Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Palliative Care, Steroids and Diabetes

Is there a problem?

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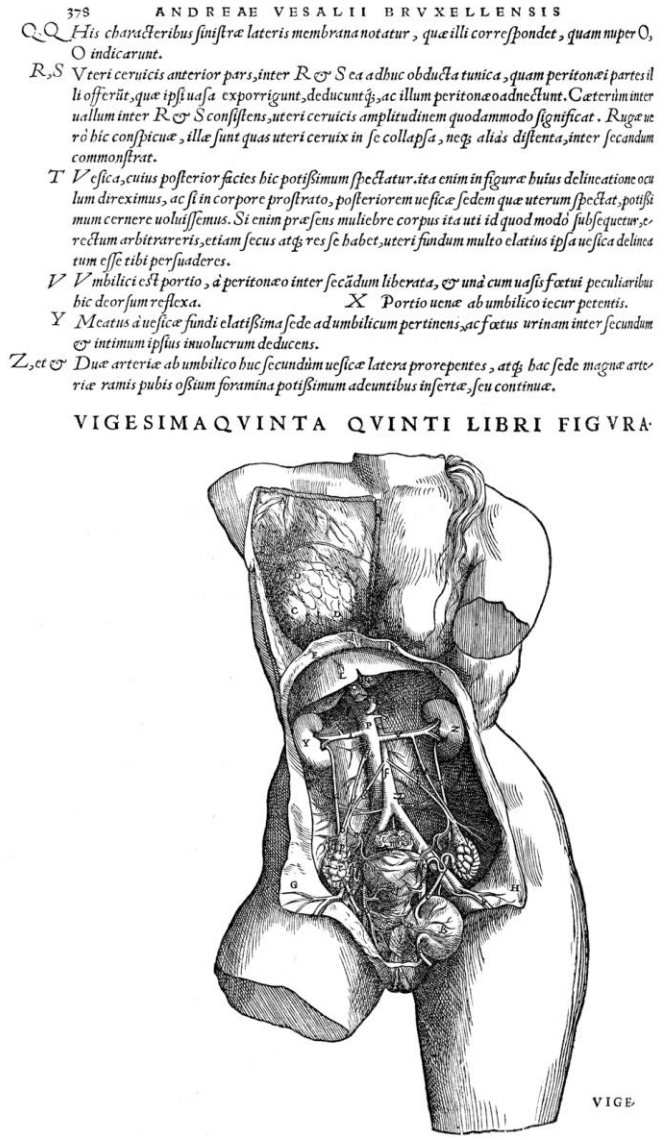
Outline

- Steroid induced hyperglycaemia
- Osteoporosis
- Weaning

Glucocorticoids and Diabetes

- Is it a problem?
- How to control hyperglycaemia associated with glucocorticoid use?


378 ANDREAE VESALII BRVXELLENSIS

Q,Q His characteribus ſiniſtræ lateris membrana notatur, quæ illi correſpondet, quam nuper O, O indicarunt.

R,S Vteri ceruicis anterior pars, inter R & S ea adhuc obducta tunica, quam peritonæi partes illi offerũt, quæ ipſi uaſa exporrigunt, deducuntq́, ac illum peritonæo adnectunt. Cæterùm inter uallum inter R & S conſiſtens, uteri ceruicis amplitudinem quodammodo ſignificat. Rugæ uerò hic conſpicuæ, illæ ſunt quas uteri ceruix in ſe collapſa, neq́ aliàs diſtenta, inter ſecandum commonſtrat.

T Veſica, cuius poſterior facies hic potiſſimum ſpectatur. ita enim in figuræ huius delineatione oculum direximus, ac ſi in corpore proſtrato, poſteriorem ueſicæ ſedem quæ uterum ſpectat, potiſſimum cernere uoluiſſemus. Si enim præſens muliebre corpus ita uti id quod modò ſubſequetur, erectum arbitrareris, etiam ſecus atq́ res ſe habet, uteri fundum multo elatius ipſa ueſica delineatum eſſe tibi perſuaderes.

V Vmbilici eſt portio, à peritonæo inter ſecãdum liberata, & unà cum uaſis fœtui peculiaribus hic deorſum reflexa.

X Portio uenæ ab umbilico iecur petentis.

Y Meatus à ueſicæ fundi elatiſſima ſede ad umbilicum pertinens, ac fœtus urinam inter ſecundum & intimum ipſius inuolucrum deducens.

Z, et & Duæ arteriæ ab umbilico huc ſecundùm ueſicæ latera prorepentes, atq́ hac ſede magnæ arteriæ ramis pubis oſſium foramina potiſſimum adeuntibus inſertæ, ſeu continuæ.

VIGESIMA QVINTA QVINTI LIBRI FIGVRA

VIGE

A Bit Of Background

- At any one time, ~0.75% of the UK population is on oral glucocorticoids (0.2% in 20-29 year olds, 2.5% in 70-79 year olds)
- 40% of glucocorticoid use is for respiratory disease, with most of the rest being musculoskeletal and cutaneous diseases and conditions requiring immunosuppression
- Most use is for <5 days, but 22% is for > 6 months and 4.3% for > 5 years

Royal College of Physicians Glucocorticoid guidelines 2002 www.nos.org.uk/NetCommunity/Document.Doc?id=422
Fardet L et al Rheumatology 2011;50(11):1982-1990

NNUH Prevalence Data (January 2014)

- All adult wards (excluding A+E, CCU, ITU/HDU)
- 120 out of 940 (12.8%) patients were receiving glucocorticoids – of whom 16 had pre-existing diabetes
- Only 25 (13 with diabetes) had their BG checked regularly
- 3 people with diabetes on glucocorticoids had no BG checked
- 95 patients had no evidence of BG checking

Swafe L et al Clinical Medicine 2014;14(3):327-328

NNUH Prevalence Data (January 2014)

