SIFC
SOCIETÀ ITALIANA
PER LO STUDIO DELLA FIBROSI CISTICA

ICS in CF: con

Napoli 20 23 ottobre 2021

Dott. ssa Sonia Volpi

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

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Effetti dei glucocorticoidi a livello delle vie aeree:

Deedbs ne bnqshbnr sdqnhc r nmf dmd sq` mr bqhoshmm

Hmbqd` rdc sq` mr bqhoshmm

- Khonbnqshm,0
- β1,@c qdmdqf hb qdbdosnqr
- Rdbqdsnqx kdt j nbxsd hmghahsnqx oqnsdhm
- **HkA,α 'hmghahsnq ne ME,κA(**
- @msh,hmek` l l `snqx nq hmghahsnqx bxsnj hmdr

HK,0/ +HK,01+HK,0 qdbdosnq` ms` f nmhrs

- L hsnf dm,` bshu` sdc oqnsdhmj hm` rd

ognrog` s` rd,0 'L J O,0+hmghahsr L @Oj hm` rd o` sgv ` xr(

Cdbqd` rdc sq` mr bqhoshmm

- Hmek` l l `snqx bxsnj hmdr

HK,1+HK,2+HK,3+HK,4+HK,5+HK,00+HK,02+HK, 04+SMEα+F L ,BRE+RBE

- Bgdl nj hmdr

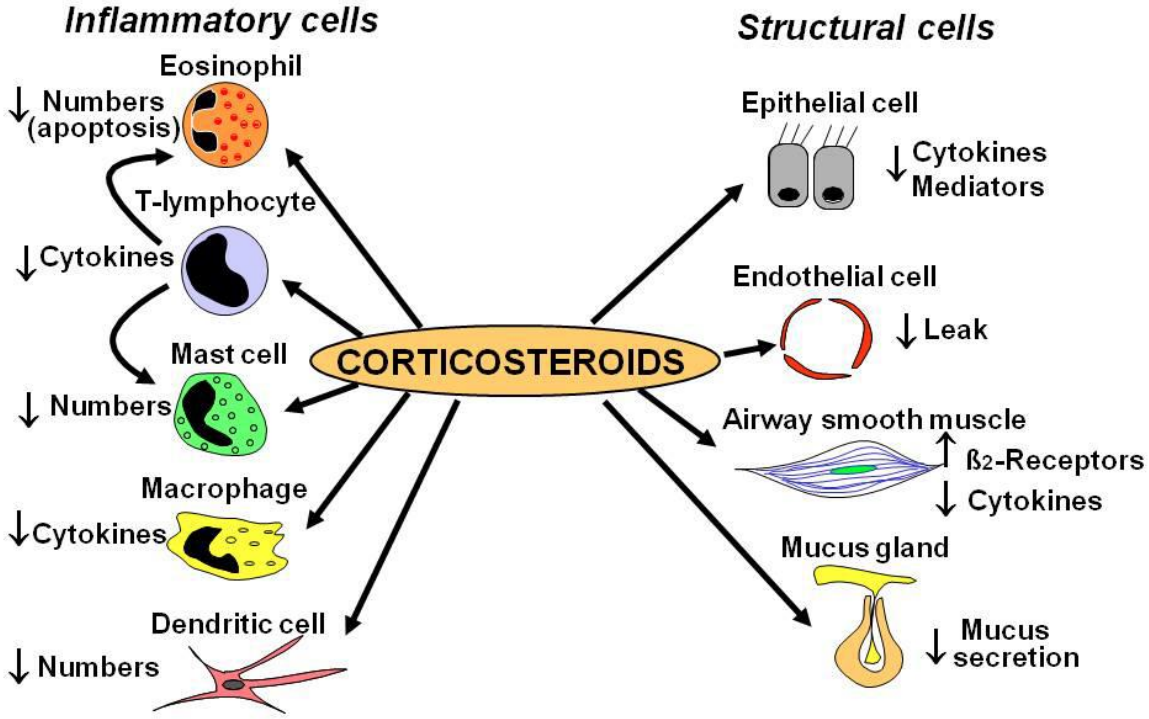
HK,7+Q@MSDR+L HO,0α+dns` whm

- Hmek` l l `snqx dmyxl dr

Hmc t bhakd mhsqfb nwhcd rxmsg` rd 'hMNR(+ hmc t bhakd bxbkn,nwxf dm` rd 'BNW,1(

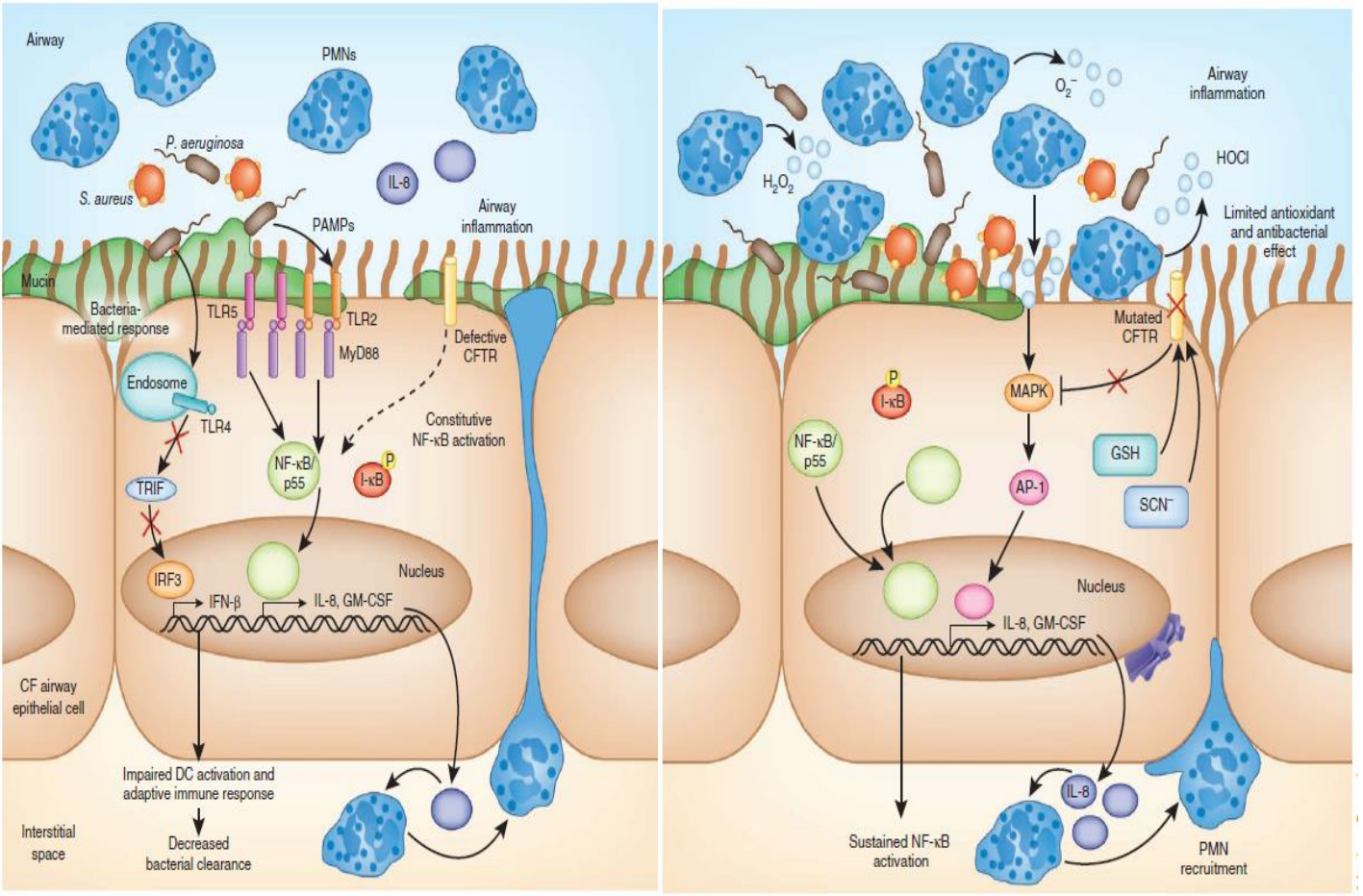
Cellular effect of corticosteroids

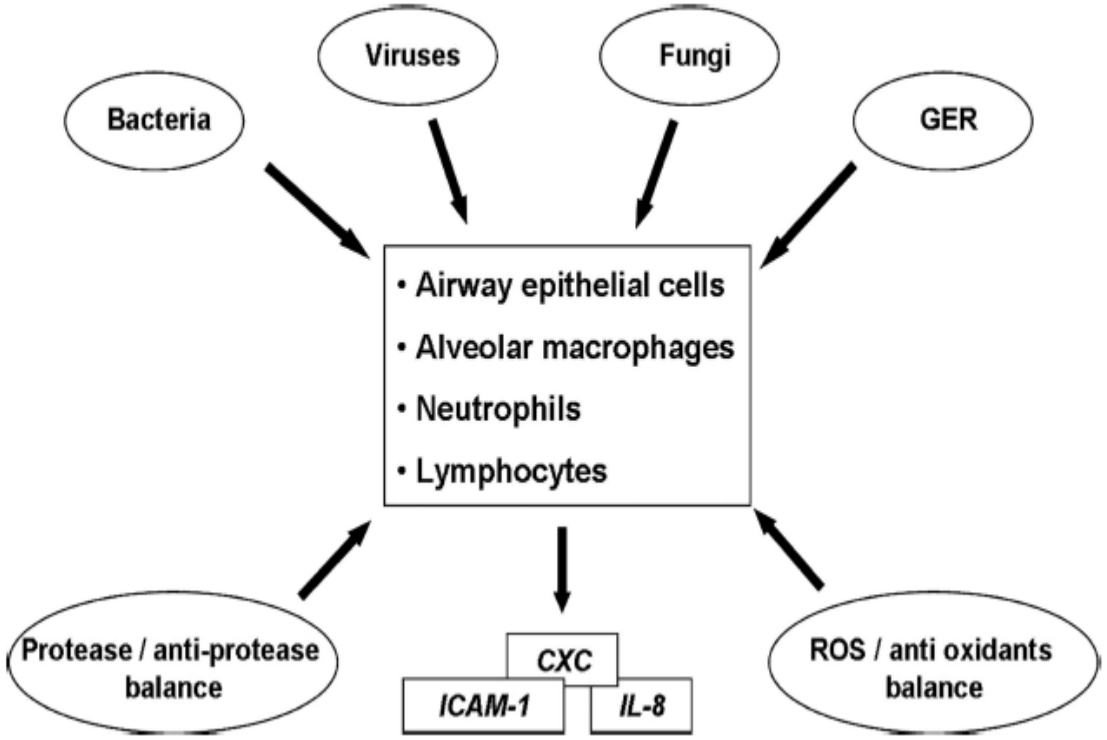
Fig. 1



Barnes PJ. Inhaled Corticosteroids. Pharmaceuticals. 2010;3(3):514-54

CF - Infiammazione neutrofila





Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. Nat Med. 2012 Apr 5;18(4):509-19.

