

# Steroids in Anaesthesia and Critical Care

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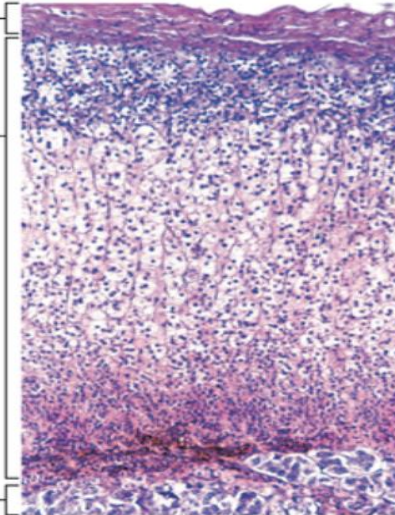
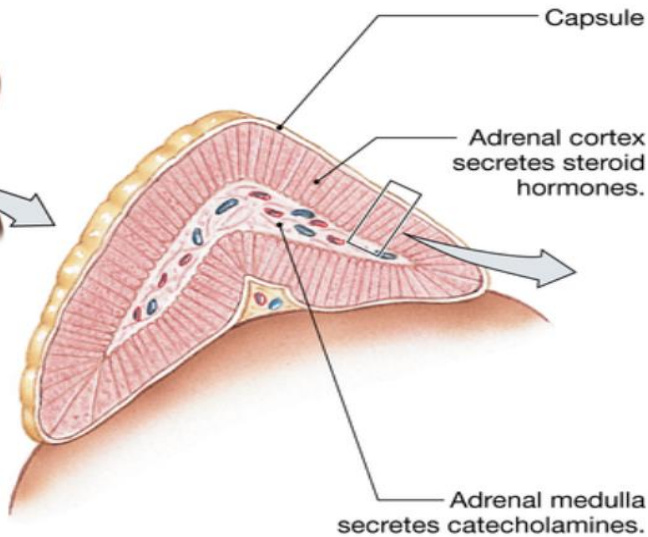
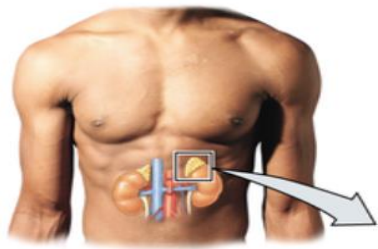
# Topics

- Definitions
- Brief anatomy and recap on R-A-A-S
- Production, control and metabolism of glucocorticoids
- Steroid cover for patients undergoing surgery
- Steroid use in Critical Care

