Asma, BPCO
ed Esercizio Fisico

Ferrara,
6 e 7 novembre 2015

Con il Patrocino di
Università degli Studi di Ferrara
Alleanza Malattie Toraco-Polmonari (ATP)

Terapia dell'Asma

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Obiettivi della gestione dell'asma

- Gli obiettivi a lungo termine nella gestione dell'asma sono:

  1. **Il controllo dei sintomi**

  2. **La riduzione del rischio**

- *Il raggiungimento di questi obiettivi richiede una buona collaborazione tra paziente e personale sanitario*

Farmaci dell'Asma	
• Steroidi	• *Beclometasone* • *Fluticasone* • *Budesonide* • *Ciclesonide* • *Mometasone* • *Triamcinolone*
• Cromoni	• *Cromoglicato* • *Nedocromile*
• Antileucotrienici	• *Montelukast* • *Zafirlukast*
• Anticorpi Monoclonali	• *Omalizumab* • *Mepolizumab* • *Lebrikizumab*
• Beta$_2$-agonisti	• *Salbutamolo* • *Terbutalina* • *Salmeterolo* • *Formoterolo* • *Vilanterolo*
• Atropinici	• *Ipratropio* • *Oxitropio* • *Tiotropio*
• Teofillinici	• *Aminofillina*

Recommended options for initial controller treatment in adults and adolescens

Presenting Symptoms	Preferred Initial Controller
• Asthma symptoms or need for SABA less than twice a month; • No waking due to asthma in last month; • No risk factors for exacerbations	No controller
• Infrequent asthma symptoms, but the patient has one or more risk factors for exacerbations	Low dose ICS
• Asthma symptoms or need for SABA between twice a month and twice a week, *or* • Patient wakes due to asthma once or more a month	Low dose ICS
• Asthma symptoms or need for SABA more than twice a week	Low dose ICS Other less effective options are LTRA or theophylline
• Troublesome asthma symptoms most days; or Waking due to asthma once a week or more, especially if any risk factors exist	Medium/high dose ICS or Low dose ICS/LABA
• Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	Short course of oral corticosteroids AND Start regular controller treatment: High dose ICS or Moderate-dose ICS/LABA

Low, medium and high daily doses of inhaled corticosteroids Adults and Adolescents (≥12 years)

Drug	Daily Dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	>500–1000	>1000
Beclometasone dipropionato (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

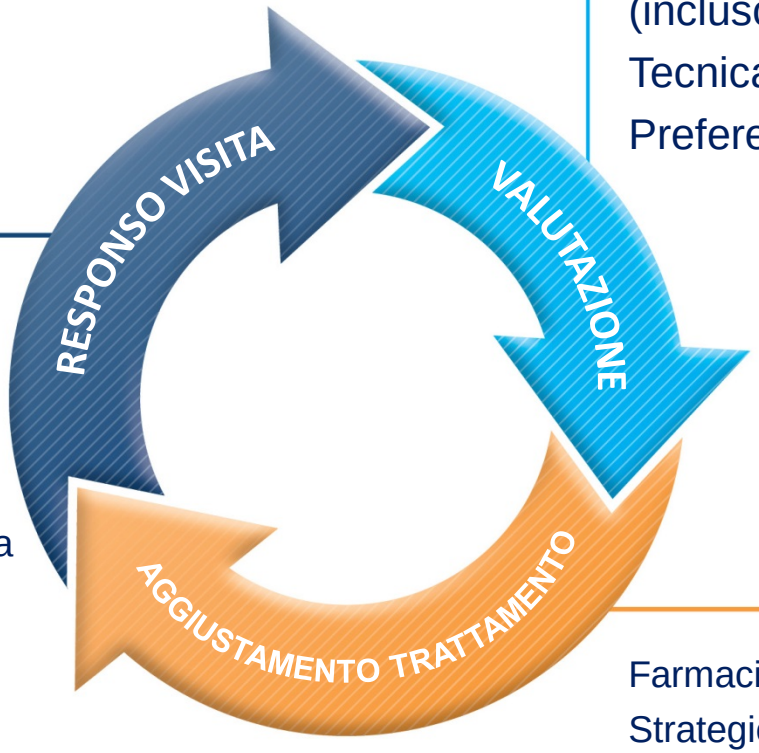
Recommendations for initial controller treatment in adults and adolescens

Before starting initial controller treatment
• Record evidence for the diagnosis of asthma, if possible
• Record the patient's level of symptom control and risk factors, including lung function
• Consider factors influencing choice of treatment
• Ensure that the patient can use the inhaler correctly
• Schedule an appointment for a follow-up visit