- 99 patients were on prednisolone
  - Mean daily dose 25mg ± 12.5 (range 0.5-60)
- 16 patients were on dexamthasone
  - Mean daily dose 9.2mg ± 6.5 (range 0.5-20)
- 4 patients on hydrocortisone
  - Mean daily dose 107.5mg ± 106.9 (range 20-200)

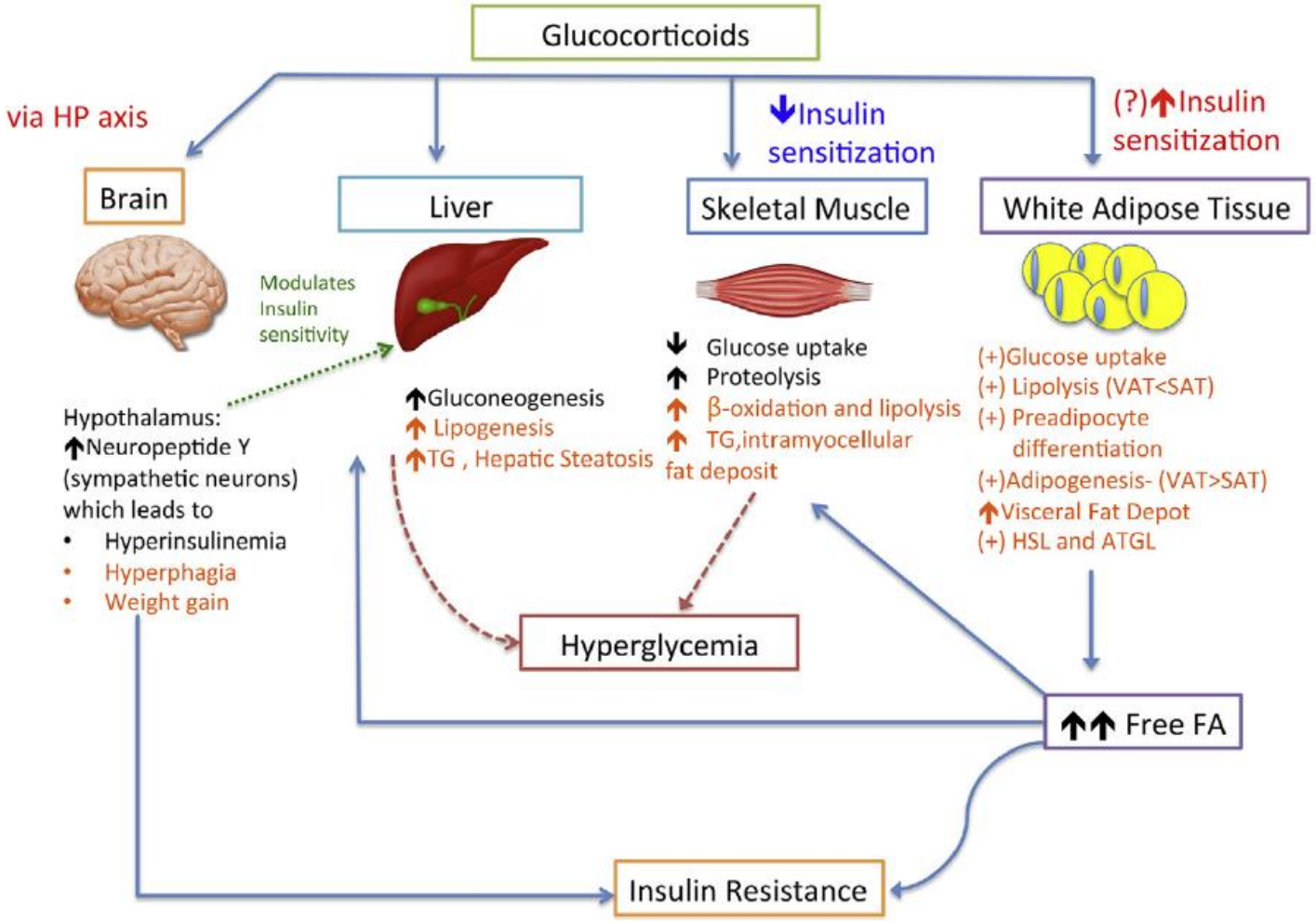
Swafe L et al Clinical Medicine 2014;14(3):327-328

Indications

Variable	Category	Number (%)
Age (years)		74.4 ± 14.3
Gender (M:F)		52:68 (43.3:56.7)
Previously diagnosis of diabetes (Yes:No)		16:104 (13.3:86.7)
Steroid type	Prednisolone	99 (82.5)
	Dexamethasone	16 (13.3)
	Hydrocortisone	4 (3.3)
Indications for steroids	Respiratory	76 (63.3)
	Musculoskeletal	14 (11.7)
	Vasculitis	7 (5.8)
	Oncology	12 (10)
	Other	11 (9.2)
Duration of course	>10 days	64 (53.3)
	<10 days	56 (46.7)
Glucose monitoring	None	95 (79.2)
	Monitored	25 (20.8)

Swafe L et al Clinical Medicine 2014;14(3):327-328

How do Glucocorticoids Affect Carbohydrate Metabolism?



Geer EB et al Endocrinol Metab Clin North Am 2014;43(1):75-102

Recognise These Regimens?

- Lenalidomide, CTD and bortezomib which use prednisolone 10-40mg for 4-8 days every 21 day cycle for myeloma
- R-CHOP for Non-Hodgkins Lymphoma (prednisolone 100mg od for 5 days)
- Docetaxel for breast cancer (dexamethasone 8mg bd for 3 days starting day before chemotherapy to prevent infusion reactions)

Recognise These Regimens?

- Docetaxel in prostate cancer (as above plus prednisolone 5mg bd continuously through treatment – up to 30 weeks)
- Paclitaxel in breast and gynaecological cancers – most commonly ovarian (dexamethasone 20mg stat IV as pre-med to prevent infusion reactions)

Spectrum of Disease

- The hyperglycaemia may be a transient rise of blood glucose levels or may result in HHS
- The best predictors of glucocorticoid-induced diabetes are family history of diabetes, increasing age, and glucocorticoid dose

Clement S Diabetes Care 2004;27(2):553-591

Now We Know the Cause, What's the Treatment?

