Carolinas HealthCare System

Dental management of patients on steroids and other immunosuppressive therapies

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ORAL MEDICINE AND IMMUNOLOGY
friends, foes and frenemies
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Statement of Disclosure

I have no actual or potential conflict of interest in relation to this presentation

Outline

- Systemic Steroid Therapy
- Biological Agents

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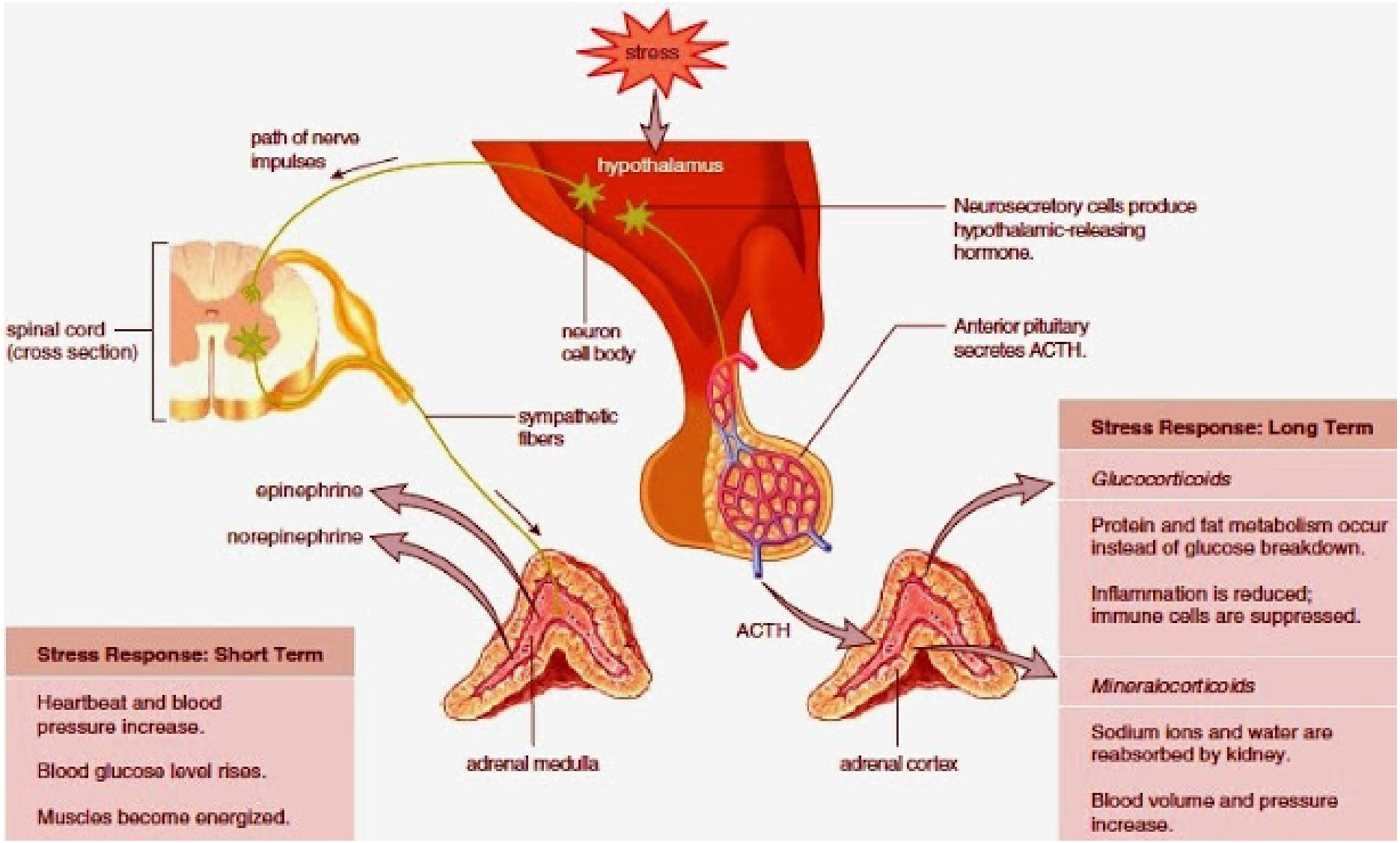
Systemic Steroid Therapy