# Definitions

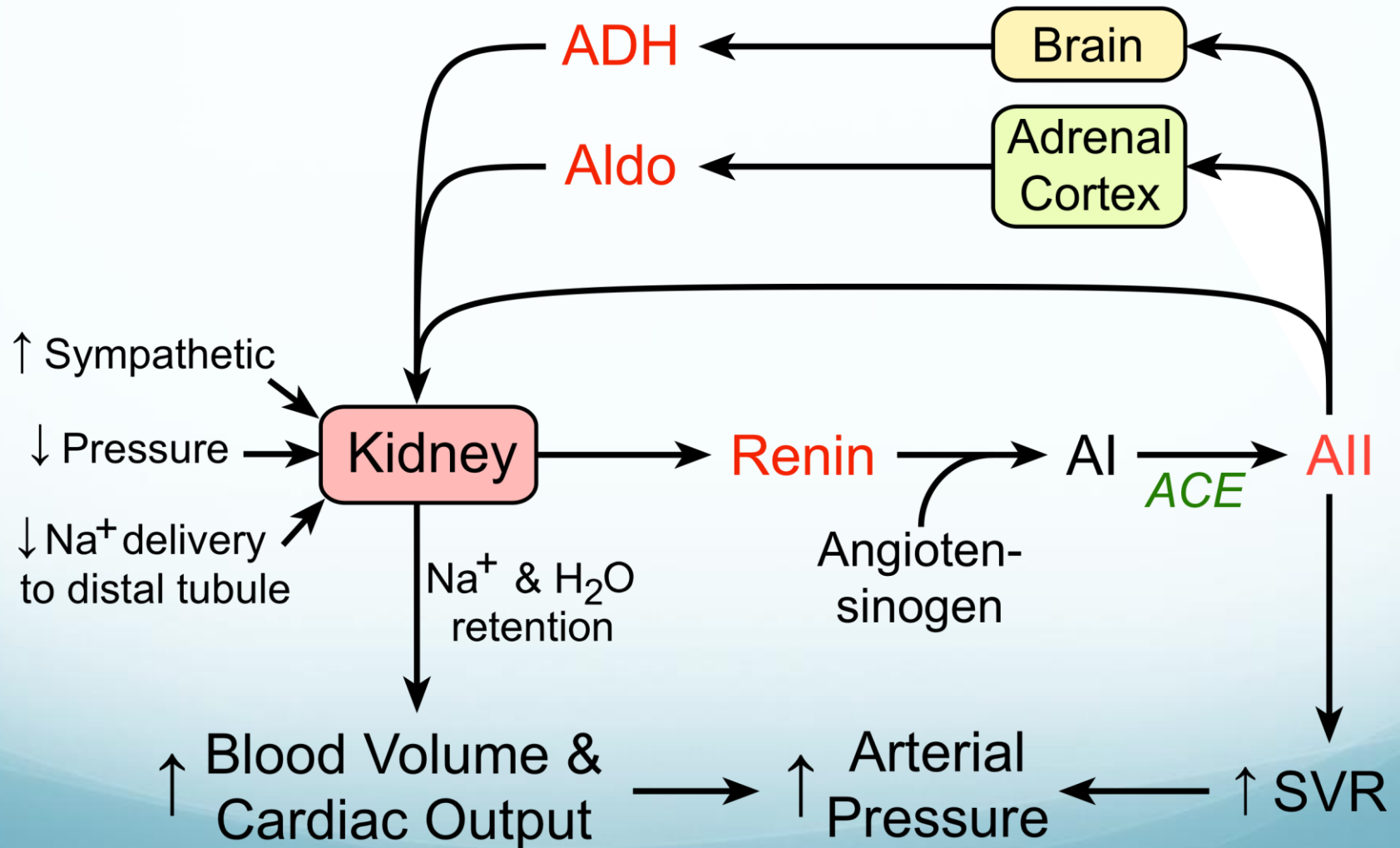
- Definitions
  - Corticosteroids – any class of steroids that are produced by the adrenal cortex. All are derivatives of cholesterol
  - Glucocorticoids – steroid which affect metabolism of glucose, fats and proteins
  - Mineralocorticoids – steroid that causes the retention of salt and water reabsorption
- For the purpose of this presentation, the term Steroid refers to Glucocorticoids

# Adrenal gland



Region	Secretes
Capsule	
Zona glomerulosa	Aldosterone
Zona fasciculata	Glucocorticoids
Zona reticularis	Sex hormones
Adrenal medulla	Catecholamines

# R-A-A-S



# Aldosterone

- The whole adrenal cortex, zona glomerulosa, requires ACTH to prevent atrophy of the tissue
- ACTH can stimulate aldosterone production, but prolonged high levels are required
- Aldosterone is produced exclusively in the zona glomerulosa under a separate control pathway from that of cortisol
- ACTH does play a role in regulation of zona glomerulosa function, angiotensin II is the most important regulator of aldosterone secretion
- Aldosterone is minimally protein bound with  $T_{1/2}$  20mins

