Addressing Adrenal Suppression with Inhaled Steroids

Program Objectives

After participating in this program, participants will:

- Appreciate the need for inhaled corticosteroids (ICS) as the mainstay therapy for the management of asthma;
- Have an increased index of suspicion for the impact of ICS on the HPA axis;
  - Examine the potential relationship between ICS and growth and bone density;
  - Identify potential patients who may be at risk of adrenal suppression from the use of high doses of ICS;
- Consider an approach to minimizing systemic risk and/or managing systemic side effects associated with ICS use.

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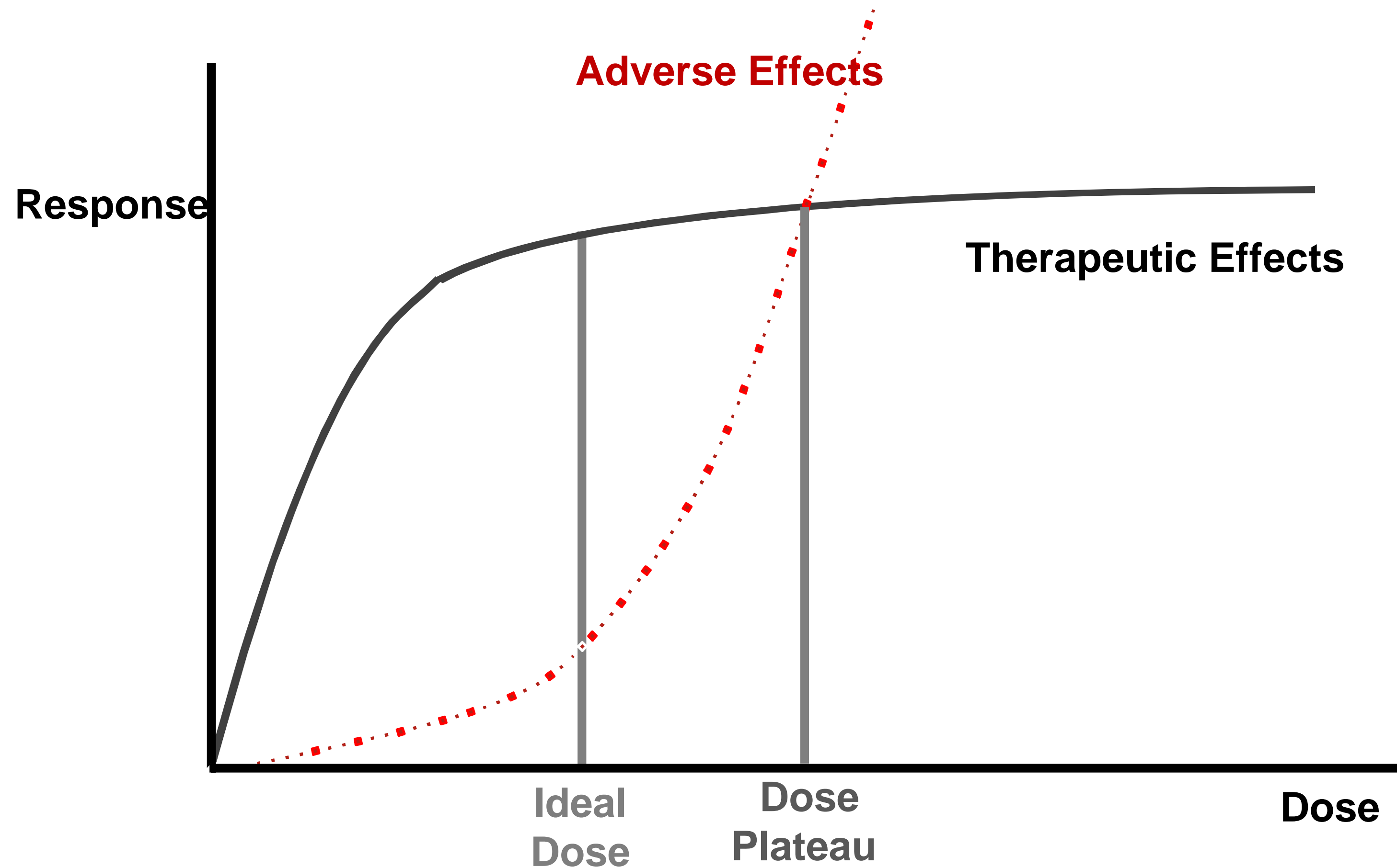
ICS: Theoretical Dose-Response Curve



Robinson DS, et al., 1996

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Possible Systemic Effects of ICS

- Adrenal suppression
- Growth suppression
- Bone effects
- Cushingoid features
- Cataracts
- Glaucoma

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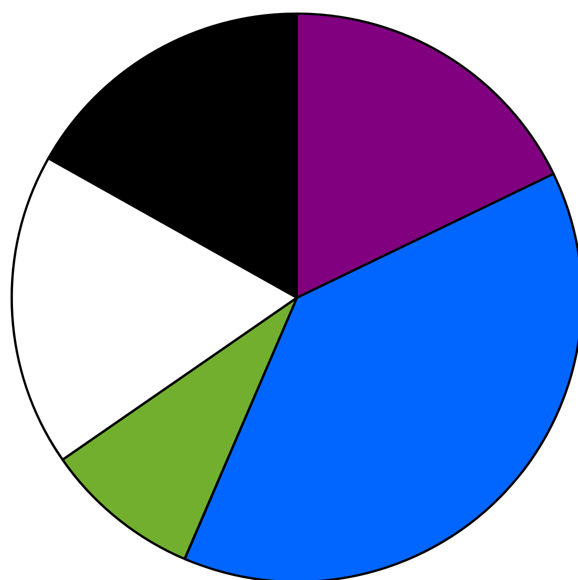
Level of Concern Regarding Steroid Medication



- Very concerned
- Quite concerned
- Neither concerned nor unconcerned
- Not particularly concerned
- Not at all concerned

Brand P, et al., 2009

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TOWARDS ADHERENCE

- **Always discuss potential side effects of using and not using ICS**
- Set goals with *patient and family*
- Step down approach
- Select appropriate device with patient
- Reinforce often at first and at every visit
- Samples
- Team approach for asthma teaching

Impact of Asthma

- **50-60% of children and adults on Canada are not in good control**
  - Landmark Study in Canada 2000
    - TRAC study 2006
    - Asthma Society of Canada 2007
- **Ask Children what bothers them**
  - Run and play
- **Ask Parents/Adults what bothers them**
  - Cough at night, missed school/work, ED visits

Prevalence of Childhood Asthma

Age Group	Boys		Girls		Total	
	%	Number	%	Number	%	Number
4-7	18.2	142,000	10.6	79,500	14.5	221,500
8-11	19.6	160,200	13.4	104,000	16.6	264,200

Numbers are rounded to the nearest 100

Prevalence among Canadian children between ages of 4 and 11 = 15.6% (485,700 children)

