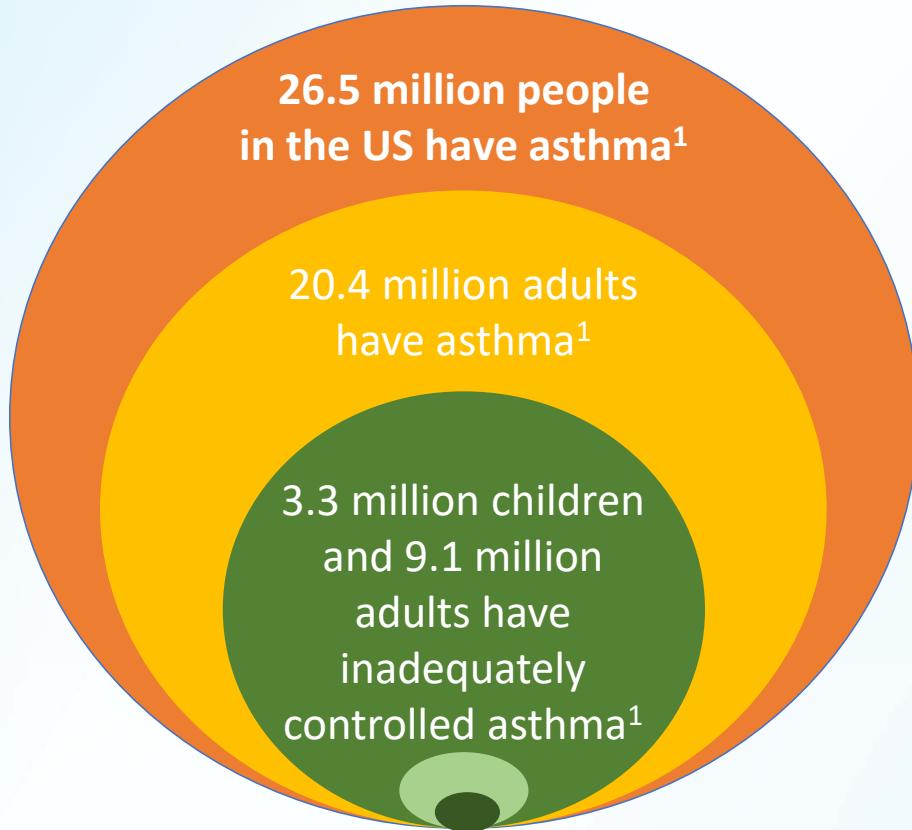


# **UTILIZZO DEI CORTICOSTEROIDI ORALI NELL'ASMA GRAVE**

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# Asthma: A Highly Prevalent and Often Inadequately Controlled Disease