# Glucocorticoids

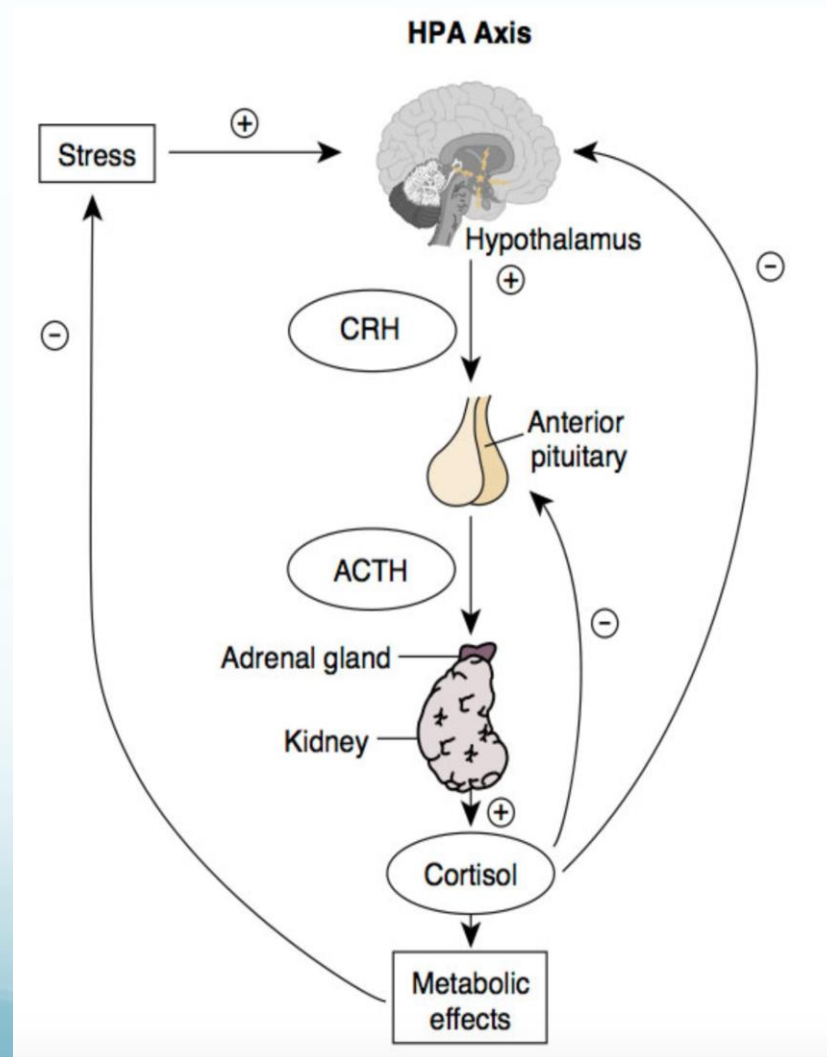
- Glucocorticoids – Cortisol
  - Cortisol is bound to an  $\alpha$ globulin – corticosteroid binding globulin
  - Released in a circadian manner & in response to physiological cues and stress
  - Serum cortisol concentrations peak in the mornings and are lowest at night.
  - Causes
    - Protein and fat catabolism
    - Gluconeogenesis in the liver
    - Increased bone resorption with decreased bone formation
    - Catecholamine production
    - Inhibition of the immune system
    - Reduction in prostaglandins leading to an anti-inflammatory response.

# Glucocorticoids

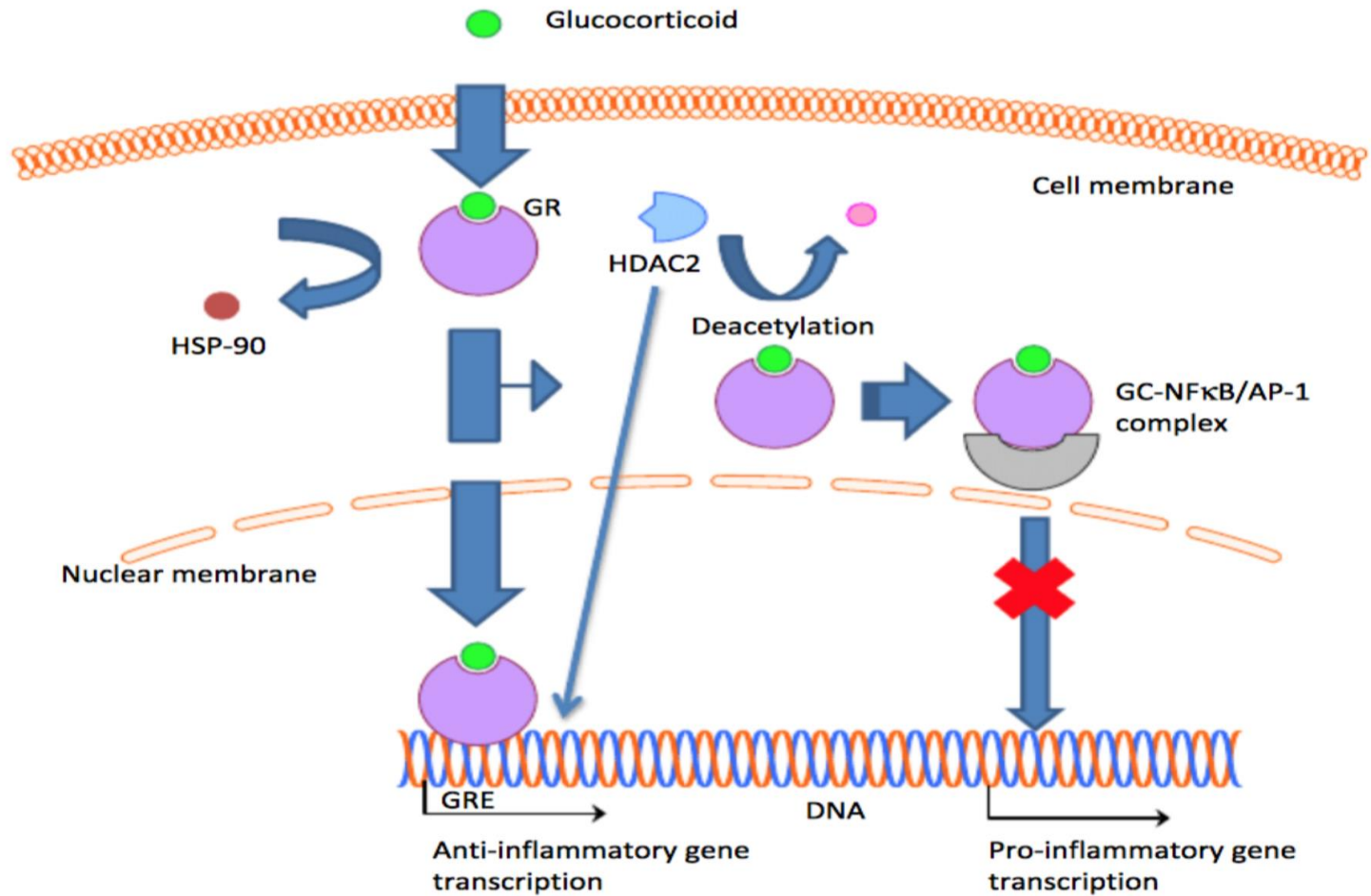
- They regulate many physiological processes
  - Metabolism
  - Immune function
  - Skeletal growth
  - Cardiovascular function
  - Reproduction
  - Cognition
- Cortisol is metabolised by the liver – reduced then conjugated with glucuronic acid & excreted in urine
- T<sub>1/2</sub> cortisol 60-90 mins



