Terapéutica del asma en el niño: entre las guías clínicas y la vida real

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Asma Bronquial

- Una de las enfermedades respiratorias crónicas más comunes, afecta a más de 300 millones de personas
- Se estima que aumentará unos 100 millones de casos especialmente pediátricos en los próximos 15 años
- Causa una de cada 250 muertes
- Tiene alto impacto en los costos de salud por las hospitalizaciones y visitas de emergencia
- 5–10% de los pacientes tienen formas severas que no se controlan con tratamiento habitual…
- Y consumen más del 50% de los costos de salud asociados al asma

Principales Guías Clínicas sobre Asma

GUIA CLINICA	Ultima edición	Páginas	Comentarios
GINA	GINA Diciembre 2009	96	Pocket Guide (Asma en niños y adultos) de 28 páginas Disponible en ppt http://www.ginasthma.org
U.S. Department of Health and Human Services National Institutes of Health National Heart, Lung, and Blood Institute	NAEPP-EPR 3 Agosto 2007	415	No Pocket Guide No disponible en ppt http://www.nhlbi.nih.gov/guidelines/index.htm
	British Guideline Mayo 2008	94	No Pocket Guide Disponible en ppt http://www.brit-thoracic.org.uk/guidelines.html
PRACTALL EAACI and AAAAI Consensus Report	Enero 2008	30	Consenso de Diagnóstico y Tratamiento del Asma en Niños. Allergy 2008;63(1):5-34 http://www.blackwell-synergy.com

Evaluación y seguimiento de los pacientes con asma

- Interrelación con 3 conceptos :

1. Severidad del asma
2. Control del asma
3. Respuesta al tratamiento

Severidad del asma

¨Intensidad intrínseca de la afección ¨

- Puede evaluarse mas fácilmente en pacientes que no están recibiendo terapia de control
- En estas circunstancias permite una estimación del tipo e intensidad de tratamiento que requerirá el paciente para mejorar sus síntomas y limitaciones actuales y reducir el riesgo.

Control del asma

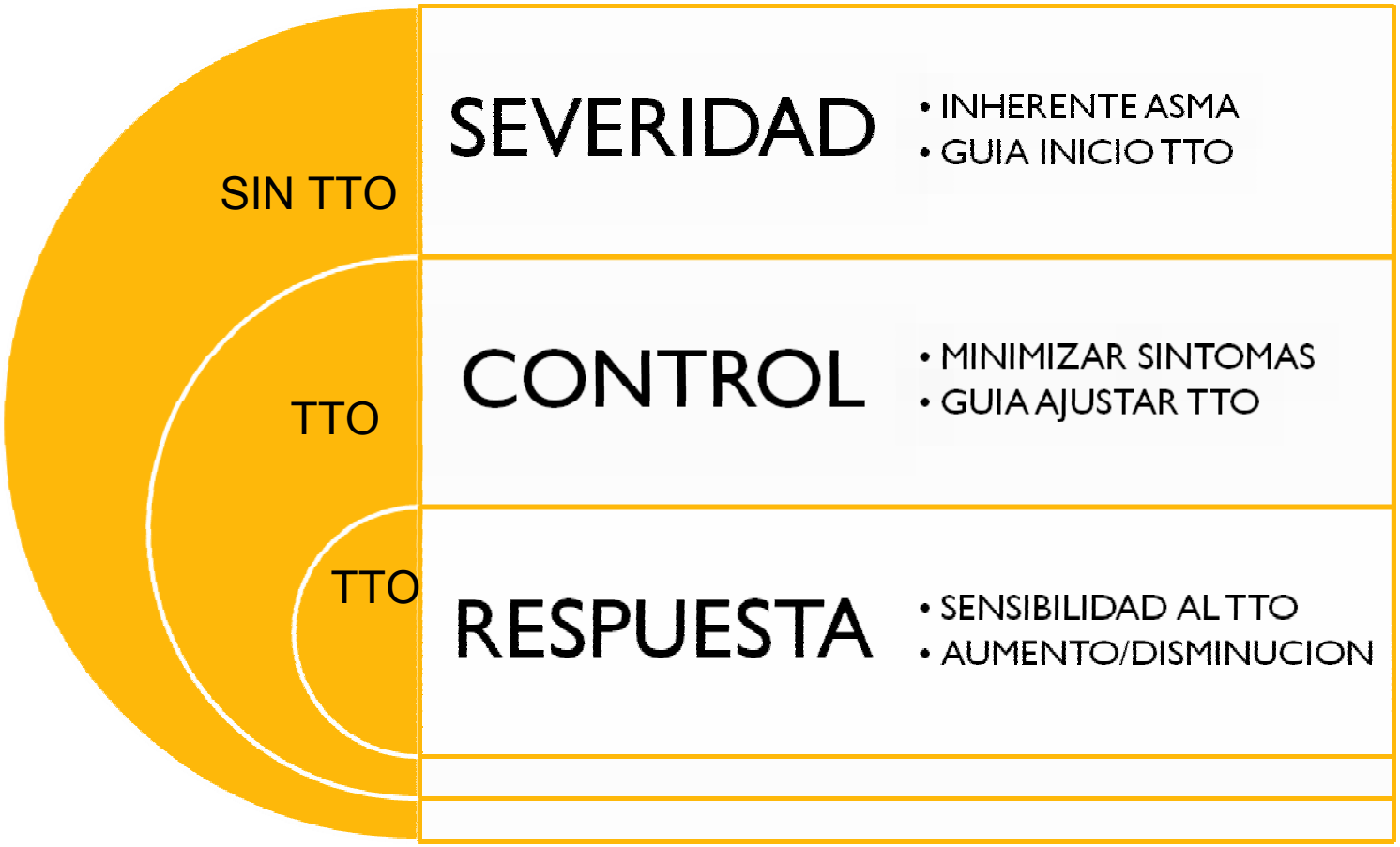
- Grado en el cual las manifestaciones del asma -Síntomas , limitación funcional y riesgo de eventos indeseados – son minimizados por el tratamiento.

Dominios de la severidad y control

- *Limitaciones* :
  - Frecuencia e intensidad de síntomas
  - Restricciones funcionales (social /laboral ,etc.)
- *Riesgo:* estimación de la posibilidad de :
  - Exacerbaciones
  - Perdida progresiva de función pulmonar
  - Eventos adversos derivados de las medicaciones
  - Muerte

Respuesta al tratamiento

- Facilidad con la cual el control del asma es alcanzado por la terapéutica
- ***ADVERTENCIA:***
  - La respuesta en un dominio (por ejemplo mejora en la limitación funcional) no implica necesariamente respuesta en el otro dominio (por ejemplo riesgo de exacerbaciones o perdida de función pulmonar)



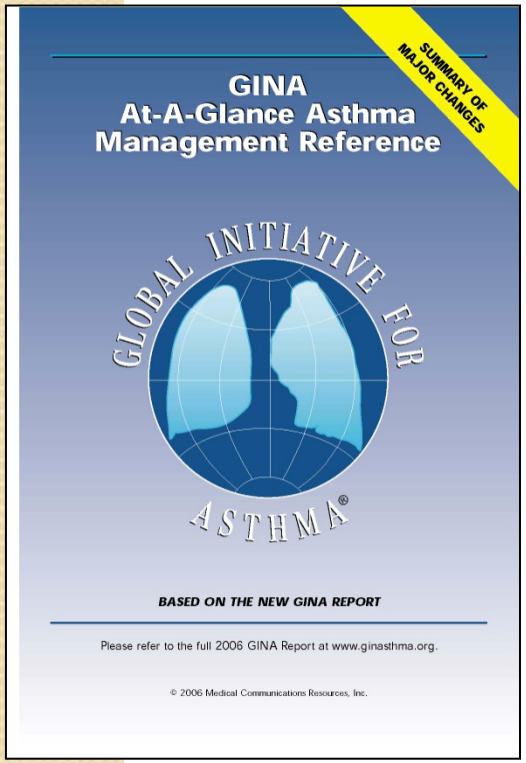
The Expert Panel Reports (EPR-3) “The Four Components of Asthma Management”

Niveles de control del Asma

Características	Controlado (todo lo siguiente)	Parcialmente Controlado (cualquiera de los siguientes en cualquier semana.)	No controlado
Síntomas diarios	Ninguno (2 o menos por semana)	Mas de dos por semana	3 o mas características del asma parcialmente controlado en cualquier semana
Limitación de las actividades	Ninguno	Cualquiera	
Síntomas o Despertares Nocturnos	Ninguno	Cualquiera	
Necesidad de medicación de rescate	Ninguno (2 o menos por semana)	Mas de dos por semana	
Función Pulmonar (PEF o FEV_1)	Normal	< 80% del predicho o del mejor personal (conocido) cualquier día	
Exacerbaciones	Ninguna	Una o mas por año	Una en cualquier semana

Componentes del control del asma:

1. **Monitoreo de signos y síntomas**
2. **Pruebas de Función Pulmonar**
3. **Historia de exacerbaciones**
4. **Calidad de vida**
5. **Seguimiento de adherencia y detección de efectos adversos de la farmacoterapia**
6. **Grado de satisfacción del paciente y comunicación con el medico del asma**



U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

SIGN

NHS
Quality Improvement Scotland

Tratamiento del asma basado en el **Control, no en severidad**

Escasos estudios sobre control del asma en niños

Objetivos de tratamiento del asma bronquial

Control del asma

ACTUAL

Ausencia de síntomas
Sin uso de BD
Actividad normal y deporte
Función pulmonar normal

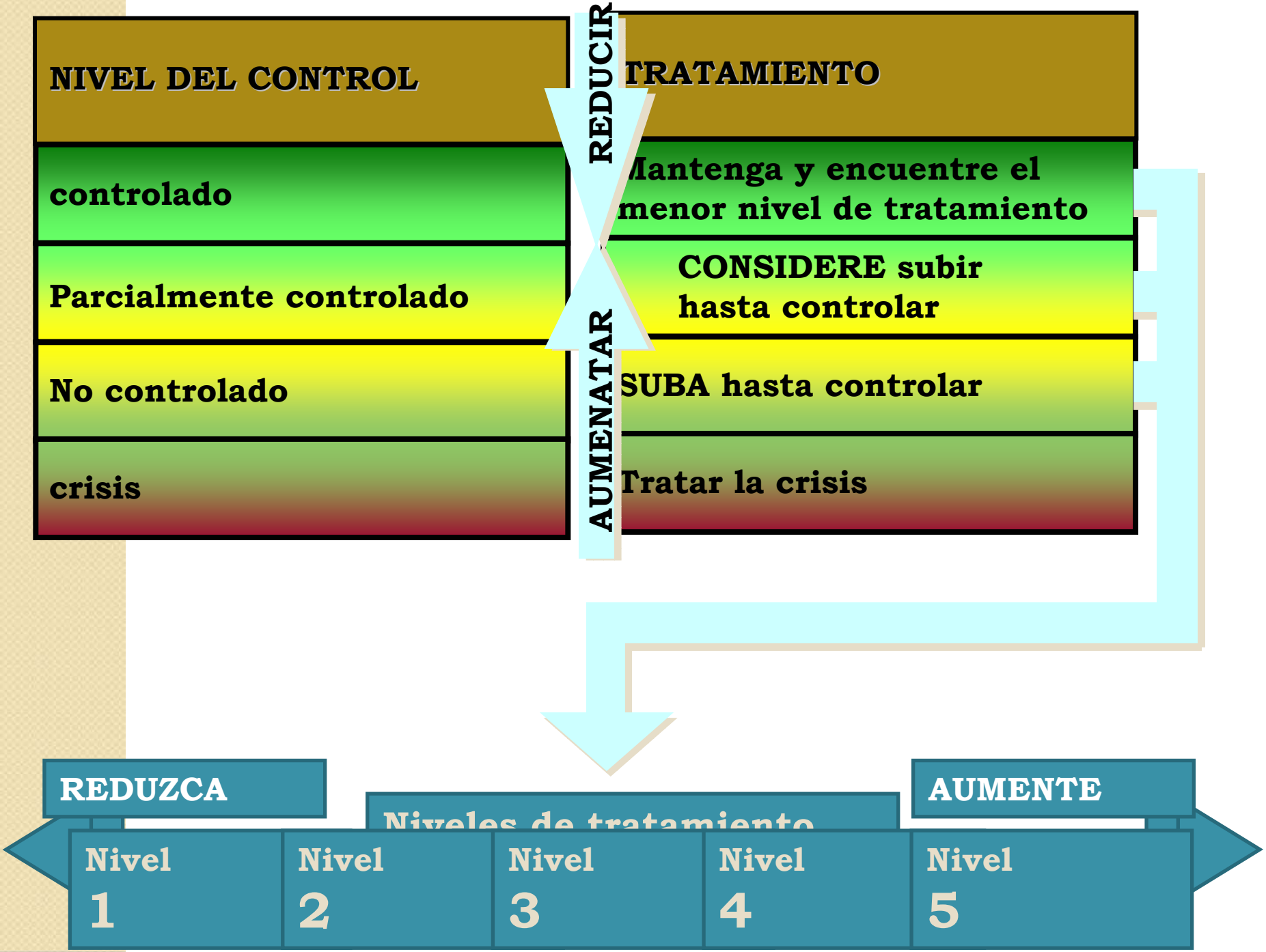
RIESGOS FUTUROS

Evitar inestabilidad o deterioro
Evitar pérdida de la función pulmonar
Evitar exacerbaciones
Efectos adversos de terapia

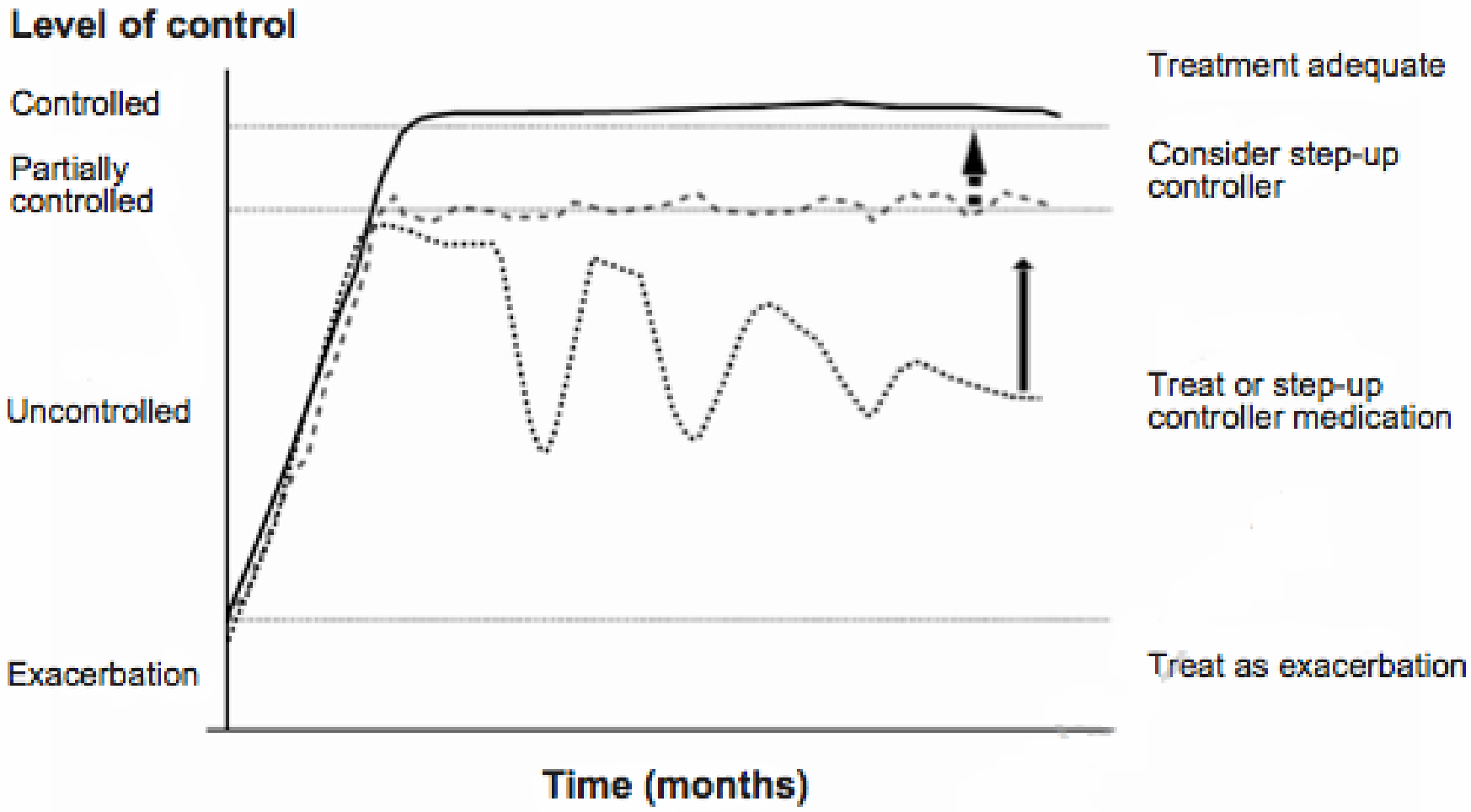
NAEPPP Expert Panel Report 3 2007

ATS/ERS Task Force AJRCCM 2009.

