Unità di Pediatria ad Alta Intensità di Cura
Università degli Studi di Milano
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

34 Congresso Nazionale di
ANTIBIOTICOTERAPIA
in età pediatrica

Gli steroidi inalatori nel bambino con allergia respiratoria

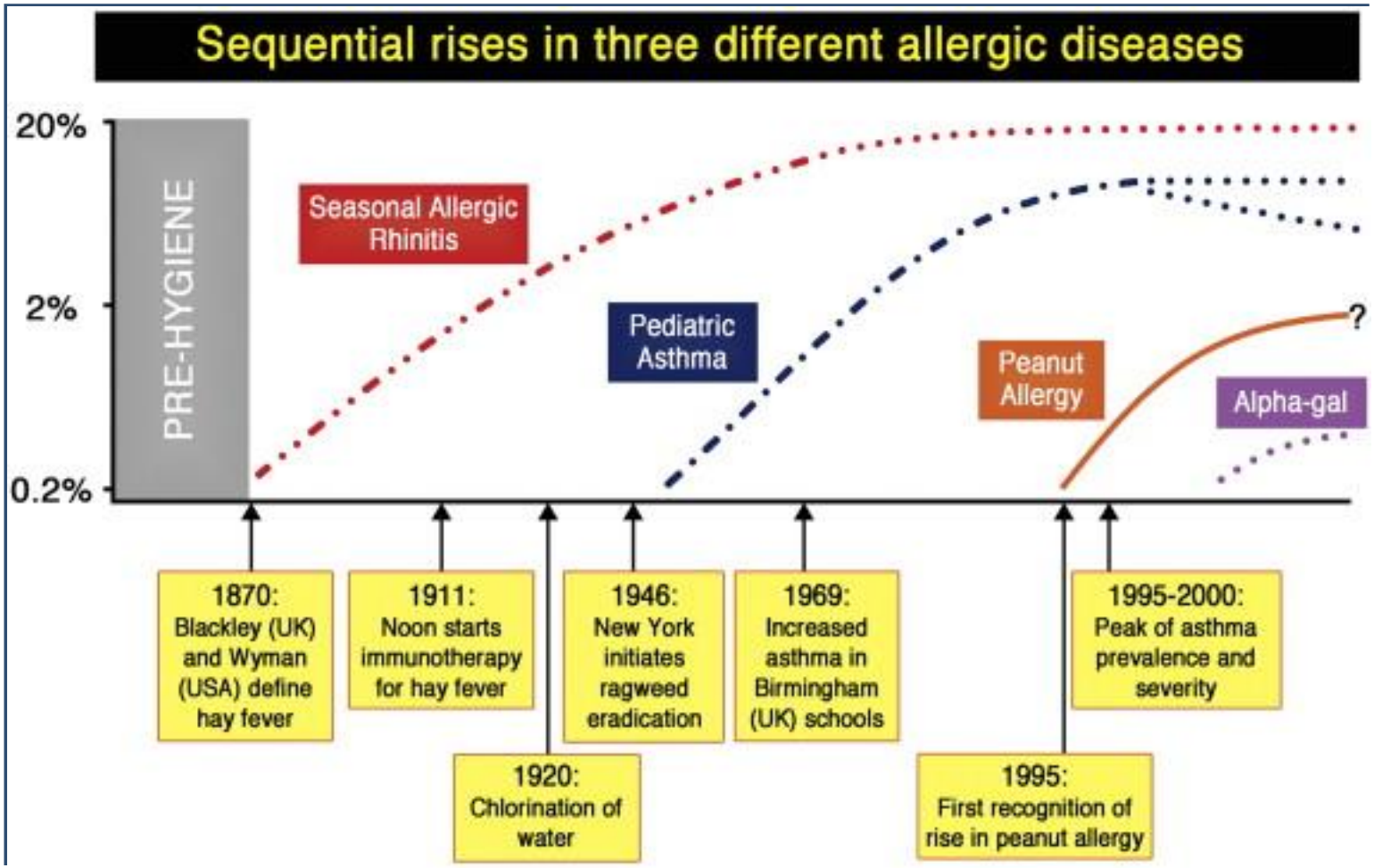
E. Novembre, Firenze

34 Congresso Nazionale di
ANTIBIOTICOTERAPIA in età pediatrica
Milano, 11 - 12 - 13 novembre 2015 | Centro Congressi AtaHotel Executive

Gli steroidi inalatori nel bambino con allergia respiratoria

Elio Novembre
SODc Allergologia
AOU Meyer Firenze

The allergy epidemics: 1870-2010



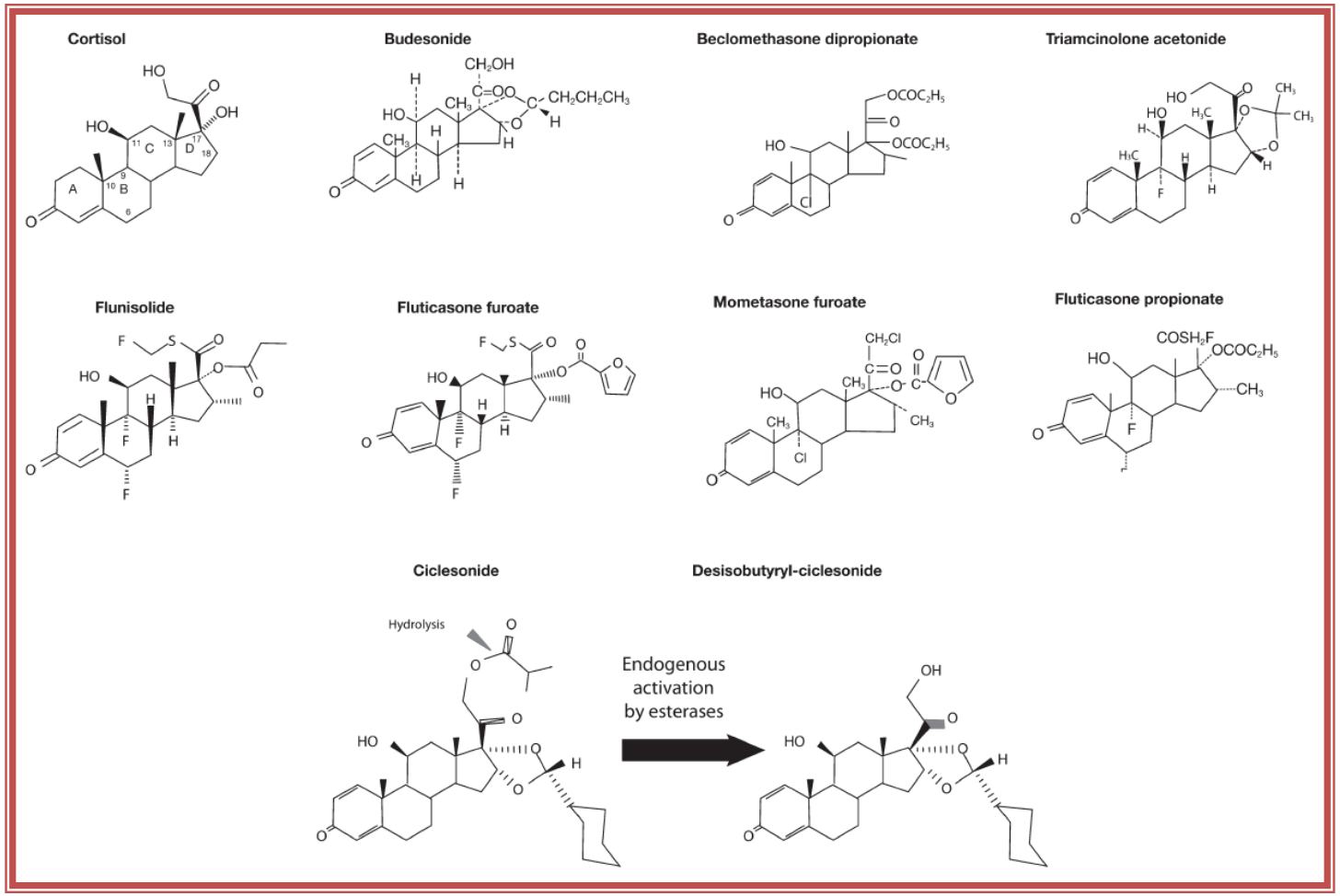
Platt Mills TA. J Allergy Clin Immunol. 2015 Jul;136(1):3-13