Cohen-Cymberknoh M, et al. Thorax 2013;68:1157–1162

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Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Patrick A. Flume[1], Brian P. O'Sullivan[2], Karen A. Robinson[3], Christopher H. Goss[4], Peter J. Mogayzel, Jr.[5], Donna Beth Willey-Courand[6], Janet Bujan[7], Jonathan Finder[8], Mary Lester[9], Lynne Quittell[10], Randall Rosenblatt[11], Robert L. Vender[12], Leslie Hazle[13], Kathy Sabadosa[14], and Bruce Marshall[13]

Am J Respir Crit Care Med Vol 176. pp 957–969, 2007

Recommendation:

For patients with CF, 6 years of age and older, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the routine use of inhaled corticosteroids to improve lung function and to reduce exacerbations. Level of evidence, fair; net benefit, zero; grade of recommendation, D.

Cystic Fibrosis Pulmonary Guidelines

Chronic Medications for Maintenance of Lung Health

Peter J. Mogayzel, Jr.[1], Edward T. Naureckas[2], Karen A. Robinson[3], Gary Mueller[4], Denis Hadjiliadis[5], Jeffrey B. Hoag[6], Lisa Lubsch[7], Leslie Hazle[8], Kathy Sabadosa[8], Bruce Marshall[8], and the Pulmonary Clinical Practice Guidelines Committee*

Am J Respir Crit Care Med Vol 187, Iss. 7, pp 680–689, Apr 1, 2013

Treatment	Recommendation	Certainty of Net Benefit	Estimate of Net Benefit	Recommendation
Inhaled corticosteroids	For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.	High	Zero	D

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Cochrane Library

Cochrane Database of Systematic Reviews

Inhaled corticosteroids for cystic fibrosis (Review)

Balfour-Lynn IM, Welch K, Smith S.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.pub6.

Balfour-Lynn IM, Welch K.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.pub5.

Balfour-Lynn IM, Welch K.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.pub4.

Balfour-Lynn IM, Welch K.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.pub3.

Balfour-Lynn IM, Welch K.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.pub2.

Balfour-Lynn I, Walters S, Dezateux C.
Inhaled corticosteroids for cystic fibrosis.
Cochrane Database of Systematic Reviews 2000, Issue 1. Art. No.: CD001915.
DOI: 10.1002/14651858.CD001915.

Evidence from these trials is of low to very low quality and insufficient to establish whether inhaled corticosteroids are beneficial in cystic fibrosis, but withdrawal in those already taking them has been shown to be safe.
There is some evidence they may cause harm in terms of growth.
It has not been established whether long-term use is beneficial in reducing lung inflammation.

2019
This is an update of a previously published review; however, due to the lack of research in this area, we do not envisage undertaking any further updates.