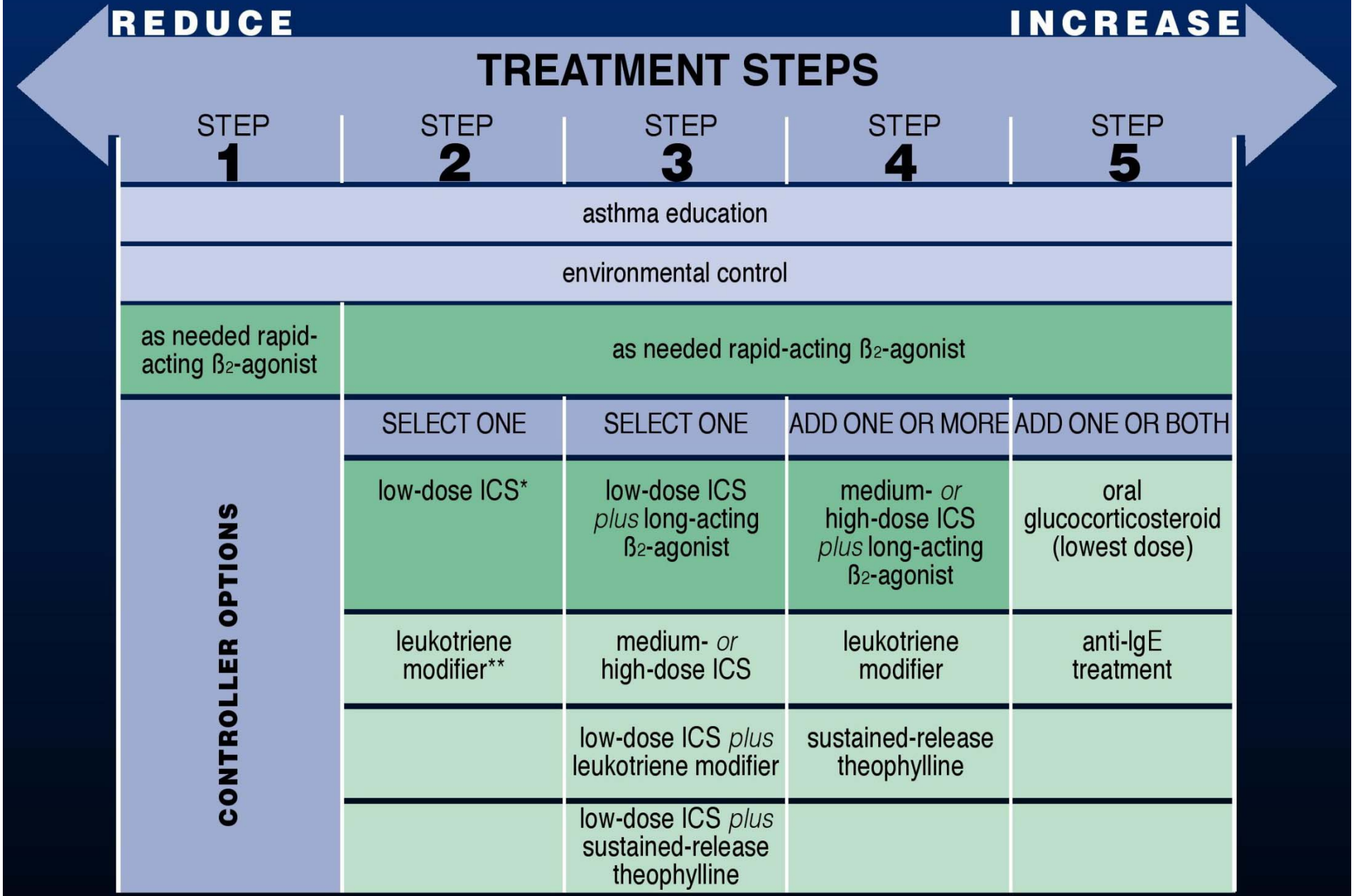
Taylor DR et al Eur Respir J 2008; 32:545.554


NIVEL DEL CONTROL
TRATAMIENTO
controlado
Mantenga y encuentre el menor nivel de tratamiento
Parcialmente controlado
CONSIDERE subir hasta controlar
No controlado
SUBA hasta controlar
crisis
Tratar la crisis
REDUCIR
AUMENATAR
REDUZCA
AUMENTE
Niveles de tratamiento
Nivel 1
Nivel 2
Nivel 3
Nivel 4
Nivel 5

El objetivo del tratamiento es minimizar la variabilidad del asma, que es característico de la enfermedad



Søren Pedersen. From asthma severity to control: a shift in clinical practice. Primary Care Respiratory Journal (2009)


REDUCE
INCREASE
TREATMENT STEPS
STEP 1
STEP 2
STEP 3
STEP 4
STEP 5
asthma education
environmental control
as needed rapid-acting ß2-agonist
as needed rapid-acting ß2-agonist
CONTROLLER OPTIONS
SELECT ONE
SELECT ONE
ADD ONE OR MORE
ADD ONE OR BOTH
low-dose ICS*
low-dose ICS plus long-acting ß2-agonist
medium- or high-dose ICS plus long-acting ß2-agonist
oral glucocorticosteroid (lowest dose)
leukotriene modifier**
medium- or high-dose ICS
leukotriene modifier
anti-IgE treatment
low-dose ICS plus leukotriene modifier
sustained-release theophylline
low-dose ICS plus sustained-release theophylline
*inhaled glucocorticosteroids
** receptor antagonist or synthesis inhibitors

Nivel del control del asma: predice futuros eventos

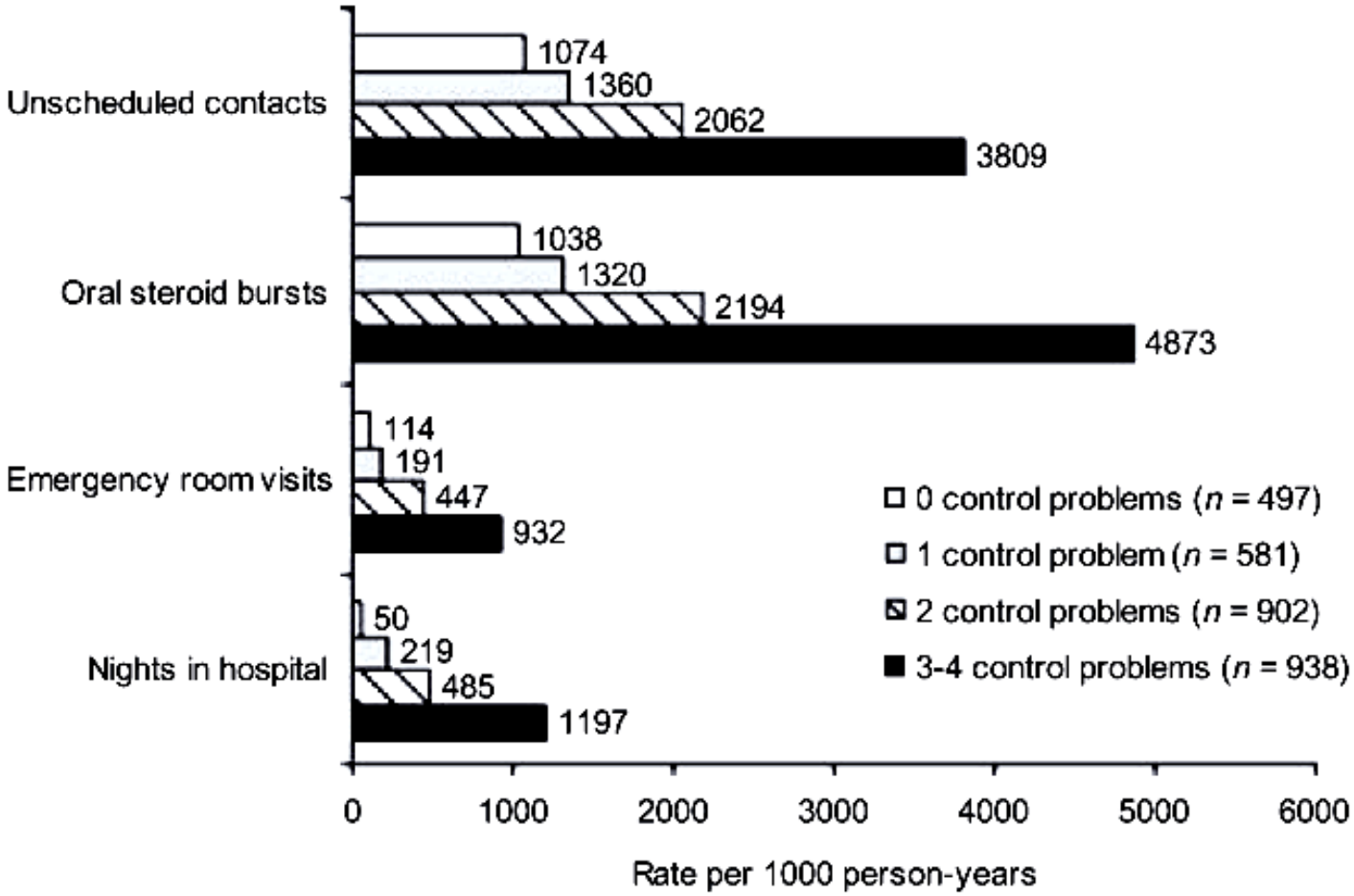


Figure 1. Unadjusted rates of acute asthma-related healthcare events per 1000 person-years of follow up by baseline level of asthma control.

Sullivan SD et al. Allergy 2007

El control del asma no alcanza lo recomendado en las guías

Alcanzan control según GINA

- **AIRE:**
  - Rabe KF et a. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J 2000;16: 802-7

(AIRE) results

GINA recommendation	AIRE result	Symptoms %	
		Children	Adults
Minimal chronic symptoms	Daytime symptoms once a week	38.2	50.1
	Sleep disturbances at least once a week	28.0	30.5
Minimal episodes	Reported episodes of coughing, wheezing, chest tightness or shortness of breath in the last month	51.5	57.2
No emergency visits	Unscheduled urgent care visits during last year	36.0	27.9
	Emergency visits during last year	18	11
Minimal need for β_2-agonists	Used as-required β_2-agonists during the last month	61.0	63.6
No limitations on activities	Limitation of activities		
	Sports	29.5	47.1
	Normal physical activity	19.1	37.9
	Choice of jobs/career	–	23.0
	Social activities	13.8	25.5
	Sleep	31.2	36.2
	Lifestyle	18.6	33.0
	Housekeeping chores	10.9	34.1
	School/work absence	42.7	17.1
Normal or near normal lung function	Never had a lung function test	60.5	45.0

- **AIRLA: 2.4%**
  - Neffen H, et al. Asthma Control in Latin America: the asthma insight and Reality in Latin America (AIRLA) survey. Rev Panam Salud Publica 2005;17(3):191-7

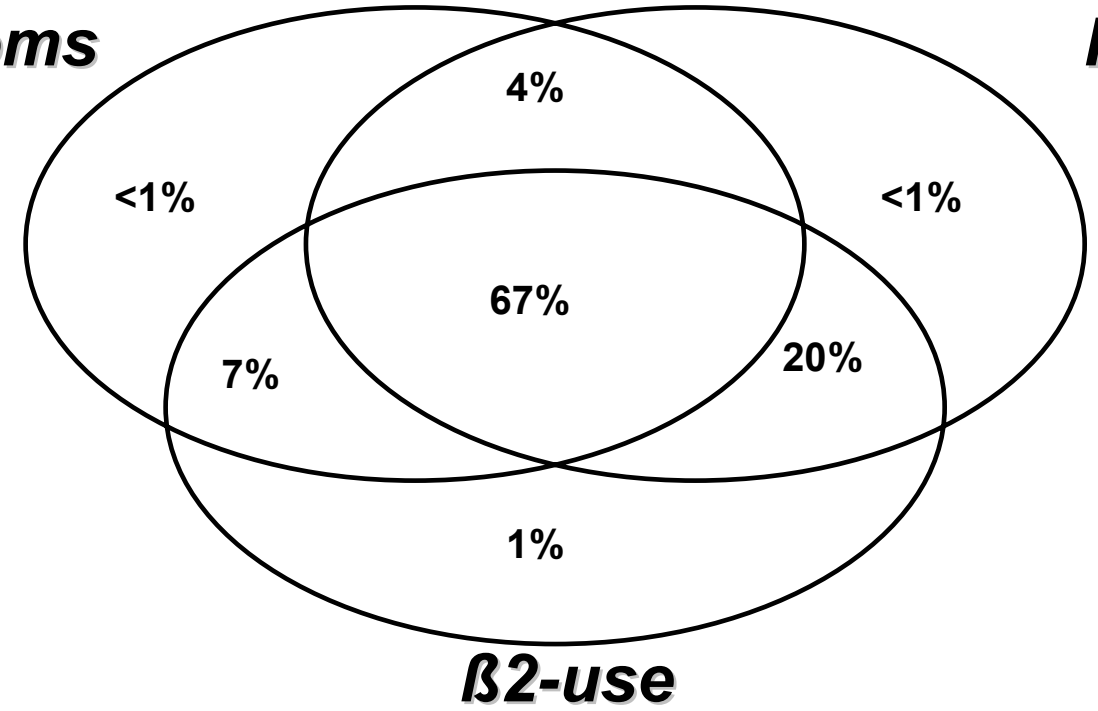
PEACE study: patient demography and baseline characteristics

Characteristic	SFC (n=281)	MON (n=267)
Age in years, mean (SD)	9.3 (2.15)	9.3 (2.12)
Male, n (%)	156 (56)	179 (67)
Diary card data, mean (SD):*		
– morning PEF (L/min)	216.0 (72.6)	214.0 (67.1)
– % predicted morning PEF	74.4 (17.8)	74.3 (17.1)
– % symptom-free days	16.8 (26.5)	15.3 (22.2)
– % nights with no awakenings	69.3 (32.8)	66.0 (32.8)
– % rescue-free days	13.4 (21.2)	11.3 (20.0)
Lung function, mean at baseline visit (SD):		
– FEV_1 (L)	1.49 (0.43)	1.48 (0.43)
– % predicted FEV_1	72.9 (6.8)	72.9 (6.9)
– % reversibility in FEV_1	26.0 (14.0)	26.3 (12.2)

***Over last 7 days of run-in**

1. Maspero J

Proportion of Patients Failing to achieve asthma control at baseline according PEF, Symptoms and β2-agonist rescue Criteria



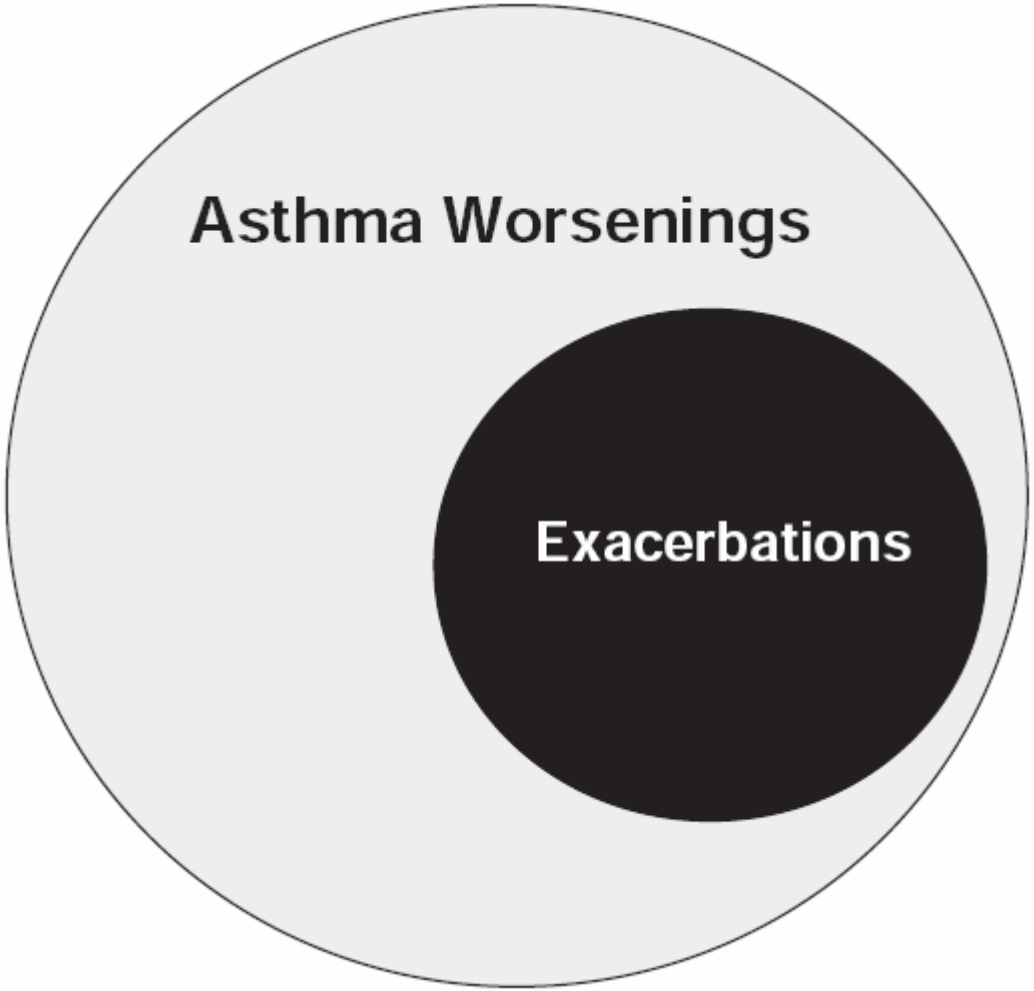
n=548 patients

Maspero J *et al. Clin Therapeutics* 2008; **30**.