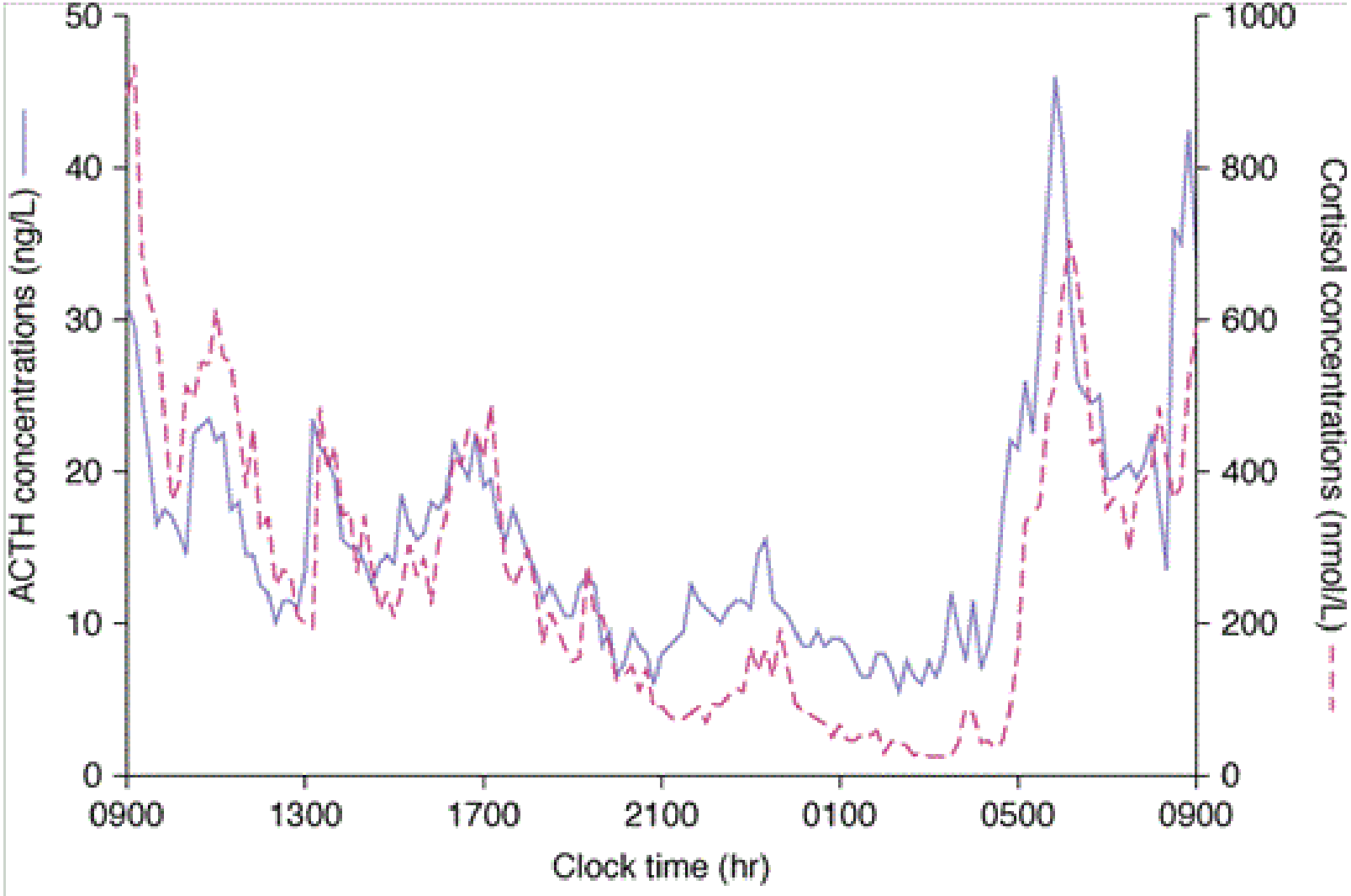
Adrenal Glands and Stress Response



Secretion and regulation

- Glucocorticoids - Cortisol
  - Daily Secretion: **15~30 mg/day**
  - May be up to **200 mg under stress**
  - Regulated by ACTH (HPA axis)
  - F=M
- Mineralcorticoids - Aldosterone
  - Daily Secretion: **50~250μg/day**
  - Secretion regulated by renin-angiotensin system (AT II)
  - Net effect: Na reabsorption (Na/K pump) at distal tubules of kidney
  - Minor influence of ACTH
  - M>F
- Androgen
  - Regulated by ACTH

Cortisol and ACTH - Circadian Rhythm



Physiology of Glucocorticoids

Immunologic
Anti-inflammatory
Metabolic
Connective tissue
Calcium and bone
Circulatory
Renal
CNS
Eye
Growth and developmental

Glucocorticoids - Anti-inflammatory activity

Hench (1949) – high dose cortisol in Cushingoid patients ameliorated RA symptoms

- Only in supraphysiological doses
- Inhibit phospholipase → dec. PG (bradykinins) and LT → dec. leukocyte migration
- Synthesize ACE, which degrades bradykinin
- Block histamine, interleukin-1 and 2, plasminogen activating factor (PAF)
- Decrease vascular permeability
- Increase WBC (ANC), platelet, WBC and RBC (dec. erythrophagocytosis)
- Decrease circulating eosinophil, basophil, and lymphocyte counts