Public Health Agency of Canada, 2007

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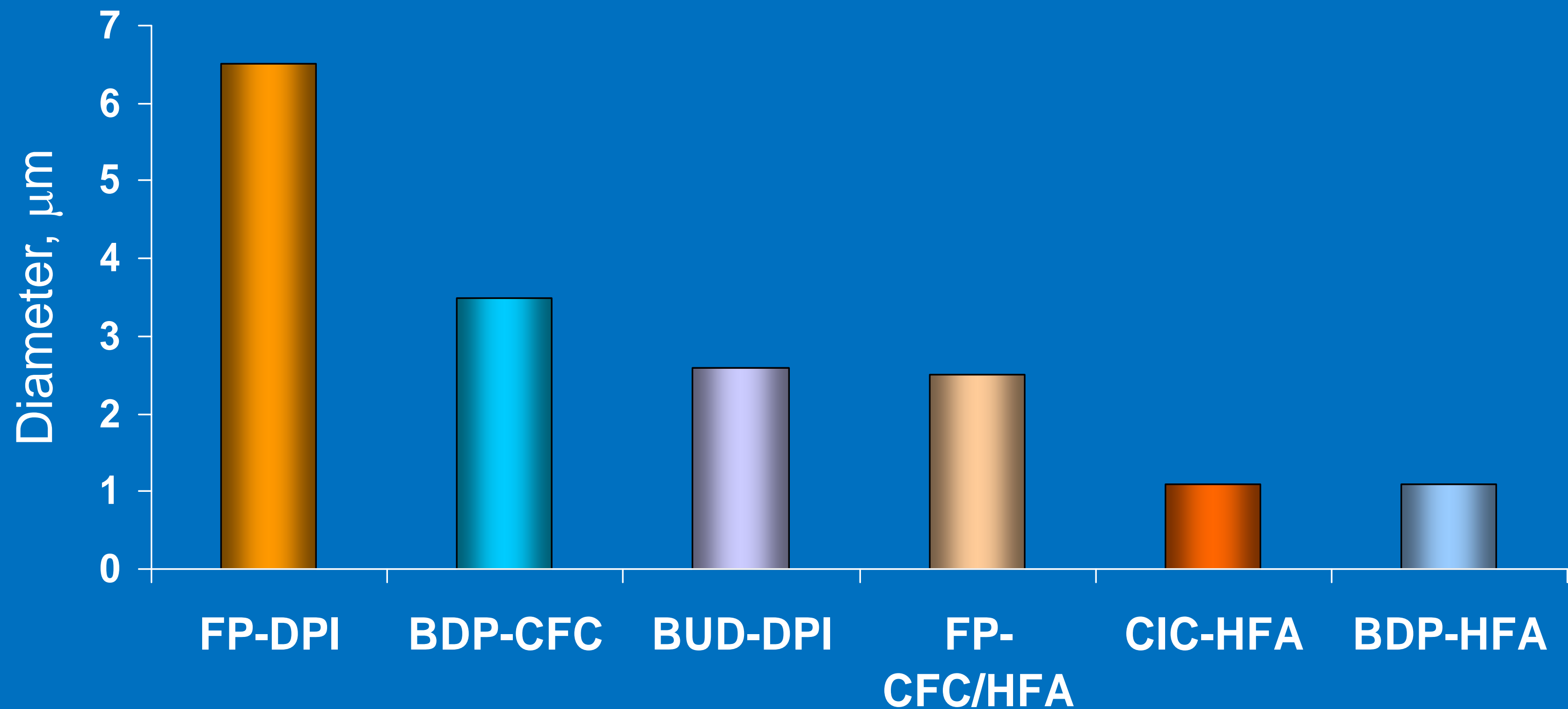
ICS SPECIAL PROPERTIES

- Relative potency
- Pro-drug
- Deposition and particle size
- Lipophilicity
- Esterification
- Half life
- Protein binding

Relative Binding of Corticosteroids to Rat Glucocorticoid Receptor

Corticosteroid	Relative Binding Affinity
(S)-CIC	2
Cortisol	10
(R)-CIC	12
Beclomethasone dipropionate	53
Beclamethasone	76
Dexamethasone (reference)	100
Flunisolide	180
(S)-des-CIC	230
Triamcinolone acetonide	233
Budesonide	935
(R)-des-CIC	1200
17-Beclomethasone monopropionate	1345
Fluticasone propionate	1800

Comparative Particle Size for ICS

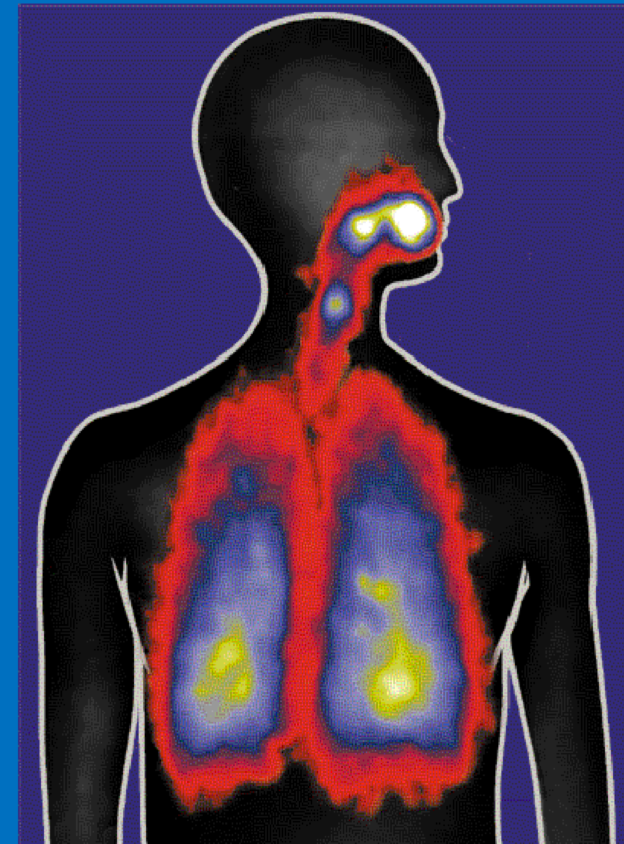


Derendorf. Available at: http://www.medscape.com/viewarticle/467714_1.
Rohatagi. *J Allergy Clin Immunol.* 2003;111:A598.