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EVENTI AVVERSI

- Locali

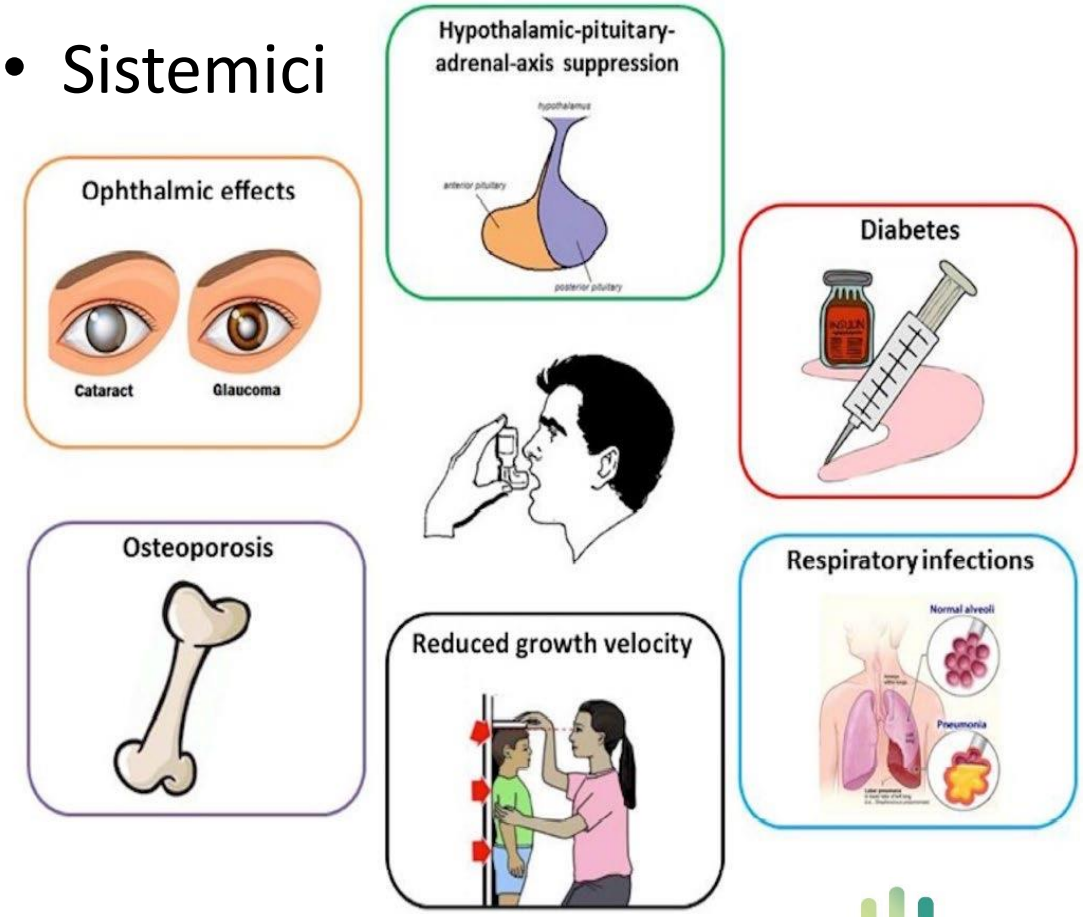
➢Disfonia

➢Tosse

➢Cadidosi orofaringea

➢Polmonite (pz COPD)

- Sistemici



J Allergy Clin Immunol Pract. 2018 May - Jun;6(3):776-781

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The new england journal *of* medicine original article

Effect of Inhaled Glucocorticoids in Childhood on Adult Height

H. William Kelly, Pharm.D., Alice L. Sternberg, Sc.M., Rachel Lescher, M.D., Anne L. Fuhlbrigge, M.D., Paul Williams, M.D., Robert S. Zeiger, M.D., Ph.D., Hengameh H. Raissy, Pharm.D., Mark L. Van Natta, M.H.S., James Tonascia, Ph.D., and Robert C. Strunk, M.D.,for the CAMP Research Group*

N Engl J Med. 2012 Sep 6;367(10):904-12

Table 1. Adjusted Mean Adult Height among 943 Study Participants.*

Variable	Mean Adult Height			Difference in Height			
	Budesonide (N=281)	Nedocromil (N=285)	Placebo (N=377)	Budesonide vs. Placebo (95% CI)	P Value	Nedocromil vs. Placebo (95% CI)	P Value
	cm			*cm*		*cm*	
All participants	171.1	172.1	172.3	−1.2 (−1.9 to −0.5)	0.001	−0.2 (−0.9 to 0.5)	0.61
Sex							
Female	162.8	163.9	164.6	−1.8 (−2.9 to −0.7)	0.001	−0.7 (−1.8 to 0.5)	0.26
Male	176.8	177.6	177.6	−0.8 (−1.8 to 0.2)	0.10	−0.0 (−0.9 to 0.9)	0.98
P value for interaction					0.10		0.49
Age at entry							
5–8 yr	170.7	171.8	172.6	−1.9 (−3.2 to −0.6)	0.004	−0.8 (−2.1 to 0.5)	0.22
9–13 yr	171.4	172.4	171.9	−0.5 (−1.7 to 0.6)	0.37	0.5 (−0.8 to 1.6)	0.48
P value for interaction					0.12		0.15

Conclusions

The initial decrease in attained height associated with the use of inhaled gluco- corticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative.

Eur J Pediatr (2007) 166:23–28
DOI 10.1007/s00431-006-0198-9

ORIGINAL PAPER

Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients?

Kris De Boeck · Frans De Baets · Anne Malfroot · Kristine Desager · Françoise Mouchet · Marijke Proesmans

Table 3 Mean (SEM) height in cm and SDS in patients treated with placebo (P) and fluticasone (F) and different time points during and after the study. Also the change in height in cm and SDS over the 12-month study period is shown in bold

	P/F	**Change 0–12 months**	0 months	3 months	6 months	9 months	12 months	18 months	24 months
Height	P	**5.49 (0.38)**	129.4 (2.9)	130.8 (2.8)	132.3 (2.8)	133.5 (2.8)	134.9 (2.9)	137.5 (0.7)	141.3 (0.7)
cm	F	**3.96 (0.29)**	127.7 (4.4)	128.8 (4.3)	130.1 (4.4)	130.8 (4.4)	131.6 (4.4)	134.2 (1.3)	137.2 (1.4)
Height	P	**−0.01 (0.07)**	−0.36 (0.19)	−0.35 (0.19)	−0.33 (0.18)	−0.39 (0.17)	−0.37 (0.17)	−0.38 (0.14)	−0.38 (0.16)
SDS	F	**−0.38 (0.09)**	0.03 (0.34)	−0.07 (0.31)	−0.05 (0.31)	−0.21 (0.32)	−0.34 (0.32)	−0.39 (0.35)	−0.38 (0.35)

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Soppressione dell'asse ipotalamo-ipofisi-surrene

Adrenal insufficiency associated with long-term use of inhaled steroid in asthma

Inseon S. Choi, MD [*,†]; Da-Woon Sim, MD [†]; Seung-Hoon Kim, MD [†]; Jin-Woo Wui, MD [†]

[*] *Department of Allergy, Chonnam National University Medical School, Gwangju, Korea*
[†] *Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea*