I Corticosteroidi inalatori

- Trattamento preferenziale delle patologie allergiche delle prime vie aeree
- Prevalente azione locale e bassa attività sistemica
- Azione su tutte le cellule infiammatorie (linfociti, cellule epiteliali, mastociti, eosinofili, basofili e cellule di Langerhan);

Mygind N, J Allergy Clin Immunol, 2001

I Corticosteroidi inalatori



Le variazioni sull'anello pentatomico D in posizione 16,17 e 21 differenziano le varie molecole.

Profilo farmacologico di alcuni CSI

Pharmacological profiles of inhaled corticosteroids (ICSs) available for asthma treatments (Chung 2009, Tamm 2012, Cazzola 2014).

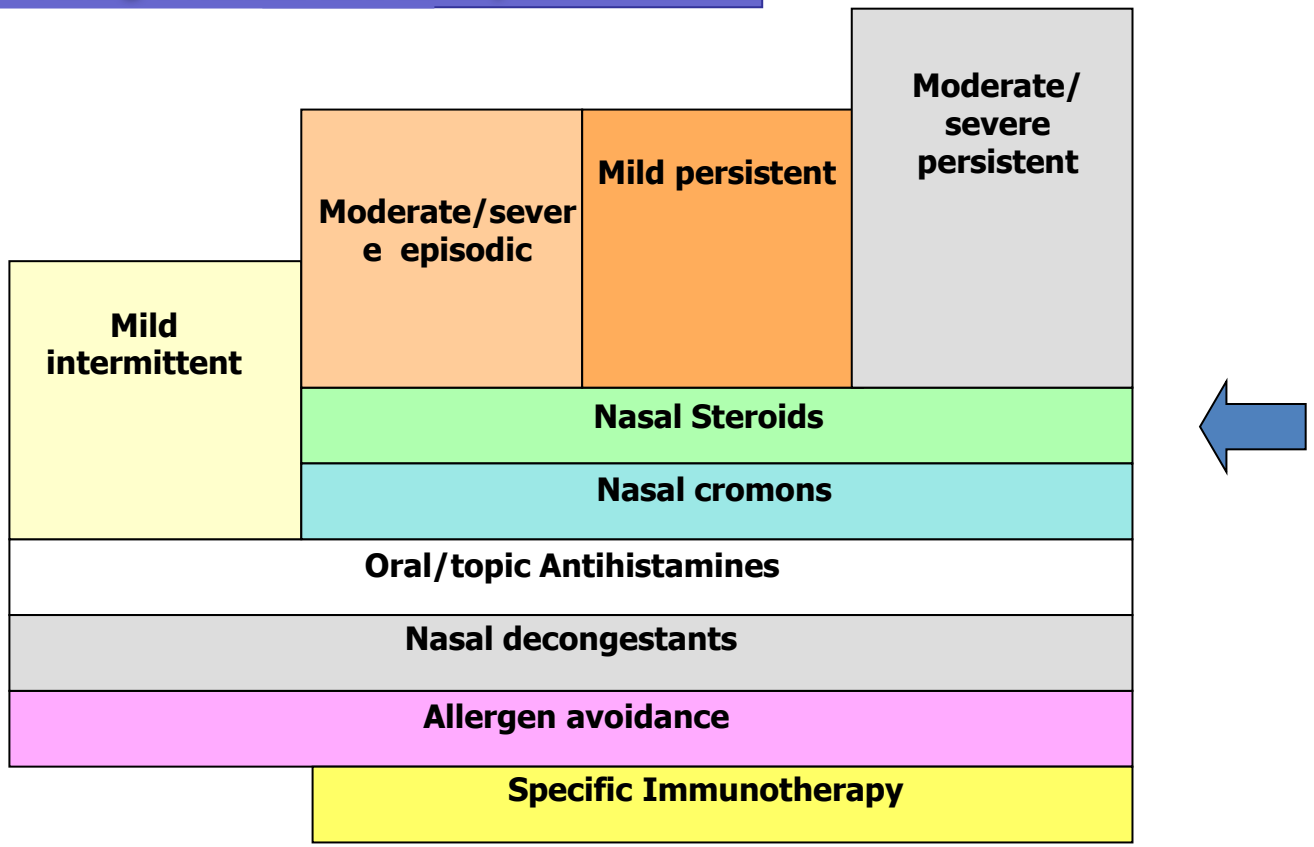
ICS	Relative receptor binding affinity[c]	Protein binding (%)	Oral bioavailability (%)	Pulmonary bioavailability (%)	Systemic clearance (L/h)	Half-life (h)	Distribution volume (L)
Beclometasone[a]	53	87	15–20	50–60	150–230	0.1	20
Beclometasone 17 mono propionate[b]	1345	na	26–40	na	120	2.7	424
Budesonide	935	88	11	15–30	84	2.0–2.8	183–280
Ciclesonide[a]	12	99	<1	50	152	0.4–0.5	207
Desciclesonide[b]	1200	99	<1	na	228–396	3.6–5.1	897–1190
Fluticasone propionate	1800	90	<1	20	66–69	14.4	318–859
Mometasone furoate	2300	99	<1	11	54	4.5	152–332

[a] This agent is activated to its active metabolite in the airway.
[b] Active metabolite.
[c] Receptor-binding affinity is relative to dexamethasone 100.