# Hypothalamic-Pituitary-Adrenal Axis



# Mode of action of Glucocorticoids



# Mode of action of Glucocorticoids

- Glucocorticoids are lipophilic
- Diffuse through cell membrane
- Bind to the intracellular Glucocorticoid Receptor
  - Transformational change allowing nuclear translocation
  - Binds to DNA causing gene transcription or repression
  - Expression of anti-inflammatory proteins IL-10
  - Suppression of pro-inflammatory proteins IL-1, IL-2, IL-6, IL-8, VEGF, COX-2, Prostaglandins, TNF, INF- $\gamma$

# Glucocorticoids

- Adrenal insufficiency (Addison's Disease)
  - Reduced or absent secretion of glucocorticoids, usually associated with deficient mineralocorticoid activity. Inadequate to regulate normal body functions
  - Signs and symptoms of Addison's disease result when approximately 90% of the adrenal cortex has been destroyed
- Primary adrenal insufficiency is due to a disorder of the adrenal glands
  - Failure to secrete cortisol AND aldosterone

# Glucocorticoids

- Secondary adrenal insufficiency results from diminished secretion of ACTH from pituitary or CRH from hypothalamus
  - If due to pituitary or hypothalamic disorders, will be deficient in cortisol but continue to secrete Aldosterone
  - Aldosterone levels typically remain normal because of stimulation from the RAAS.
  - Exogenous steroids is the most common cause of secondary adrenal suppression
- Acute (Addisonian crisis)
  - Abdominal pain,
  - Vomiting,
  - Dehydration
  - Hypotension (particularly postural)

# Glucocorticoids

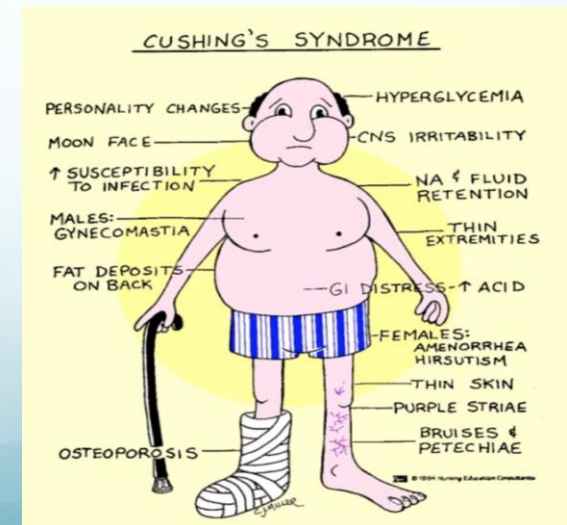
- Chronic condition
  - Insidious onset
  - Fatigue,
  - Anorexia,
  - Weight loss
  - Postural hypotension
  - Increased pigmentation – palmar creases and the buccal mucosa
    - high plasma concentrations of ACTH mimic melanocyte-stimulating hormone
  - Hypoglycaemia,
  - Hyponatraemia,
  - Hyperkalaemia
  - Raised serum urea.