Glucocorticoids - Immunologic activity

- Impairs cell-mediated immunity (T-lymphocyte dependent)
- Lymphotoxic
- Little effect on humoral immunity
  - no decrease in existing Ab levels
  - B-cell response to antigen not inhibited

Systemic Corticosteroid Use

Conditions with evidence-based benefits include:

- Asthma
- Croup
- Crohn's disease
- Ulcerative colitis
- Giant cell arteritis (temporal arteritis)
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Wegener's granulomatosis
- Sarcoidosis
- Eczema
- Otitis externa
- Pemphigus
- Dermatomyositis
- Minimal change glomerulonephritis
- Acute leukemia
- Acquired hemolytic anemia
- Idiopathic thrombocytopenic purpura
- Cerebral edema
- Cluster headache
- Congenital adrenal hyperplasia
- Anaphylaxis and allergic reactions

Comparative steroid potencies			
Name	**Glucocorticoid potency**	**Mineralocorticoid potency**	**Duration of action** ($t_{1/2}$ in hours)
Hydrocortisone (cortisol)	1	1	8
Cortisone acetate	0.8	0.8	oral 8, intramuscular 18+
Prednisone	3.5-5	0.8	16-36
Prednisolone	4	0.8	16-36
Methylprednisolone	5-7.5	0.5	18-40
Dexamethasone	25-80	0	36-54
Betamethasone	25-30	0	36-54
Triamcinolone	5	0	12-36
Beclometasone	8 puffs 4 times a day=14 mg oral prednisone once a day	-	-
Fludrocortisone acetate	15	200	-
Deoxycorticosterone acetate (DOCA)	0	20	-
Aldosterone	0.3	200-1000	-