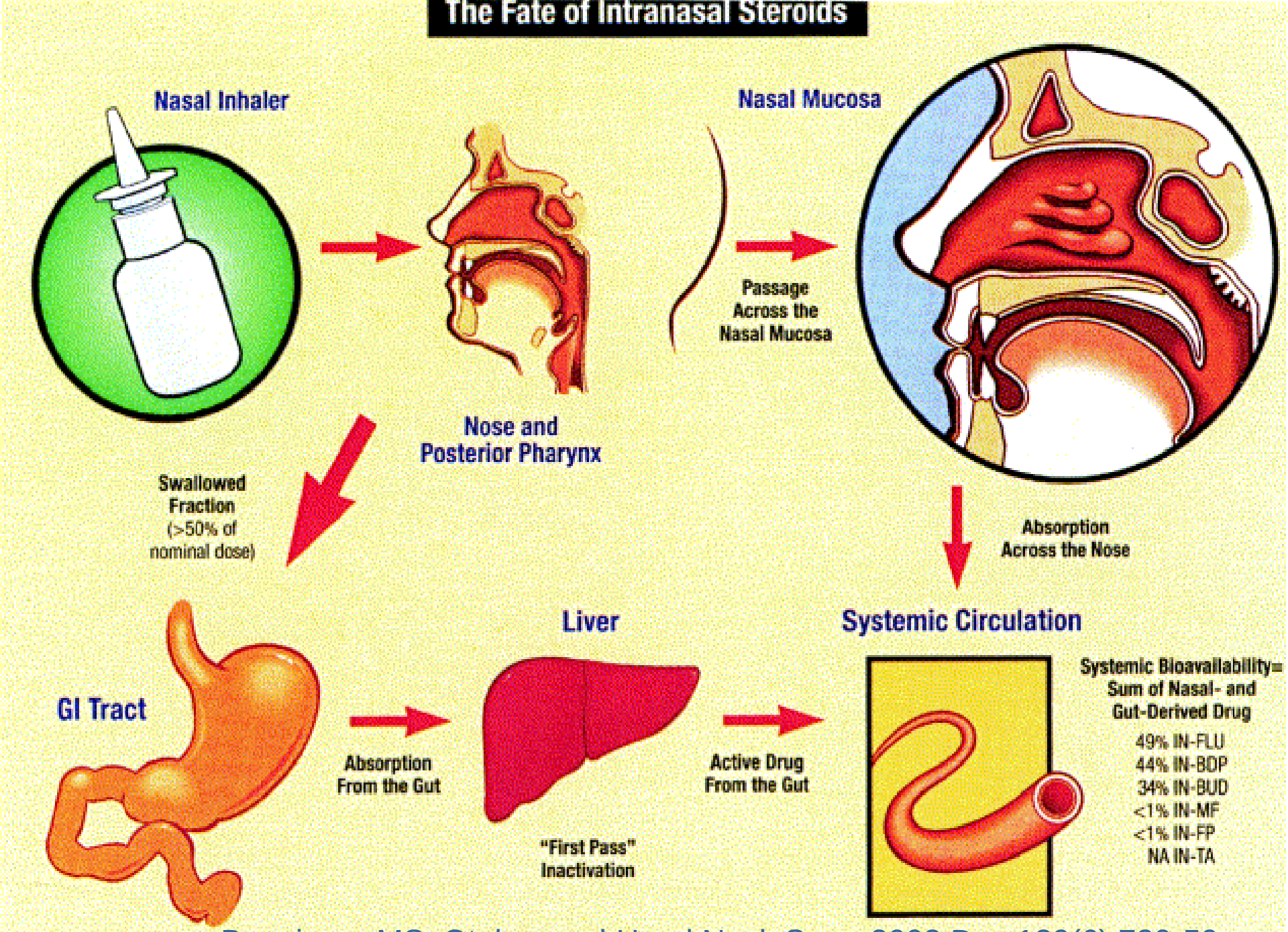
CS intranasali

ARIA

Allergic rhinitis and its impact on asthma



Bousquet J. J Allergy Clin Immunol 2001;108:S147-334.



Benninger MS, Otolaryngol Head Neck Surg. 2003 Dec;129(6):739-50

CS nasali efficacia clinica

In base ai dati della Letteratura, non vi è una chiara evidenza che un particolare CSN sia superiore ad un altro nella terapia della rinite allergica nonostante le varie differenze farmacologiche tra i diversi composti

H. Derendorf Allergy, 2008

CS nasali: sicurezza

Differenze nella sicurezza tra i vari CSN sono più teoriche che basate sull'evidenza, in particolare per quello che riguarda i possibili effetti sulla crescita.

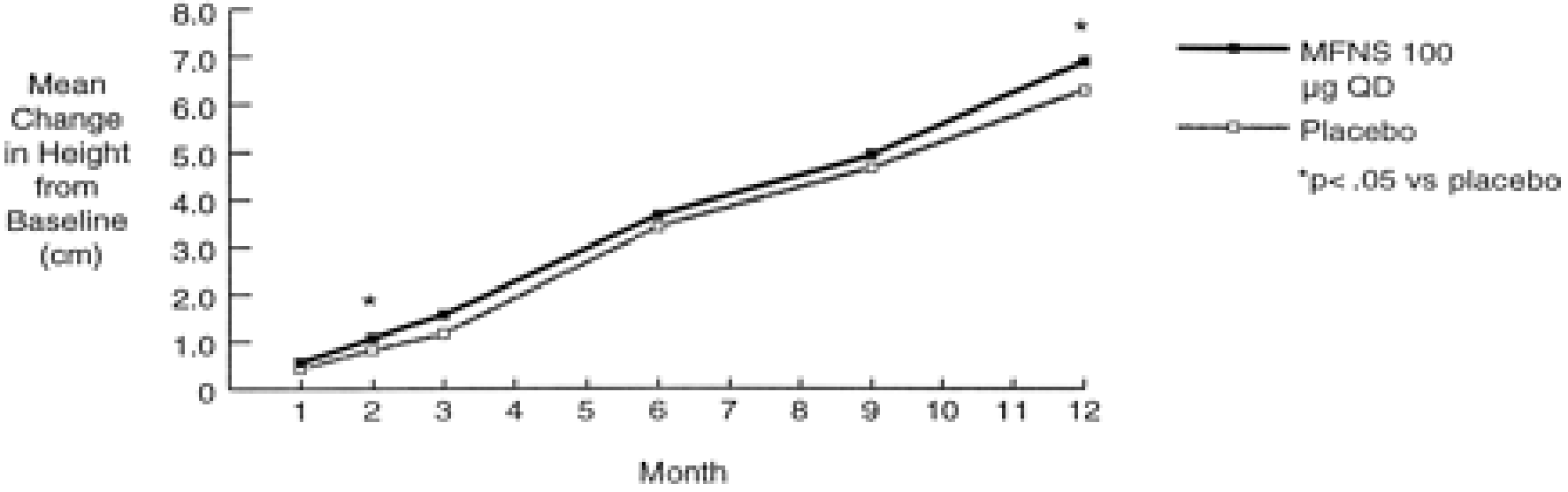
H. Derendorf Allergy, 2008

CS nasali : effetti sulla crescita

Nessuna evidenza di effetti sulla crescita in numerosi studi a lungo termine con MF, FP, Bud, Cic in bambini e adolescenti quando i CSN sono stati usati alle dosi raccomandate.