After starting initial controller treatment
• Review patient's response after 2–3 months, or earlier depending on clinical urgency
• Step down treatment once good control has been maintained for 3 months

Ciclo di gestione dell'asma basato sul controllo

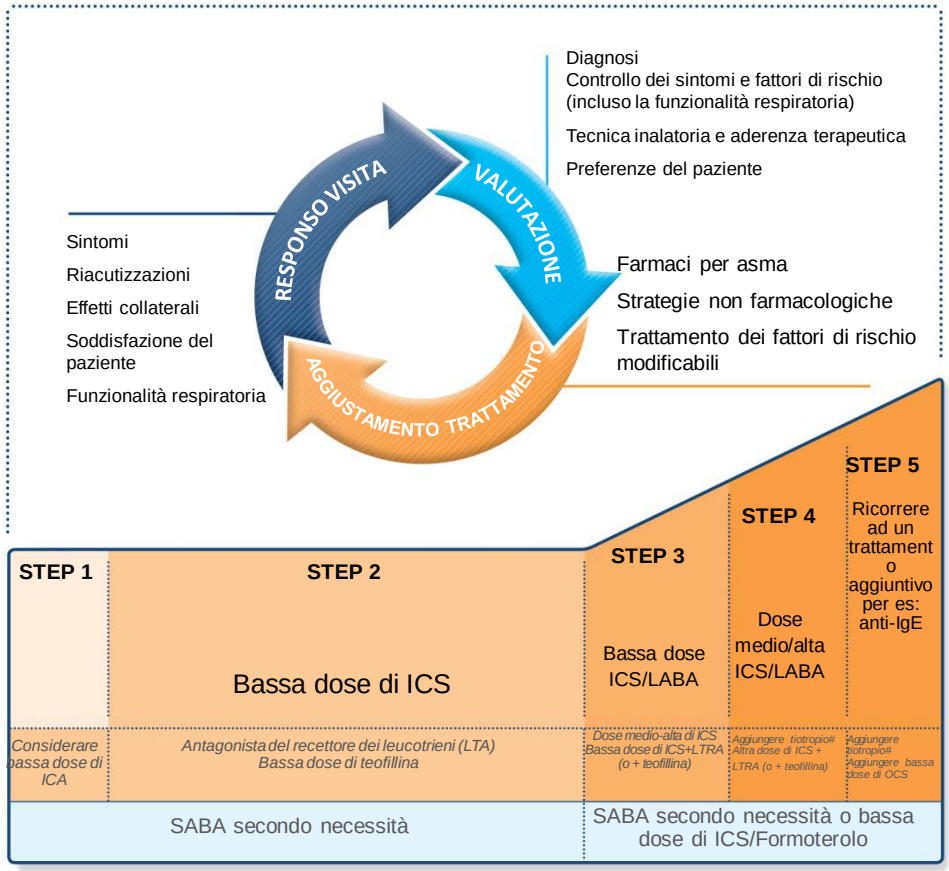
Diagnosi
Controllo dei sintomi e fattori di rischio (incluso la funzionalità respiratoria)
Tecnica inalatoria e aderenza terapeutica
Preferenze del paziente



Sintomi
Riacutizzazioni
Effetti collaterali
Soddisfazione del paziente
Funzionalità respiratoria

Farmaci per asma
Strategie non farmacologiche
Trattamento dei fattori di rischio modificabili

Gestione graduale farmacoterapia



RICORDARSI DI…

. Fornire una educazione guidata di auto gestione (auto monitoraggio + piano d'azione scritto + controllo regolare).
. Trattare i fattori di rischio modificabili e comorbidità, per es.: fumo, obesità, ansia.
. Informare sulle terapie non farmacologiche e le strategie per es.: attività fisiche, perdita di peso, evitare sensibilizzanti quando possibile.
. Considerare terapia "step-up" se… sintomi non controllati, esacerbazioni o rischi, ma prima controllare le diagnosi, la tecnica inalatoria, e l'aderenza.
. Considerare la terapia "step-down" se… i sintomi sono controllati per 3 mesi + basso rischio per iacutizzazioni. La cessazione di ICS non è consigliata.