- Education and pre-empting the (almost) inevitable
- Letting teams know that when someone starts glucocorticoid treatment that blood glucose levels are very likely to rise and to watch for it
- When it happens, treat early

This meets with quite a lot of resistance – so be prepared!

Sulphonylureas

- Little published evidence but widely used
- We asked for examples of guidelines used at different hospitals – and we got lots!
- All variations around a theme with some minor differences
- Most often used first line

The Best Treatment?

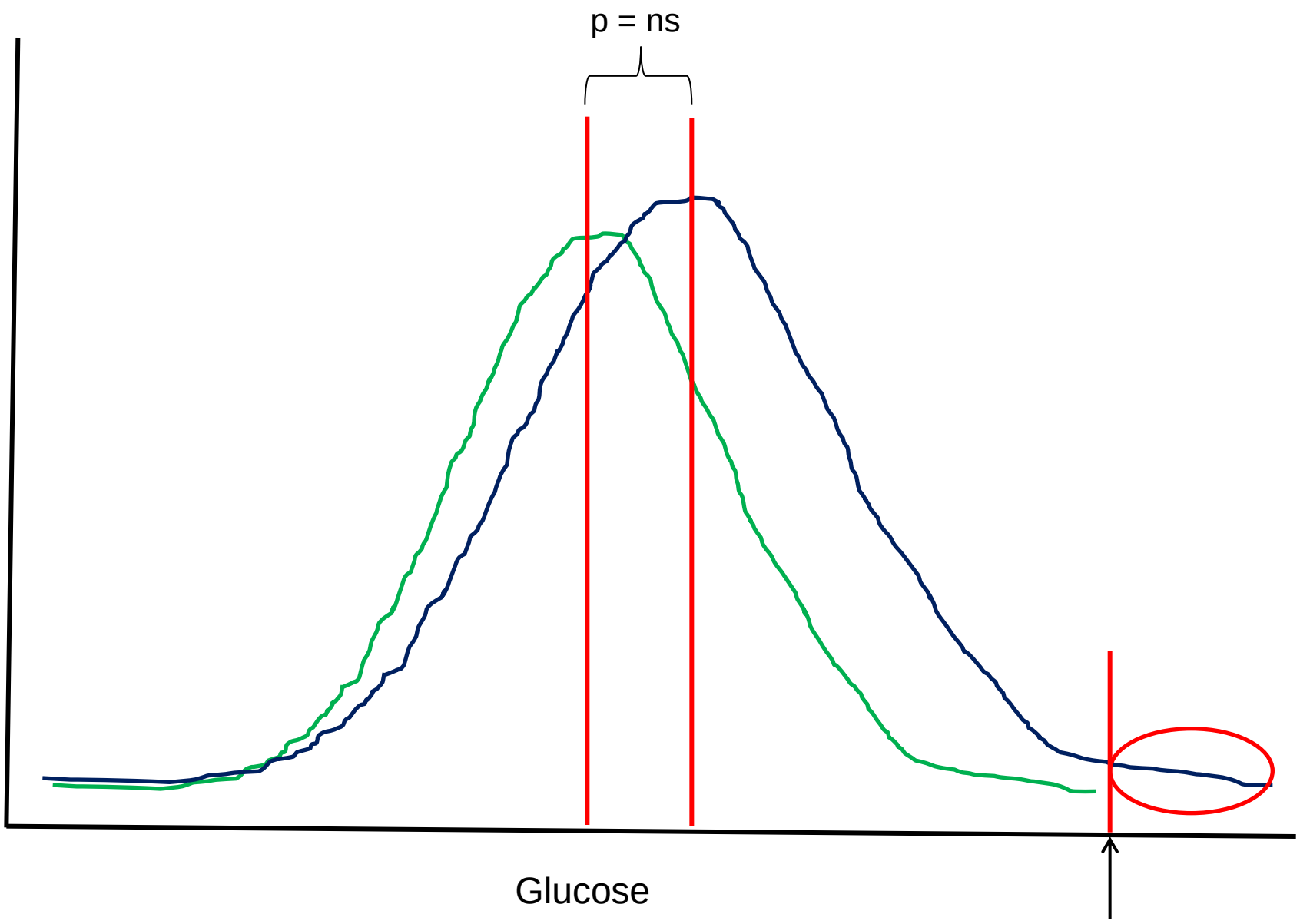
- Insulin is recommended in the US as the drug of choice for the treatment of glucocorticoid-induced hyperglycaemia
- Theoretically, prandial insulin should minimise the effects of the postprandial rise in glucose
- For patients receiving high-dose intravenous glucocorticoids, an intravenous insulin infusion may be appropriate

Hirsch IB et al Endocr Metab Clin North Am 1997;26:631–645
Archer JR et al BMJ Open 2011 DOI: 10.1136/bmjopen-2011-000210

Where's the Evidence?