Sastre J et al, J Investig Allergol Clin Immunol 2012; Vol. 22(1): 1-12

Absence of growth retardation in children with perennial rhinitis after 1 year of treatment of mometasone furoate nasal spray



Schenkel EJ et al, Pediatrics 2000;105:E22

Local adverse effects of INC: Epistaxis

- In most clinical trials of INC, the incidence of epistaxis is modestly above or similar that of placebo, and most episodes are mild and transient

Sastre J et al, J Investig Allergol Clin Immunol 2012; Vol. 22(1): 1-12

Beclometasone dipropionato

Fluticasone furoato

Budesonide

Triamcinolone acetonide

Fluticasone dipropionato

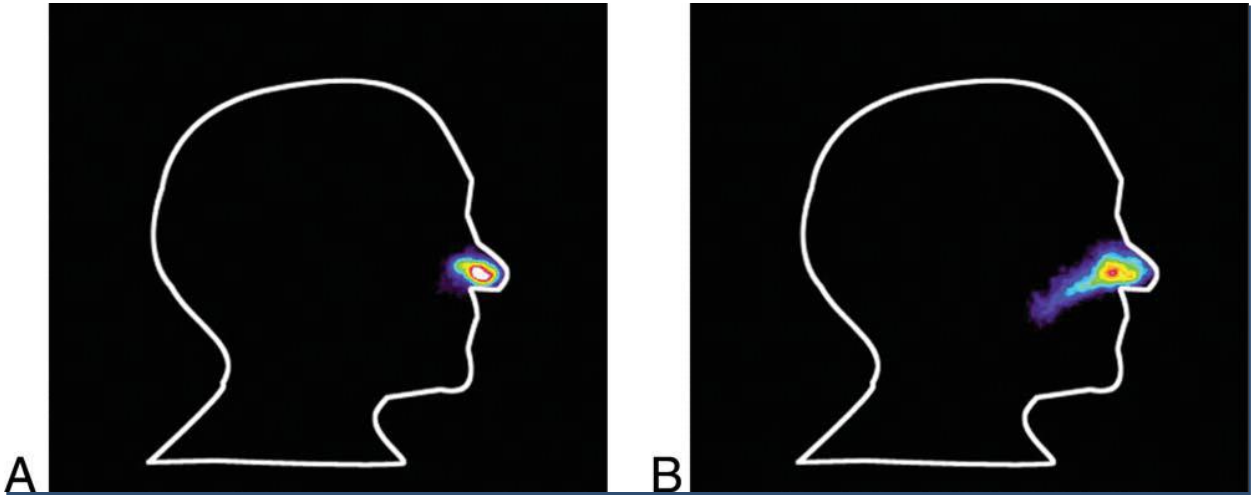
Mometasone furoato

Cicloesanide

CIC nasal aerosol using a nasal MDI with an HFA propellant (CIC-HFA) is now available for the treatment of symptoms associated with PAR and SAR in individuals aged ≥12 years.

Sunovion Pharmaceuticals, Inc. Zetonna (ciclesonide) nasal aerosol package insert. Marlborough, MA; January 2012.

Nasal deposition of ciclesonide nasal aerosol and mometasone aqueous nasal spray in allergic rhinitis patients



In this scintigraphy study, radiolabeled CIC-HFA delivered via a nasal MDI resulted in significantly higher deposition and retention in the nasal cavity compared with radiolabeled MFNS. The CIC-HFA nasal aerosol offers an alternative treatment for patients with AR who may find nasal runoff and rundown to the back of the throat to be bothersome

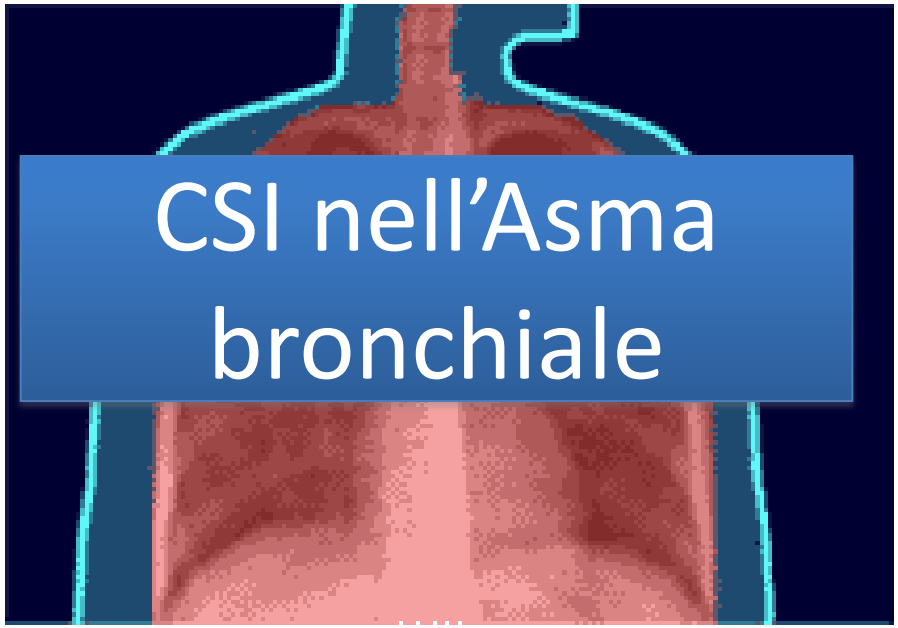
S.; Meltzer, American Journal of Rhinology & Allergy 2014

Nasal CS:Tecnique of administration

Table 3. Recommended Technique for Using Topical Intranasal Corticosteroid Sprays [51]

1. Hold head in a neutral, upright position
2. Clear nose of any thick or excessive mucus, if present, by gently blowing the nose
3. Insert spray nozzle into the nostril
4. Direct the spray laterally or to the side, away from the middle of the nose (septum) and toward the outer portion of the eye or the top of the ear on that side. (If possible, use the right hand to spray the left nostril and left hand to spray the right nostril, to direct the spray away from the septum)
5. Activate the device as recommended by the manufacturer, and use the number of sprays recommended by the doctor
6. Gently breathe in or sniff during the spraying
7. Breathe out through the nose

(Adapted from *Benninger MS et al. Techniques of intranasal steroid use. Otolaryngol Head Neck Surg. 2004;130:5-24.*)



CSI nell'Asma bronchiale

- Riducono i sintomi asmatici
- Riducono il rischio di ospedalizzazione
- Migliorano la funzione polmonare
- Riducono la iperreattività bronchiale
- Migliorano la qualità di vita

GINA 2015

- Non prevengono lo sviluppo di asma in bambini ad alto rischio
- Non inducono una remissione dell'asma
- Effetti controversi sul rallentamento della perdita di funzione polmonare

Stoloff SW and Kelly HV. COACI 2011

Trattamento dell'asma

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Farmaci di controllo di prima scelta		Bassa dose ICS	Bassa dose ICS/LABA*	Dose medio-alta ICS/LABA	Trattamento add-on per es.: Anti-IgE
Altre opzioni	Considerare bassa dose ICS	Antileucotrieni (LTRA) Bassa dose di Teofillina*	Dose medio-alta ICS Bassa dose ICS+LTRA (o + Teofillina*)	Alta dose ICS+LTRA (o + Teofillina*)	Aggiungere bassa dose steroide orale
Farmaci al bisogno	SABA secondo necessità		SABA secondo necessità o Bassa dose ICS/formoterolo**		