Stepping up asthma treatment

- *Sustained step up (for at least 2–3 months)*: some patients may fail to respond adequately to initial treatment. A step up in treatment may be recommended if the symptoms are confirmed to be due to asthma; *inhaler technique* and *adherence* are satisfactory; and modifiable *risk factors* such as smoking have been addressed. Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2–3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.
- *Short-term step up (for 1–2 weeks)*: an occasional short-term increase in maintenance ICS dose for 1–2 weeks may be necessary; for example, during *viral infections* or *seasonal allergen exposure*.
- *Day-to-day adjustment:* for patients prescribed combination budesonide/formoterol or beclometasone/formoterol as maintenance and reliever treatment, the patient adjusts the number of as-needed doses of ICS/formoterol from day to day according to their symptoms, while continuing the maintenance dosage.

General principles of stepping down asthma treatment

- Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. If the patient has risk factors for exacerbations or fixed airflow limitation, do not step down without close supervision.
- Choose an *appropriate time* (no respiratory infection, patient not travelling, not pregnant).
- Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function and risk factors); provide clear instructions; provide written asthma action plan and ensure patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit.
- Stepping down *ICS doses by 25–50% at 3 month intervals* is feasible and safe for most patients

Current step	Current medication and dose	Options for stepping down	Ev
Step 5	High dose ICS/LABA plus oral corticosteroids (OCS)	• Continue high dose ICS/LABA and reduce OCS dose • Use sputum-guided approach to reducing OCS • Alternate-day OCS treatment • Replace OCS with high dose ICS	D B D D
	High dose ICS/LABA plus other add-on agents	• Refer for expert advice	D
Step 4	Moderate to high dose ICS/LABA maintenance treatment	• Continue combination ICS/LABA with 50% reduction in ICS component, by using available formulations • Discontinuing LABA is more likely to lead to deterioration	B A
	Medium dose ICS/formoterol as maintenance and reliever	• Reduce maintenance ICS/formoterol to low dose, and continue as needed low dose ICS/formoterol* reliever	D
	High dose ICS plus second controller	• Reduce ICS dose by 50% and continue second controller	B
Step 3	Low dose ICS/LABA maintenance	• Reduce ICS/LABA to once daily • Discontinuing LABA is more likely to lead to deterioration	D A
	Low dose ICS/formoterol* as maintenance and reliever	• Reduce maintenance ICS/formoterol* dose to once daily and continue as-needed low dose ICS/formoterol* reliever	C
	Moderate- or high-dose ICS	• Reduce ICS dose by 50%	B
Step 2	Low dose ICS	• Once-daily dosing (budesonide, ciclesonide, mometasone)	A
	Low dose ICS or LTRA	• Consider stopping controller treatment only if there have been no symptoms for 6–12 months, and patient has no risk factors. Provide a written asthma action plan, and monitor closely. • Complete cessation of ICS in adults is not advised as the risk of exacerbations is increased	D A