Lung Deposition of Inhaled Corticosteroids

Dose to the lung

Fluticasone DPI	12%
Fluticasone MDI	12-20%
Budesonide DPI	22-42%
BDP HFA MDI	53-60%
Ciclesonide HFA MDI	52%

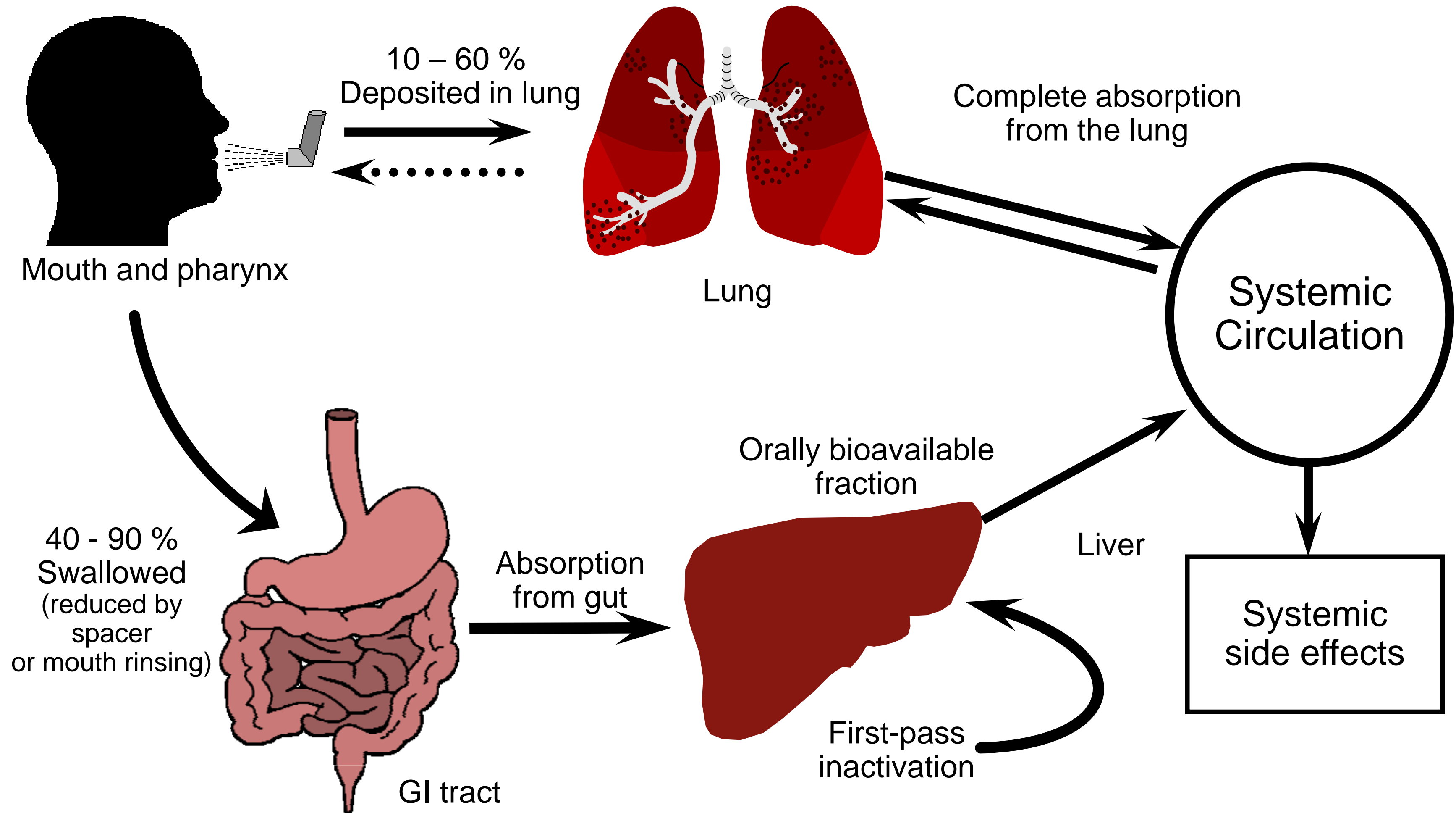


DOSE EQUIVALENCIES

Budesonide	DPI		2
Fluticasone	DPI		1?
BDP (Qvar)	pMDI	+/- spacer	1
Ciclesonide	pMDI	+/- spacer	1
Fluticasone	pMDI	+ spacer	1

The Fate of Inhaled Steroids

How do inhaled steroids cause systemic effects?