How many patients are well controlled in clinical trials?

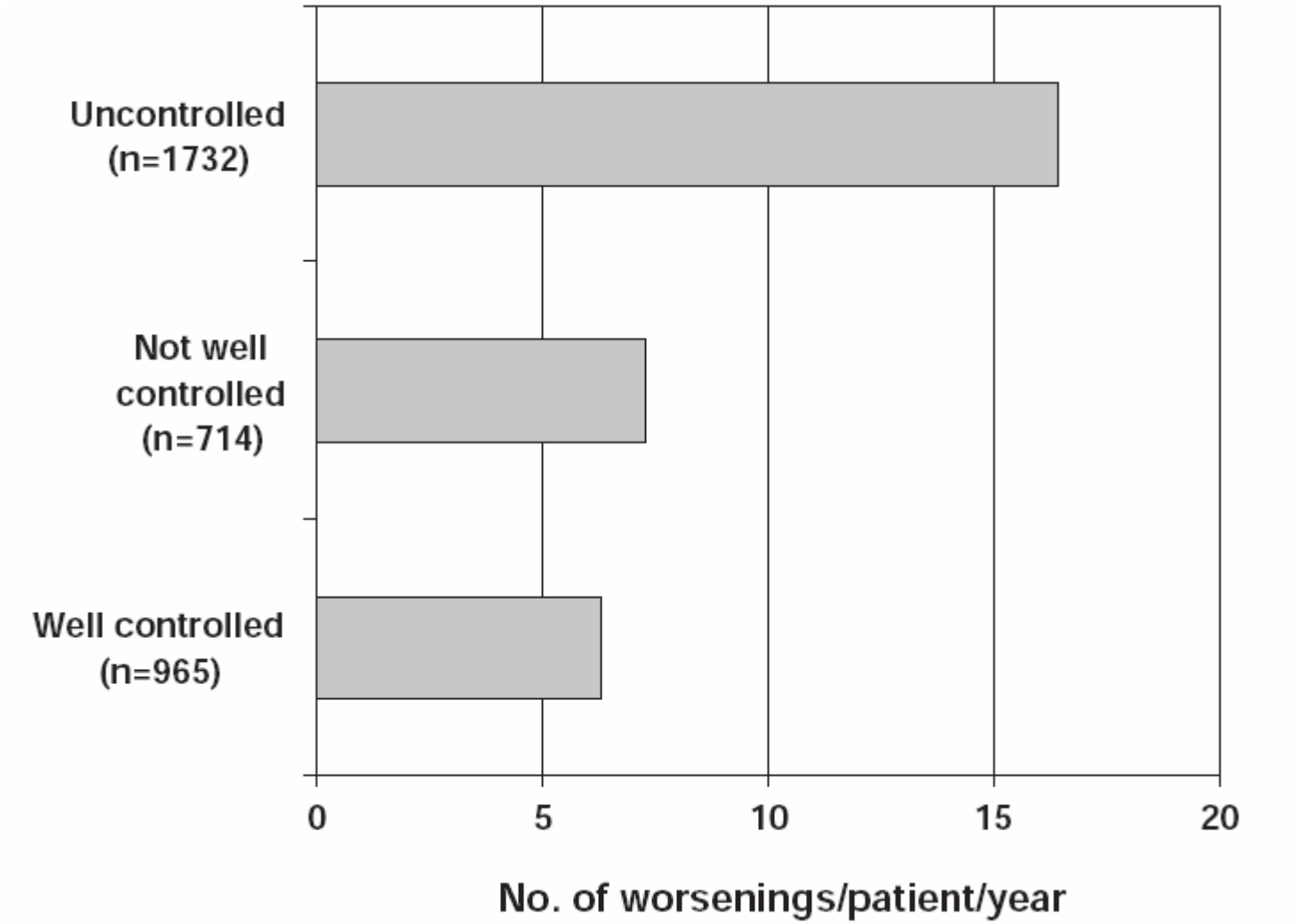
- 38% of patients well controlled with FP 200 mcg (Run in De Blic study)
- 40% achieve asthma control with FP 400 mcg – 15% Total Controlled Asthma - (De Blic study)
- 43% achieve asthma control with SFC - 19% Total controlled asthma- (De Blic study)
- 36 % were well controlled with montelukast 5 mg (PEACE)
- 59% achieve well controlled asthma with SFC (PEACE)
- 71 % achieve well asthma control after an year (GOAL)
- But after the first 12 weeks only around 50% of the SFC treated

Las exacerbaciones son un subgrupo de los empeoramientos



The Reality of Asthma Control (TRAC) study: Asthma worsenings and exacerbations during the past year by asthma control status

Asthma worsening and exacerbation	Patients with uncontrolled asthma	Patients with controlled asthma	P
Patients with worsening asthma and exacerbations, n (%)	474 (53)	418 (47)	
Asthma worsening			
Patients who experienced at least one, %	95	82	<0.01
Mean duration, days	13.6	8	<0.02
Asthma exacerbation			
Patients who had at least one urgent office visit, %	72	15	<0.01
Patients who had at least one emergency-room visit, %	32	3	<0.01
Patients who had at least one hospitalization, %	7	0	<0.01



Partridge MR et al , Inspire Study , BMC PULM MED 2006,6:13

Initial treatment in Asthmatic Adults poor relation with guidelines recommendations

	Mild intermmitent	Mild Persistent	Moderate Persistent	Severe Persistent
	Percent of patients treated with:			
Albuterol (salbutamol)	78%	41%	39%	42%
Combination Therapy (ICS + LABA)				
Seretide®	24%	48%	81%	87%
Singulair®	22%	25%	21%	34%
Inhaled steroids	17%	49%	27%	26%
LABAs*	8%	11%	15%	17%
Xolair® (Anti I g E)	*	*	1%	3%
Oral steroids	-	-	-	3%

Como usamos los esteroides?

- Budesonida y fluticasona se administran 2 veces al día,
- la beclometasona 2-3 veces por día
- ciclesonide es el único corticoide inhalado con eficacia comprobada cuando se lo administra una vez por día.

Arch Argent Pediatr 2008;106(2):162-175

BRONCODILATADORES DE ACCION LARGA

- están aprobados siempre asociados a corticoides inhalados.
- su indicación se limita a pacientes con asma persistente moderada o grave que no logren controlar sus síntomas con dosis moderadas de CTC inhalados.
- La asociación de ambos fármacos ha demostrado mejorar el control del asma, y permitido utilizar menores dosis de CTC tópicos.
- Esta terapia combinada ha sido ampliamente estudiada en adultos pero las publicaciones en niños son escasas.
- Las formas de presentación corresponden a la vía inhalatoria, en aerosoles de dosis medida, o en polvo para inhalar.

Arch Argent Pediatr 2008;106(2):162-175

- Salmeterol y formoterol se pueden prescribir a partir de los 4-6 años, respectivamente.

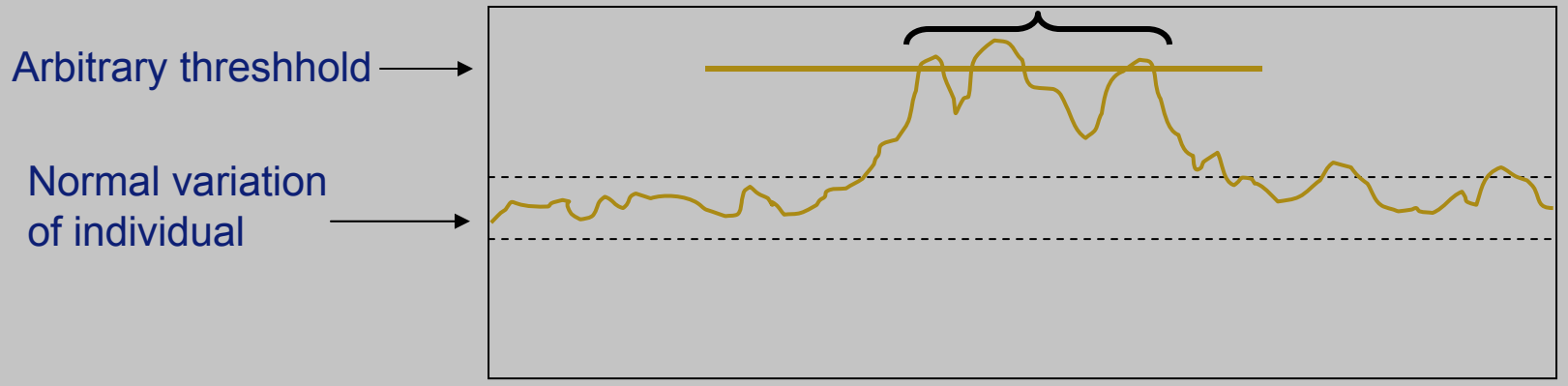
Health care resource use in patients with appropriate and inappropriate use of asthma medications

Use of health care resources	Appropriate use (n=4671)	Inappropriate use (n=763)	P
Hospital resources			
Hospital admissions			
Patients admitted at least once, n (%)	257 (5.5)	64 (8.4)	0.002
Admissions per patient	0.07±0.34	0.11±0.42	0.006
Urgent admissions			
Patients with at least 1 urgent admission, n (%)	154 (3.3)	44 (5.8)	0.001
Urgent admissions per patient	0.04±0.26	0.08±0.33	0.005
Prescribing physicians*			
"Prescribing physicians" seen per patient	1.4±0.7	1.8±1.4	<0.001
Prescriptions† per physician	2.5±1.5	5.2±4.2	<0.001
Prescriptions per patient	3.3±1.9	7.5±4.9	<0.001
All physicians‡			
Physicians seen per patient	5.1±4.2	4.8±4.3	0.16
Visits per physician	3.2±3.0	3.9±3.8	<0.001
Visits to all physicians per patient	14.9±15.9	16.7±19.3	0.015

Definiciones: exacerbación moderada

"Event which, when recognized, should result in a temporary change in treatment in an effort to prevent the exacerbation from becoming severe"

ATS/ERS taskforce on asthma control and exacerbations 2007

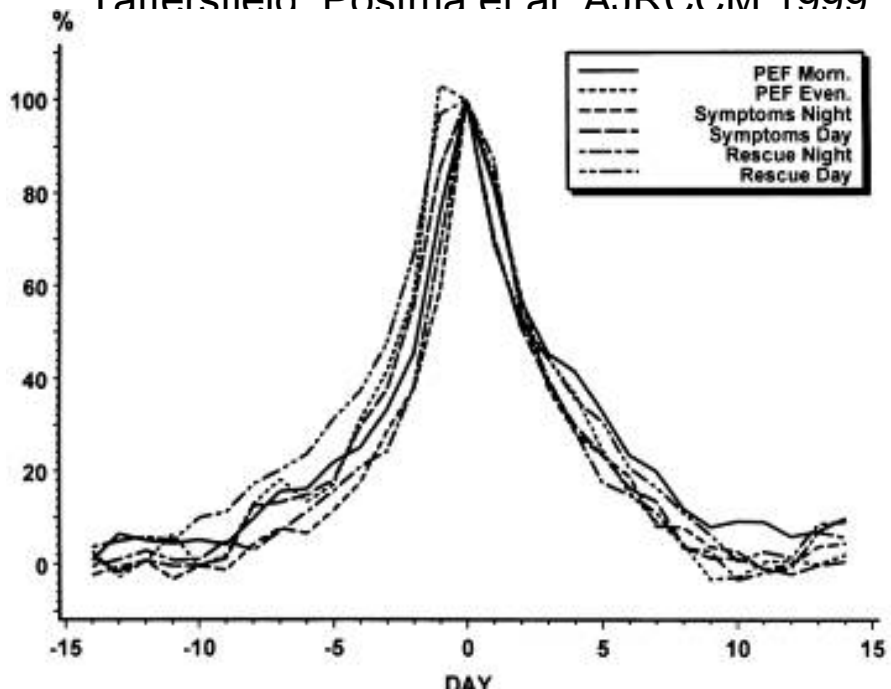


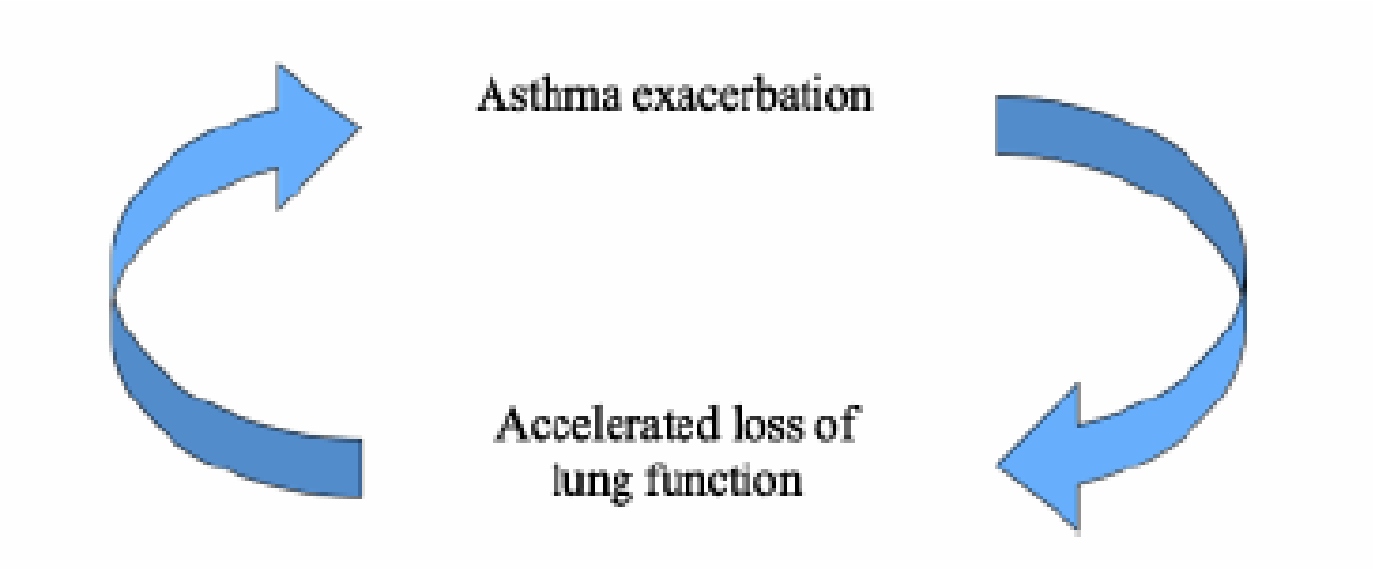
Definiciones – exacerbación severa

"Event which requires urgent action on the part of the patient and physician to prevent a serious outcome such as hospitalization or death from asthma. The occurrence of severe exacerbations should be used as a marker of poor asthma control"

ATS/ERS taskforce on asthma control and exacerbations 2007

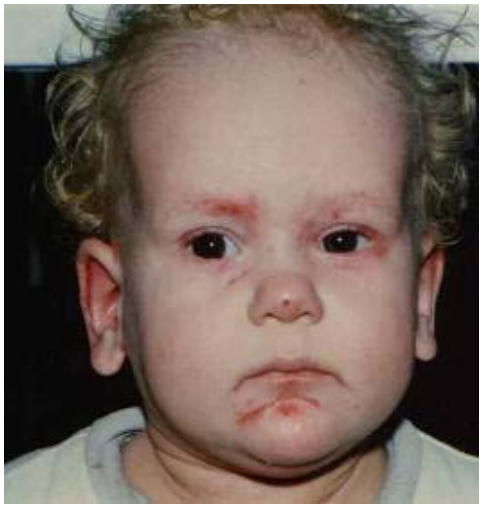
Tattersfield, Postma et al. AJRCCM 1999





Verdad en adultos , que pasa en niños?