Eur Respir Rev 2012; 21: 123, 66–74
DOI: 10.1183/09059180.00008111

REPORT

Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years

P. Demoly*, K. Annunziata#, E. Gubba¶ and L. Adamek+

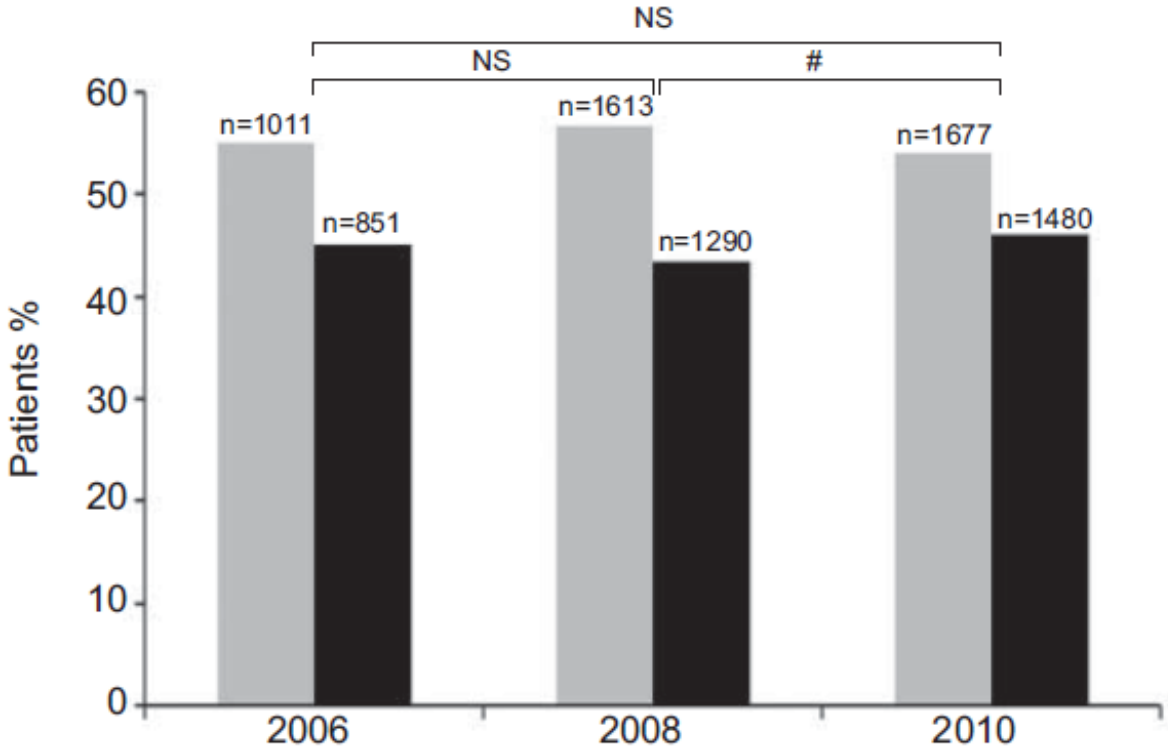


FIGURE 1. Proportion of treated patients with not well-controlled asthma (■) and at least well-controlled asthma (■) in 2006, 2008 and 2010 in all countries. NS: nonsignificant. #: p=0.035.

Definizione di asma

L'asma è una *malattia eterogenea*, caratterizzata normalmente da un infiammazione cronica delle vie aeree.

Viene definita dalla storia dei sintomi respiratori come sibili, dispnea (respiro corto), costrizione toracica e tosse che variano nel tempo e nell'intensità associati ad una limitazione al flusso aereo.

Factors affecting adherence

Weinstein AG, Curr Opin Pulm Med 2015

Drug-related factors	Interventions to improve adherence
Difficulties with inhaler devices	• Identify appropriate device for patient. • Demonstrate use and have patient demonstrate technique in turn
Awkward regimens, for example, 4 times daily, or multiple drugs	• Simplify regimen or tailor to patient preference
Fears about side-effects	• Determine whether concern is theoretical or specific. If specific, relate the persistence of the symptoms vs. likelihood of side-effects. • Use motivational interviewing to assess 'pros and cons' and reduce ambivalence. • Consider referral to support group
Cost of medication	• If patient has prescription plan, select least expensive drug. If not, refer to discount pharmacy plans or pharmaceutical programs
Dislike of medication	• Reduce allergic or irritant exposure to decrease symptoms or medication • Use motivational interviewing to assess 'pros and cons' and reduce ambivalence
Distant pharmacies	• Identify capability of receiving prescription by mail

Factors affecting adherence

Weinstein AG, Curr Opin Pulm Med 2015

Nondrug-related factors	Interventions to improve adherence
Misunderstanding or lack of instruction	• If lack of instruction, provide instruction. Assess level of literacy. If low, provide suitable education strategy. Review pathophysiology and rationale for treatment as well as consequences of no treatment. • Provide instruction and have patient demonstrate technique
Dissatisfaction with healthcare professionals	• Have patient speak to administrator regarding issue. May require patient to see another provider if interactions do not improve
Unexpressed/undisclosed fears or concerns	• Identify concerns and address each. Determine if they are theoretical or actual. Consider referral to a support group. May require psychological intervention if fears or concerns persist
Inappropriate expectations	• Clarify expectations from a medical perspective. If patient expects greater or quicker improvement, attempt to reset expectations. Review role of allergen/irritant exposure as factor
Poor supervision, training, or follow-up	• Encourage supervision for children/elderly. Review use of medication in office. Schedule appropriate follow-up
Anger about condition or its treatment	• Identify reason for anger. Express that treatment may improve condition. Assess ambivalence about treatment and review possible alternatives
Underestimation of severity	• Relate symptoms with pulmonary function or use exercise challenge to demonstrate severity of condition
Cultural issues	• Appreciate that varying cultures have different concepts of development of asthma, factors that exacerbate it, and treatment choices. Take advantage of community health workers to clarify issues
Concerns about stigmatization	• Assess patient reaction to diagnosis. Understand the patient's concerns and refer to support group if the concerns persist
Forgetfulness or complacency	• Determine whether the problem is forgetting to follow treatment vs. other reasons. Consider tailoring medication use to patient's daily activities. Address complacency by withdrawing treatment to determine actual need for treatment
Attitudes toward ill health	• Assess patient's health beliefs about asthma and treatment. For patients who question the diagnosis or efficacy of treatment, consider stopping treatment and having patient monitor lung function at home
Religious issues	• Clarify how patient's religious beliefs may affect attitudes about diagnosis and treatment. Discussing this with patient's religious leader may give insight and source of support for the patient