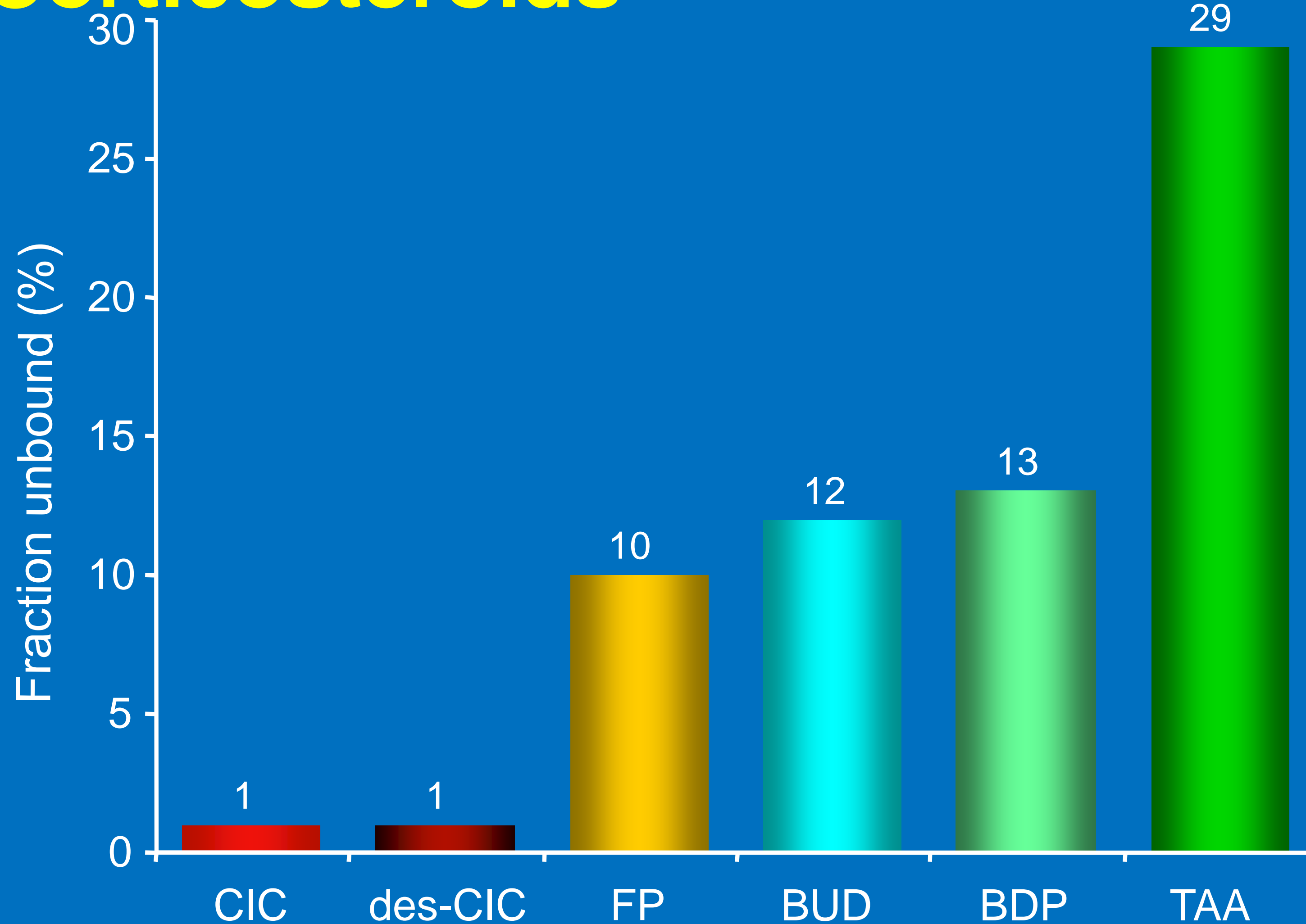


Barnes NC, 2007; Gulliver T, et al., 2007; Salvatoni A, et al., 2003

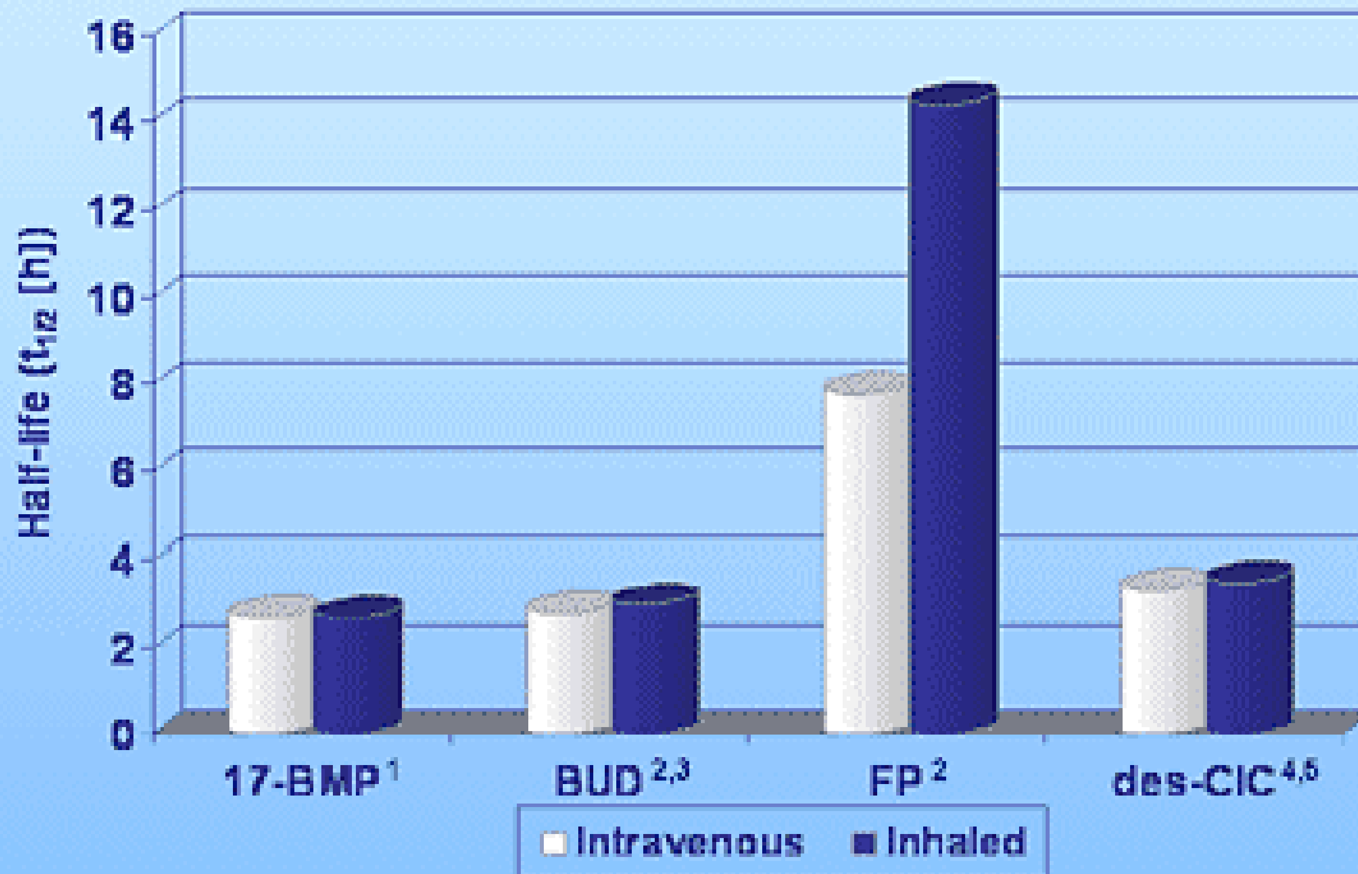
BIOAVAILABLITY

ICS	LUNG	GI
BDP	70-100%	30%
BUD	70-100%	10%
FLUTIC	70-100%	1%
CICLES	70-100%*	1%

Protein Binding of Inhaled Corticosteroids



Derendorf H et al. J Allergy Clin Immunol. 101:S500-6, 1998.



Half-life
Half-life (t1/2 [h])
16
14
12
10
8
6
4
2
0
17-BMP 1
BUD 2,3
FP 2
des-CIC 4,5
Intravenous
Inhaled

Impact of ICS on Short-Term Growth

Summary of literature

Inhaled Corticosteroid	Studies < 1 year
Beclomethasone[1]	Growth suppression at 400 and 800 mcg
Budesonide[2]	Growth suppression at 200, 400 and 800 mcg
Ciclesonide[3]	No detectable effect on childhood growth at 200 and 400 mcg
Fluticasone[4]	Growth suppression at 375, 500 and 1000 mcg

[1]Sharek PJ, et al., 2000
[1]Doull IJM, et al., 2004
[1]Pedersen S, 2002
[1]Wolthers OD, 2006*

[2]Wolthers OD, et al., 1991*
[2] Bisgaard, 2004
[2] MacKenzie C, 1998
[2] Agertoft and Pedersen, 2000
[2] CAMP, 2000
[2] Volovitz, 1993

[3] Agertoft, 2005*
[3]von Berg, 2007
[3]Skoner, 2008
[3] Agertoft, 2009

[4]Allen, et al., 1998
[4]Bisgaard, et al., 2004
[4]Agertoft, 2009
[4] Visser, 2004
[4]Ducharme FM, et al., 2009
[4]Guilbert TW, et al., 2006
[4]Volovitz, 1993

* Indicates study used knemometry

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ICS and Growth

- Dose related short-term effects
  - Most studies low-moderate doses
- It remains to be determined if final adult height will be affected, further study is required
- Consider adrenal suppression if growth is poor

Agertoft L, et al., 2000 CAMP Research Group, 2000; Verberne AA, et al., 1997; Weldon D, 2009

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ICS and Bone

- Several studies have shown no difference in bone mineral density in children treated with ICS
- Reduction in rate of bone mass accretion with ICS use in prepubertal children (prospective cohort) but clinical significance unknown
- Need longer-term prospective studies

Allen, 2000; CAMP Research Group, 2000; Gregson, 1998

Case: 5 ½ Year Old Girl

- Identify:
  - 5 ½ year old girl with asthma
- History of presenting illness:
  - Unwell x 12 hours
  - Unable to rouse in AM
- ER:
  - Treated for hypoglycemic seizure
- ICU x 2 months:
  - Encephalopathic
  - w/u metabolic/infectious/neurological negative