Definiciones en niños



- **Síntomas referidos por los padres**
- **No suele haber pruebas de funcion pulmonar en menores de 6-7 años**
- **Diagnostico de asma es muchas veces incierto**
- **Respuesta al tratamiento puede variar con la edad y fenotipos**

→ ***Es necesario un enfoque edad- especifico para la definición , diagnostico y tratamiento de las exacerbaciones de asma en niños***

Boluyt et al, Pediatrics 2007

Pocket Guide for Asthma Management and Prevention in Children 5 Years and Younger

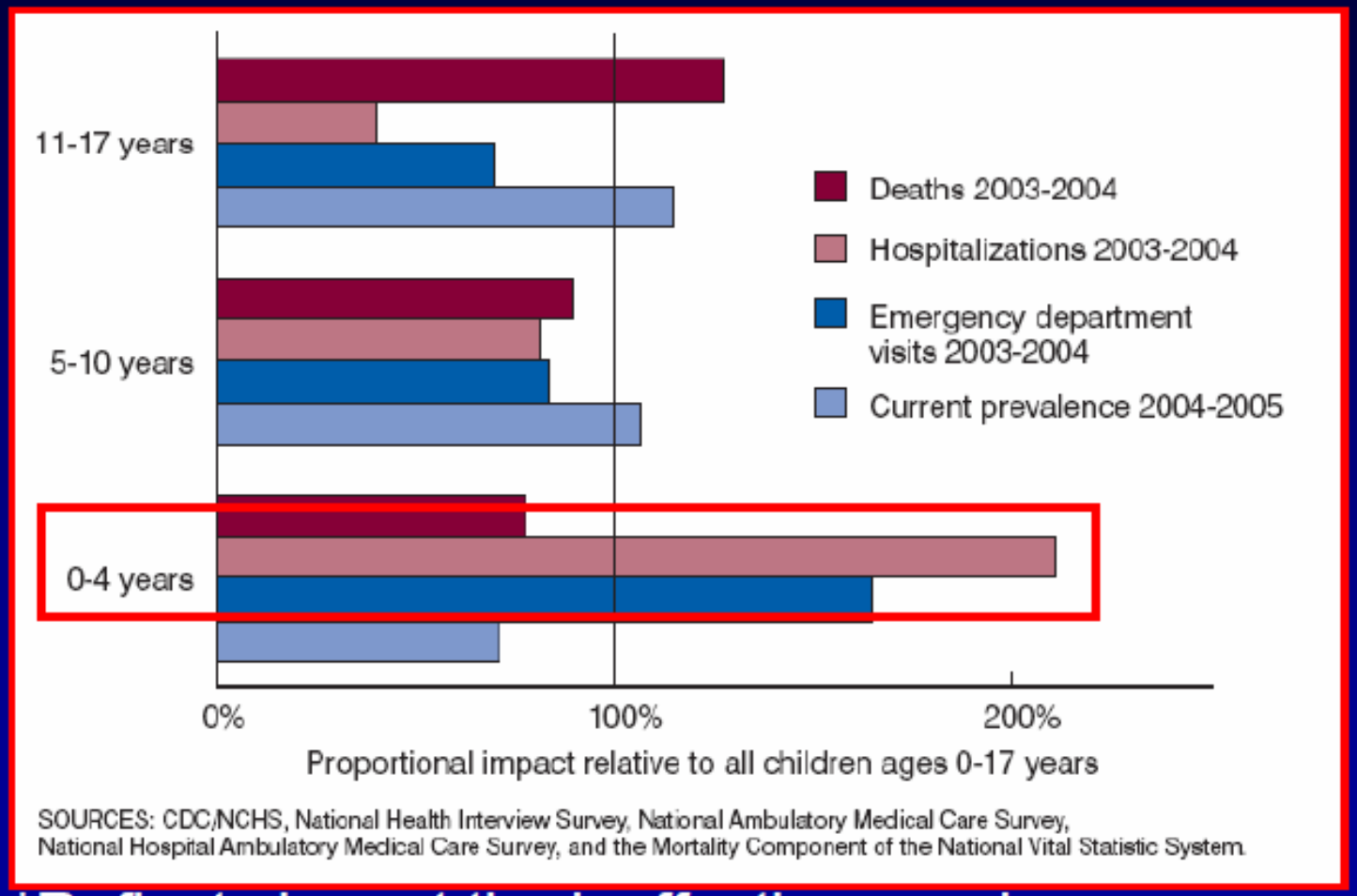
A Pocket Guide for Physicians and Nurses

2009

BASED ON THE GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION IN CHILDREN 5 YEARS AND YOUNGER

Available from www.ginasthma.org

Disproportionate Use of Health Care Resources



*Reflects in part the ineffectiveness in age group

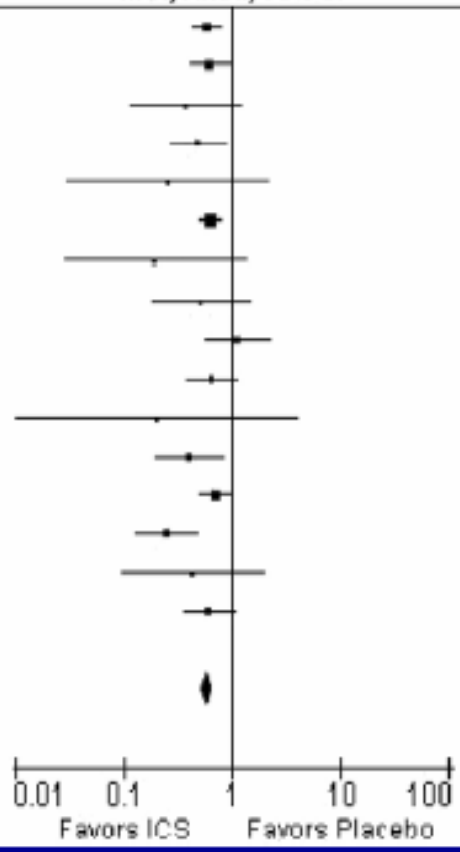
L Akinbami, *Advance Data* 2006

ICS in Infants and Preschoolers with Recurrent Wheezing and Asthma-Metanalysis

Study or Subgroup	ICS Events	ICS Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baker et al[30]	89	306	37	95	15.1%	0.59 [0.43, 0.81]
Bisgaard et al[31]	36	156	30	81	10.0%	0.62 [0.42, 0.93]
Connett et al[25]	3	20	8	20	2.0%	0.38 [0.12, 1.21]
de Blic et al[27]	8	20	15	18	4.0%	0.48 [0.27, 0.85]
Gleeson et al[20]	1	39	4	39	1.0%	0.25 [0.03, 2.14]
Guilbert et al[9]	57	132	89	130	22.8%	0.63 [0.50, 0.79]
Kraemer et al[28]	1	9	8	14	1.6%	0.19 [0.03, 1.30]
Carlsen et al[41]	5	79	10	81	2.5%	0.51 [0.18, 1.43]
Murray et al[10]	16	101	14	99	3.6%	1.12 [0.58, 2.17]
Nielsen et al[34]	9	19	14	19	3.6%	0.64 [0.37, 1.11]
Noble et al[24]	0	24	2	24	0.6%	0.20 [0.01, 3.96]
Qaqundah et al[43]	12	239	15	120	5.1%	0.40 [0.19, 0.83]
Roorda et al[36]	38	152	54	153	13.7%	0.71 [0.50, 1.00]
Shapiro et al[29]	12	134	16	44	6.1%	0.25 [0.13, 0.48]
Teper et al[42]	2	14	4	12	1.1%	0.43 [0.09, 1.94]
Wasserman et al[44]	25	219	21	113	7.0%	0.61 [0.36, 1.05]
Total (95% CI)		**1743**		**1062**	**100.0%**	**0.59 [0.52, 0.67]**
Total events	314		341			

Heterogeneity: $Chi^2 = 16.63$, $df = 15$ ($P = 0.34$); $I^2 = 10\%$

Test for overall effect: $Z = 8.15$ ($P < 0.00001$)



Castro-Rodriguez, J. A. et al. Pediatrics 2009;123:e519-e525

Factors that affect the efficacy of inhaled corticosteroids for infants and young children

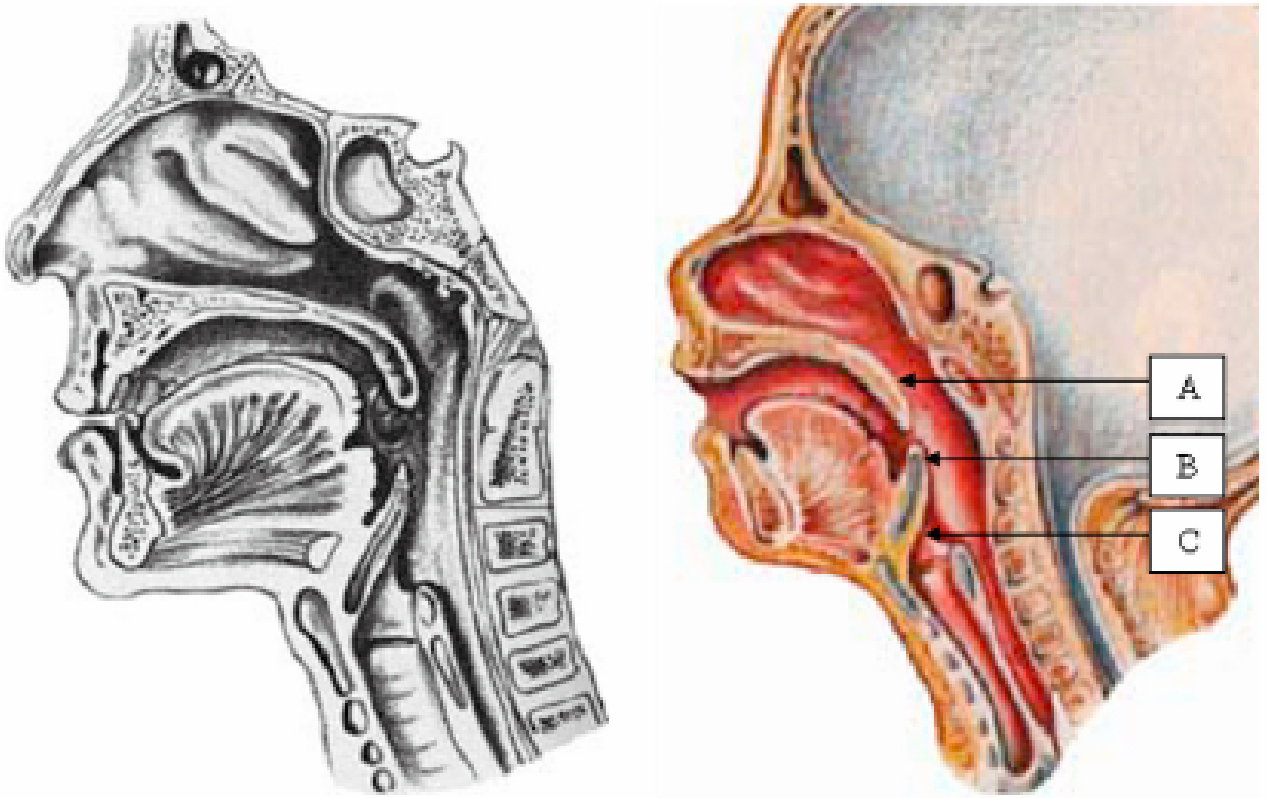
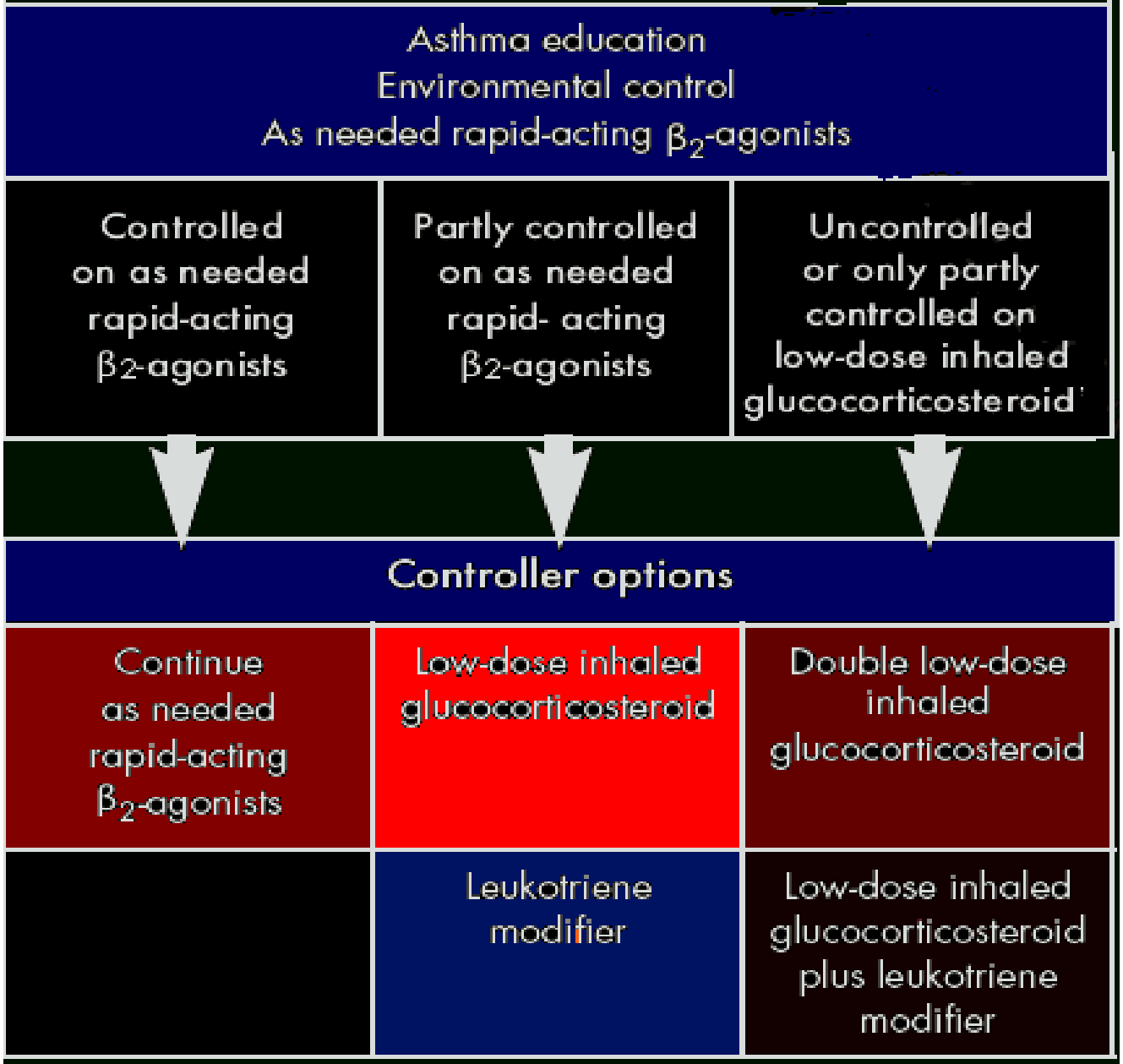


FIG 1. The upper airway of adults *(left)* compared with that of infants *(right)*: *A*, pharynx and supraglottic—less rigid; *B*, epiglottis—narrow, floppy, and closer to the palate; *C*, larynx—higher and very close to the base of the tongue.