Factors affecting adherence

Weinstein AG, Curr Opin Pulm Med 2015

Patient behaviors	Interventions to improve adherence
Erratic nonadherence: Forgetfulness, busy lives, changing schedules	• Simplification of the regimen; tailoring treatment to a specific daily activity (tooth brushing); memory aids
Unwitting nonadherence: Failure to understand the specifics of the treatment or the necessity for adherence	• Provide clear communication and use patient-centered communication techniques to verify comprehension
Intelligent nonadherence: Deliberate choice to not follow treatment; patients no longer feel the need; concern about side-effects; believe that variation in regimen works better than prescribed	• Use communication skills (open-ended questions, active listening) to identify patient concerns and motivational interviewing to address patient ambivalence

Severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics

Wenzel SE et al, AJRCCM 1999

PHYSIOLOGIC CHARACTERISTICS OF SEVERE ASTHMA SUBGROUPS

	Eosinophil (−)* (*n* = *14*)	Eosinophil (+)* (*n* = *20*)	p Value
FEV_1, % pred	42 (33–58)	56 (34–66)	0.05
BD response, %	25 (12–50)	22 (15–35)	0.69
RV, % pred	191 (155–294)	210 (167–242)	0.95
Vtg, % pred	109 (93–150)	108 (393–131)	0.68
FVC/SVC	97 (89–100)	88 (71–94)	0.03

CLINICAL CHARACTERISTICS OF SEVERE ASTHMA GROUPS

	Eosinophil (−) (*n* = *14*)	Eosinophil (+) (*n* = *20*)	p Value
Age, yr*	28 ± 3	34 ± 3	0.22
M/F	7/7	8/12	0.68
Cauc/AA + Hisp	12/2	16/4	0.67
Asthma duration, yr*	22 ± 3	19 ± 3	0.51
Steroid dose, mg/d*	27 ± 4	29 ± 5	0.85
Intubation (Y/N)	1/13	12/8	0.004

Inflammatory subtypes in asthma. Assessment and identification using induced sputum

Simpson JL et al, Respirology 2006

Inflammatory Phenotype	Cell Profile	No. (%)
Eosinophilic asthma	*Eosinophils > 1%*	*38 (41)*
Paucigranulocytic asthma	*Normal levels of Neutrophils & Eosinophils*	*29 (31)*
Neutrophilic asthma	*Neutrophils > 61%*	*19 (20)*
Mixed granulocytic asthma	*Neutrophils > 61% & Eosinophils > 1%*	*7 (8)*

Inflammatory subtypes in asthma. Assessment and identification using induced sputum

Simpson JL et al, Respirology 2006

	Eosinophilic asthma	Neutrophilic asthma	Paucigranulocytic asthma	Mixed granulocytic asthma	*P*
Total cells ($\times 10^6$/mL)	1.9 (1–3.3)	14.9 (5.8–25.5)†‡	2.8 (1.4–3.7)	13.5 (8.3–20)††‡‡	<0.001
Viability (%)	70 (59–86)	98 (88–98)†‡	76 (71–86)	87 (81–99)††	<0.001
Neutrophils (%)	24.5 (14.3–36.4)	81 (70–93)†‡	28.7 (15.7–44.1)	71.8 (64–87.8)†‡‡	<0.001
Neutrophils ($\times 10^4$/mL)	39.6 (19.2–82.7)	1265 (390–2416)†‡	58.6 (26.7–129.3)	819 (482–1385)†‡‡	0.001
Eosinophils (%)	3.4 (2.2–12.8)¶	0.3 (0–0.5)†	0.3 (0–0.5)	4.8 (2.1–21)§	<0.001
Eosinophils ($\times 10^4$/mL)	10.7 (5.3–30.5)¶	1.1 (0–9.5)†	0.5 (0–1.45)	34.4 (11.4–96.4)§‡	<0.001
Macrophages (%)	59.1 (38–74)	18 (6.5–27.3)†‡	64.6 (53.6–80.6)	18.5 (12–25.5)†‡‡	<0.001
Macrophages ($\times 10^4$/mL)	120 (62.2–205)	196 (107–274)	181 (95.3–262)	204 (109–300)	>0.05
Lymphocytes (%)	0.5 (0–1.6)	0.3 (0–1)	0.5 (0–1)	0.5 (0.3–3)	>0.05
Columnar epithelials (%)	2.2 (0.8–4.1)	0.3 (0–1)†‡	1.3 (0.5–3)	1.3 (0.5–2.1)††	<0.001
Squamous (%)	8.3 (2.8–15)	1 (0.5–3.5)†	4.5 (2–14.5)	1 (0.8–2)††	<0.001
Intracellular bacteria (%)	1 (0.5–2.3)	1 (0.3–3.3)	1.3 (0.3–1.7)	1 (0.7–4)	>0.05