- La soppressione dell'asse HPA può insorgere in pazienti in trattamento con steroidi inalatori **anche a dosi medio-basse**, soprattutto se somministrati per un **lungo periodo**

- **monitorare** costantemente i livelli di **cortisolo sierico** al mattino per confermare o escludere una condizione di iposurrenalismo centrale iatrogeno

- *fluticasone propionato* è maggiormente correlato alla comparsa di tale reazione avversa, se confrontato con *budesonide* e *ciclesonide*

Ann Allergy Asthma Immunol. 2017 Jan;118(1):66-72.e1

Risk factors for persistent *Aspergillus* respiratory isolation in cystic fibrosis

Gina Hong [a,*], Kevin J. Psoter [b], Mark T. Jennings [c], Christian A. Merlo [c], Michael P. Boyle [c,d], Denis Hadjiliadis [a], Steven M. Kawut [a], Noah Lechtzin [c]

Journal of Cystic Fibrosis 17 (2018) 624–630

	Odds ratio	95% confidence interval	p-Value
Treatments			
Macrolide	1.23	1.14, 1.32	<0.001
Inhaled corticosteroid	1.12	1.04, 1.20	0.001
Oral steroids	1.13	1.04, 1.23	0.006

Inhaled corticosteroids and *Aspergillus fumigatus* isolation in cystic fibrosis

Maria Noni[1,*], Anna Katelari[1], George Dimopoulos[2], Georgia Kourlaba[1], Vana Spoulou[3], Helen Alexandrou - Athanassoulis[4], Stavros-Eleftherios Doudounakis[1] and Chryssa Tzoumaka - Bakoula[5]

Medical Mycology, 2014, 52, 715–722

Table 4. Multiple logistic regression: determining independent effects of the duration of inhaled corticosteroid treatment on *Aspergillus fumigatus* first isolation and chronic colonization.

Outcome	Odds Ratio (95% confidence interval)	*P* value
First isolation*		
Duration of inhaled corticosteroid treatment (months)	1.165 (1.015–1.337)	0.029
Chronic colonization†		
Duration of inhaled corticosteroid treatment (months)	1.180 (1.029–1.353)	0.018

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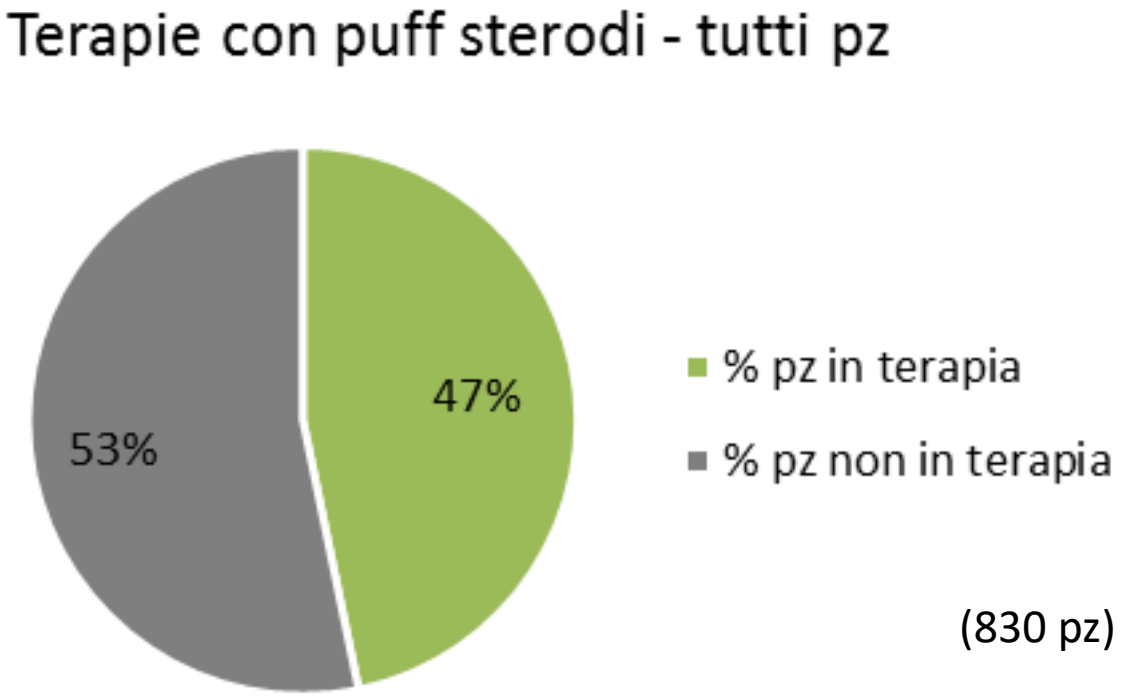
REAL LIFE