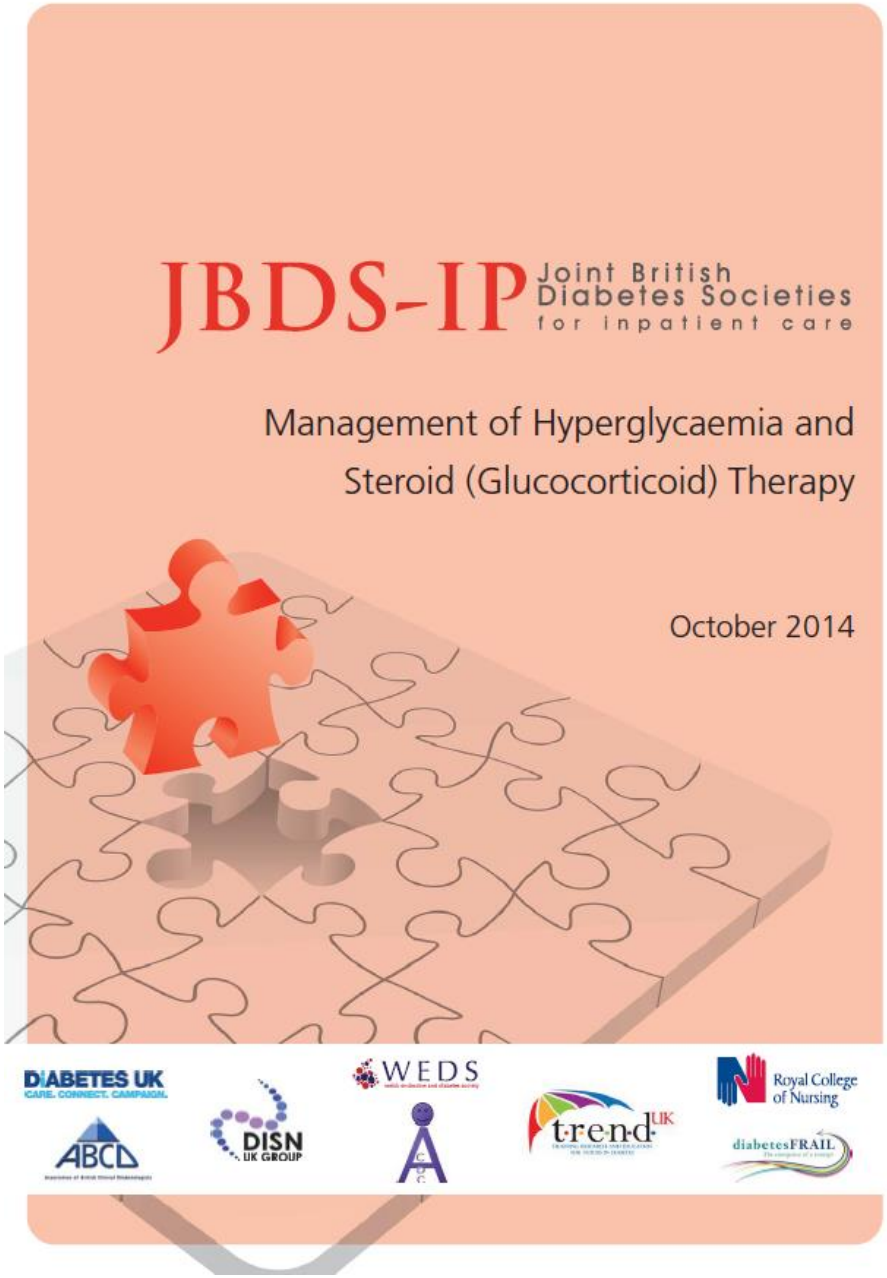
- Naturally, there isn't any
- But there is evidence that hyperglycaemia in a hospital setting (for any cause) is associated with poor mortality, morbidity, and health economic outcomes
- Improving glycaemic control improves these outcomes

Umpierrez GE et al J Clin Endocrinol Metab 2002; 87:978–982
Bruno A et al Diabetes Care 2008;31(11):2209-2210
Dhatariya K BMJ 2013;346:f134


p = ns
Glucose
Diabetes / hyperglycaemia

What Should the Targets Be?

- Targets similar to those of outpatients are unrealistic in hospital due to the effects of
  - Stress hyperglycaemia
  - Altered nutritional intake
  - Multiple interruptions to medical care
- Aiming for a range of 6.0 – 10.0 mmol/L with an acceptable range of 4.0 – 12.0 mmol/L if they can be safely achieved
- For end of life care, a range of 6.0 – 15.0 mmol/L is acceptable



http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf

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Steroid (glucocorticoid) Induced Diabetes

NO KNOWN DIABETES

- Check HbA1c prior to the commencement of steroids in patients perceived to be at high risk
- On commencement of steroid, recommend CBG once daily pre or post lunch or evening meal, in those at "high risk" or with symptoms suggestive of "hyperglycaemia"
- If the capillary blood glucose (CBG) is below 12mmol/L consider the patient to be at low risk and record the CBG daily post breakfast or post lunch
- If CBG consistently <10mmol/L consider cessation of CBG testing
- If a capillary blood glucose is found to be greater than 12mmol/L the frequency of testing should be increased to four (4x) times a day
- If a capillary blood glucose is found to be consistently greater than 12mmol/L (i.e. on 2 occasions during a 24hr period), then the patient should enter the treatment algorithm below

CBG readings above desired target (6 - 10mmol/L - acceptable range 4 - 12mmol/L)

- Add in gliclazide 40mg with breakfast and increase the dose by 40mg increments daily if targets are not reached

If no symptoms of hypoglycaemia are experienced by the patient despite being on 160mg of gliclazide in the morning, consider titration to 240mg in the morning. (You may wish to seek specialist advice on dose titration at this stage)

If still no improvement on maximum dosage consider

- Adding an evening dose of gliclazide or add morning human NPH insulin e.g. Humulin I / Insulatard / Insuman Basal
- For NPH - commence 10 units daily in the morning and titrate every 24 hours by 10-20% to achieve desired CBG target

Discharge - Monitoring will need to be continued in patients remaining on glucocorticoids post discharge

- If steroid treatment is ceased in hospital and hyperglycaemia has resolved CBG can be discontinued post discharge
- If steroids are discontinued prior to discharge and hyperglycaemia persists then continue with monitoring until normal glycaemia returns or until a definitive test for diabetes is undertaken (fasting blood glucose, OGTT or HbA1c)

If steroids are reduced or discontinued:

- Continue CBG testing if CBG >12mmol/L in 24 hours
- Any changes made should be reviewed and consideration given to reverting to previous therapy or doses

If unsure at any stage about next steps or want specific advice on how to meet with patients needs or expectations please discuss with the team who usually looks after their diabetes (GP/Specialist Team).

