prolonged courses of dexamethasone (>10 days) for the treatment of severe Covid-19

- Patients taking inhaled corticosteroids at doses described in Table 4 and any other form of glucocorticoid treatment (incl potent/very potent topical glucocorticoids, intra-articular injection, regular nasal glucocorticoids).

- Topical high-dose (>/= 200g/ week) potent or very potent glucocorticoids used across a large area of skin for 4 weeks or more, or factors increasing absorption assessed on a case by case basis, and for 12 months after stopping.

- Potent or very potent topical glucocorticoids applied to the rectal or genital areas and used at high dose (more than 30g per month) for more than 4 weeks, and for 12 months after stopping

- Patients prescribed any form of ongoing glucocorticoid treatment (except small amounts of a mild or moderate topical glucocorticoid which should be assessed on a case by case basis) in conjunction with medicines known to be potent CYP3A4 inhibitors

Who should be given a Steroid Emergency Card and "sick day rules" advice

- Patients taking oral prednisolone 5mg or above (or equivalent dose of other oral glucocorticoids) for more than 4 weeks, and for 12 months after stopping oral steroids (see Table 1)
- Patients receiving intra-articular or intramuscular glucocorticoid injections who also use glucocorticoids by another route (eg inhaled steroids, oral steroids etc)
- Concomitant use of CYP3A4 enzyme inhibitors (see list below) and glucocorticoids (any route of administration except small amounts of topical mild or moderate potency glucocorticoid which should be assessed on a case by case basis)
- Patients with respiratory disease such as COPD and asthma on high dose inhaled steroids receiving repeated courses of oral steroids (3 or more courses over the past 6 months).

Challenges….

- Advice is pragmatic
- Little firm evidence base to guide us further
- Trying to collect more data
  - Trying to obtain funding for CPRD study
  - Other ways of auditing harm from admissions in patients with asthma

Oral glucocorticoid for more than 4 weeks

Medicine	Dose (*)
Betamethasone	750 microgram per day or more
Deflazacort	6mg per day or more
Dexamethasone	500 microgram per day or more (**)
Hydrocortisone	15mg per day or more (**)
Methylprednisolone	4mg per day or more
Prednisone	5mg per day or more
Prednisolone	5mg per day or more

Short-term oral corticosteroids (1 week course or longer and has been on long-term course within the last year OR has regular need for repeated courses)

MEDICINE	DOSE (*)
Betamethasone	6mg per day or more
Deflazacort	48mg per day or more
Dexamethasone	4mg per day or more (**)
Hydrocortisone	120mg per day or more (**)
Methylprednisolone	32mg per day or more
Prednisone	40mg per day or more
Prednisolone	40mg per day or more

(*) dose equivalent from BNF except (**) where dose reflects that given associated Guidance (Simpson et al 2020) and (***) based on best estimate

Inhaled glucocorticoid doses

Medicine	Dose (*)
Beclometasone (as non-proprietary, Clenil, Easihaler, or Soprobec)	1000 microgram per day or more
Beclometasone (as Qvar, Kelhale or Fostair)	500 microgram per day or more (check if using combination inhaler and MART regimen)
Budesonide	1000 microgram per day or more (check if using combination inhaler and MART regimen)
Ciclesonide	480 microgram per day or higher (**)
Fluticasone	500 microgram per day or more
Mometasone	800 microgram per day or more

(*) dose equivalent from NICE Inhaled corticosteroid doses for NICE's asthma guideline (2018)

Enzyme inducers: Patients prescribed any form of ongoing corticosteroid treatment at any dose and these drugs:

- **Potent Protease inhibitors:**
- Atazanavir
- Darunavir
- Fosamprenavir
- Ritonavir (+/- lopinavir)
- Saquinavir
- Tipranavir

- **Antifungals:**
- Itraconazole
- Ketoconazole
- Voriconazole
- Posaconazole
-
- **Antibiotics:**
- Clarithromycin—long term courses only

Patient information

- https://www.endocrinology.org/adrenal-crisis

Sheffield Respiratory information:

- https://publicdocuments.sth.nhs.uk/pil4794.pdf
- https://publicdocuments.sth.nhs.uk/pil4795.pdf

Addison's Disease Self Help Group:

- https://www.addisonsdisease.org.uk/newly-diagnosed-sick-day-rules
- https://www.addisonsdisease.org.uk/news/new-nhs-steroid-card-released

Pituitary Foundation:

- https://pituitary.org.uk/information/publications/essential-free-publications/hydrocortisone-sick-day-rules/
- https://pituitary.org.uk/information/publications/essential-free-publications/keeping-safe-with-adrenal-insufficiency/

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- Yasser Elhassan
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