# Glucocorticoids

- Cushing's Syndrome
  - Prolonged increase in plasma glucocorticoids
  - ACTH-independent
    - Glucocorticoid secreting adrenal tumours
    - Adrenal hyperplasia
    - Prolonged exogenous steroids
  - ACTH-dependent
    - ACTH secreting tumours of the anterior pituitary (Cushing's Disease) and lung

# Glucocorticoids

- Features of excess glucocorticoid
  - Protein depletion – Thin skin, proximal muscle wasting, poor wound healing & thin hair
  - Redistribution of body fat – “buffalo hump”, abdominal fat (purple striae)
  - Mineralocorticoid effect – water retention, plethoric “moon face”, HTN
  - Bone resorption – osteoporosis
  - Insulin-resistance





# Perioperative Management of Steroids

- Doses equivalent to 5mg prednisolone per day are not significant and no steroid cover is required
- 10mg prednisolone or equivalent is the threshold for needing steroid cover
- Steroid cover is required if taken within 3 months of the surgery.
  - Adrenal suppression can occur after only a week and can take up to 3 months to recover
- Normal cortisol secretion ~ 30mg/day
- Rise in ACTH is proportional to severity of surgery – rarely >150mg/day & last 3 days

# Perioperative Management of Steroids

- Patients on corticosteroids at a dose of 10 mg or more of prednisolone daily (equivalent to betamethasone 1.6 mg, dexamethasone 1.6 mg, hydrocortisone 40 mg, methylprednisolone 8 mg daily).
- Patients who have received corticosteroids 10 mg daily within the three months preceding surgery.
- Patients on high-dose inhaled corticosteroids (for example, beclometasone 1.5 mg a day).

# Perioperative Management of Steroids

- **Minor surgery** - 25 mg hydrocortisone at induction of anaesthesia and then resume normal medication postoperatively.
- **Moderate surgery** - usual dose of steroids pre-operatively and then 25 mg of hydrocortisone intravenously (IV) at induction, followed by 25 mg IV every 8 hours for 24 hours. Usual pre-operative dose is then continued.
- **Major surgery** - usual dose of steroids pre-operatively, then a bigger 50 mg of hydrocortisone IV at induction, followed by 50 mg IV every 8 hours for 48-72 hours. Continue this infusion until the patient has started light eating, then restart the normal pre-operative dose.

# Perioperative Management of Steroids

- **Minor surgery**
  - Hand surgery
  - Uterine curettage
  - Colonoscopy
  - Inguinal hernia repair
- **Moderate surgery**
  - Lower extremity revascularisation
  - Total joint replacement
  - Cholecystectomy
  - Colon resection
  - Hysterectomy
- **Major surgery**
  - Oesophagectomy
  - Trauma
  - Major cardiac/vascular
  - Proctocolectomy
  - Delivery
  - Hepatic surgery

# Equivalent dose and relative potency

Agent	Equivalent dose (mg)	Relative Glucocorticoid Potency	Relative Mineralocorticoid Potency
Hydrocortisone	100	1	1
Prednisolone	25	4	0.6
Methylprednisolone	20	5	0.25
Betamethasone	3.75	25	0
Dexamethasone	3.75	25	0
Fludrocortisone		10	125
Aldosterone		0	100

# Indications for use in Critical Care

- Septic shock
  - Aims to improve cardiovascular function and improve mortality
  - 2 trials in early 2000 reported dichotomous results
    - Early administration in vasopressor-resistant septic shock improved mortality
    - No improvement in mortality despite faster reversal of shock
  - 2016 – administration in severe sepsis did not prevent progression to septic shock
  - ADRENAL trial 2018 – no difference in mortality however faster resolution of shock & weaning from mechanical ventilation

# Indications for use in Critical Care

- Cardiac surgery
  - Aims to suppress inflammatory response to CPB
  - 2 large trials, neither of which have shown improvement in mortality
- Anapylaxis
  - Cornerstone of treatment
  - Shortens protracted reactions & helps prevent biphasic response
- Respiratory
  - Airway oedema on tracheal extubation – significantly reduces risk of stridor and reintubation