Glycaemic targets:

- **Aim for 6 - 10mmol/L (acceptable range 4 - 12mmol/L)**
- **End of life care: Aim for 6 - 15mmol/L and symptom relief**

Managing Glucose Control in People with Known Diabetes On Once Daily Steroids (glucocorticoids)

KNOWN DIABETES, reassess glucose control and current therapy

- Set target blood glucose e.g. 6-10mmol/L (see glycaemic targets box below)
- Check capillary blood glucose (CBG) 4 times a day and use this flowchart to adjust diabetes medication accordingly
- In Type 1 diabetes also check daily for ketones if CBG> 12mmol/L

Type 2 diet control
OHA +/- GLP1

If no 'hypo' symptoms and NOT on an SU:

- Commence gliclazide 40mg a.m., titrate daily until a maximum dose of 240mg a.m. or glycaemic targets are reached
- Seek specialist advice if you are concerned about dose titration in those taking 160mg with no improvement in glycaemic control
- If on twice daily gliclazide and targets not reached consider referral to specialist care for titration to 240mg morning dose plus 80mg p.m.

If no 'hypo' symptoms and taking maximum dose (320mg/day)

- Add Insuman Basal, Humulin I or Human Insulatard
- Aim for CBG appropriate to patients' needs

If CBG remains above desired target before the evening meal

- Increase insulin by 4 units or 10 - 20%
- Review daily
- If remains above target titrate daily by 10 - 20% until glycaemic target reached

Insulin controlled (Type 1 and Type 2). In Type 1 diabetes always test for ketones, if blood ketones more than 3mmol/L or urinary ketones >++ assess for DKA
In Type 2 diabetes check for ketones if CBG levels >12mmol/L and the patient has osmotic symptoms

Once daily night time insulin, transfer this injection to the morning:

- Titrate by 10 - 20% daily according to pre-evening meal CBG readings
- If targets not achieved consider BD, or basal bolus regimen

Twice daily insulin:

- Morning dose will need to increase 10 - 20% daily according to pre-evening meal CBG readings
- Aim for CBGs to individual needs as stated above, unless patient experiences 'hypo' despite snacks

Basal bolus insulin:

- Consider transferring evening basal dose insulin to the morning and increase short/fast acting insulin by 10 - 20% daily until glycaemic target reached
- Aim for agreed CBGs target to patients needs pre-meal, unless patient has hypo despite snacks or has long gaps between meals

If steroids are reduced or discontinued:

- Blood glucose monitoring may need to be continued in inpatients and, in discharged patients assessed by their GP
- Any changes made should be reviewed and consideration given to reverting to previous therapy or doses

If unsure at any stage about next steps or want specific advice on how to meet with patients needs or expectations please discuss with the team who usually looks after their diabetes (GP/Specialist Team).

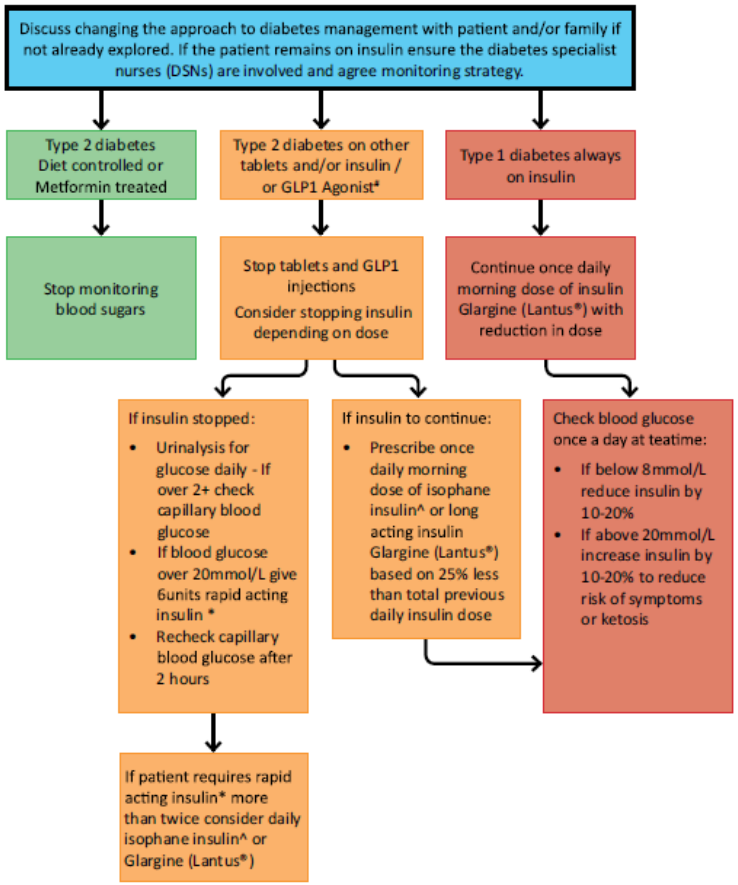
Glycaemic targets:

- **Aim for 6 - 10mmol/L (acceptable range 4 - 12mmol/L)**
- **End of life care: Aim for 6 - 15mmol/L and symptom relief**

[Version 2.0] 25/09/2014

Algorithm to show End of life Steroid Management

End of Life Diabetes Management



Key

* Bydureon (Exenatide ER), Byetta (Exenatide) / Victoza, (Liraglutide), Lyxumia (Lixisenatide)

* Humalog/Novorapid/Apidra
^ Humulin I /Insulatard/ Insuman Basal

- Keep tests to a minimum. It may be necessary to perform some tests to ensure unpleasant symptoms do not occur due to low or high blood glucose
- It is difficult to identify symptoms due to "hypo" or hyperglycaemia in a dying patient
- If symptoms are observed it could be due to abnormal blood glucose levels
- Test urine or blood for glucose if the patient is symptomatic
- Observe for symptoms in previously insulin treated patient where insulin has been discontinued

For queries relating to the diabetes flowchart please contact the Diabetes Specialist Nurses
For queries relating to palliative care please contact the Palliative Care Team

http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf

Steroid Induced Osteoporosis

Burden of Disease

- Up to 50% of women and 30% of men with osteoporosis have a secondary cause
- Glucocorticoids account for up to 25% of all cases of osteoporosis in the UK

Scane AC et al Osteoporosis Int 1999;9:91-97
Baillie SP et al Age Ageing 1992;21:139-141
Caplan GA et al JRSM 1994;87:200-202
Eastell R et a J Int Med 1998;244:271-292

At What Dose Does This Occur?