	Eosinophilic asthma	Neutrophilic asthma	Paucigranulocytic asthma	Mixed granulocytic asthma	*P*
No. subjects	38	19	29	7	
Age (years, mean (range))	38 (19–72)	49 (21–74)‡	39 (18–77)	59 (38–77)§¶	0.005
Sex (female, *n* (%))	33 (87)	13 (68)	23 (78)	4 (57)	>0.05
Atopic (*n* (%))	24 (86)	12 (92)	15 (88)	6 (100)	>0.05
Ex-smoker (*n* (%))	14 (37)	8 (42)	13 (45)	4 (57)	>0.05
FEV_1% predicted (mean (SD))	78 (21)	73 (21)	79 (18)	60 (19)	>0.05
ICS dose (mg/day,† median (IQR))	1.5 (1.0–2.0)	2.0 (1.0–2.0)	1.5 (1.0–2.0)	2.0 (1.6–4.0)	>0.05
PD_{15} (mL, median (IQR))	3.4 (1–9)	9.1 (7.4–16)	7.6 (4.3–15.7)	10 (8.5–15.7)	>0.05

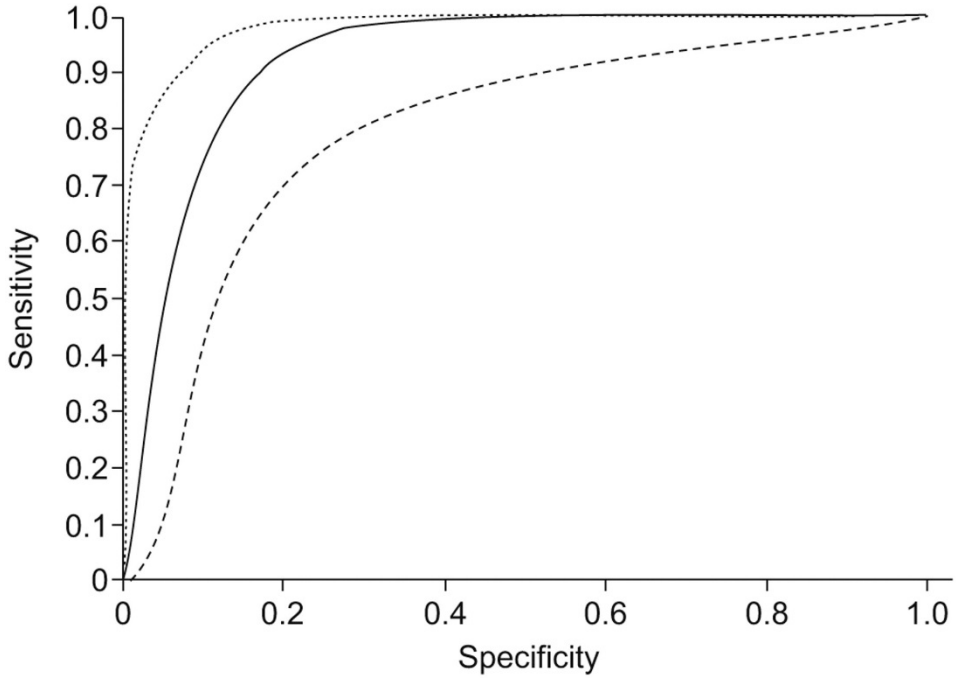
Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma