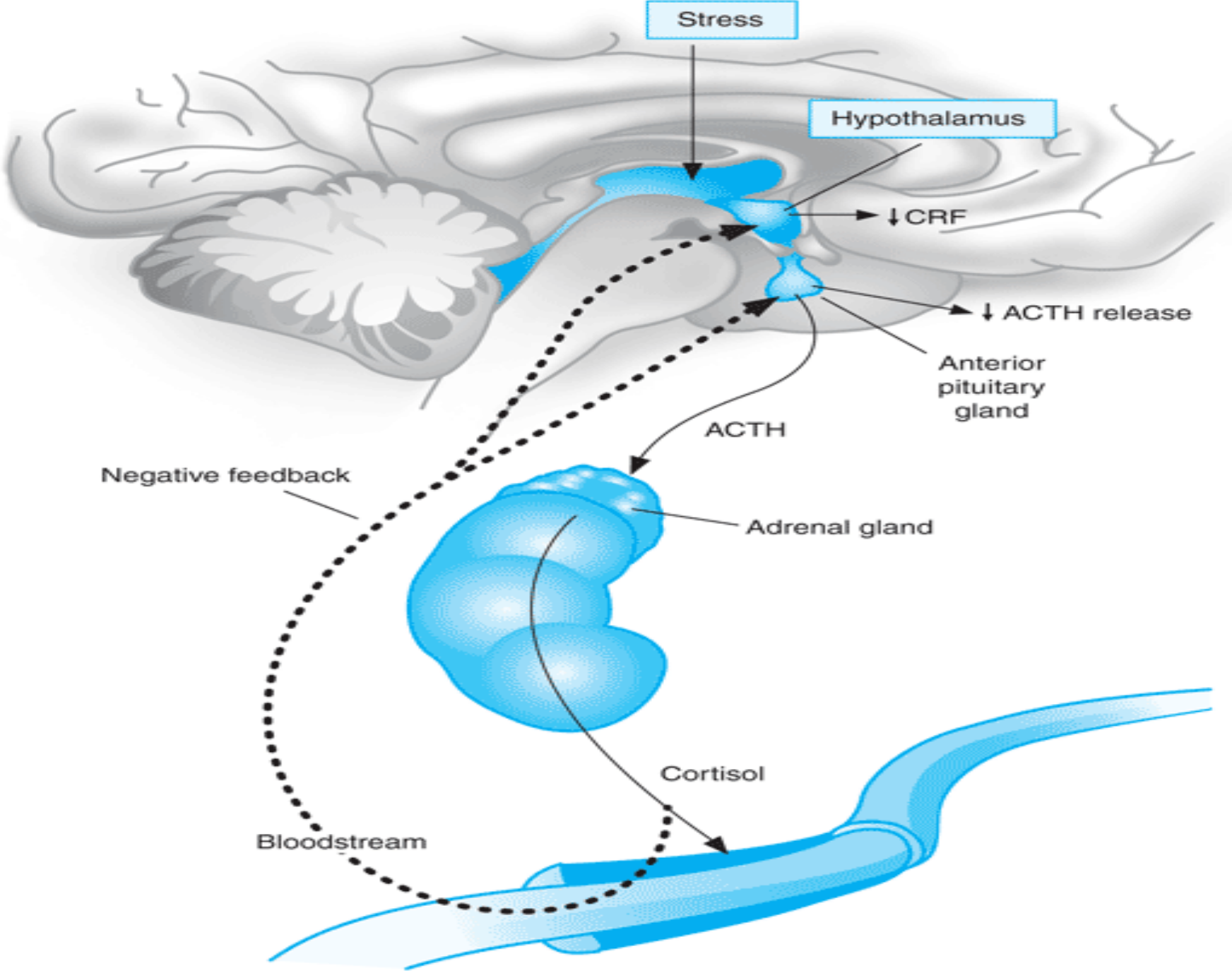
Adrenal Insufficiency

Primary

- Pituitary necrosis
- Bilateral adrenalectomy
- Removal of a functioning adrenal tumor that had suppressed the other adrenal
- Injury to both adrenals (trauma, hemorrhage, infection, anticoagulant, thrombosis or metastatic carcinoma)
- Thyroid hormone replacement is given to a patient with adrenal insufficiency

Secondary

- Administration of exogenous steroids


Stress
Hypothalamus
↓CRF
↓ ACTH release
Anterior pituitary gland
ACTH
Negative feedback
Adrenal gland
Cortisol
Bloodstream

Adrenal Insufficiency

- Chronic adrenal insufficiency (Addison's disease)
  - Primary - adrenal function↓, ACTH↑, MSH
  - Secondary - ACTH↓
    - glucocorticoid deficiency, mineralcorticoids relatively maintained
    - 2-3X more common than primary

- Acute adrenal insufficiency
  - Adrenal crisis (Addisonian crisis)

Adrenal Crisis - Causes

May occur in the course of treatment of chronic insufficiency or as its presenting manifestation

Primary adrenal insufficiency >> secondary

Stressors:

Infection

Surgery

Trauma

Prolonged fasting

ADRENAL INSUFFICIENCY

ADRENAL CRISIS - PATHWAY OF EVENTS

Life Sustaining Cortisol replacement therapy needed with either:- Hydrocortisone, Prednisolone or Dexamethasone

Vital Aldosterone replacement therapy with Fludrocortisone is needed to maintain a proper balance of body salts and fluid i.e. electrolytes and blood volume

ADRENAL GLANDS

Defective production of

GLUCOCORTICOIDS → **CORTISOL** ***IMPAIRED*** OR ***NO*** PRODUCTION

- **LIVER** Function decreases → **Hypoglycaemia** Low blood glucose → Seizures, convulsions Loss of consciousness → **SHOCK**
- Nausea and vomiting Diarrhoea and cramps → Low body fluid volume → Low Blood Pressure → **SHOCK**

MINERALCORTICOIDS → **ALDOSTERONE** ***IMPAIRED*** OR ***NO*** PRODUCTION

- **KIDNEY** Water and Sodium loss → **Hyponatremia** Low sodium level → Low body fluid volume
- **Hyperkalaemia** Increase in potassium → **HEART** Irregular output → **CARDIAC ARREST**