Table 5. Asthma Management Approach Based on Control for Children 5 Years and Younger



Preescolares

- Long-acting inhaled β2-agonists Formoterol and salmeterol have shown long-lasting bronchodilatory and bronchoprotective effects in preschool children
- *There are no published double-blind randomised placebo-controlled trials in preschool children on the addition of long-acting inhaled β2-adrenergic agents to ICSs.*

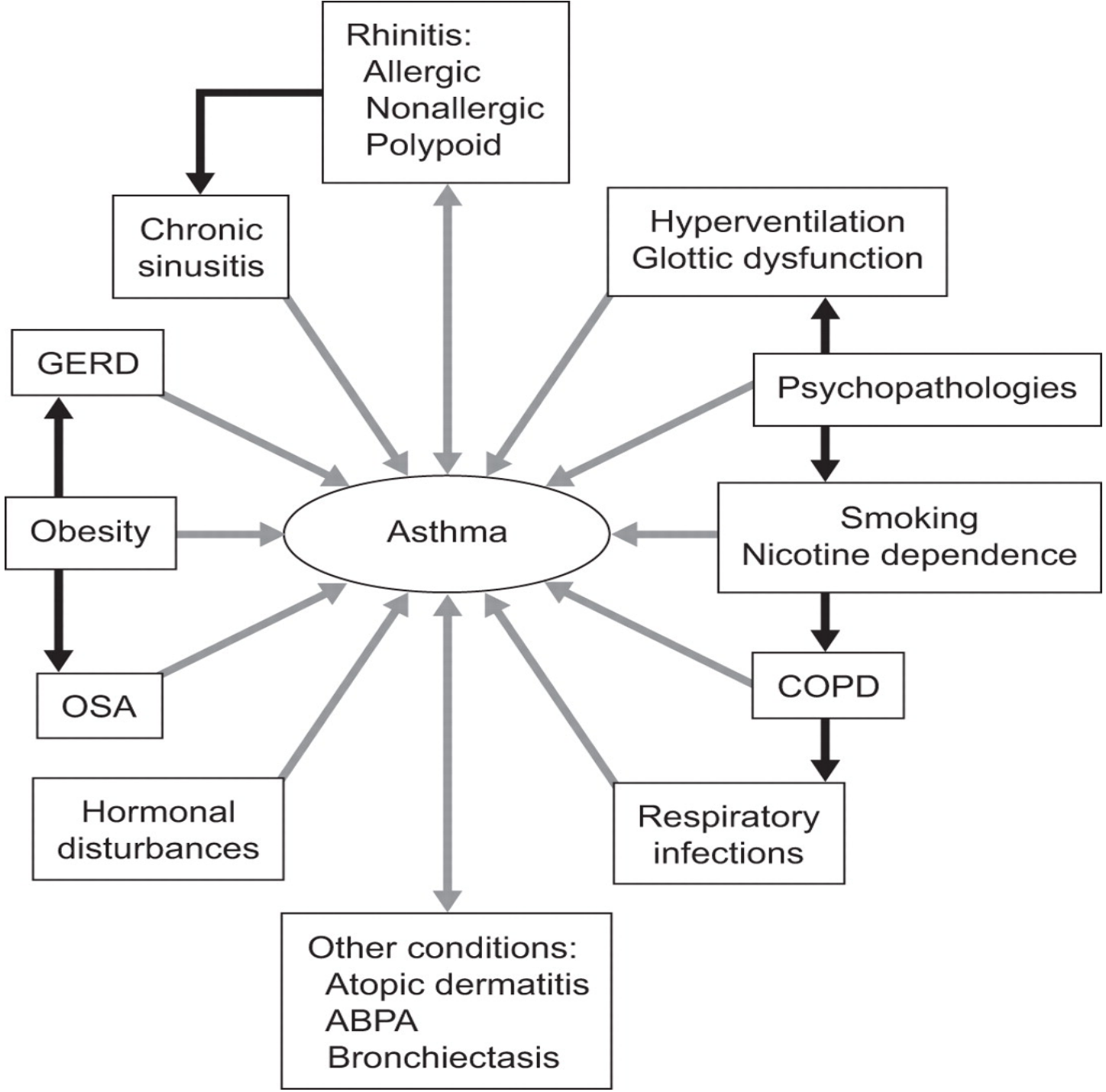
Eur Respir J 2008; 32:1096-1110

Que cuestiones restan en la práctica

- Comorbilidades
- Predicción de remisión o persistencia:
  - En escolares y adolescentes
  - En preescolares
- Fenotipos o endotipos
- Guía para el step down
- Validez externa
- Aplicación a las realidades sociales y ambientales de Argentina
-

Asma y morbilidades relacionadas

Boulet LP,
Eur Respir J 2009;
33:897-906



Los niños con sibilancias y aparición de atopia en los 2 o 3 primeros años de vida estan en riego de presentar asma persistente con hiperreactividad bronquial y perdida de función pulmonar

A su vez los niños *no atópicos* con sibilancias suelen perder los sínomas para la edad escolar y mantienen función pulmonar normal en la infancia.

Illi et al, Lancet 2006

API original (Castro-Rodriguez et al.)

Criterios mayores:

- Historia familiar de asma.
- Diagnóstico médico de dermatitis atópica.
- **Criterios menores:**
- Diagnóstico médico de rinitis alérgica.
- Sibilancias sin resfrío.
- Eosinofilia sanguínea ≥ 4%.

API modificado (Guilbert et al.)

Criterios mayores:

- Historia familiar de asma.
- Dermatitis atópica.
- Sensibilización a ≥ 1 aeroalergeno.

Criterios menores:

- Sensibilización a leche, huevo o maní.
- Sibilancias sin resfrío.
- Eosinofilia sanguínea ≥ 4%.

**Las diferencias en los índices están en colores.*

Predictors of remitting, periodic, and persistent childhood asthma

- Asthma was identified as
  - remitting in 6%,
  - periodic in 39%,
  - and persistent in 55% of the 909 participants,
  - no effect noted from earlier anti-inflammatory treatment.
- improvements in airway hyperresponsiveness, eosinophilia, and asthma morbidity were observed over time in all cathegories

Associated with remitting versus persistent asthma were:

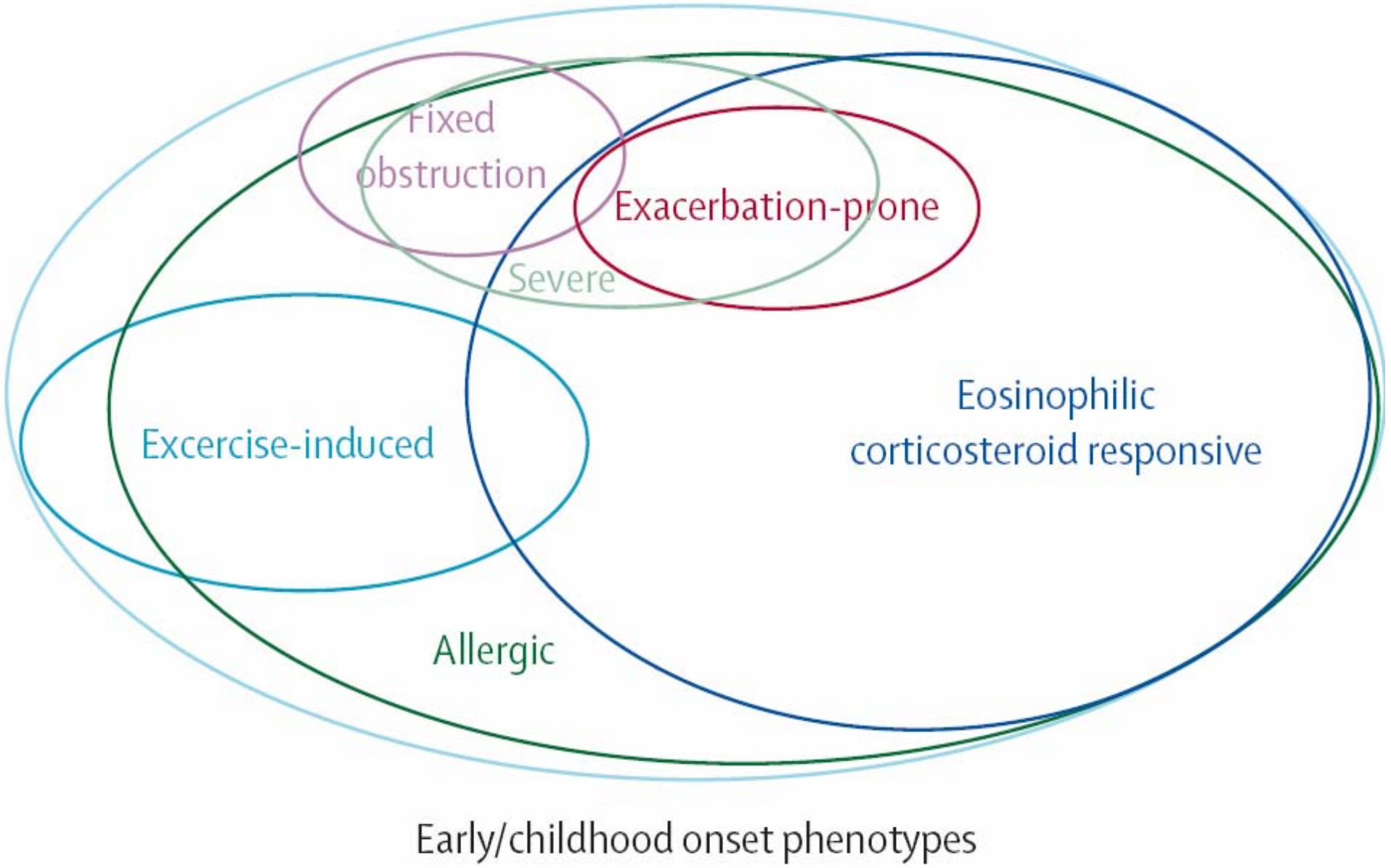
- lack of allergen sensitization and exposure to indoor allergens (odds ratio [OR], 3.23; $P < .001$),
- milder asthma (OR, 2.01; $P = .03$)
- older age (OR, 1.23; $P = .01$)
- less airway hyperresponsiveness (higher log methacholine FEV1, PC20 (OR, 1.39; $P = .03$)
- higher pre-bronchodilator FEV1 percent predicted (OR, 1.05; $P = .02$)
- lower forced vital capacity percent predicted (OR, 0.96; $P = .04$).

Asma: ¿una o varias?

Se han descrito muchos subtipos clínicos de asma o fenotipos

- clínicos o fisiológicos
- relacionados con desencadenantes
- inflamatorios

Son expresiones de una sola enfermedad o representan enfermedades distintas con similar sintomatología?



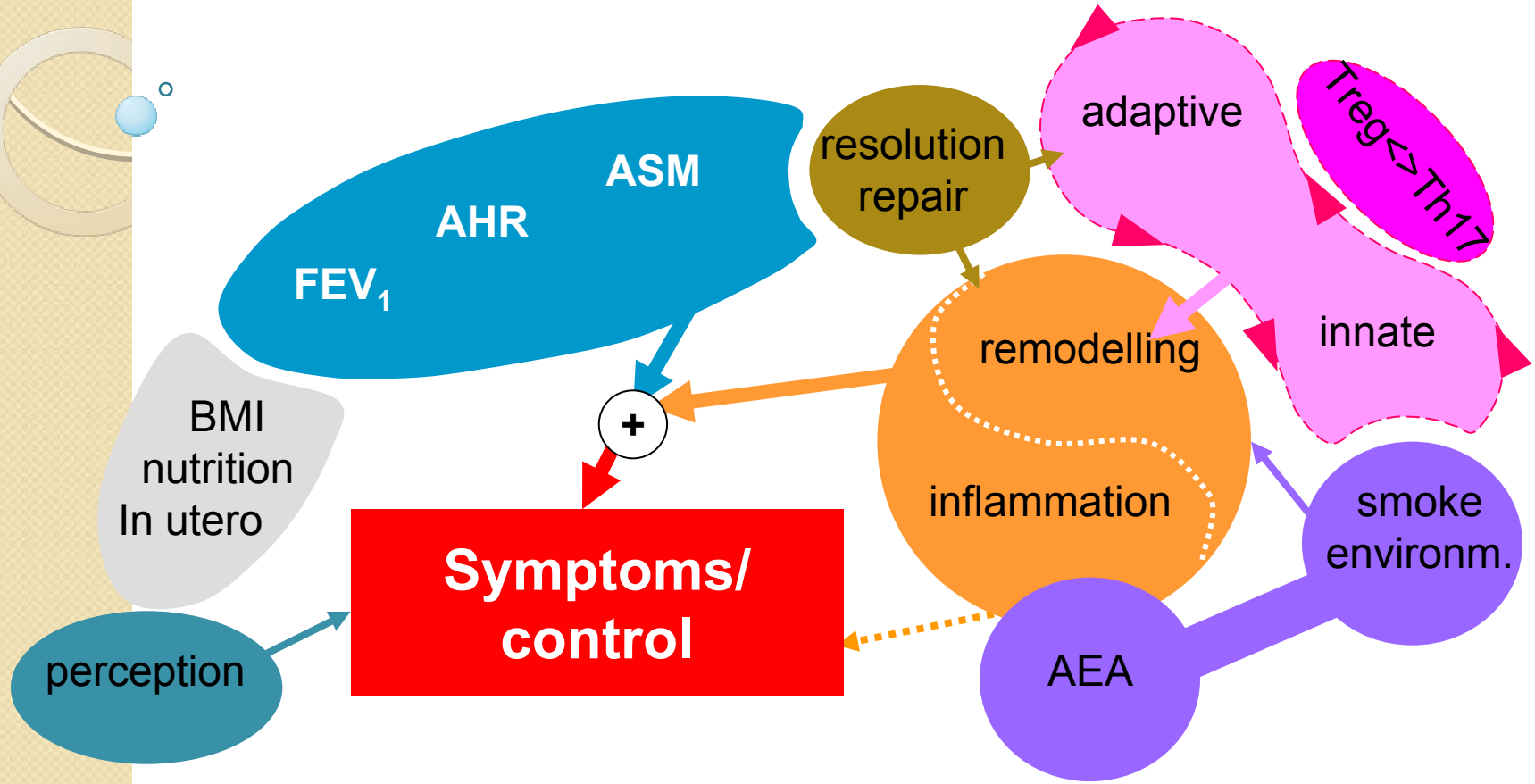
Sally E Wenzel Lancet 2006; 368: 804–13

¿Que es un endotipo?

- Endotipo (contracción de endofenotipo) es un subtipo de enfermedad definido funcional y patológicamente por un mecanismo molecular o por la respuesta a un tratamiento.
- El asma es una afección heterogénea y genéticamente compleja en la cual muchos genes (>100) contribuyen en forma variable a sus diferentes manifestaciones.
- En el Asma probablemente hay muchos endotipos específicos asociados a características clínicas *distintivas* ,causas y mecanismos moleculares subyacentes *divergentes* y *diferentes* respuestas a los tratamientos

Endotipos en Asma

Distintos endotipos se originan por la variable interrelación de estos componentes



- BMI, nutrition, in utero
- Lung Function
- Resolution and repair
- Inflammo-pathology
- Immune effector pathways
- Immune suppression and tolerance
- Exacerbations, smoke, environment
- Perception of dyspnea

Getting the basics right in childhood asthma management

- Important issues to consider in children in whom inhaled corticosteroid therapy is unsuccessful before adding other medications:
  1. Adherence to treatment
  2. Poor inhalation technique
  3. Co-morbid conditions, such as allergic rhinitis
  4. Exposure to environmental allergic and nonallergic stimuli (cigarette smoke)
  5. Addressing parental concerns and beliefs regarding medication

Estudio BADGER

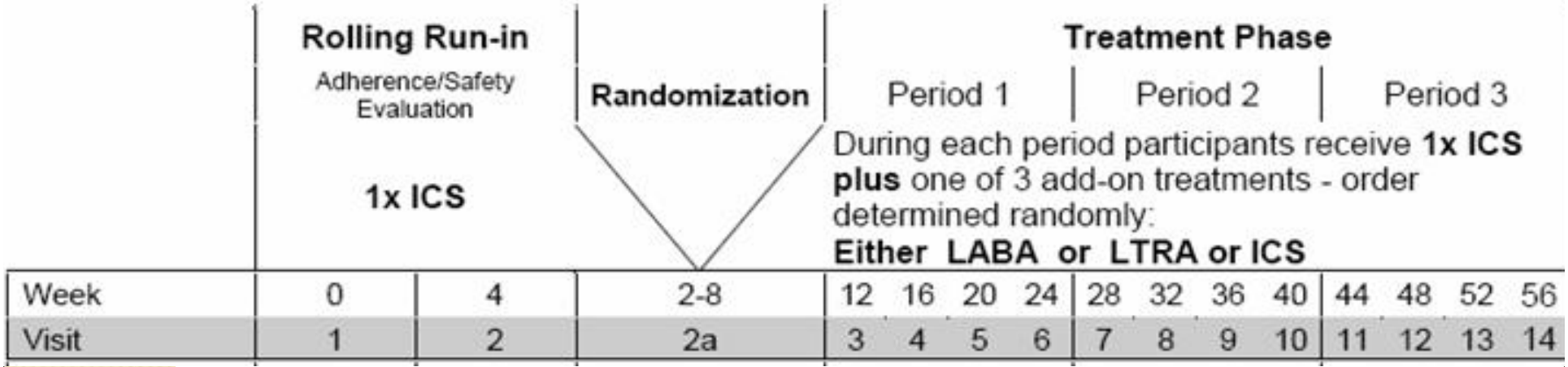
The NEW ENGLAND JOURNAL of MEDICINE

Step-up Therapy for Children with Uncontrolled Asthma while Receiving Inhaled Corticosteroids

Robert F. Lemanske, Jr., M.D., David T. Mauger, Ph.D., Christine A. Sorkness, Pharm.D., Daniel J. Jackson, M.D., Susan J. Boehmer, M.S., Fernando D. Martinez, M.D., Robert C. Strunk, M.D., Stanley J. Szefler, M.D., Robert S. Zeiger, M.D., Ph.D., Leonard B. Bacharier, M.D., Ronina A. Covar, M.D., Theresa W. Guilbert, M.D., Gary Larsen, M.D., Wayne J. Morgan, M.D., Mark H. Moss, M.D., Joseph D. Spahn, M.D., and Lynn M. Taussig, M.D., for the Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute

Childhood Asthma Research and Education (CARE) Network Best ADd-on Therapy Giving Effective Response (BADGER)

- ## NULL HYPOTHESIS
- In children 6-18 years of age, whose asthma symptoms are not acceptably controlled by low dose inhaled corticosteroid (ICS) therapy, the following three step-up therapies will not differ with respect to asthma control: (1) doubling the dose of the current ICS regimen; (2) adding a long-acting beta-agonist and not increasing the ICS dose; (3) adding a leukotriene receptor antagonist and not increasing the ICS dose.