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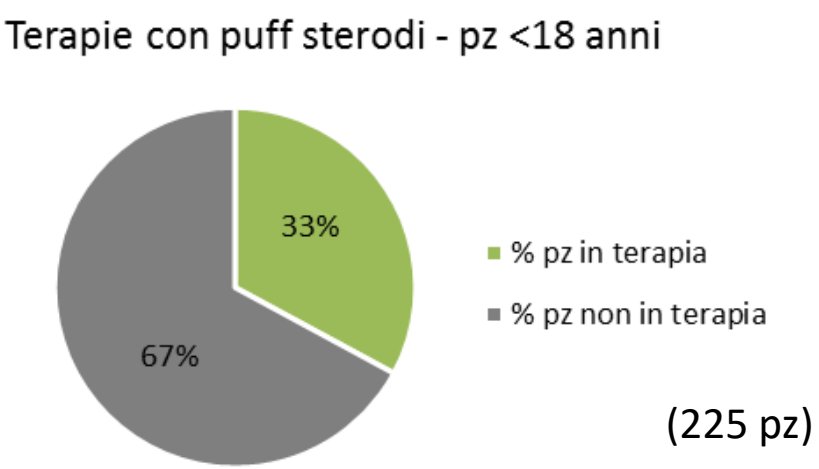
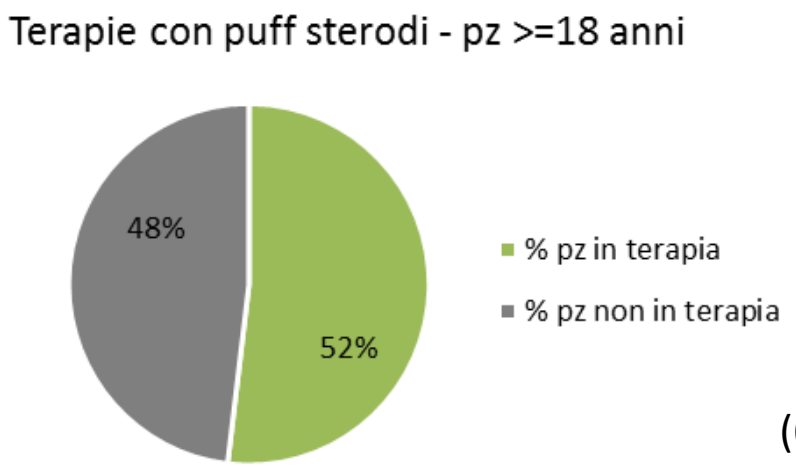
REAL LIFE



(225 pz)



(605 pz)

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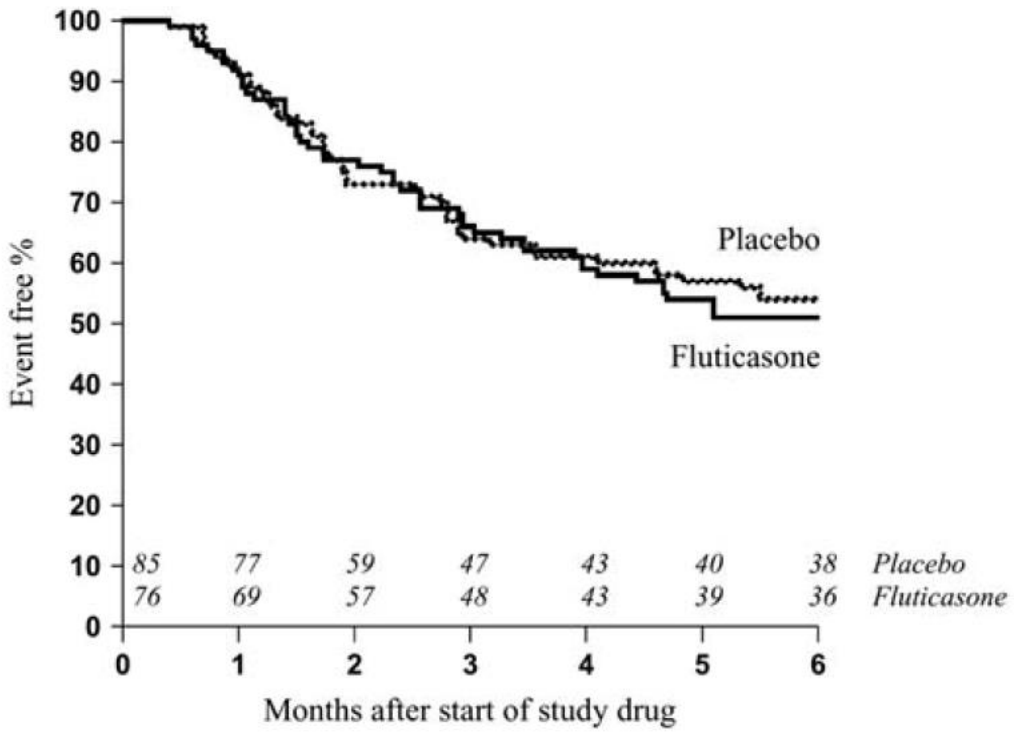
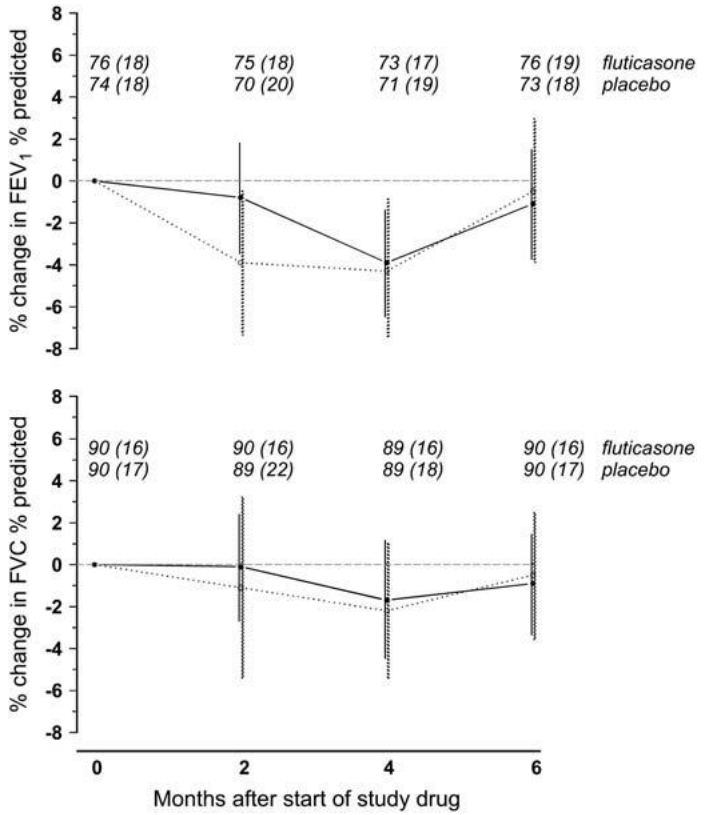
Multicenter Randomized Controlled Trial of Withdrawal of Inhaled Corticosteroids in Cystic Fibrosis