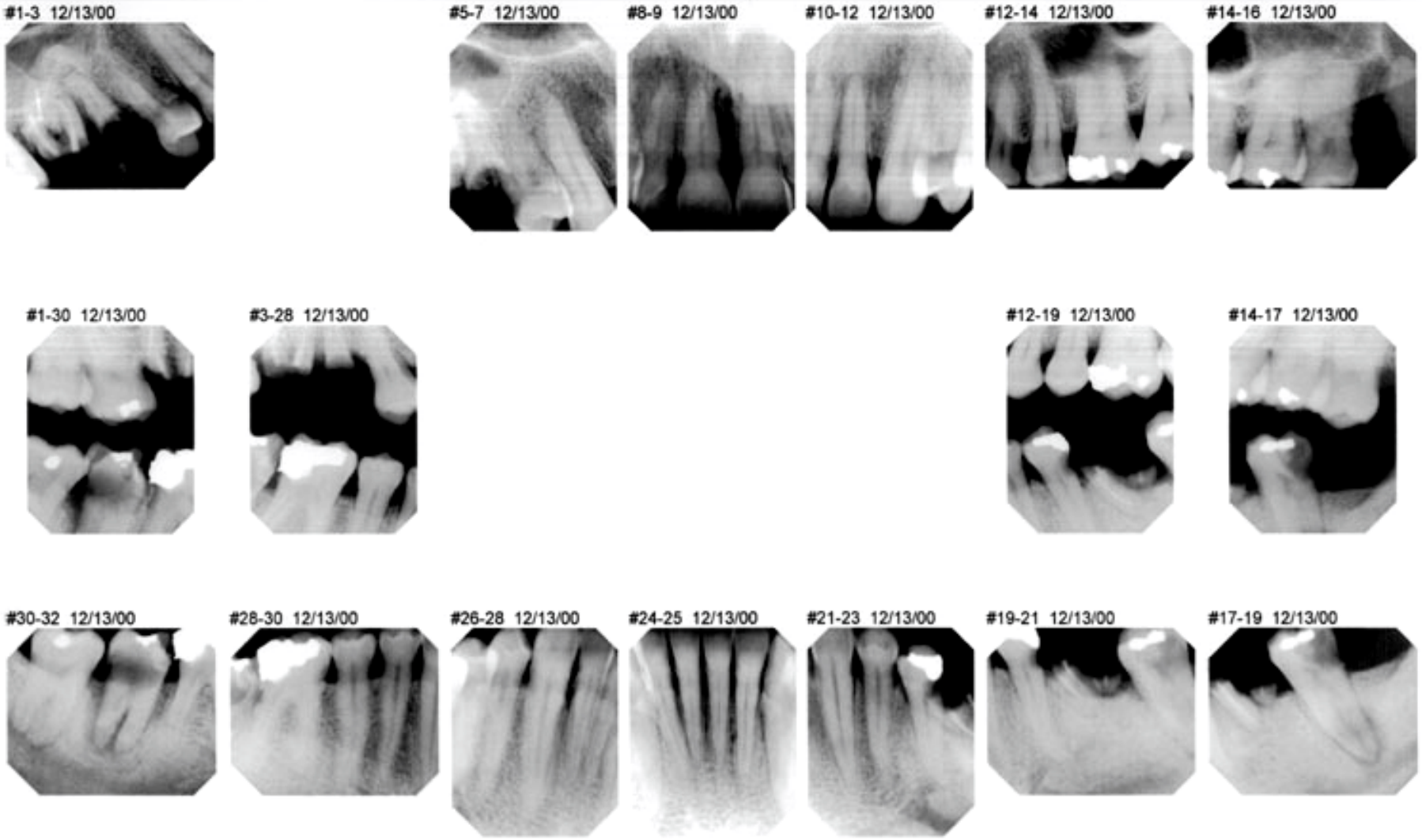
SHOCK → **BRAIN COMA ORGAN FAILURE** → **DEATH**

CARDIAC ARREST → **DEATH**

http://www.cahisus.co.uk/pdf/Adrenal%20Crisis%20Pathway%20Professor%20Peter%20Hindmarsh.pdf

Scenario

- 65 y/o female
- PMH:
  - Rheumatoid arthritis
  - Hypertension
- Medications:
  - Prednisone 10 mg daily (5 years)
  - HCTZ
  - Captopril
  - Meloxicam



1. Perio – S/RP
2. Extract non restorable teeth
3. Implants vs. removable or fixed prosthodontic therapy

Dentistry and Steroid Supplemenation
Areas of confusion

Do we cover or not cover?

If we decide to cover, then:

Which appointments do we cover?

How do we cover? (when, how much, how long?)

Rule of Twos

Adrenal suppression may occur if:

- patient is taking **2**0 mg of cortisone or its equivalent daily
- for **2** weeks
- within **2** years of dental treatment

Steroid cover regimen:

Doubling the dose of current regimen on the day of surgery

Adrenal Crisis, Steroid Supplementation and Dentistry
Khalaf et al. JADA 2013:144(2)

Case reports (N=6)

- ‘suggestive’ of adrenal crisis – 4
- ‘consistent’ with adrenal crisis – 2
- prophylactic steroid supplementation - 4
- First 3 cases between 1964-1973
  - All ‘suggestive’
  - All involved general anesthesia
  - All involved prophylactic steroid supplementation
- No fatalities

Adrenal Crisis, Steroid Supplementation and Dentistry
Khalaf et al. JADA 2013:144(2)

Case reports (N=6)

- secondary AI – 3
  - ‘suggestive’ of adrenal crisis – 3
  - pre and perioperative steroid supplementation – 3
  - type of secondary AI:
    - irradiated pituitary gland w/ steroid therapy (13 y) - 1
    - steroid therapy (4-5 y) - 2
      - general anesthesia - 2