- The standard answer is at doses of greater than 7.5 mg of prednisolone per day
- Chronic use at this dose is associated with an increased fracture risk, but most bone (up to 30% of total) is lost within 6 months of starting treatment – so treat early!
- The cumulative dose is also important

Don’t Forget…

- Established risk factors for non-glucocorticoid related fractures
  - Age
  - Sex
  - Caucasian race
  - History of prior fracture
  - Recurrent falls
  - Family history
  - Poor health status

Table 1. Risk Factors for Glucocorticoid-Induced Osteoporosis.*

Risk Factor	Evidence of a Contribution
Advanced age	Patients 60 to 80 years of age receiving glucocorticoid therapy, as compared with patients 18 to 31 years of age, had a relative risk of vertebral fracture of 26 and a shorter interval between initiation of treatment and the occurrence of fracture[8]
Low body-mass index (<24)†	Low body-mass index is a risk factor for glucocorticoid-induced osteoporosis and probably fractures as well[9]
Underlying disease	Rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, chronic pulmonary disease, and transplantation are independent risk factors[4]
Prevalent fractures, smoking, excessive alcohol consumption, frequent falls, family history of hip fracture	All are independent risk factors for osteoporosis but have not been extensively studied in patients receiving glucocorticoids
Glucocorticoid receptor genotype	Individual glucocorticoid sensitivity may be regulated by polymorphisms in the glucocorticoid receptor gene[10]
Increased 11β-HSD1 expression	11β-HSD1 expression increases with the age of the patient and with glucocorticoid administration[11]
High glucocorticoid dose (high current or cumulative dose; long duration of therapy)	Risk of fracture escalates with increased doses and duration of therapy; alternate-day or inhaled therapies also confer risks of glucocorticoid-induced osteoporosis[4,12]
Low bone mineral density	Glucocorticoid-induced fractures occur independently of a decline in bone mass, but patients with very low bone mineral density may be at higher risk[4,8]

Weinstein RS NEJM 2011;365(1):62-70

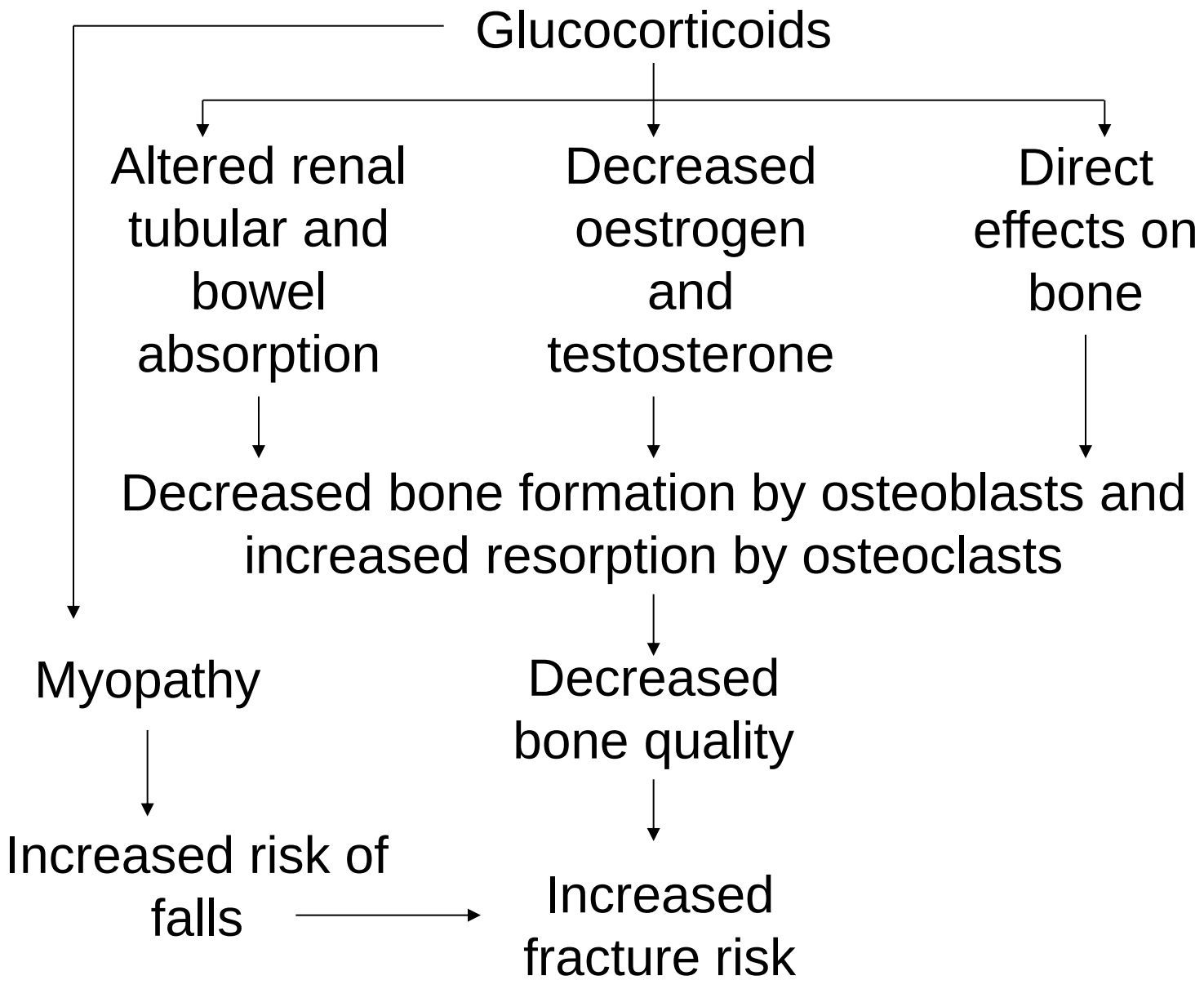

Glucocorticoids
Altered renal tubular and bowel absorption
Decreased oestrogen and testosterone
Direct effects on bone
Decreased bone formation by osteoblasts and increased resorption by osteoclasts
Myopathy
Decreased bone quality
Increased risk of falls
Increased fracture risk