Ian M. Balfour-Lynn, Belinda Lees, Pippa Hall, Gillian Phillips, Mohammed Khan, Marcus Flather, and J. Stuart Elborn, on behalf of the CF WISE (Withdrawal of Inhaled Steroids Evaluation) Investigators*

Am J Respir Crit Care Med Vol 173. pp 1356–1362, 2006





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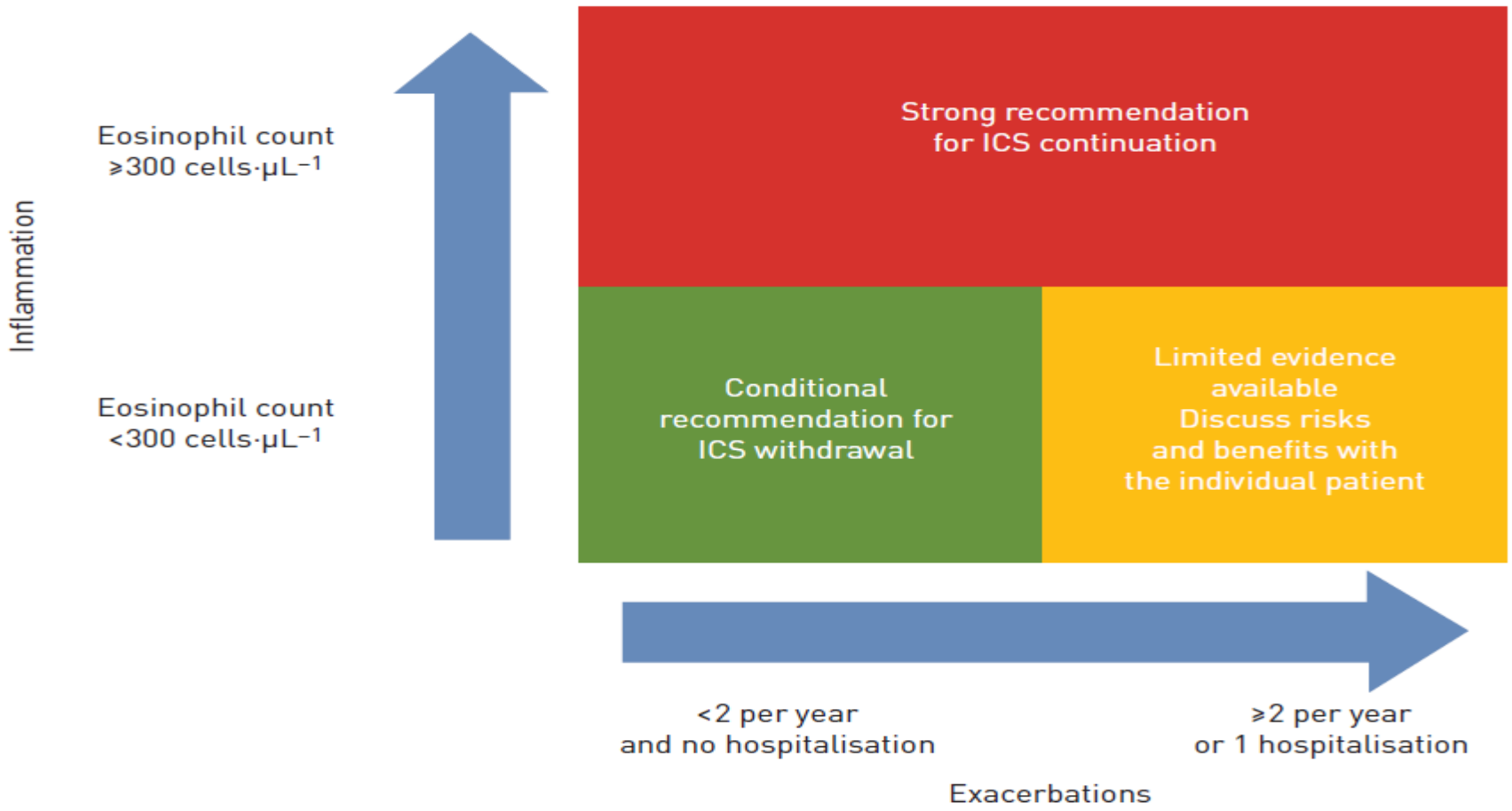
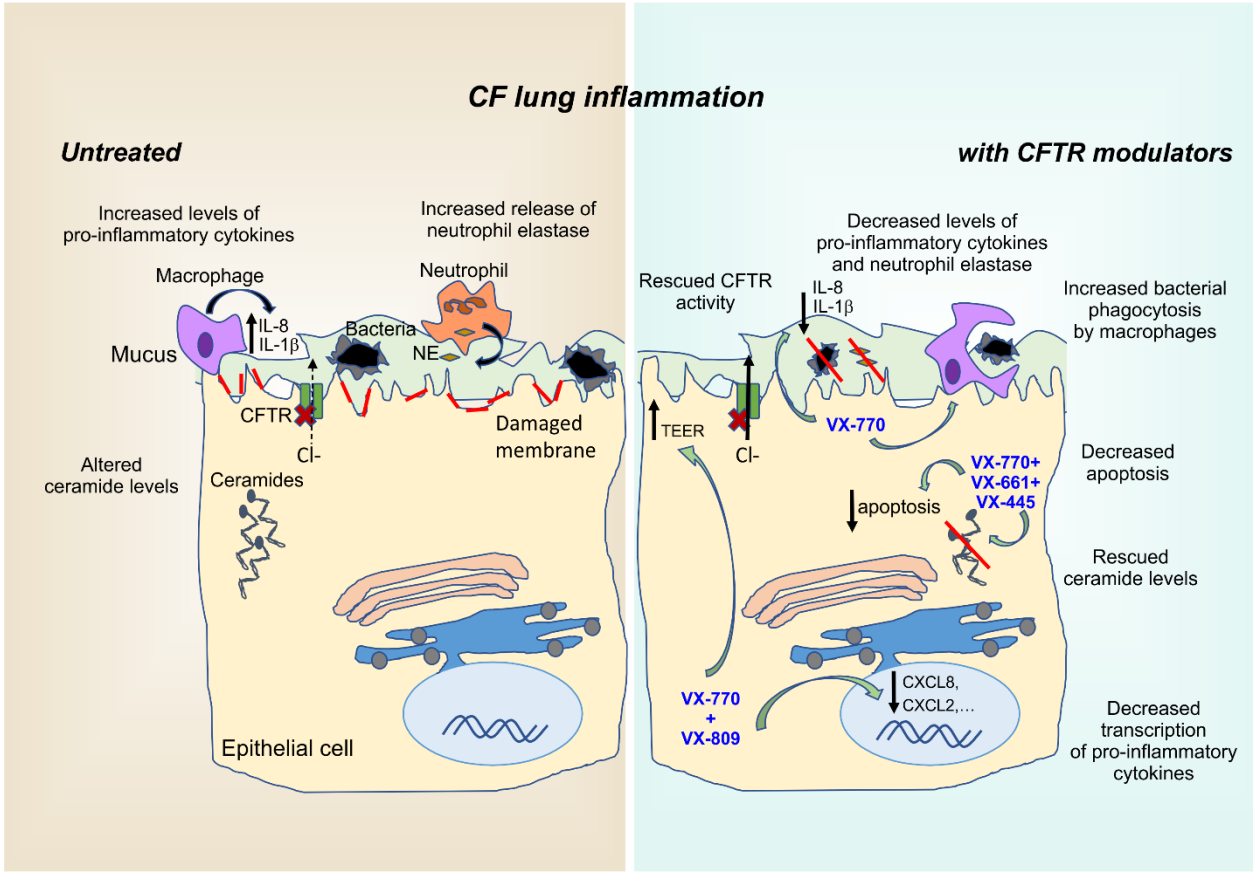
Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline