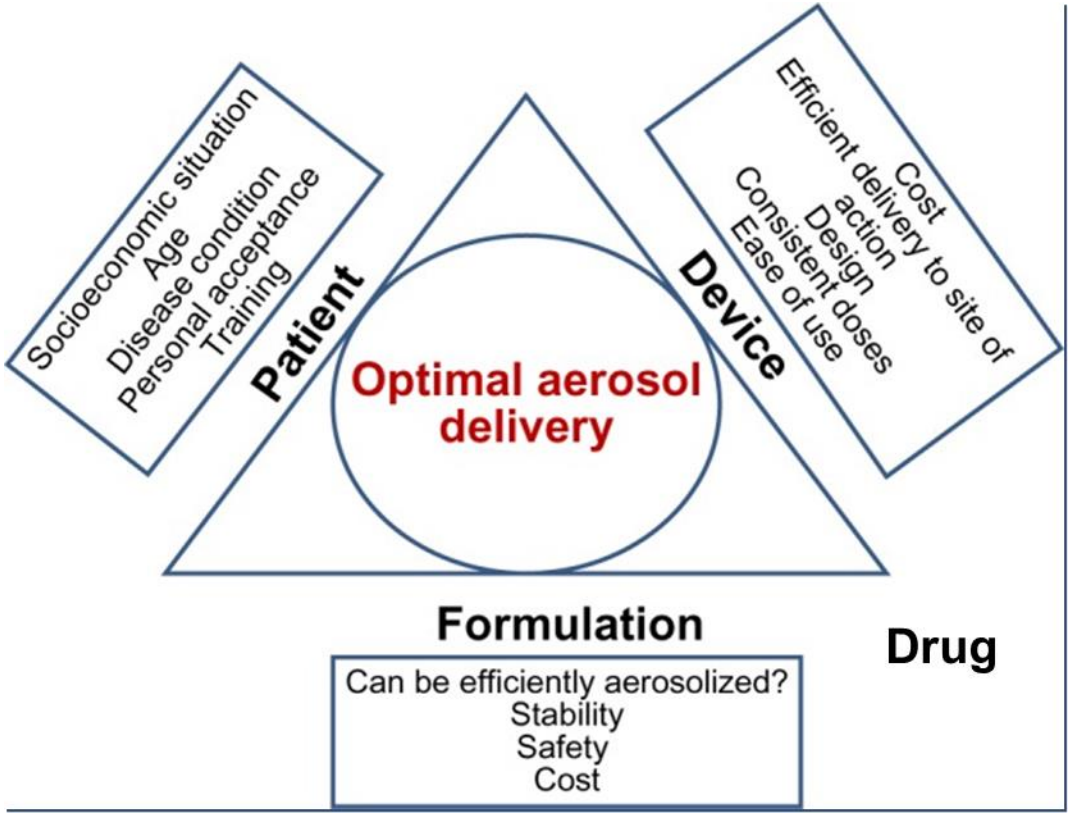
*Per bambini fra 6 e 11 anni la teofillina non è raccomandata e il trattamento di step 3 consigliato è la dose media di ICS ** Nei pazienti in terapia con bassa dose di budesonide/formoterolo o bassa dose di beclometasone/formoterolo il trattamento al bisogno è rappresentato da ICS a bassa dose/formoterolo

Basse, medie e alte dosi di corticosteroidi inalatori
Bambini 6–11 anni

Corticosteroidi inalatori	Dose giornaliera totale (mcg)		
	Bassa	Media	Alta
Beclometasone dipropionato (CFC)	100–200	>200–400	>400
Beclometasone dipropionato (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (HFA)	80	>80–160	>160
Fluticasone propionato (DPI)	100–200	>200–400	>400
Fluticasone propionato (HFA)	100–200	>200–500	>500
Mometasone furoato	110	≥220–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

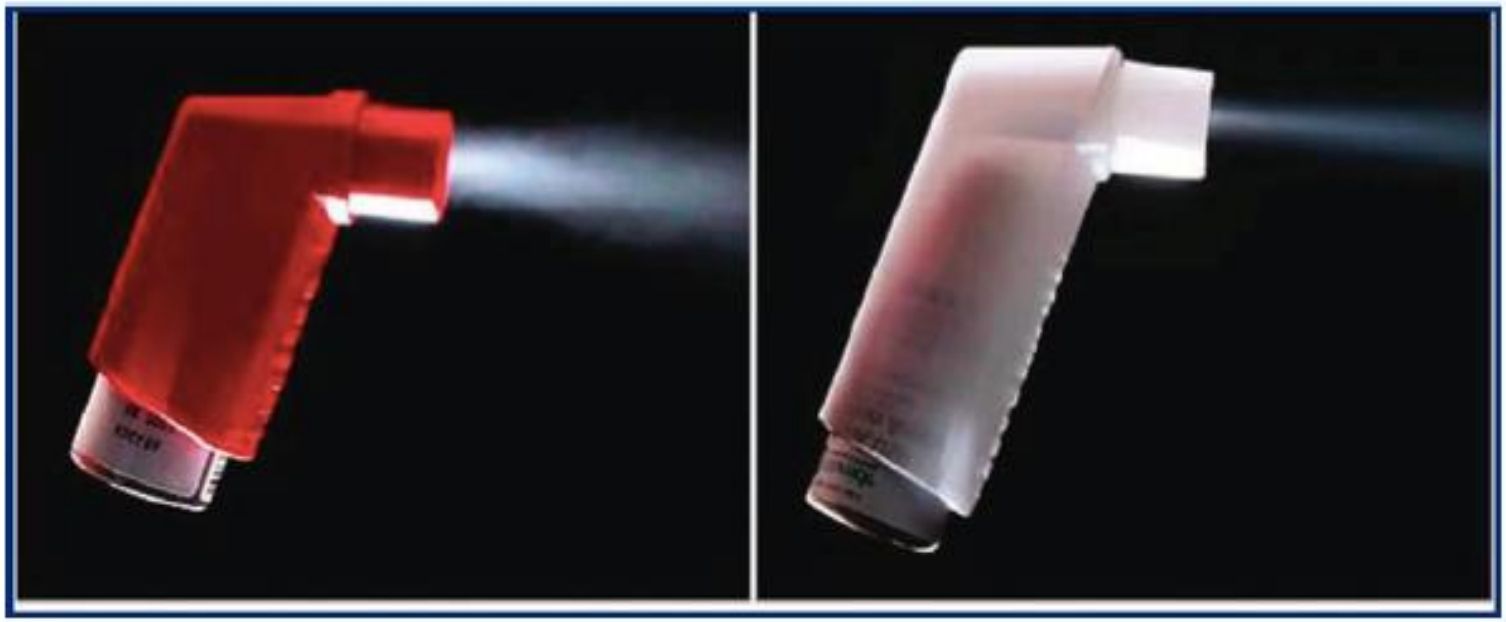
- Non è una tabella di equivalenza,ma una comparazione clinica stimata
- La maggior parte dei benefici clinici da ICS è evidenziabile a basse dosi
- Le alte dosi sono arbitrarie, ma nella maggior parte di ICS l'uso prolungato è associato ad un aumentato del rischio di effetti avversi sistemici


Asthma Nurse - Real Life
Humidose
Nasonex


Socioeconomic situation
Age
Disease condition
Personal acceptance
Training
Patient
Optimal aerosol delivery
Device
Cost
Efficient delivery to site of action
Design
Consistent doses
Ease of use
Formulation
Can be efficiently aerosolized?
Stability
Safety
Cost
Drug

Nuovi Propellenti per MDI

Negli ultimi anni la proibizione dei CFC per motivi ambientali ha favorito l'uso di HFA (composti in soluzione e non in sospensione) che genera particelle molto più piccole con frazioni respirabili molto diverse.