Perez-de-Llano LA, et al ERJ 2010

TABLE 2 Pulmonary function test

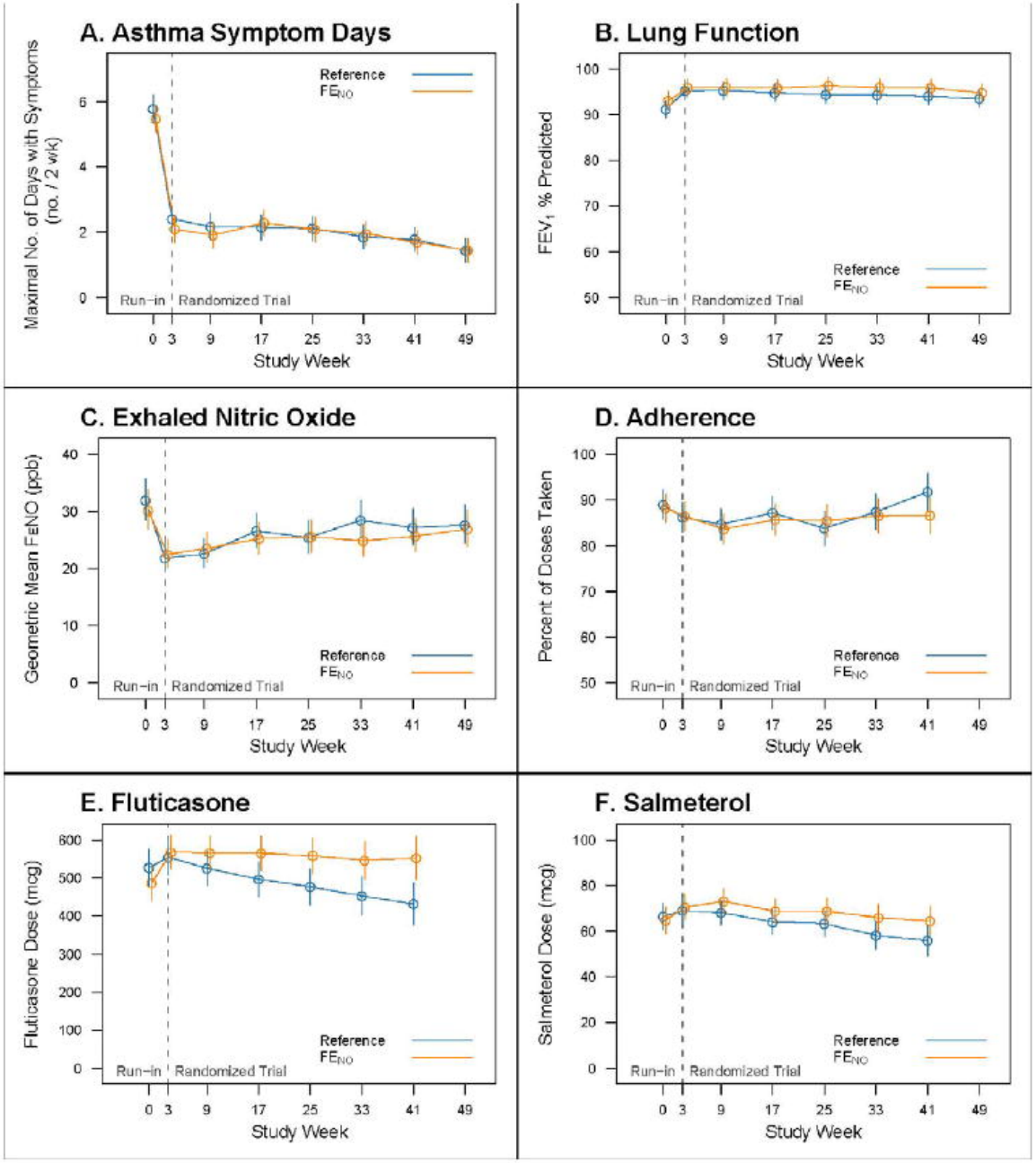
	All subjects	Controlled	Uncontrolled	Controlled *versus* uncontrolled
FEV_1 % pred	72±24	75±20	69±27	p=0.18 (NS)
FEV_1/FVC <70%	51 (50)	25 (49)	26 (51)	p=1.0 (NS)
Positive bronchodilator test	47/99	30 (57.1)	17 (35.8)	p=0.02 (NS)
PEF variability >20%	58 (59)	32 (71.1)	26 (49.1)	p=0.04
Positive methacholine test	69/71	35 (72.9)	34 (66.7)	p=0.37 (NS)
F_{ENO} ppb	43.1 (4–222)	68.4 (11–222)	19.7 (4–160)	p<0.01

Data are presented as n, n (%), mean±SD or median (range), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; PEF: peak expiratory flow; F_{ENO}: exhaled nitric oxide fraction; NS: nonsignificant.



An F_{eNO} value **≥30** ppb demonstrated a sensitivity of 87.5% and a specificity of 90.6% for the identification of responsive asthmatics.