BADGER Design

Triple Crossover Design

Treatment Phase: Three 16-week periods

Asthma Uncontrolled

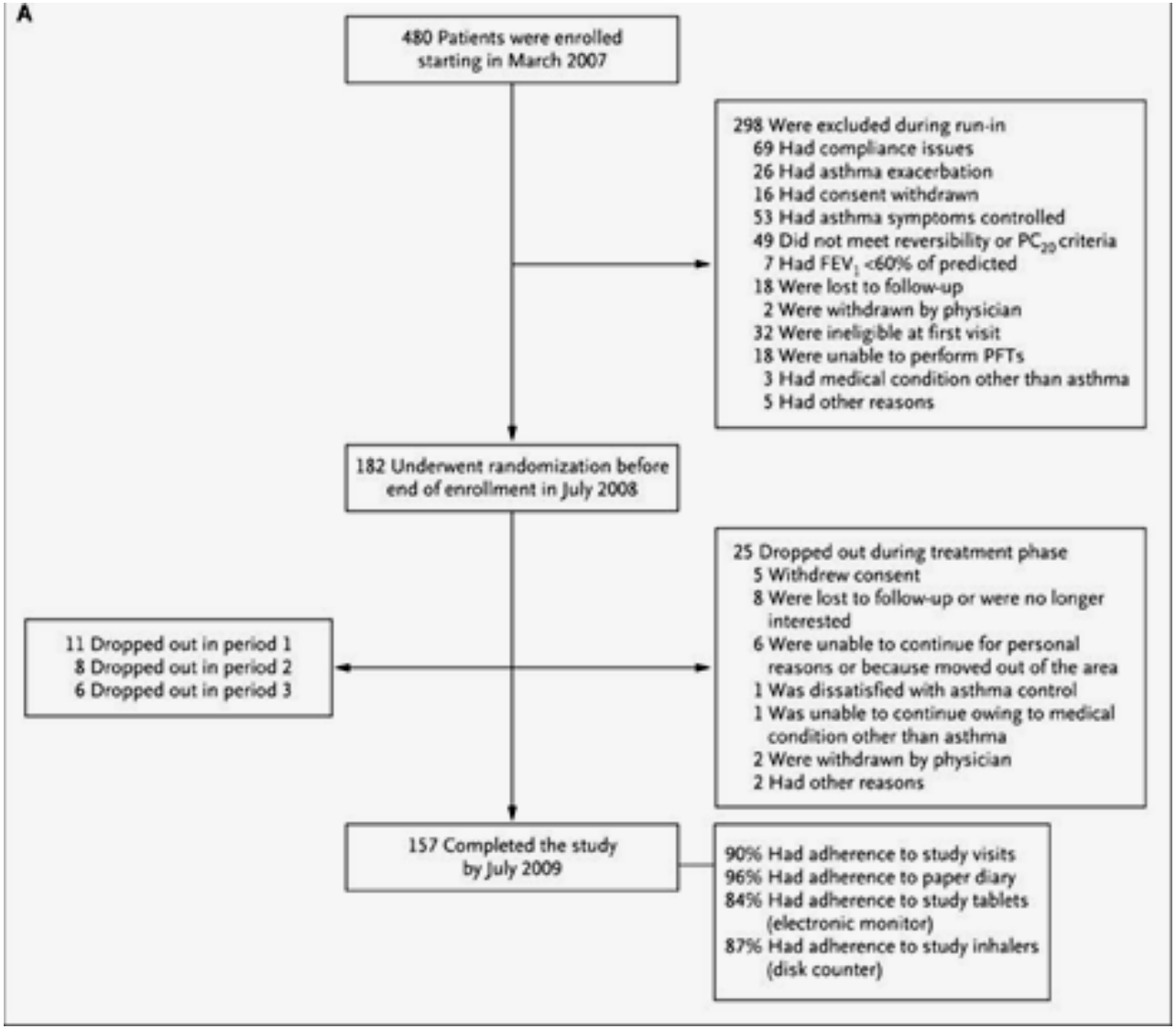
Characterization on 1X ICS to determine eligibility

Randomization

	Period 1	Period 2	Period 3
	1x ICS+LTRA	1x ICS +LABA	2xICS
	1x ICS +LABA	2xICS	1x ICS+LTRA
	2xICS	1x ICS+LTRA	1x ICS +LABA
	1x ICS+LTRA	2xICS	1x ICS +LABA
	1x ICS +LABA	1x ICS+LTRA	2xICS
	2xICS	1x ICS +LABA	1x ICS+LTRA

3 Outcomes: Exacerbations, FEV1, Asthma control days

Enrollment and Outcomes and Schedule of Evaluations



Lemanske R et al. N Engl J Med 2010;10.1056/NEJMoa1001278

The NEW ENGLAND JOURNAL of MEDICINE

Enrollment and Outcomes and Schedule of Evaluations

B

	Run-in: 2–8 weeks		Randomization	Treatment Phase: 48 Weeks												
	Adherence and safety evaluation			Period 1				Period 2				Period 3				
	1x ICS			*During each period, patients received ICS plus one of three add-on treatments: ICS or LABA or LTRA*												
Week	0	4	2–8	4	8	12	16	20	24	28	32	36	40	44	48	
Visit	1	2	2a	3	4	5	6	7	8	9	10	11	12	13	14	
Skin Test			+													
FeNO, FO, and Spirometry	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
BR4P	+					+				+				+		
Methacholine			+				+				+				+	
QOL			+				+				+				+	
ACT or c-ACT			+	+	+	+	+	+	+	+	+	+	+	+	+	

Lemanske R et al. N Engl J Med 2010;10.1056/NEJMoa1001278

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Age Group	
	6–11 Yr (N=126)	12–17 Yr (N=56)
Age — yr	9.1±1.5	14.7±1.7
Male sex — no. (%)	83 (66)	36 (64)
Race or ethnic group — no. (%)†		
Hispanic or Latino	38 (30)	22 (39)
Non-Hispanic white	54 (43)	20 (36)
Black	37 (29)	12 (21)
Hispanic white	28 (22)	15 (27)
Other	7 (6)	9 (16)
Height — cm	134.3±10.8	164.2±11.0
Weight — kg	36.1±12.7	63.4±17.2
Body-mass index	19.6±4.5	23.3±4.8
Age at asthma diagnosis — yr	3.3±2.2	4.7±4.1
Age at onset of asthma symptoms — yr	2.4±2.2	3.8±3.6
Family history of asthma — no. (%)		
Father	33 (26)	17 (30)
Mother	44 (35)	12 (21)
Eczema — no. (%)	69 (55)	24 (43)
Positive aeroallergen skin test		
Any — no.	2.6±2.1	3.7±2.4
≥1 — no./total no. (%)	95/122 (78)	48/55 (87)
Positive perennial skin test		
Any — no.	1.4±1.3	2.0±1.4
≥1 — no./total no. (%)	82/122 (67)	48/55 (87)

Serum IgE — IU/ml	493.4±690.5	530.5±589.0
Blood eosinophils — %	5.1±3.7	5.3±4.8
Eligibility classification — no. (%)‡		
Step-up	35 (28)	14 (25)
Step-neutral	16 (13)	11 (20)
Step-down	75 (60)	31 (55)
Medication use in previous year — no. (%)		
Inhaled or nebulized corticosteroid	82 (65)	39 (70)
Leukotriene modifier	46 (37)	14 (25)
Salmeterol	5 (4)	5 (9)
Theophylline	0	0
Cromolyn or nedocromil	0	1 (2)
Salmeterol plus fluticasone, or budesonide plus formoterol	41 (33)	18 (32)
Prednisone (≥1 courses)	56 (44)	25 (45)
Prebronchodilator FEV_1 — % of predicted value	98.5±13.1	95.0±14.8
Prebronchodilator FEV_1:FVC ratio	81.6±7.1	78.2±7.1
Bronchodilator response, 4 puffs — %	11.2±11.2	13.5±10.2
Asthma-control days during worst 2 weeks of run-in period — %	30±21	36±23
Score on Asthma Control Test or Childhood Asthma Control Test§	20.5±3.8	19.8±3.4
Exhaled nitric oxide — ppb		
Median	8.5	17.7
Interquartile range	5.8–13.1	11.4–26.2
Methacholine PC_{20} — mg/ml		
Median	1.24	2.06
Interquartile range	0.56–3.83	0.70–5.44
β_2-adrenergic–receptor genotype — no. (%)¶		
Arg/Arg	19 (15)	10 (18)
Arg/Gly	71 (57)	31 (55)
Gly/Gly	34 (27)	15 (27)

Outcome Measures

The primary outcome was the differential response to each of the three step-up therapies on the basis of fixed threshold criteria for the following three asthma-control measures:

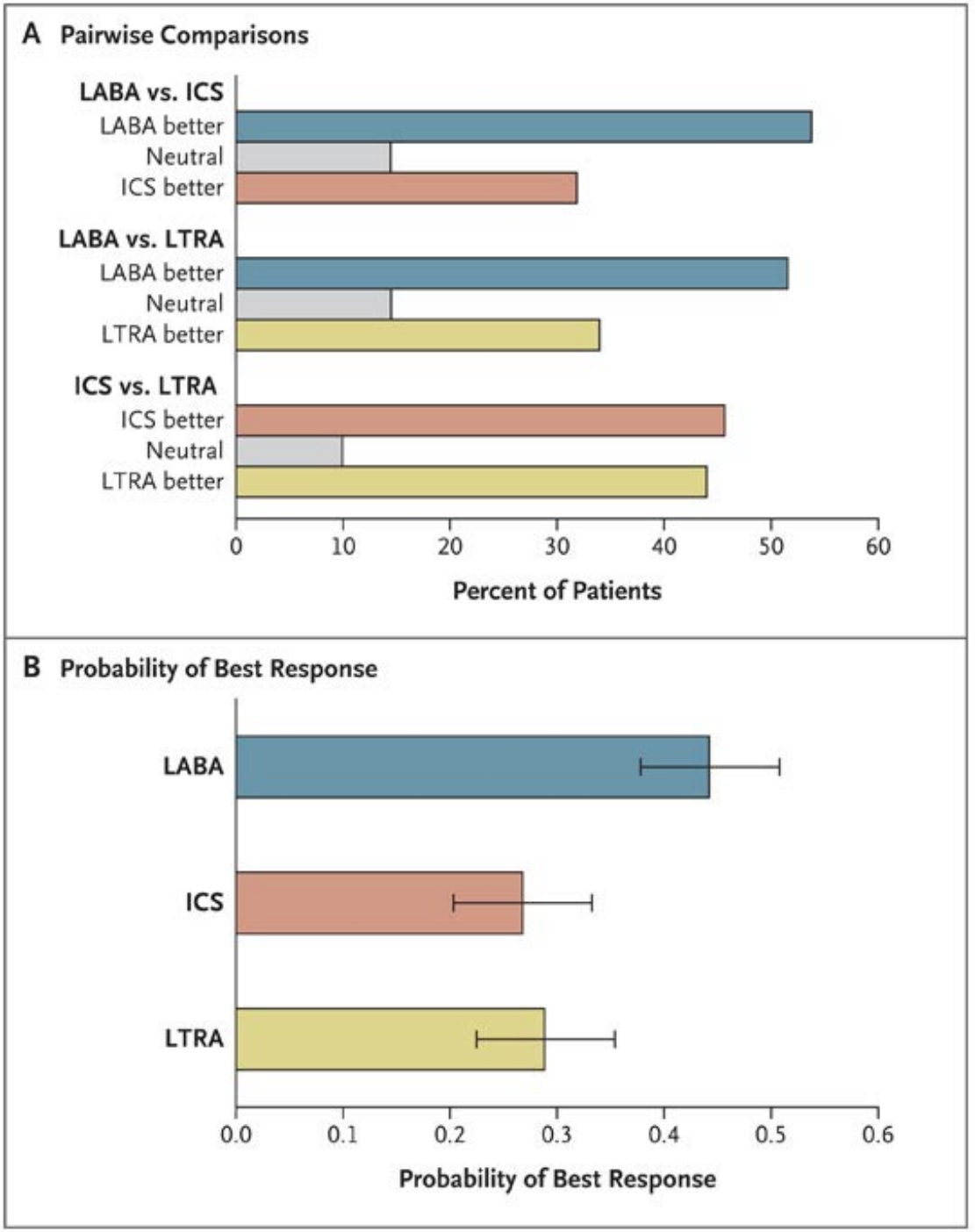
- ✓ **Need for oral prednisone for acute asthma exacerbations**
- ✓ **Number of asthma-control days,**
- ✓ **FEV_1**

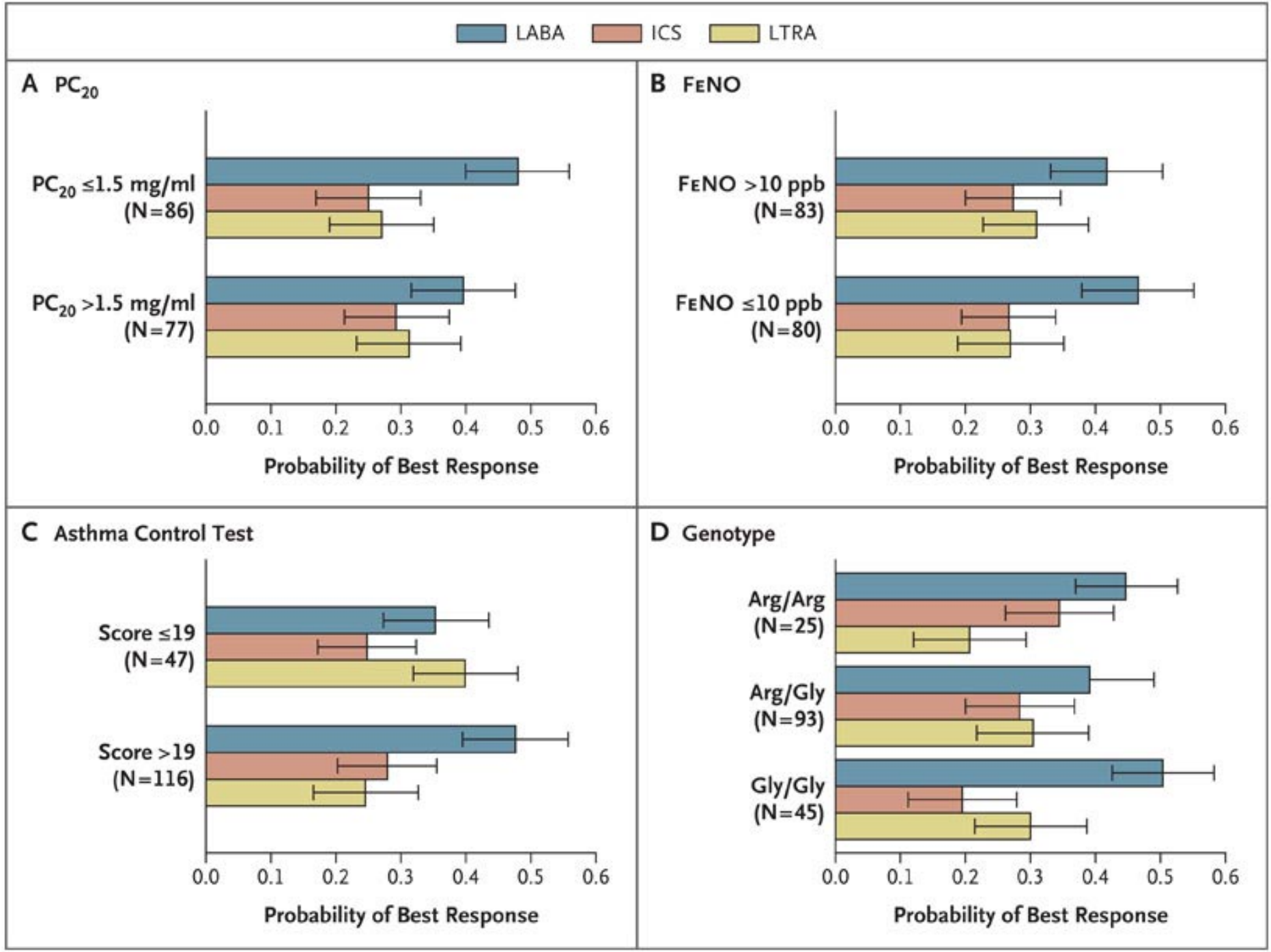
One treatment period was ranked as better than another if :