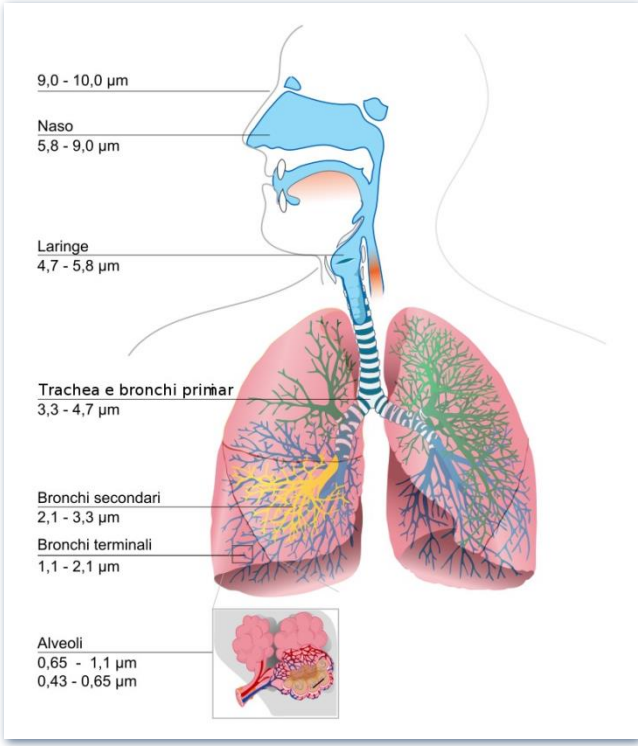
HFA: MMAD= 1,1 µm , frazione respirabile 50%

CFC: MMAD= 3.5–3.9 µm ,frazione respirabile 10%

Extra fine particle inhaled corticosteroids, pharmacokinetics and systemic activity in children with asthma.

Table 1. Median mass aerodynamic diameter (MMAD) (µm) of fine particle size inhaled ,corticosteroids currently available;

Ciclesonide pMDI (Alvesco®):	1.1
Beclometasone dip. pMDI (Qvar®; Aerobec®):Clenilexx	1.1
Beclometasone dip.+formot. pMDI (Fostair®; Innovair®):	1.1-1.5
Fluticasone furoate+vilanterol trifenatate (Relvar Ellipta®):	2.3
Fluticasone propionate pMDI (Flixotide®):	2.4
Budesonide+formoterol dry powder (DuoResp Spiromax®):	2.5
Fluticasone propionate+formoterol pMDI (Flutiform®):	3.2
Budesonide dry powder (Giona Easyhaler®):	4.0
Budesonide dry powder (Spirocort Turbuhaler®):	4.0
Fluticasone propionate dry powder (Flixotide Discus®):	5.4



Wolthers OD. Pediatr Allergy Immunol. 2015 Sep 11. doi: 10.1111/pai.12491.

Ciclesonide inhalation aerosol

Ad oggi si dispone di dati insufficienti relativamente al trattamento con ciclesonide dei bambini al di sotto di **12 anni di età**

Beclomethasone dipropionate HFA autohaler

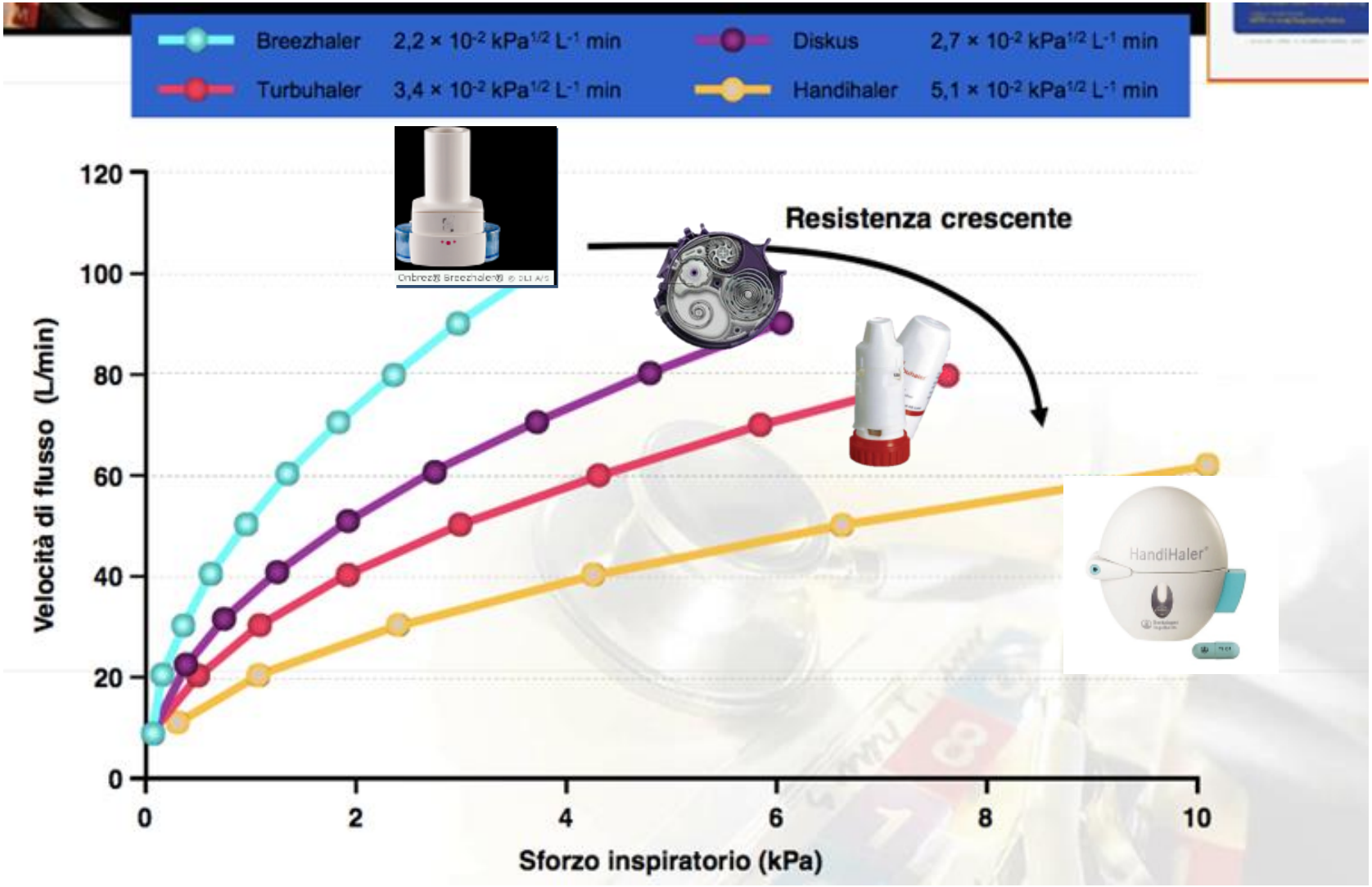
Adults (including the elderly) and children over **12 years**