Adrenal Crisis, Steroid Supplementation and Dentistry
Khalaf et al. JADA 2013:144(2)

Conclusions:

- Adrenal crisis in dental patients a rarely reported event (6 in 66 years)
- Very rare when attributed to secondary steroid supplementation
- Uncertainty regarding efficacy of prophylactic steroid supplementation

Surgery and Steroid Supplementation

Bromberg et al (1991, 1995)[1,2]

- 5 to 10 mg prednisolone daily > than 3 months
- Renal transplant recipients undergoing surgery
- Moderate surgery
- Usual daily dosage with no additional adjustments
- No evidence of adrenal suppression
- Comparative cortisol levels between treatment and controls in response to stress
- No signs of adrenal crisis

1. Bromberg JS et al. J Am Coll Surg. 1995;180(5):532-6.
2. Bromberg JS et al. Transplantation. 1991;51(2):385-90.

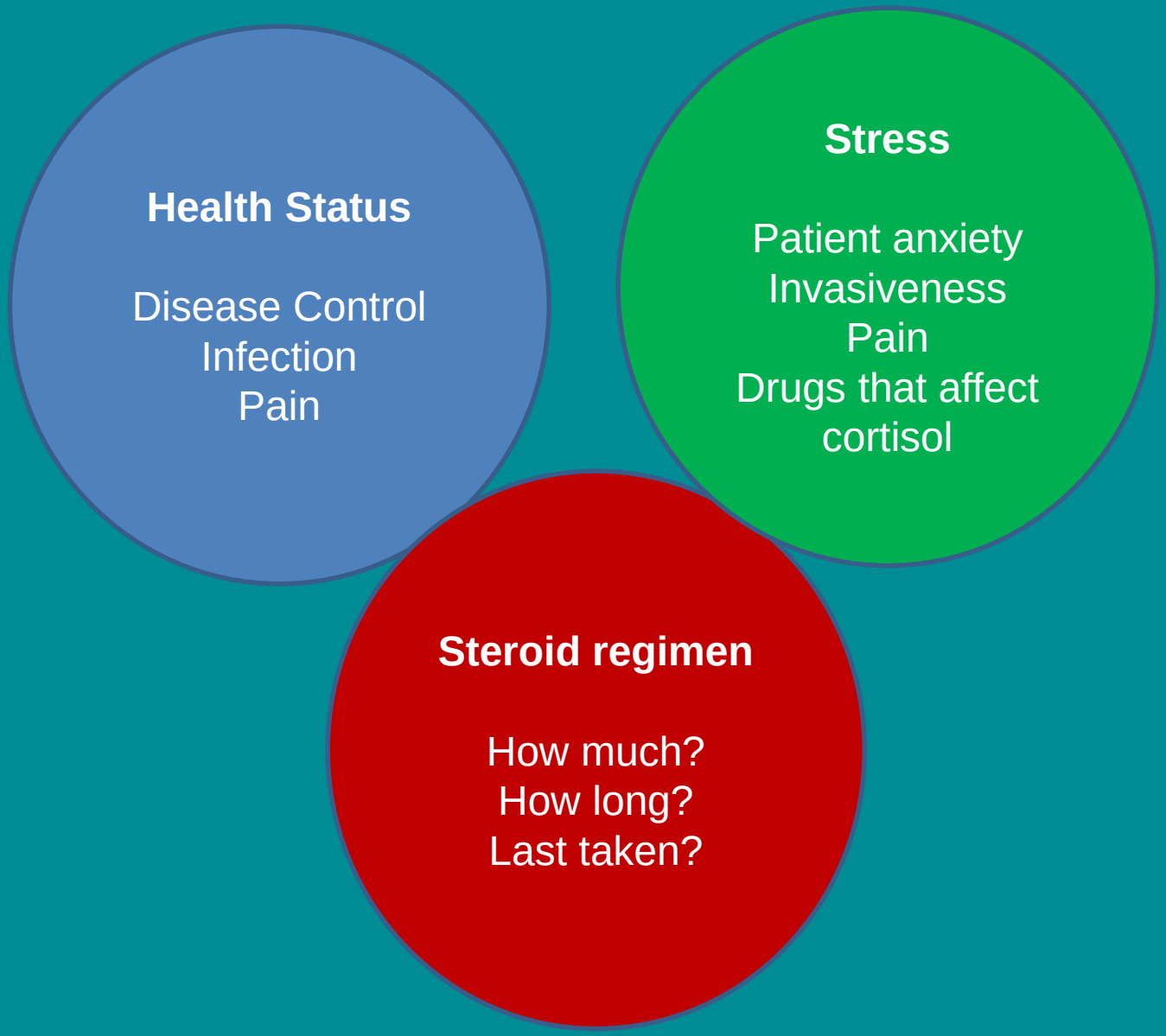
Current Recommendations

Cochrane Review (2012) –

- 2 RCTs with N=37 - (High risk of bias)
- Unable to support or refute use of supplemental corticosteroids
- No adverse events from treatment and control groups
- Short courses (< 48hours) of increased glucocorticoid therapy rarely cause significant problems
- Consider coverage for:
  - glucocorticoid therapy patients suspected of having iatrogenic adrenal insufficiency (AI)
  - patients who have received glucocorticoid therapy for more than 3 weeks by any route.