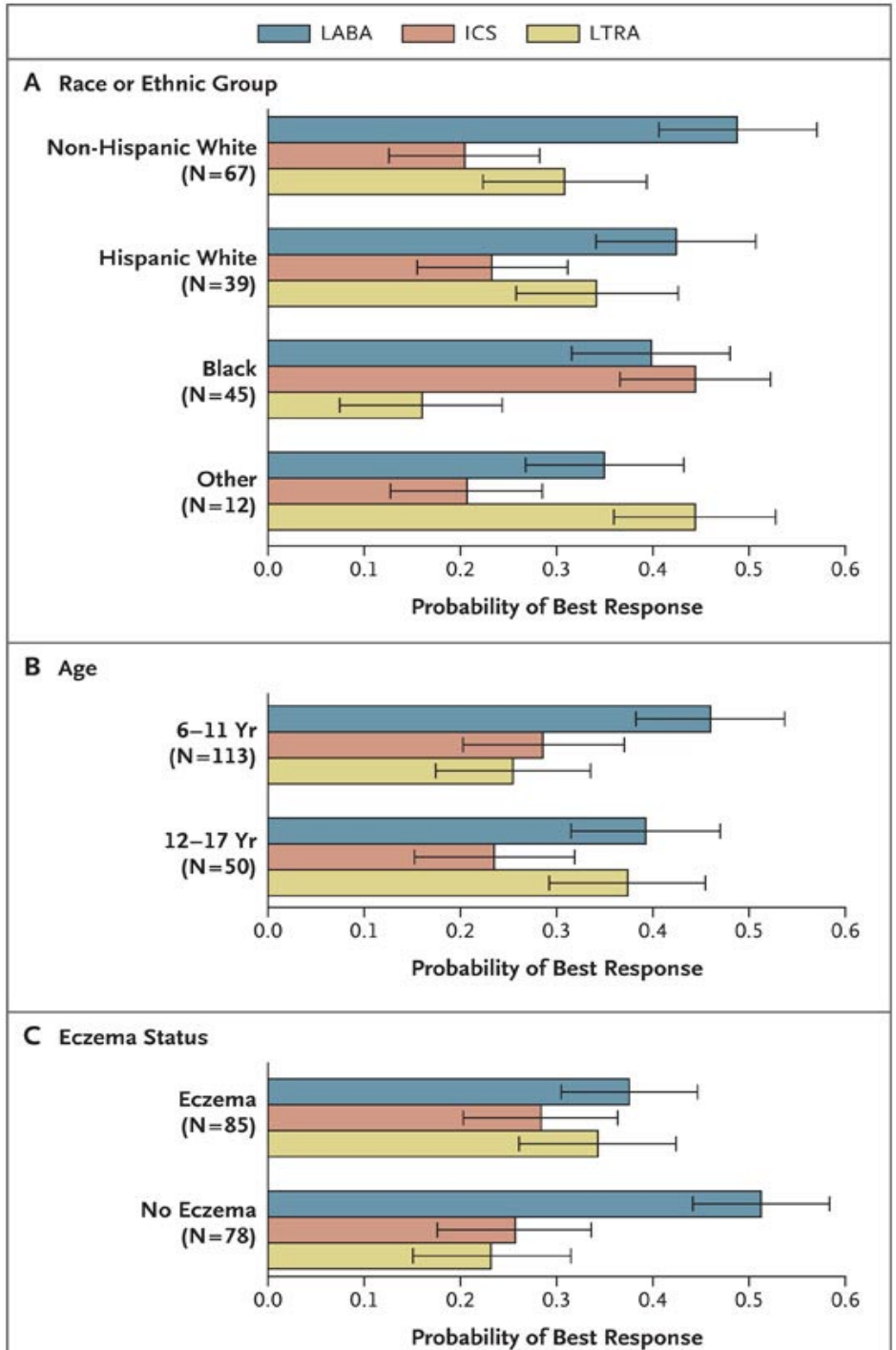
- ✓**Total amount of prednisone received during the period was at least 180 mg less**
- ✓**Number of annualized asthma-control days during the final 12 weeks of the period was increased by at least 31 days.**
- ✓ **FEV_1 at the end of the period was at least 5% higher.**

A patient was considered to have had a differential response if at least one treatment period was ranked as better than another.

Pairwise Comparison of Three Step-up Therapies and the Overall Probability of Best Response




LABA
ICS
LTRA
A PC20
PC20 ≤1.5 mg/ml (N=86)
PC20 >1.5 mg/ml (N=77)
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Probability of Best Response
B FeNO
FeNO >10 ppb (N=83)
FeNO ≤10 ppb (N=80)
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Probability of Best Response
C Asthma Control Test
Score ≤19 (N=47)
Score >19 (N=116)
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Probability of Best Response
D Genotype
Arg/Arg (N=25)
Arg/Gly (N=93)
Gly/Gly (N=45)
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Probability of Best Response


LABA
ICS
LTRA
A Race or Ethnic Group
Non-Hispanic White (N=67)
Hispanic White (N=39)
Black (N=45)
Other (N=12)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Probability of Best Response
B Age
6–11 Yr (N=113)
12–17 Yr (N=50)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Probability of Best Response
C Eczema Status
Eczema (N=85)
No Eczema (N=78)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Probability of Best Response

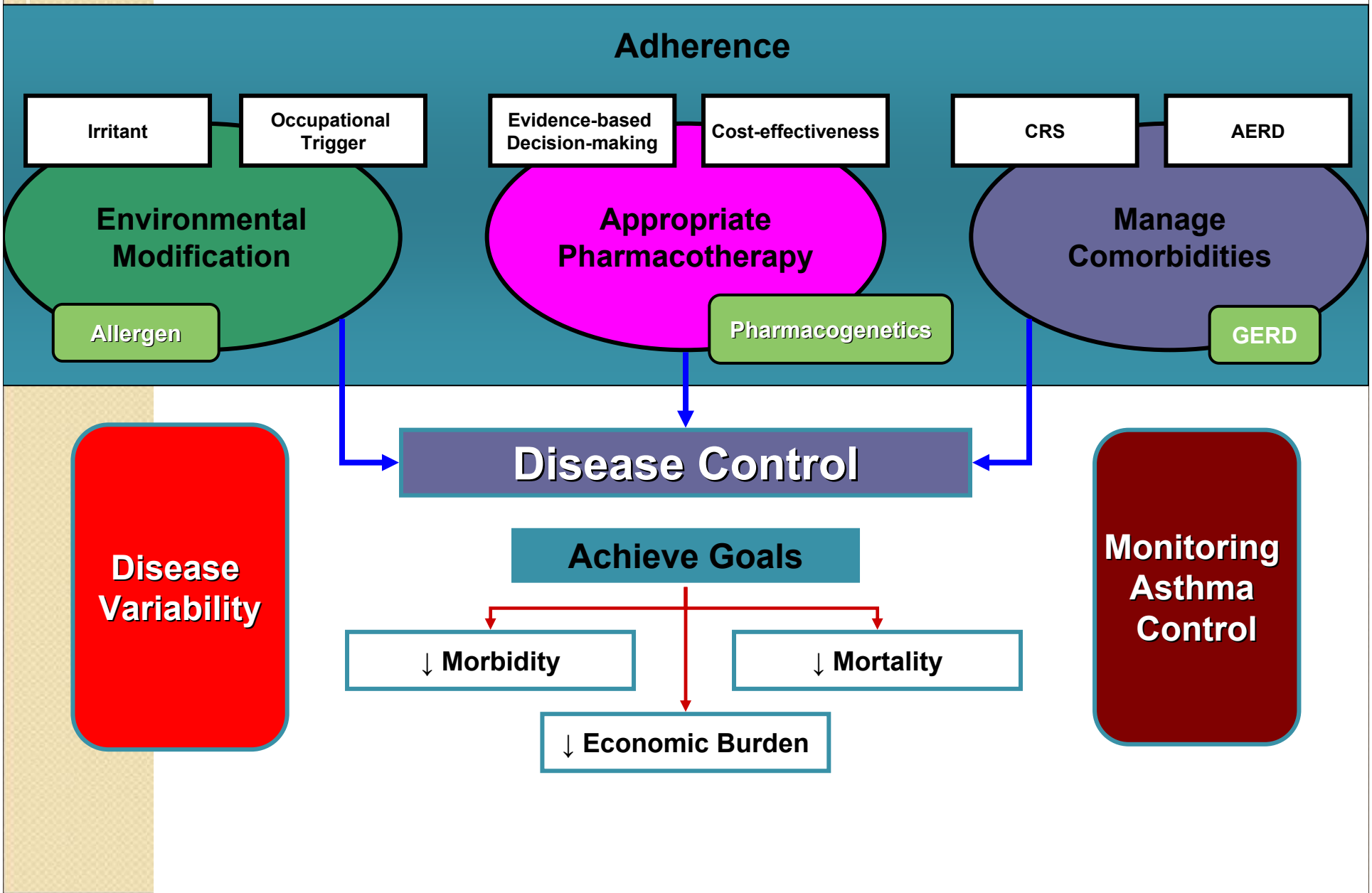
EXACERBACIONES

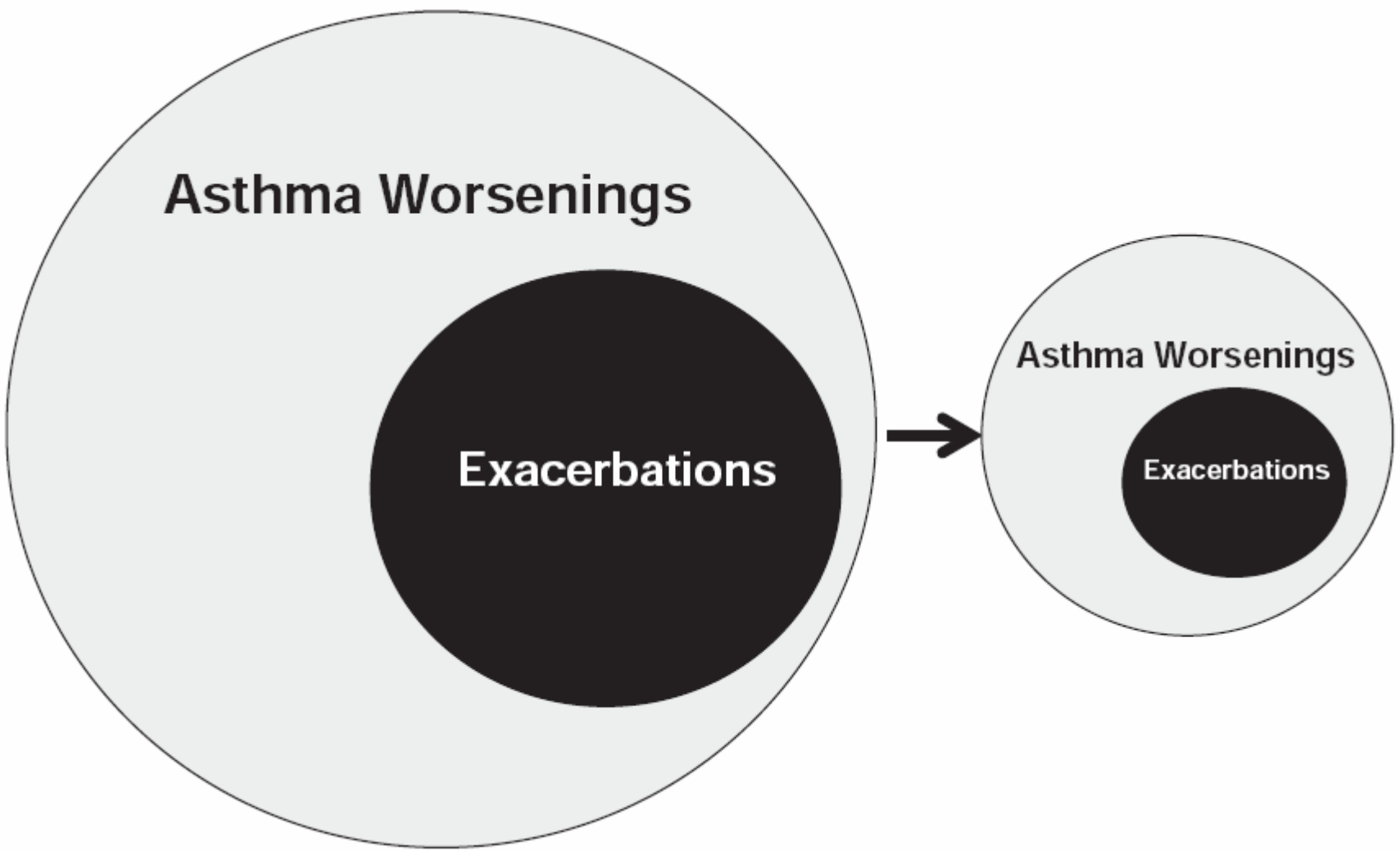
	LABA step-up	ICS step-up	LTRA step-up	Total
Number of Treatment Failures	4	9	12	25
Number of TF's due to Hospitalization for Asthma	1	1	1	3
Number of TF's due to 2nd prednisone burst	3	8	11	22
Number of Prednisone Bursts	30	47	43	120