James D. Chalmers[1,14,15], Irena F. Laska[1,15], Frits M.E. Franssen[2,3], Wim Janssens[4], Ian Pavord[5], David Rigau[6], Melissa J. McDonnell[7], Nicolas Roche[8], Don D. Sin[9], Daiana Stolz[10], Samy Suissa[11], Jadwiga Wedzicha[12] and Marc Miravitlles[13,14,15]



Ghigo, A.; Prono, G.;Riccardi, E.; De Rose, V.
Dysfunctional Inflammation in Cystic. Fibrosis Airways: From Mechanisms to Novel Therapeutic Approaches.
Int. J. Mol. Sci. 2021, 22, 1952



CFTR modulators exert various anti-inflammatory effects by targeting intracellular processes, such as ceramide accumulation, cytokine transcription, membrane integrity, and macrophage-mediated phagocytosis of bacteria.

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Management of bronchiectasis in adults

James D. Chalmers[1], Stefano Aliberti[2] and Francesco Blasi[3]

Eur Respir J 2015; 45: 1446–1462

Inhaled corticosteroids and bronchodilators

The role of inhaled corticosteroids (ICS) in bronchiectasis is less clear. they have not shown any significant improvement in lung function, or exacerbation frequency.

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Conclusioni ICS e FC

- Assenza di dimostrazioni di efficacia
- Documentati effetti collaterali
- Dati real life → uso diffuso

In quali pazienti FC sono indicati?

- Ipereattività bronchiale
- Asma allergico
- ABPA
- Biomarcatori

Possiamo sospenderli?

- Sospensione senza conseguenze
- Terapia con modulatori

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- Grazie per l’attenzione