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Case: 5 ½ Year Old Girl

Past medical history

- Past medical history
  - Asthma
  - Fluticasone >500 mcg/day

- Chest clinic
  - Malaise/fatigue/headache/ poor growth
  - Suspected adrenal suppression

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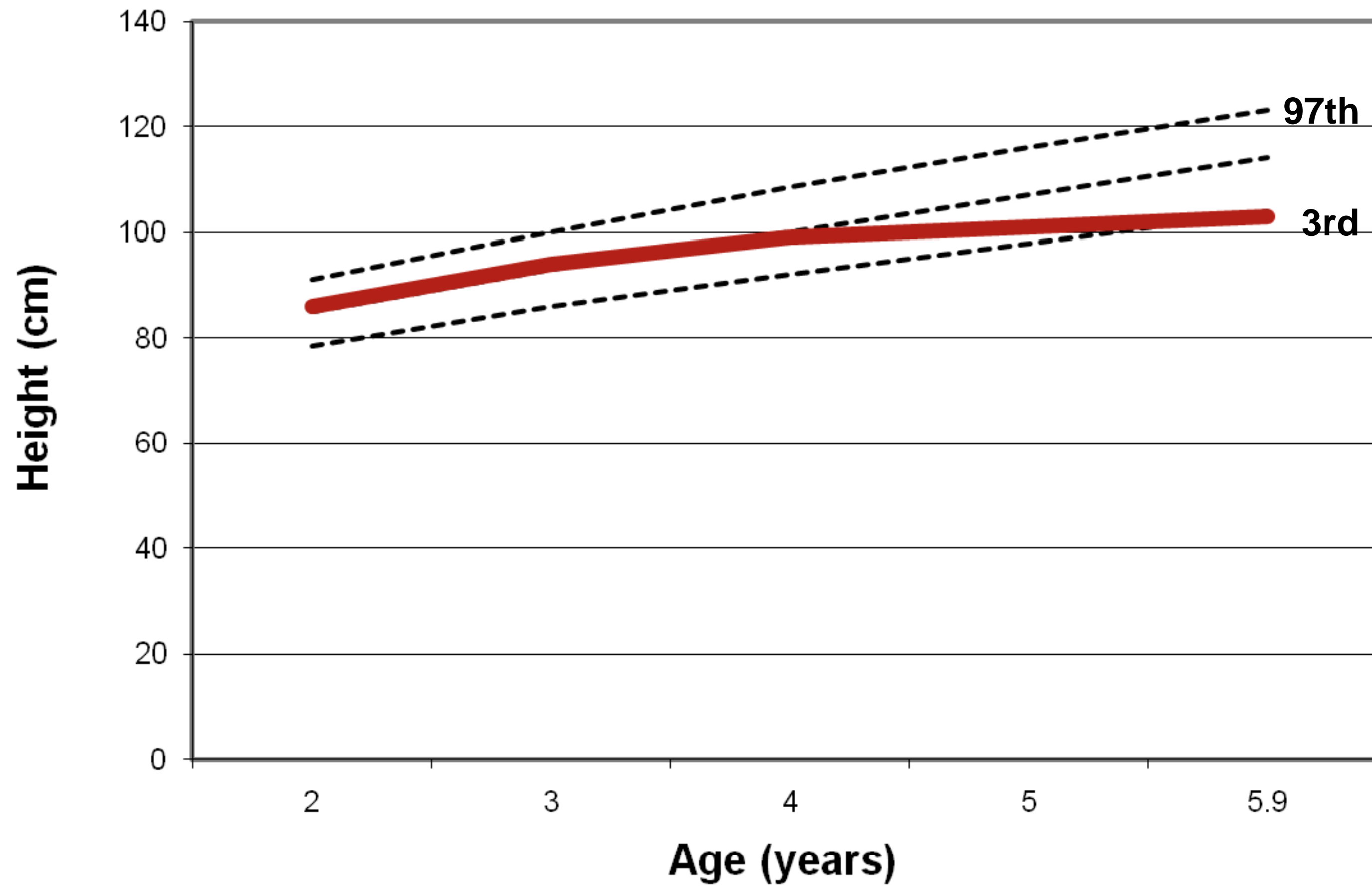
Case: 5 ½ Year Old Girl

Growth



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Case: 5 ½ Year Old Girl

The answer

- ACTH stimulation test:
  - Basal and peak cortisol levels <25nmol/L

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Case: 5 ½ Year Old Girl

The aftermath

- Fluticasone gradually weaned
- Gradual normalization of ACTH stimulation test
- Stress steroids for infection
- 8 months (off steroids x 2mo)
  - cortisol peak >500nmol/L
  - energy much improved
  - asthma well controlled on steroid sparing agents

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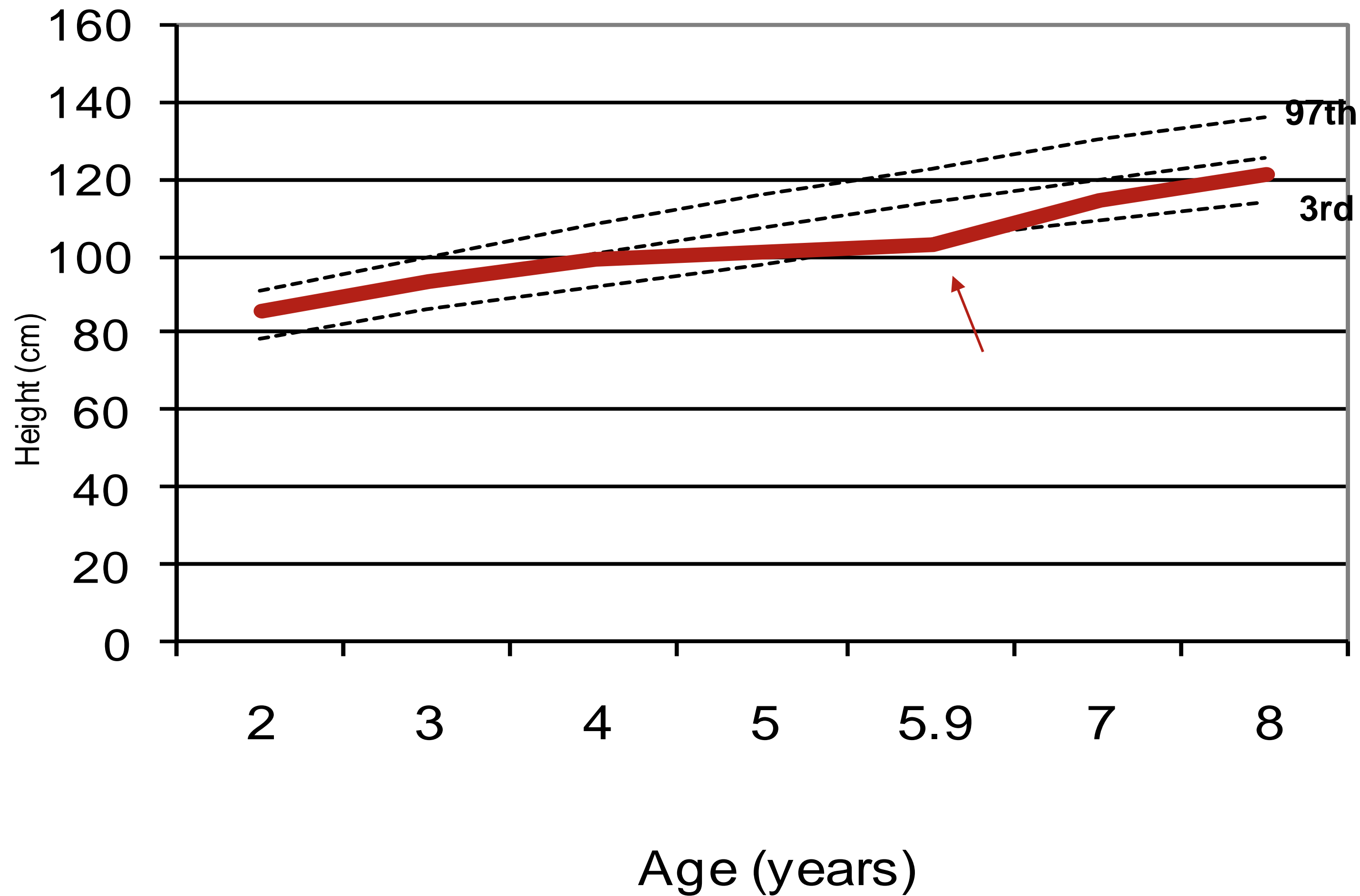
Case: 5 ½ Year Old Girl