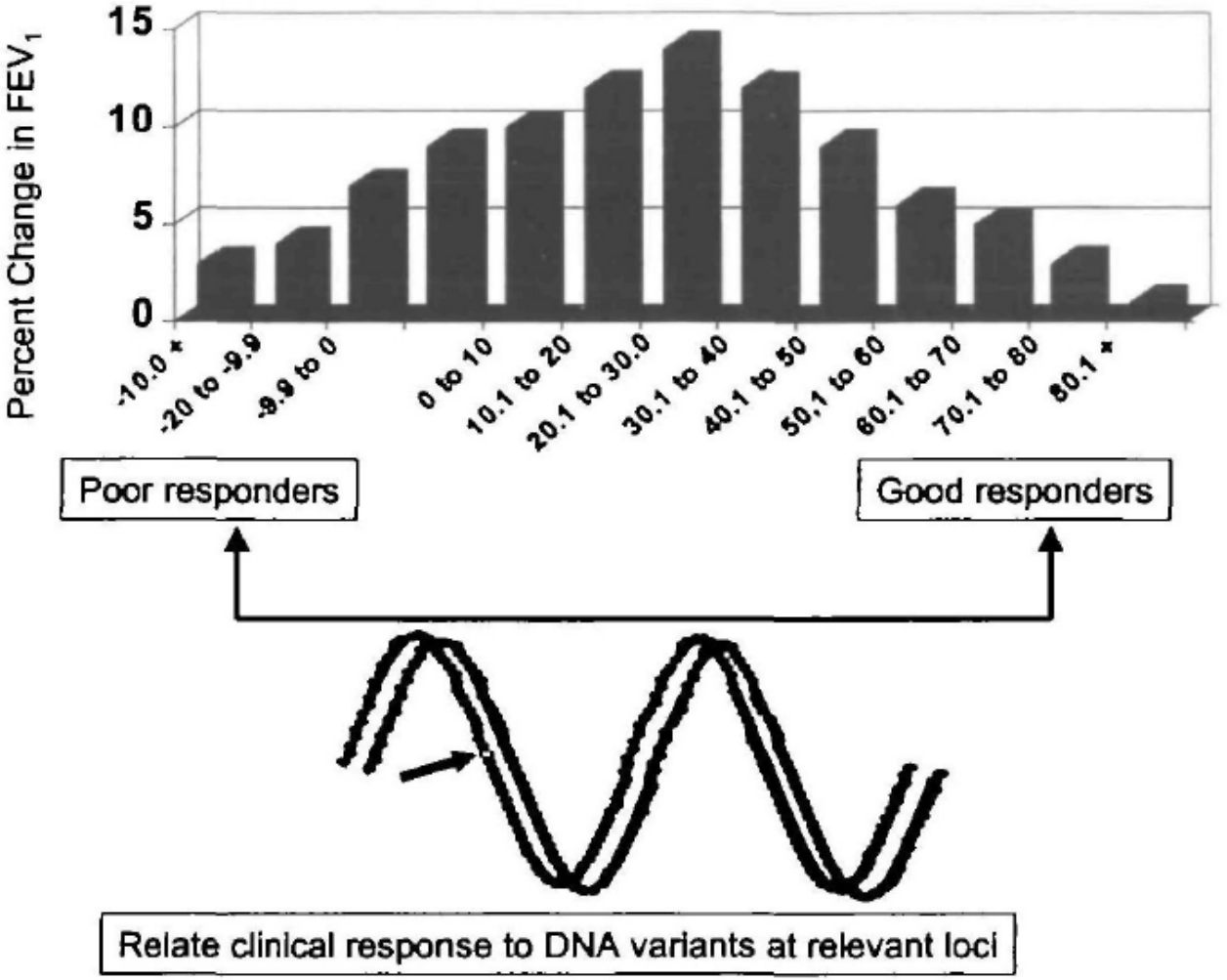
Adding Exhaled Nitric Oxide to Guideline-based Asthma Treatment in Inner-City Adolescents and Young Adults: a randomized controlled trial



Szefler SJ, Lancet 2008

Heterogeneity of therapeutic responses in asthma

Jeffrey M Drazen[1], Edwin K Silverman[1] and **Tak H Lee[2]**



British Medical Bulletin 2000; **56** (No. 4): 1054–1070

Conclusioni

- La terapia dell'asma bronchiale si avvale di un ampio ventaglio di classi di farmaci

- L'approccio terapeutico si basa fondamentalmente su corticosteroidi inalatori e $ß_2$-agonisti, secondo una logica a gradini crescenti o decrescenti in relazione alle condizioni clinico-funzionali

- La risposta alla terapia è influenzata dall'aderenza terapeutica, da distinti profili infiammatori e da poliformismi genetici