1. Yong SL et al. Cochrane Database Syst Rev. 2012 Dec 12;12:CD005367

Risk Assessment



Risk Assessment – Health Status

Specific risk factors increase the risk of an adverse event in patients with AI

- presence of oral infection
- hypovolemia
- inadequate circulating cortisol due to adrenal insufficiency
- fasting state

Surgical stress

- Minor surgical stress:
  - surgical extractions, multiple extractions
- Moderate surgery procedures:
  - mandible, zygoma
- Major oral surgery procedures:
  - multiple extractions, quadrant periodontal surgery, extraction of bony impactions, osseous surgery, osteotomy, bone resections, cancer surgery, surgical procedures involving GA, procedures lasting > 1 hour, procedures assoc with significant blood loss
  - orthognathic surgery, severe facial trauma, head and neck, orthognathic surgery

Gualandro DM, Yu PC, Calderaro D, et al. Bras Cardiol. 2011;96:43-54.

Cortisol equivalents – Salem (1994)

Review of multiple studies

75-150mg/24hr cortisol secretion after major surgery

cortisol level rarely exceed **200mg/24hr**
(50mg prednisone)

Salem M. Ann Surg. 1994 Apr;219(4):416-25.

Perioperative Steroid Supplementation Guidelines

- No need for mineralocorticoid supplementation[1]
- Insufficient evidence to support or refute the use of supplemental perioperative steroids in patients with adrenal insufficiency[2]
- Administration of the patient's daily maintenance dose may be sufficient[2]
- Supplemental doses may not be required[2]

1. Gualandro DM, Yu PC, Calderaro D, et al. Bras Cardiol. 2011;96:43-54.
2. Yong SL et al. Cochrane Database Syst Rev. 2012 Dec 12;12:CD005367

Perioperative Steroid Supplementation Guidelines

General Dental Procedures

- Does not warrant supplementation with additional glucocorticoids[1]

Minor surgery under LA

- Patients are at very low risk, if any, for developing adrenal crisis[1]
- Supplementation is unnecessary[1]
- Maintain their usual dose of glucocorticoids[1]

Surgery under GA

- No evidence that supplementation is beneficial[1]
- Should be determined by the severity of the surgery and the preexisting glucocorticoid dose[1]

1. Gibson N, Ferguson JW. Br Dent J 2004;197:681-685.

Major oral surgery under LA?

Treat like surgery under GA

Recommended cortisol equivalent doses Salem (1994) –

Daily physiologic – 10-20 mg

Minor stress – 25 mg on day of procedure (5 mg prednisone)

Moderate stress – 50-75 mg for 1-2 days (10-15 mg prednisone)

Major stress – 100-150 mg daily for 2-3 days (20-30 mg prednisone)

Salem M. Ann Surg. 1994 Apr;219(4):416-25.

Conclusions

- Adrenal crisis from dental treatment of patients on supplemental steroids is rare
- Adverse events from short term courses of steroids is rare however a concern
- Steroid supplementation rarely indicated for routine dental treatment
- Consideration based on individual risk assessment of patient (medical, surgical stress, steroid regimen)
- Control of pain and stress peri and post operatively
- Monitoring post operatively for high risk patients (BP)

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Biological Agents

Biological Agents (BA)

- Manufactured in or extracted from a biological source (i.e.: blood, stem cells, vaccines, DNA recombinant technology)

- Target immunocytes or their products and steps in pro-inflammatory pathways

Biological Agents – Immune Mediation

Binding to:

- immunocytes (T lymphocytes, B cells, granulocytes, APCs, etc.)
- immune mediators (cytokines, chemokines, growth factors)

Objectives:

- Depletion
- Suppression
- Prevent binding to lymphoid organs or inflammatory sites
- Create unresponsiveness