Growth



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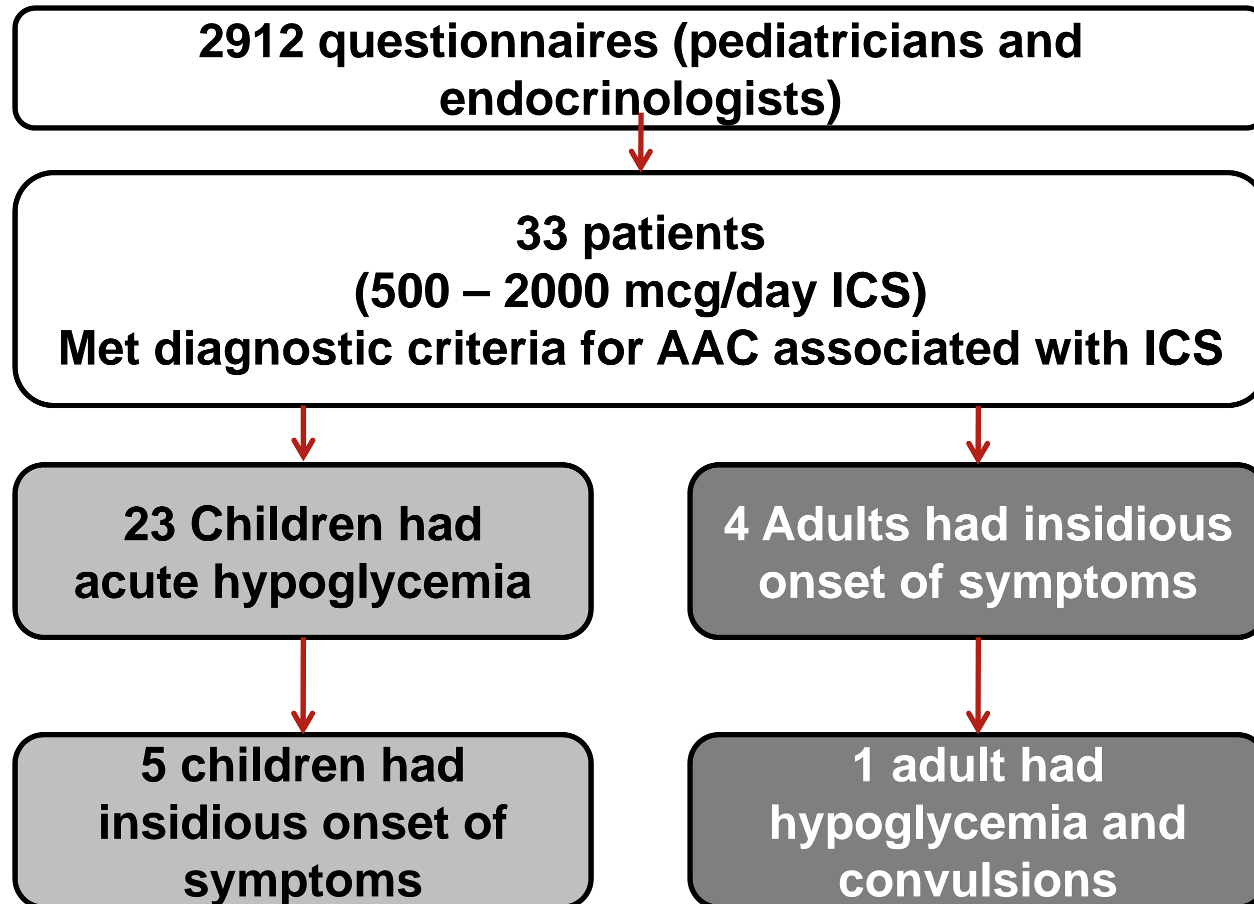
Side effects

- Ritonavir
  - Cyt P450 34A
  - >15 case reports adults and children total > 25 cases from many countries
  - Cushingoid within 2 weeks
  - All Fluticasone from 200 mics/day except 1 Budesonide

CNS SIDE EFFECTS

- Alberta Children’s Hospital
- 2 years
- 814 FP; 427 other
- 18 CNS side effects – ALL FP
  - 16 moody
  - 14 behaviour change
  - 13 hyperactive
  - 12 aggressive
  - 8 attention problems
- Change to Qvar – symptoms disappear