Clenilexx 100 mcg

Beclometasone dipropion.+formot. pMDI **100/6** inhalation aerosol

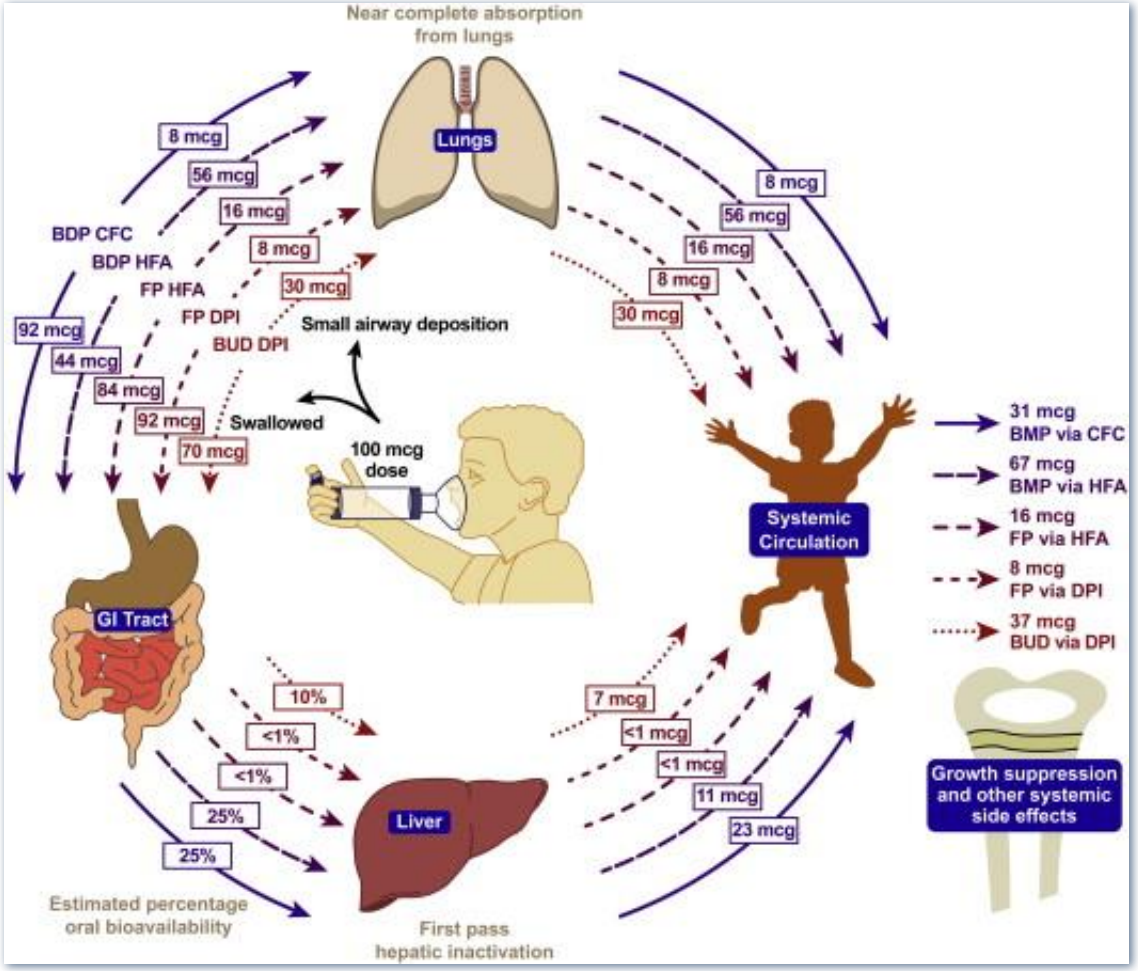
The safety and efficacy of Fostair in children and adolescents under 18 years of age have not been established yet. No data are available with Fostair in children under 12 years of age. Only limited data are available in adolescents between 12 and 17 years of age**.** Therefore **Fostair is not recommended for children and adolescents under 18 years** until further data become available.

Resistenza di alcuni DPI e flussi necessari per l'attivazione



Singh D et al. ATS 2010

Effects of drug and device characteristics on systemic bioavailability of a conceptual 100 µg dose of various ICS preparations



BDP, beclomethasone diproprionate; *BMP*, beclomethasone monopropionate (active metabolite of BDP); *BUD*, budesonide; *FP*, fluticasone propionate; *GI,*gastrointestinal

Allen, J Pediat 2015

Pharmacokinetics of extrafine ciclesonide (CIC) and beclomethasone dipropionate (BDP).

	CIC	BDP
Active metabolite(s)	des-CIC	17-BMP
Pulmonary deposition	52%	51%
Bioavailability of oral deposition	<1%	26%
Bioavailability of pulmonary deposition	100%	100%
Bioavailability of oral and pulmonary deposition	52%	82%
First pass hepatic metabolism	>99%	60%
Pulmonary retention time	>24h	hours*
Esterification	Yes	Yes
Lipophilicity (LogP)	3.2	4.6
Receptor binding affinity	12 times Dexamethasone	13 times

Wolthers DO. Pediatr Allergy Immunol. 2015

Cochrane Database Syst Rev. 2013 Feb 28;
Ciclesonide versus other inhaled corticosteroids for chronic asthma in children.
Kramer S[1], **:**

Six studies were included in this review (3256 children, 4 to 17 years of age).

AUTHORS' CONCLUSIONS:
An improvement in asthma symptoms, exacerbations and side effects of ciclesonide versus budesonide and fluticasone could be neither demonstrated nor refuted and the trade-off between benefits and harms of using ciclesonide instead of budesonide or fluticasone is unclear.

Effetti locali di alcuni CSI

1) Irritazione faringe/mal di gola
2) Disfonia-raucedine
3) Candidosi orofaringea
4) Tosse/broncospasmo

	Incidence (%)			
Drug	Oropharyngeal candidiasis	Dysphonia/hoarseness	Pharyngitis/sore throat	Bronchospasm/cough
FP* (37)	2–5	3–8	10–14	<3
BUD† (38)	2–4	1–6	5–10	<3
BDP‡ (39, 40)	§	<2	14	<2
TAA ¶ (41)	1–3	1–3	7–25	<1
CIC** (42, 43)	0–1	0–2	4–5	–

Buhl R. Allergy. 2006 May;61(5):518-26

Potenziali effetti sistemici CSI

- Soppressione o ritardo di crescita
- Osteoporosi
- Cataratta
- Assottigliamento del derma
- Insufficienza surrenale