Table 3. Guidelines for Management of Glucocorticoid-Induced Osteoporosis.*

Variable	American College of Rheumatology[24]	National Osteoporosis Foundation[25]	Royal College of Physicians of London[26]	Belgian Bone Club[27]
Dose and duration of glucocorticoid treatment warranting pharmacologic intervention†	≥7.5 mg/day for at least 3 months, but patients at increased risk require treatment with any dose or duration	≥5 mg/day for at least 3 months	Any oral dose for at least 3 months in patients ≥65 years of age and those with a prior fragility fracture	≥9.3 mg/day for at least 3 months
BMD threshold for treatment if dose and duration qualify	Threshold to be based on the FRAX algorithm in addition to "higher daily and cumulative dose, intravenous usage, and declining BMD"	T score, −2.5, unless patient is at high risk on the basis of a modified FRAX model	T score, −1.5	T score, −1.0 to −1.5
Yearly BMD testing recommended	Yes	Yes	Yes	Yes
Prevalent vertebral fractures as justification for pharmacologic intervention	Yes	Yes	Yes	Yes
Calcium and vitamin D supplementation	1200–1500 mg of calcium per day and 800–1000 units of vitamin D per day for all patients‡	1200 mg of calcium per day and 2000 units of vitamin D per day for all patients‡	Only for patients with low calcium intake (<1 g/day) or vitamin D deficiency (not defined)‡	For all patients
Pharmacologic intervention	Bisphosphonates; teriparatide reserved for patients at highest risk	Bisphosphonates; teriparatide only for patients at high risk	Bisphosphonates as first-line options, followed by teriparatide	Bisphosphonates

Weinstein RS NEJM 2011;365(1):62-70

Weaning off Steroids

Adrenal Suppression

- Weaning is advised
- A test of adrenal reserve will help – do a 9am cortisol prior to the administration of the next dose of steroid
  - If it is >100nmol/l – short Synacthen® test

Risk of Adrenal Suppression – Route of Administration

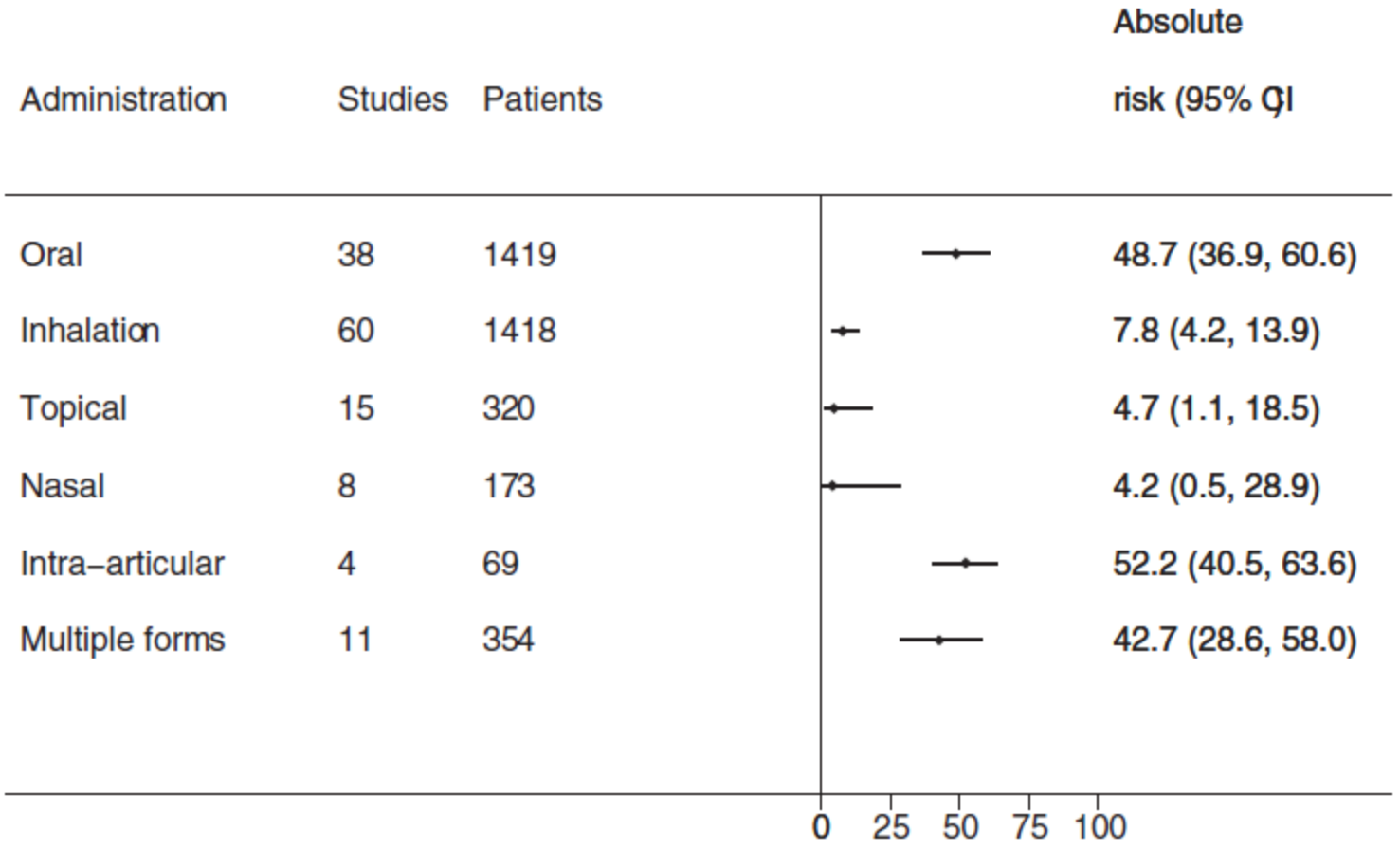


Figure 1. Meta-analysis, adrenal insufficiency after corticosteroids use by administration form.