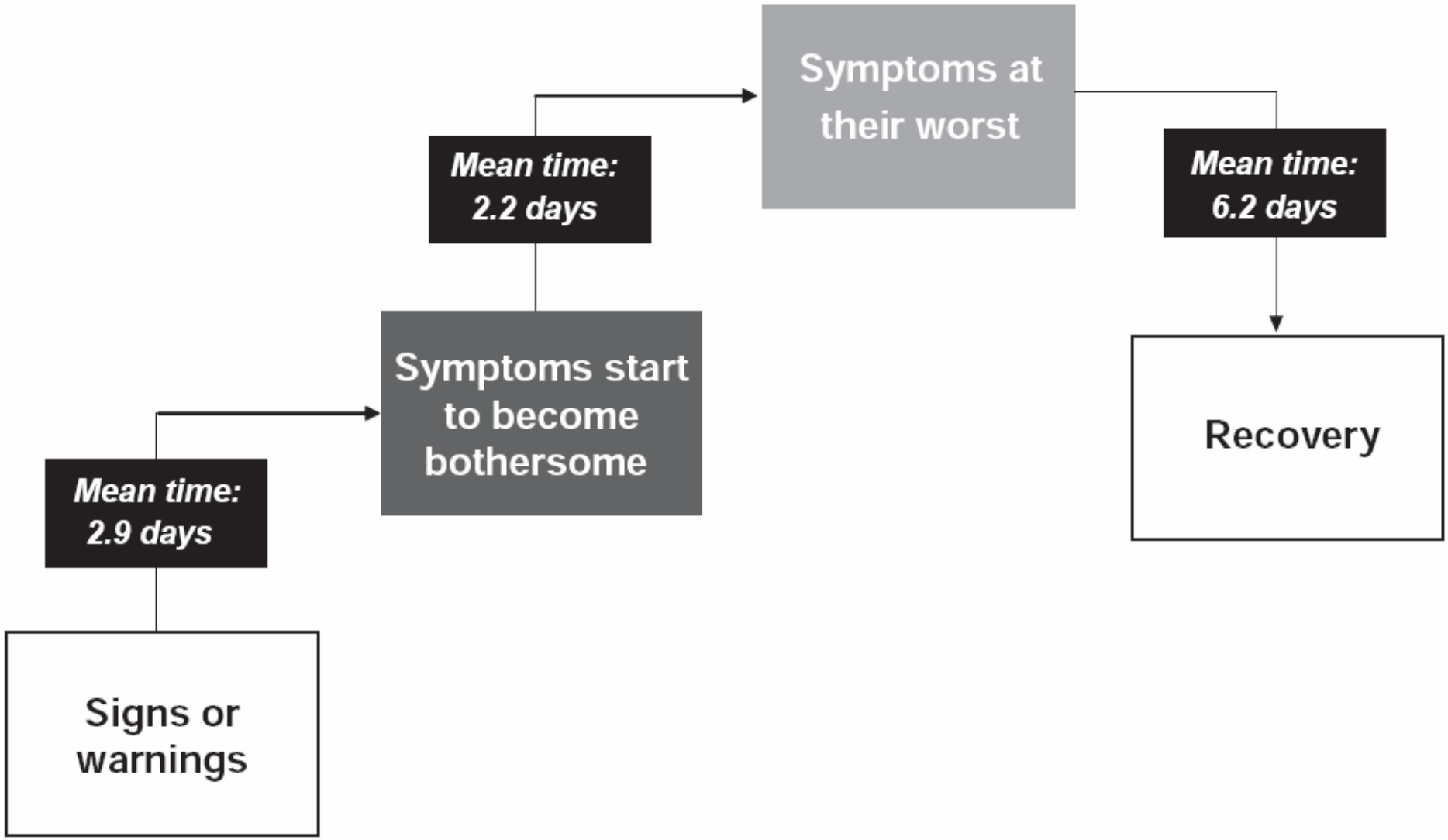
Conclusions

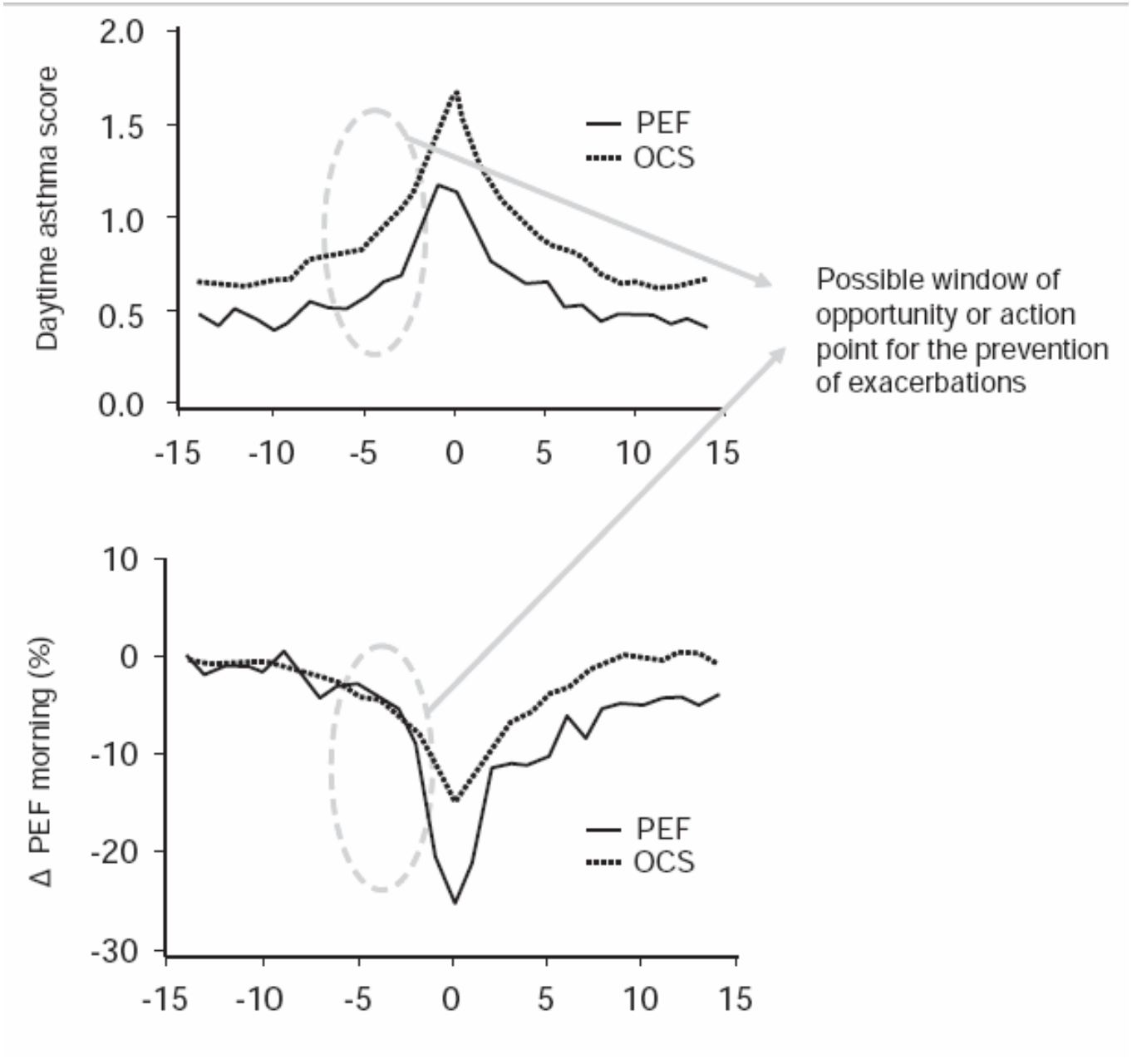
- Nearly all the children had a differential response to each step-up therapy.
- LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up.
- However, many children had a best response to ICS or LTRA step-up therapy.
- Highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy.

Asthma Management Paradigm



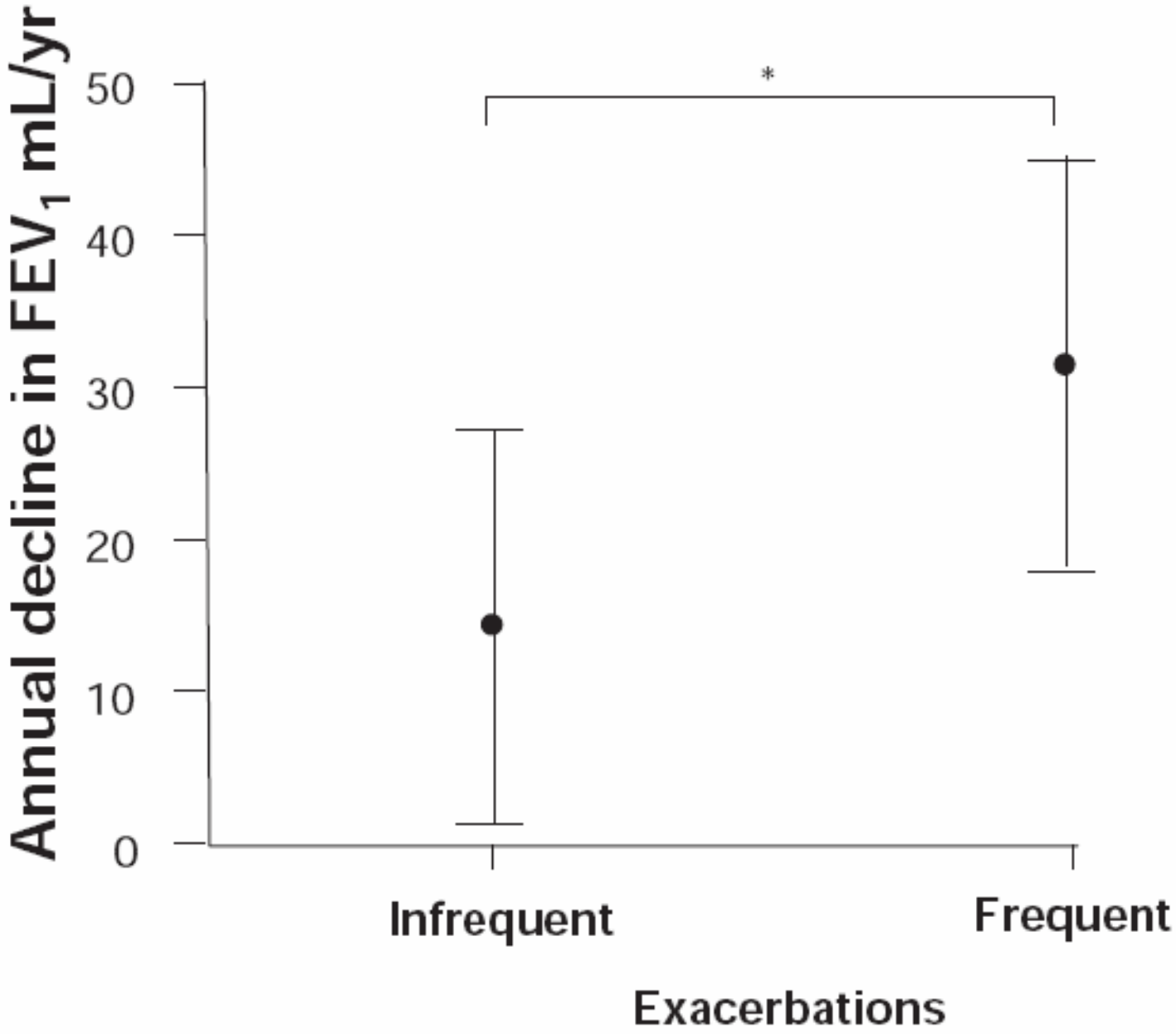

Asthma Worsenings
Exacerbations
Asthma Worsenings
Exacerbations


Signs or warnings
Mean time: 2.9 days
Symptoms start to become bothersome
Mean time: 2.2 days
Symptoms at their worst
Mean time: 6.2 days
Recovery


Daytime asthma score
2.0
1.5
1.0
0.5
0.0
-15
-10
-5
0
5
10
15
PEF
OCS
Possible window of opportunity or action point for the prevention of exacerbations
Δ PEF morning (%)
10
0
-10
-20
-30
-15
-10
-5
0
5
10
15
PEF
OCS

Main characteristics of patients with slow-onset and sudden-onset acute asthma

Type 1: Slow progression	Type 2: Sudden progression
Slow-onset acute asthma	Sudden-onset, asphyxic, brittle or hyperacute asthma
Progressive deterioration: >6 h (usually days or weeks)	Rapid deterioration: <6 h
80% to 90% who presented to an emergency department	10% to 20% who presented to an emergency department
Female predominance	Male predominance
More likely to be triggered by an upper respiratory tract infection	More likely to be triggered by respiratory allergens, exercise and psychosocial issues
Less severe obstruction at presentation	More severe obstruction at presentation
Slow response to treatment and higher hospital admissions	Rapid response to treatment and lower hospital admissions
Airflow inflammation mechanism	Bronchospastic mechanism of deterioration

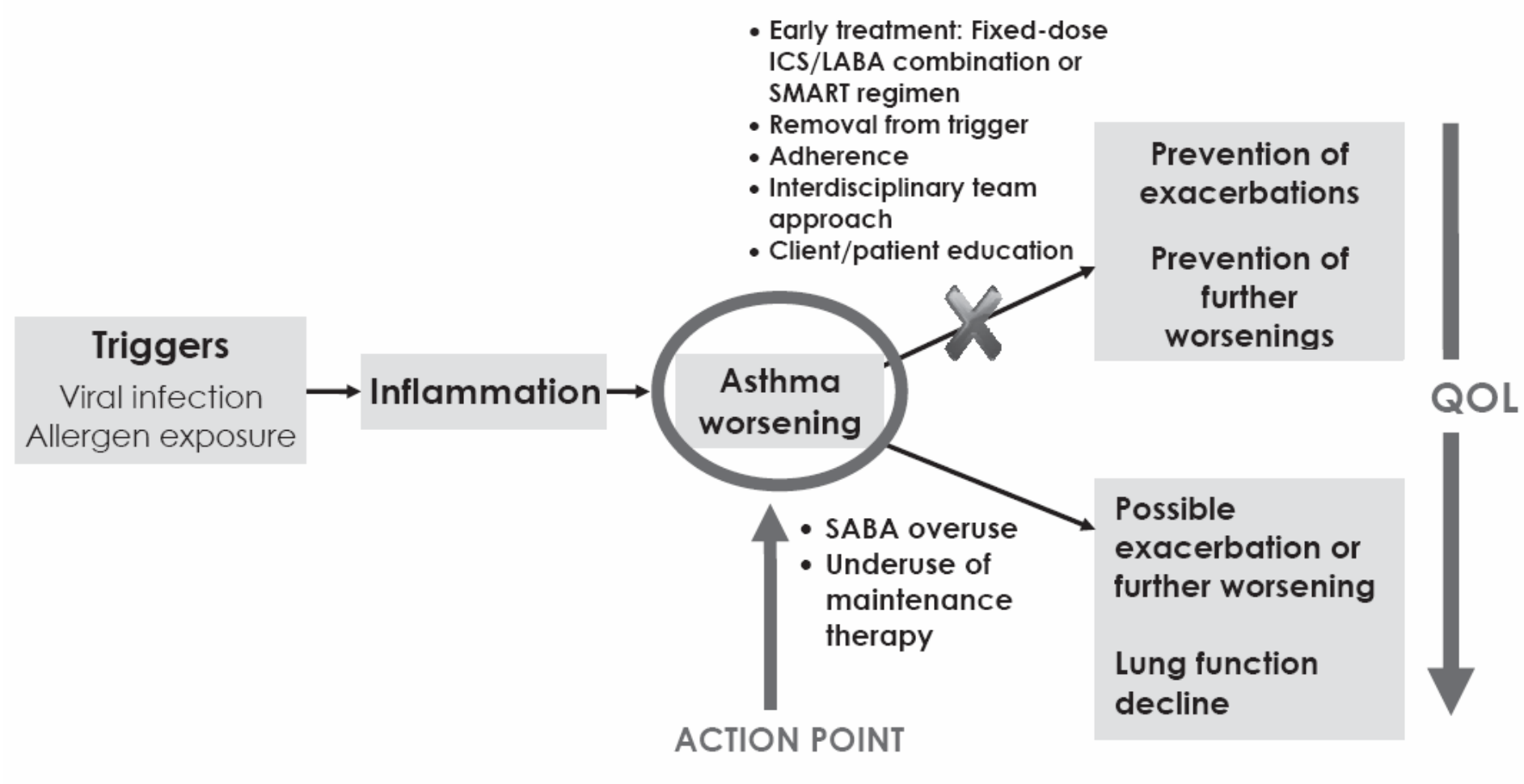

Annual decline in FEV_1 mL/yr
50
40
30
20
10
0
*
Infrequent
Frequent
Exacerbations

Proportion of patients reporting that worsening asthma limited/prevented their daily activities

Activity	Percentage of patients
Exercise and physical activity	73 (n=2476)
Leisure activities	49 (n=1671)
Social commitments	39 (n=1340)
Intimacy with partner	29 (n=999)
Work	28 (n=973)
Time spent with family	16 (n=535)

Gaining Optimal Asthma Control (GOAL) study: Definitions of well-controlled and totally controlled asthma based on Global Initiative for Asthma (GINA) and National Institutes of Health (NIH) guideline aims of treatment

	Goals of GINA/ NIH	Totally controlled: each week all of	Well controlled each week 2 or more of
Daytime symptoms	Minimal (ideally none)	None	≤ 2 days with symptom score > 1*
Rescue β_2-agonist use	Minimal (ideally none)	None	Use on ≤ 2 days and ≤ 4 occasions/wk
Morning PEF	Near normal	≥ 80% predicted† every day	≥ 80% predicted† every day
Night-time awakening	Minimal (ideally none)	None	None
Exacerbations‡	Minimal (infrequent)	None	None
Emergency visits	None	None	None
Treatment-related adverse events	Minimal	None enforcing change in asthma therapy	None enforcing change in asthma therapy


• Early treatment: Fixed-dose ICS/LABA combination or SMART regimen
• Removal from trigger
• Adherence
• Interdisciplinary team approach
• Client/patient education
Triggers
Viral infection
Allergen exposure
Inflammation
Asthma worsening
Prevention of exacerbations
Prevention of further worsenings
QOL
Possible exacerbation or further worsening
Lung function decline
• SABA overuse
• Underuse of maintenance therapy
ACTION POINT

FDA Meta-Analysis Results:
Number of Patients Experiencing an Event

Event defined as the composite endpoint
(asthma-related death, intubation, and hospitalization)

Patient Population	LABA Patients experiencing an event	Non-LABA Patients experiencing an event	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients n = 30,148 LABA patients n = 30,806 non-LABA patients	381	304	***2.80***	1.11 – 4.49
Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	***5.57***	0.21 – 10.92
Patients ages 4 to 11 years n = 1,626 LABA patients n = 1,789 non-LABA patients	**61**	**39**	***14.83***	**3.24 – 26.43**

- ***The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs.***
- ***The largest risk difference per 1000 treated patients was seen in children 4-11 years of age,***
- ***The results of the meta-analysis were primarily driven by asthma-related hospitalizations.***
- ***Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.***

Recommendations for Practitioners Managing Patients With Asthma

- Symptom control is the primary objective for patients with asthma.
- Treatment should follow the NAEPP guidelines.
  - Therapy should be stepped up or stepped down according to NAEPP guidelines to achieve symptom control with the fewest interventions possible.
  - Stepping down therapy should be done with caution and patients should be followed closely for potential worsening of symptoms.
- All patients with persistent asthma should be managed with a long-term controller agent, such as an inhaled corticosteroid.
  - LABAs should be added when symptom control is not achieved using a controller agent alone.
- LABAs should not be used as monotherapy for anyone with persistent asthma.
  - LABAs should not used on a long-term basis unless the patient's condition cannot be adequately controlled with controller medications.
- Patients requiring LABAs should be counseled regarding the potential risks of these agents.

3 How to use Seretide

- Use your Seretide every day, until your doctor advises you to stop.
- Always use Seretide exactly as your doctor has told you.

Adults and adolescents aged 12 years and over

- Seretide Evohaler 25/50 - 2 puffs twice a day
- Seretide Evohaler 25/125 - 2 puffs twice a day
- Seretide Evohaler 25/250 - 2 puffs twice a day

Children 4 to 12 years of age

- Seretide Evohaler 25/50 - 2 puffs twice a day
- Seretide is not recommended for use in children below 4 years of age.

Your symptoms may become well controlled using Seretide twice a day. If so, your doctor may decide to reduce your dose to once daily. The dose may change to:

- once at night - if you have **night-time** symptoms
- once in the morning - if you have **daytime** symptoms.

- Recordaremos que todo niño con una “exacerbación grave” de asma será clasificado como “asma persistente”, por el lapso de un año y se le indicará tratamiento preventivo según esquema correspondiente.
- El tratamiento preventivo antiinflamatorio deberá iniciarse precozmente en cuanto se confirme el diagnóstico y mantenerse en forma continua y por tiempo prolongado, no menor de seis meses; su duración será determinada en función de la evolución clínica y funcional.
- Aproximadamente cada 3 meses se evaluará la evolución de la enfermedad.
- En caso de control óptimo, se sugiere evaluar un descenso de la dosis o descomplejizar el tratamiento (*step-down*).
- En caso de control aceptable, pero no óptimo, no se modificarán las dosis y si la evolución no es favorable se evaluará incrementar la dosis o aumentar la complejidad del tratamiento (*step-up*).
- Ante una clínica compatible con remisión de la enfermedad, se iniciará una suspensión gradual de tratamiento, que estará sujeta a la evaluación clínica y funcional periódica.

TABLE 1 "Getting the basics right" in childhood asthma management

Important issues to consider in children in whom inhaled corticosteroid therapy is unsuccessful before adding other medications:

- Adherence to treatment
- Poor inhalation technique
- Comorbid conditions, such as allergic rhinitis
- Exposure to environmental allergic and nonallergic stimuli (cigarette smoke)
- Addressing parental concerns and beliefs regarding medication