Inhaled Corticosteroids and Growth: Still an Issue after All These Years

Allen, J Pediat 2015

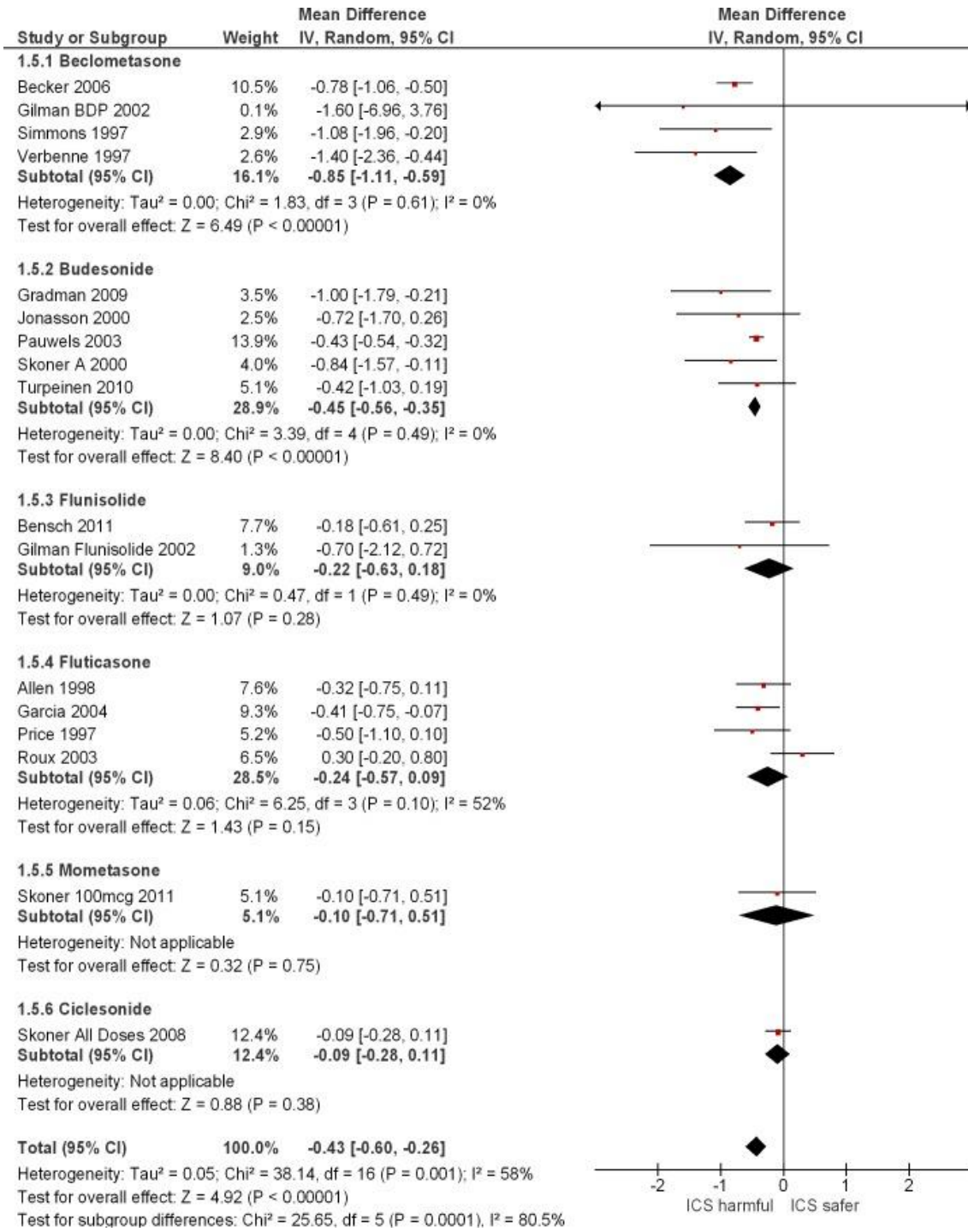
PLoS One. 2015 Jul 20;10(7):e0133428.

Impact of Inhaled Corticosteroids on Growth in Children with Asthma: Systematic Review and Meta-Analysis.

Loke YK et al

Growth Velocity in RCTS at 12 months follow-up

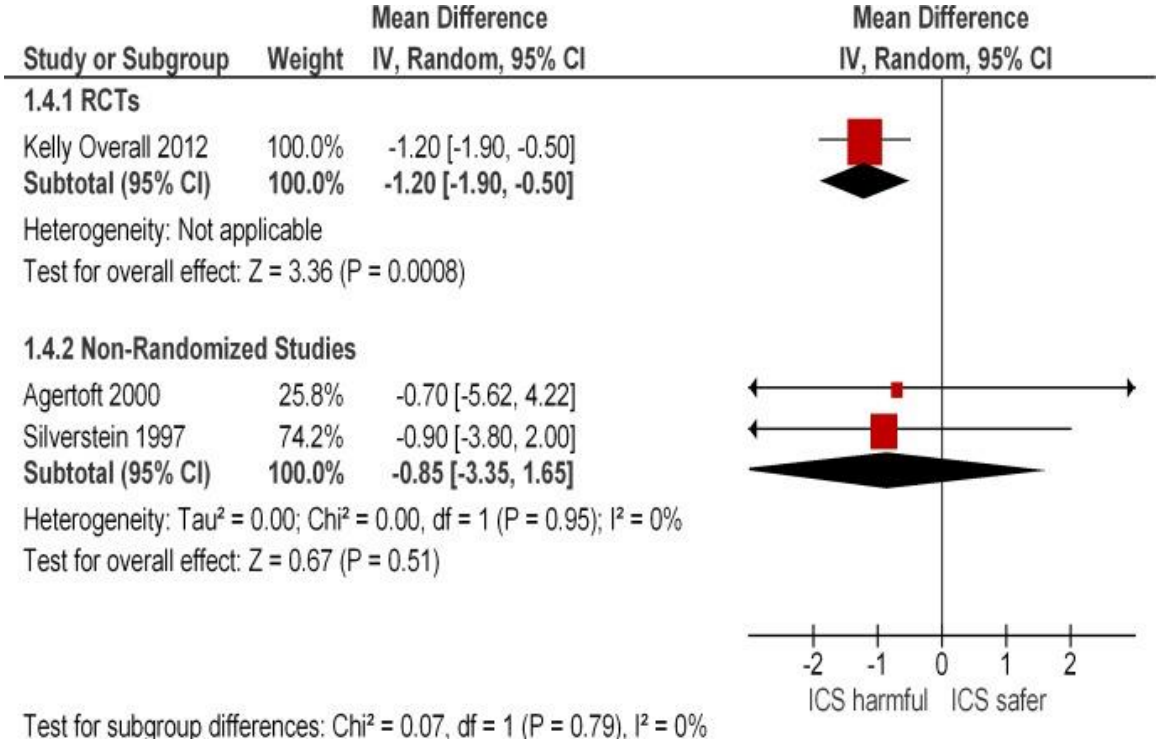
significantly reduced growth velocity at one year follow-up (mean difference -0.48 cm/year



Impact of Inhaled Corticosteroids on Growth in Children with Asthma: Systematic Review and Meta-Analysis.

Final adult height showed a mean reduction of -1.20 cm (95% CI -1.90 cm to -0.50 cm) with budesonide versus placebo in a high quality RCT

Final Adult Height, ICS users vs. non-users.



Meta-analysis of two lower quality observational studies revealed uncertainty in the association between ICS use and final adult height, pooled mean difference -0.85 cm

Loke YK et al PLoS One. 2015 Jul 20;10(7):e0133428.

Come usare correttamente i CSI

(1)Utilizzare preparati di CSI con bassa biodisponibilità orale

(2) **Aggiustare** il dosaggio in base allo specifico farmaco e al relativo dispositivo inalatorio

(3) **Stabilire** un piano di adeguato follow-up per identificare la dose minima efficace per il controllo dei sintomi fino ad una possibile sospensione se il controllo persiste per > 3 mesi

(4) **Monitorare la crescita** con sufficiente frequenza (ogni 4 mesi) e accuratezza (stadiometro a muro) per identificare precocemente eventuali rallentamenti.

Allen, J Pediat 2015

THANKS