Evidence: Acute Adrenal Crisis (AAC) Associated with ICS



Todd GRG, et al., 2002

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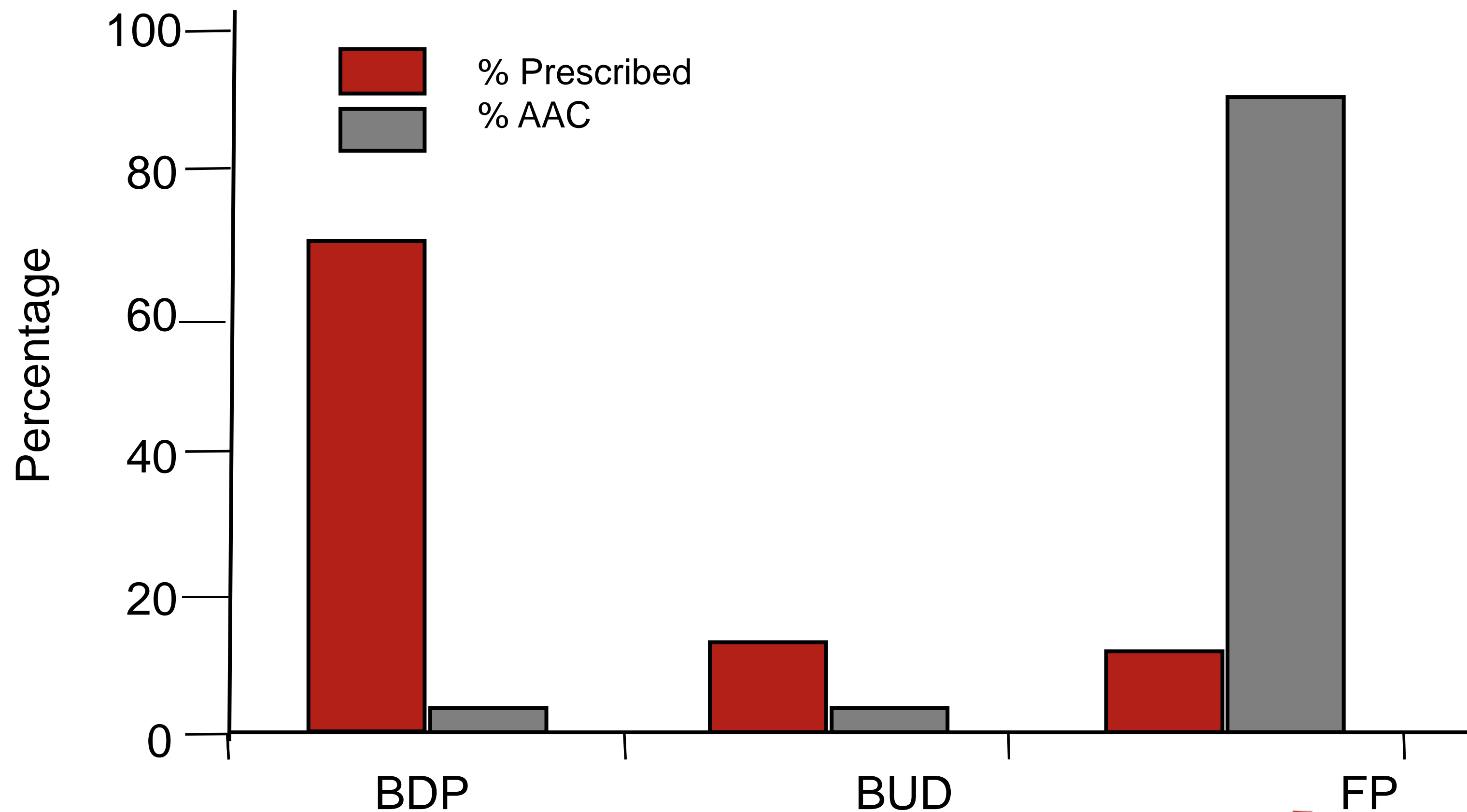
Acute Adrenal Crisis (AAC) Associated With ICS in UK

% Prescriptions compared with % of AAC cases for BDP, BUD, FP



Todd GRG, et al., 2002

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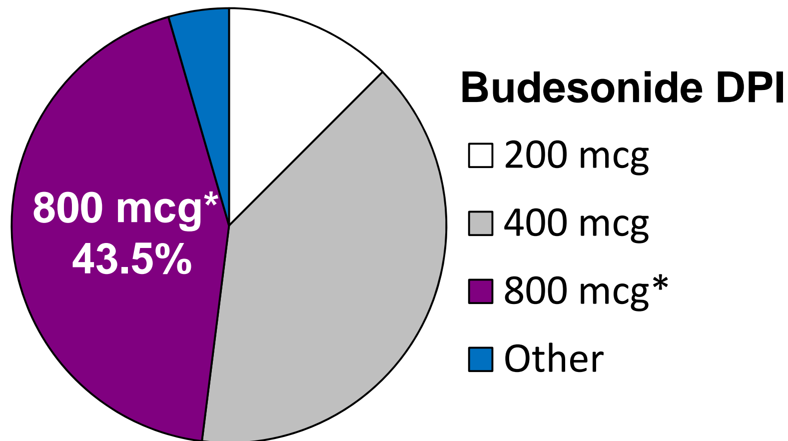
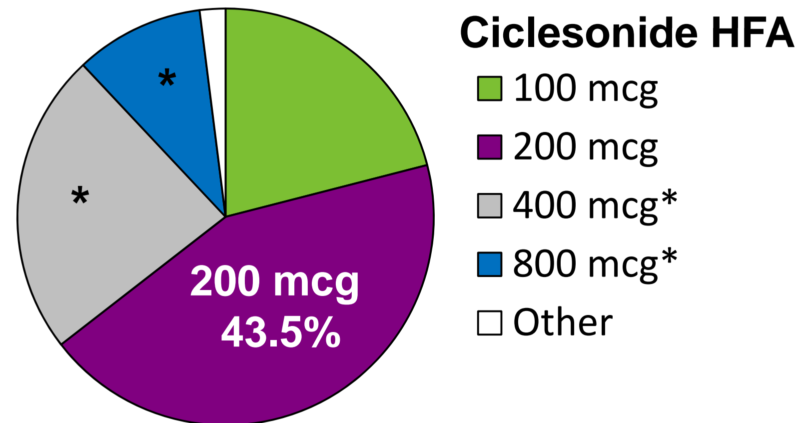
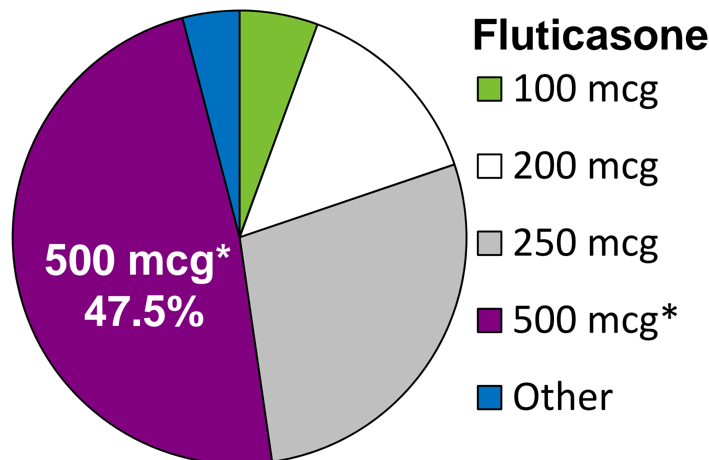
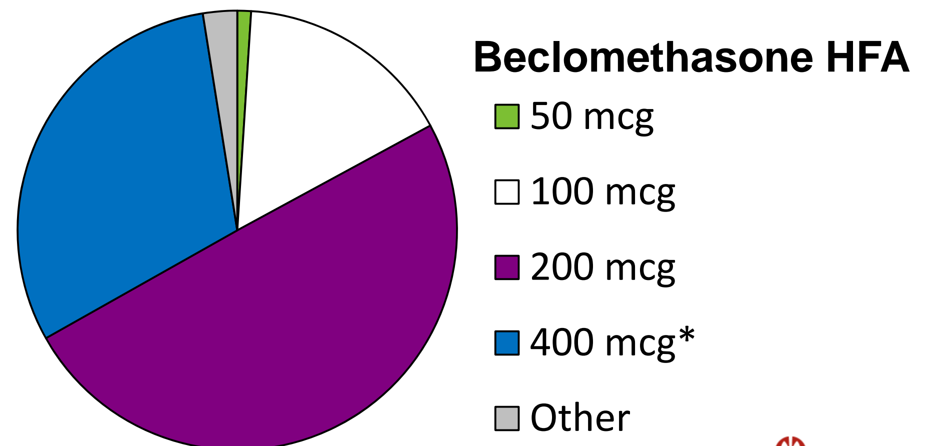
Breakdown of Common ICS Doses

Total average daily dose for ages 0-11 (all indications)









Source: IMS Health Canada, October 2009

considered high dose

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Definitions: Adrenal Insufficiency

Adrenal Insufficiency – Adrenal glands unable to produce a sufficient amount of cortisol secondary to ANY etiology (genetic, iatrogenic, acquired). May be associated with other adrenal hormone deficiencies.