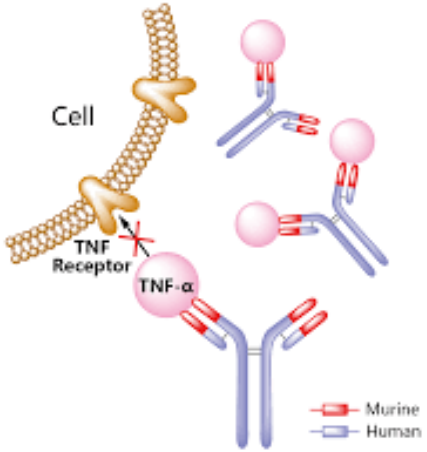
Biological Agents

1. Biologics
   - Erythropoeitin
   - CSFs
   - GH

2. Monoclonal antibodies
   - Counteract or block a biologic substance
   - Target and/or damage a cell type

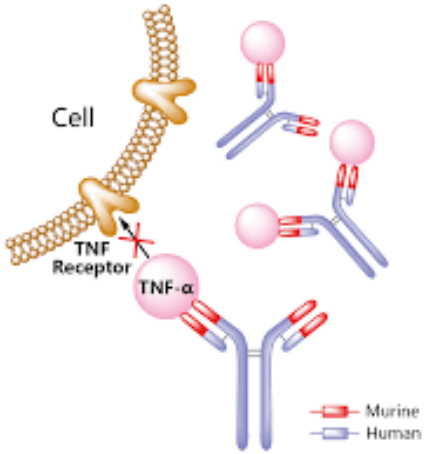
Monoclonal Antibodies (mAbs)

1. Human derived – ‘-mab’
2. Humanised – ‘-zumab’
3. Chimeric – mouse-human – ‘ximab’



Monoclonal Antibodies (mAbs)

- Expensive
- IV or SC administration due to size
- Adverse Reactions:
  - infusion reactions
  - fatigue
  - arthralgias
  - immunosuppression
  - autoimmunity
  - infections
  - malignancies



Main Biological Agents

- TNF-α inhibitors
- Interleukin inhibitors (e.g.: basiliximab)
- T-cell modulators
- T-cell co-stimulators (e.g.: abatacept)
- B-cell modulators (e.g.: rituximab)
- Cluster of differentialtion (CDs)
- Others (anti-coagulant, anti-epidermal GF, NF-ΚB blockers, interferons, vaccines, anti-microbials)

BA Targets and Conditions

TNF-α

Crohn's, RA, psoriasis

CDs

Transplant rejection, RA, AML, NHL,

VEGF

Cancers

ILs

RA, Transplant rejection, Juvenile arthritis, Lymphoma, other autoinflammatory disease, Psoriasis

Biologic Uses in Oral Healthcare

Mainly TNF-α inhibitors

- Behcet's disease, RAS - infliximab, etanercept, adalimumab
- Vesicullobullous disease – rituximab, etanercept (pemphigoid)
- Lichen Planus – etanercept, adalimumab
- Crohn's disease – infliximab, adalimumab
- Sjogren's syndrome – infliximab, etanercept, rituximab??

Dental Management of Patients on BAs

No official guidelines

Main concerns:

1. Infections
2. MRONJ
3. Impaired wound healing
4. Other (bleeding, drug eruption)

BAs and Infection

Post-transplant patients undergoing active therapy (anti IL-2, anti-CD3 agents)[1]

- Pre transplant evaluation
- Conservative treatment of infections during therapy

Cutaneous infections[2]

Increased incidence of oral candidiasis[3]

1. Georgakopoulou E A et al. *Stomatologija* 2011; **13:** 107–112.
2. Hagen JW et al. Dermatologic Clinics. 2012;30(4):695-730, vii.
3. Moen K et al. OOOOE 2005; 100: 433–440.

BAs and Other Adverse Effects

Bleeding - One case report of gingival bleeding due to abciximab related thrombocytopenia[1]

Cutaneous or mucosal drug eruptions - varies and may manifest as a lichenoid reaction, vesicle/bullae, or ulcer[2]

1. Oh Y-J et. Al. *Korean Circ J* 2009; **39:** 75–78.
2. Boussemart L et al. Dermatology. 2010;221(3):201-5.

BAs and MRONJ

RANKL inhibitors (denosumab)

- Final mediator of osteoclastic bone resorption

Angiogenesis inhibitors (bevacizumab, sorafenib, sunitinib)

- VEGF inhibitor

BAs and Impaired Wound Healing

- VEGF inhibitors
- Bevacizumab – $T_{1/2}$ – 20 days (11-50)

Recommendation to reduce risk of wound complications (surgical oncology, plastic surgery)[1]:

  - 6-8 week interruption before surgery
  - Resume 4 weeks after surgery

1. Sharma K et al. *Ann Plast Surg* 2013; **71:** 434–440.

Conclusions

- Rapid development of biological agents → > 900 agents in development
- Discontinuation of agents is often not an option
- Definitive recommendations and guidelines for dental management are lacking
- Consideration for management of adverse effects individually as they relate to dental management

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