Broersen LH et al JCEM 2015;100(6):2171-2180

Risk of Adrenal Suppression – Dose and Length of Time

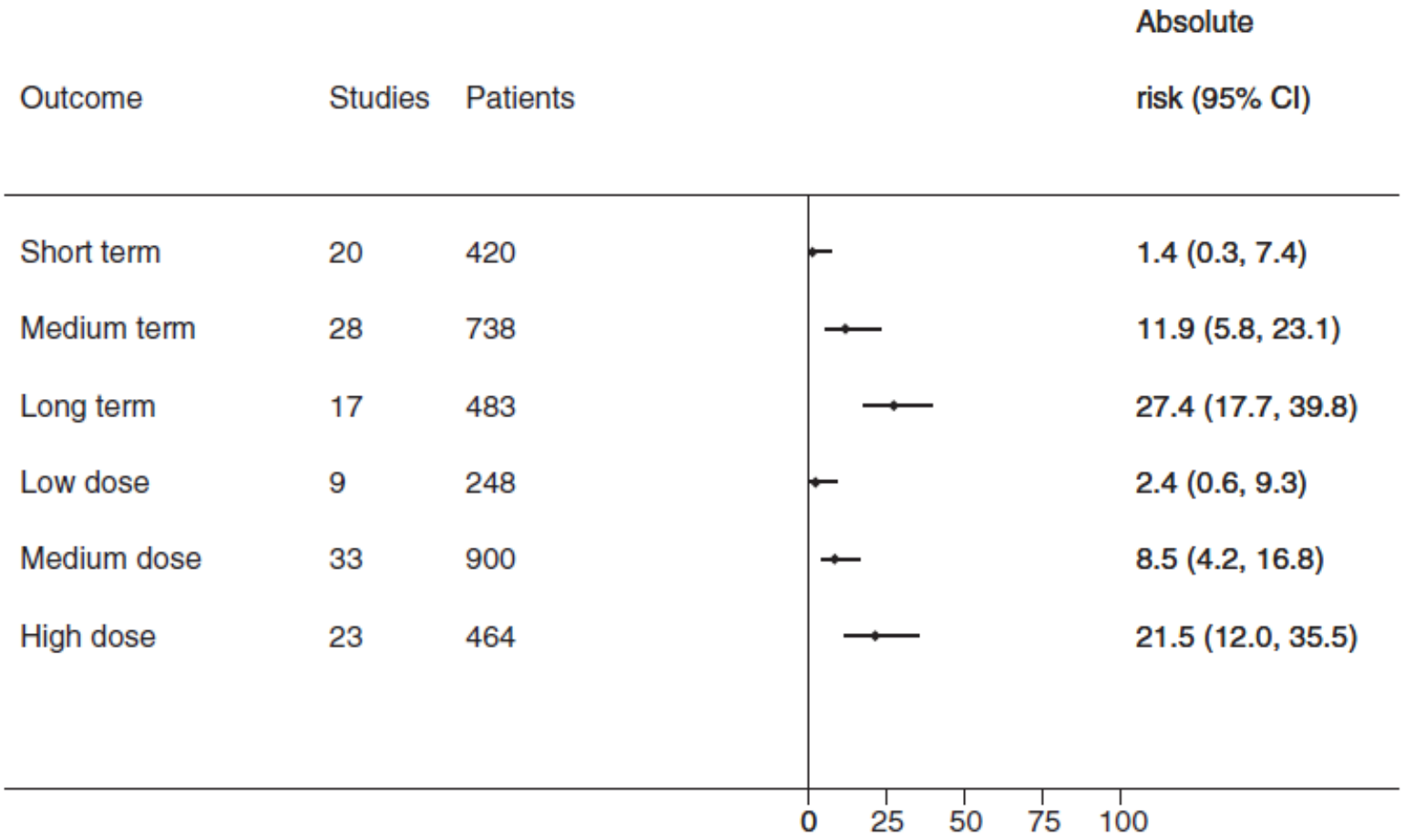


Figure 2. Meta-analysis, adrenal insufficiency after corticosteroids use per condition.

Broersen LH et al JCEM 2015;100(6):2171-2180

Risk of Adrenal Suppression – Indication

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)

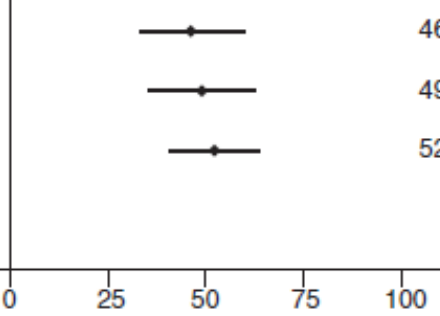


Figure 3. Meta-analysis, adrenal insufficiency per dose and duration in asthma patients.

Broersen LH et al JCEM 2015;100(6):2171-2180

Adrenal Reserve

- Do a 9am cortisol (done prior to them taking their steroid)
  - If the value is >100nmol/l then they can have an SST
  - If the value is <100nmol/l they are very unlikely to have sufficient adrenal reserve to come off the steroid thus SST is not necessary
- We often change people to hydrocortisone due to the shorter half life and thus easier titration

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors
- SGLT2 inhibitors

Palliative Care, Steroids and Diabetes

Is there a problem?

www.norfolkdiabetes.com