# Indications for use in Critical Care

- Respiratory
  - Obstructive airway disease – in both asthma and COPD reduce the extent of airway inflammation & mucus plugging in bronchospasm not relieved by beta-agonist therapy
- ARDS
  - Aims to reduce inflammation therefore halting the progress through the exudative, proliferative and fibrotic phases
  - Multiple trials with mixed results
    - 2016 trial suggested that prolonged methylprednisolone reduces hospital mortality & increases ventilator-free days
    - Ongoing – Dexamethasone to treat ARDS in conjunction with lung-protective ventilation



# Indications for use in Critical Care

- Community-acquired pneumonia
  - Aims to reduce pulmonary and systemic inflammation associated with severe pneumonia
  - NICE (2014) does not recommend routine administration
  - Recent meta-analyses suggest reduced mortality and incidence of need for mechanical ventilation and ARDS
  - Ongoing trials in France, Netherlands and USA
- Pneumocystis jirovecii pneumonia in HIV
  - Significantly reduced rates of mechanical ventilation
    - Thought to be due to the reduction in inflammatory damage sustained as the organism undergoes necrosis

# Indications for use in Critical Care

- Neurological
  - Bacterial meningitis
    - Cochrane 2015 concluded that steroids reduced mortality when caused by *Streptococcus pneumoniae*
    - Also the neurological sequelae such as hearing loss, cognitive impairment and focal neurological deficits are significantly reduced with any bacterial cause
  - Traumatic brain injury
    - Aims to reduce secondary brain injury caused by swelling and oedema
    - Study 2005 of methylprednisolone vs placebo showed significantly higher mortality at both 2 weeks and 6 months. The trial was stopped

# Indications for use in Critical Care

- Neurological
  - Spinal cord injury
    - Trial in 1990s and subsequent Cochrane review concluded that high-dose methylprednisolone is the only pharmacological therapy to be efficacious if administered within 8hrs of injury
    - NICE recommend that methylprednisolone should NOT be given as the risks outweigh the benefits
    - Concerns also that many patients with spinal-cord injury will also have TBI therefore making steroids contraindicated
  - Guillain-Barre syndrome
    - Aim to modulate the inflammatory polyneuropathy
    - Cochrane 2016 – no significant effect on time to recovery or long-term outcome

# Indications for use in Critical Care

- Raised ICP
  - Contraindicated when associated with trauma or spontaneous ICH
  - Symptomatic rise in ICP caused by oedema surrounding intracerebral tumours – Dexamethasone
  - Dexamethasone also reduced the mass effect of vasogenic oedema caused by abscesses
- Immune modulation
  - Used in many autoimmune diseases and also to reduce the rejection of transplanted organs
- Endocrine
  - Severe hypothyroidism
    - Myoedema coma – 1<sup>o</sup> or 2<sup>o</sup>

# Indications for use in Critical Care

- Endocrine
  - Adrenal crisis
    - Primary adrenal insufficiency (Addison's Disease)
      - Autoimmune
      - TB
      - Surgery
    - Secondary insufficiency is caused by reduced release of ACTH
      - Exogenous steroids
      - Pituitary tumours
      - Sheehan's syndrome
- Organ donation
  - Part of the optimisation bundle which improves viability of donor organs

# Indications for use in Critical Care

Indication	Dose	Duration
Septic shock	Hydrocortisone 200mg/24 <sup>0</sup> IV	Taper when vasopressors not needed
Anaphylaxis	Hydrocortisone 200mg IV	Stat
Airway oedema	Methylprednisolone 40mg IV	≥4 hours before extubation
Exacerbation of asthma	Prednisolone 40-50mg PO OD or 100mg Hydrocortisone IV QDS	≥5 days≥≥
Exacerbation of COPD	Prednisolone 30mg PO OD	7-14 days

# Indications for use in Critical Care

Indication	Dose	Duration
Pneumocystis pneumonia in HIV	Prednisolone 40mg PO BD or Methylprednisolone 60mg IV OD	Taper after 4 days on advice
s. Pneumoniae meningitis	Dexamethasone 10mg IV QDS	4 days
↑ ICP cerebral tumour	Dexamethasone 16mg PO OD	Taper when symptoms improve
Adrenal crisis	Hydrocortisone 100mg IV then 200mg/24 <sup>0</sup>	Endocrine advice
Myxodema coma	Hydrocortisone 100mg IV	Endocrine advice
Organ donor optimisation	Methylprednisolone 15mg/kg (max 1g)	Stat dose