Adrenal Suppression (AS) – Adrenal glands unable to produce a sufficient amount of cortisol secondary to exposure of the HPA axis to exogenous glucocorticoids leading to suppression and, in turn, adrenal insufficiency. Isolated to cortisol deficiency.

Adrenal Crisis – Severe adrenal insufficiency leading to hypoglycemia or hypotension. Can occur with AS.

Fauci AS, et al., 2008

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Adrenal Suppression

- Sustained deficiency of HPA axis function following exposure to exogenous glucocorticoids
- Consider after 2 or more weeks of glucocorticoid therapy, *(depends on the type, schedule of glucocorticoid administration and individual factors)*
- May last from days to one year
- This can predispose an individual to life-threatening acute adrenal insufficiency (crisis)

Under-recognized and under-reported

Alexrod L, 1976, 2003; Kino T, et al., 2001; Sim, et al., 2003

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Symptoms of Adrenal Suppression

<u>Glucocorticoid</u>

- Weakness/fatigue
- Malaise
- Nausea
- Headache
- Poor weight gain

- **Hypoglycemia** *
- **Hypotension** *

** Note: Symptoms often presented in adrenal crisis are indicated in red*

Donohoue PA, 2009; Niewoehner CB, 2004

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Symptoms of Adrenal Insufficiency

Glucocorticoid

- Weakness/fatigue
- Malaise
- Nausea
- Headache
- Poor weight gain

- **Hypoglycemia** *
- **Hypotension** *

Mineralocorticoid

- Salt craving
- Weight loss
- Volume depletion

- **Hyponatremia** *
- **Hyperkalemia***
- **Hypotension***

* ***Note: Symptoms often presented in adrenal crisis are indicated in red***

Donohoue PA, 2009; Niewoehner CB, 2004

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Oral Steroids:

Factors that influence adrenal suppression

- Dose
- Duration
- Timing
- Frequency
- Time for recovery

Consider total body steroid load (oral, nasal, topical, inhaled, etc)

Oral glucocorticoids are frequently used in the treatment of asthma, especially during an exacerbation

Axelrod L, 1976; Carter ME, et al., 1972; Cunha CDF, et al., 2004; Felner EI, et al., 2000; Graber AL, et al., 1965; Livanou T, et al., 1967; Myles AB, et al., 1971; Nichols T, et al., 1965; Plager JE, et al., 1962

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Growth and HPA Suppression of ICS

- Height standard deviation score (SDS) change is NOT a sensitive predictor of adrenal suppression
- Growth and adrenal suppression can be independent side effects of ICS

Dunlop KA, et al., 2004

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Adrenal Suppression (AS) Diagnosis

Cortisol values

Best Test:

- Low Dose (1 mcg) ACTH stimulation test >500nmol/L

Other:

- **8 AM** cortisol < 85nmol/L
- Cortisol value < lab norm *may* indicate AS–consider endocrine consult
- A normal non-stimulated cortisol does NOT rule out AS

Note:

- Urinary cortisol in NOT a specific marker of AS

Agwu JC, 1999; Elhadd T, et al., 1999; Erturk E, et al., 1998; Thaler LM. 1998; Tordjman K, Jaffe A, et al., 2000

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Faculty Recommendations:

Minimizing risk of systemic effects with ICS

All Patients:

- Maintain good control of asthma at the lowest possible dose of ICS (regular re-evaluation)
- Consideration of ICS with minimal systemic effects
- Educate patients and family on potential systemic side effects of ICS – but compare to social benefits

Allen, DB, 2005

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Screening For Adrenal Suppression?

Children and Adolescents

When to Screen?

- **Persistent symptoms of suppression**
- **Patients receiving high dose ICS** (eg >500 mcg fluticasone, >800-1200 mcg beclomethasone/budesonide)

How to Screen?

- **Complete <u>8 am</u> cortisol test**
- **Do at 8 am or earlier, no CS night before**
  - <137 nmol/L or repeat value < Lab Normal – **urgent endocrine consult – phone call**
  - 137 nmol/L - Lab normal (400)– repeat within one week
  - within lab normal range - repeat every 6 months

Allen, DB, 2005; Gulliver T, et al. 2005; Derendorf H, 2007

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Treatment of Adrenal Suppression

Proven Adrenal Suppression:

- "stress steroids" – illness and surgery
- +/- daily steroids
- Consider MedicAlert bracelet
- Education

PO Steroids:

- >3 weeks (cumulative within 1yr) should consider testing
- <3 weeks (cumulative within 1yr) awareness of possible adrenal suppression

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Treatment of Adrenal Suppression

- Major stress (surgery, hypotension):
  - 50-100 mg/m^2 x1 and then 25 mg/m^2 every 6 hours IV hydrocortisone
- Minor stress (fever, intercurrent illness):
  - 20-30 mg/m^2/day IV/PO hydrocortisone divided every
    8 hours
- Family education - If vomiting and on high dose ICS, consider Dexamethasone .6 mg/kg/day, especially if URTI.

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Adrenal Crisis

Symptoms of crisis:

- Suspect if on high dose ICS, vomiting
- Draw a cortisol level immediately
- Stress-dose of hydrocortisone (100 mg/m^2)
- Call endocrinologist
- **Hypoglycemia**
- **Hypotension**

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Faculty Recommendations:

Bone and growth

- Standard of care: take growth measurements and plot on curve every 6 months
- If poor growth consider all etiologies (AS, asthma, other)
- Growth velocity < 4cm/yr consider endocrine referral
  - Please pass along growth charts to endocrinologist

- Avoid all controllable risk factors for osteoporosis
- Adequate calcium and vitamin D
- Bone mineral density (BMD) only if systemic steroids

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Faculty Conclusions:

1. Inhaled corticosteroids should be the mainstay pharmacological treatment for the management of asthma.
   - In moderate doses, these are safe medications
2. Consider total body steroid load of asthmatic patients (oral/topical, nasal and inhaled).
   - Individualized therapy with goal of asthma control using minimal effective dose
   - Consider clinically important differences between ICS
3. Ensure adequate growth measurements, 6 months apart, and plot on curve.
4. In children on high doses of ICS (eg >500 mcg Fluticasone) screen & monitor for adrenal suppression every 6 months. Consider referral to endocrinologist.

Allen DB, 2005

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