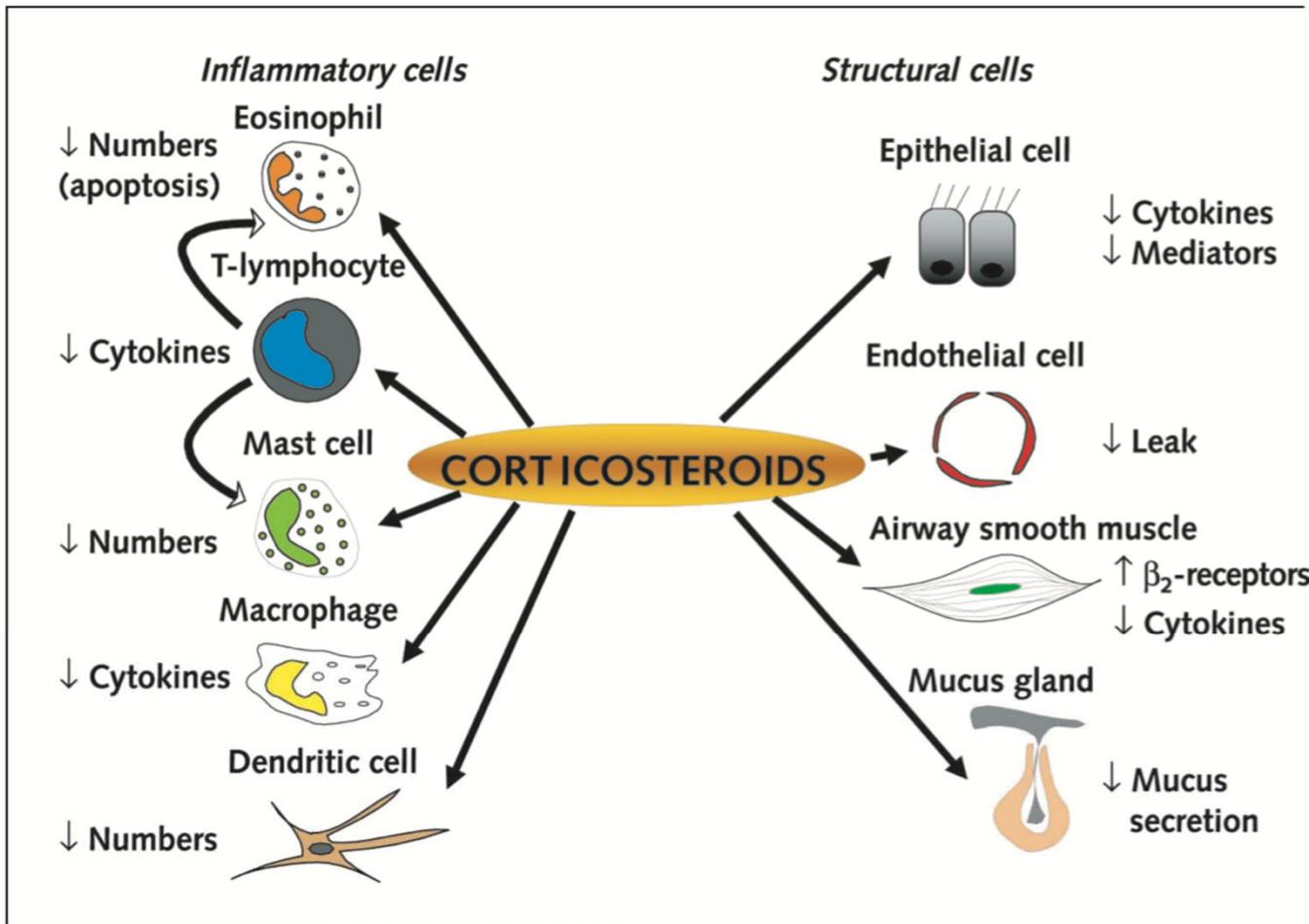


1. Centers for Disease Control and Prevention (CDC). [https://www.cdc.gov/asthma/most\\_recent\\_data.htm](https://www.cdc.gov/asthma/most_recent_data.htm). Accessed August 14, 2018.

## Storia dell'uso dei corticosteroidi orali nell'asma

- Prima degli anni '50, il trattamento dell'asma era limitato a composti derivati da piante o dall'adrenalina.
- Gli OCS costituiscono di gran lunga la formulazione più comune di corticosteroidi sistematici utilizzati nel trattamento dell'asma da quando McCombs nel 1952 notò un marcato miglioramento dei sintomi dell'asma usando corticosteroidi o l'ormone adreno- corticotropo
- nel 1958 si notò l'associazione tra il successo del trattamento con OCS e una riduzione degli eosinofili nell'espettorato. Questa importante osservazione clinica aprì la porta a un trattamento diffuso con OCS, su base sia protracta (cronica) sia di breve durata (acuta); ma con l'inizio di questa terapia emerse anche l'evidenza degli effetti collaterali dei corticosteroidi sistematici.
- La diffusione del trattamento con corticosteroidi sistematici ha esposto i pazienti a potenziali numerosi effetti collaterali

## Cellular effect of corticosteroids.

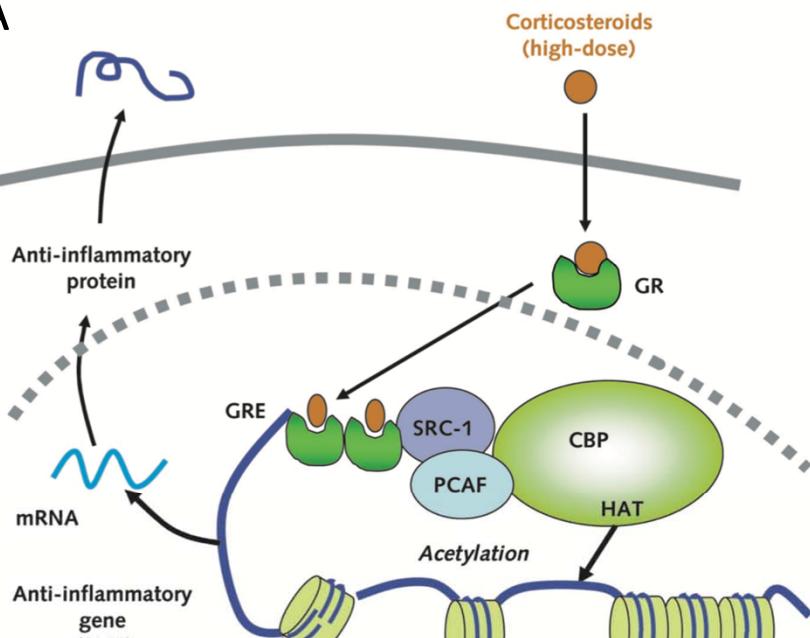


Paul Epstein, *Ann Intern Med.* 2003

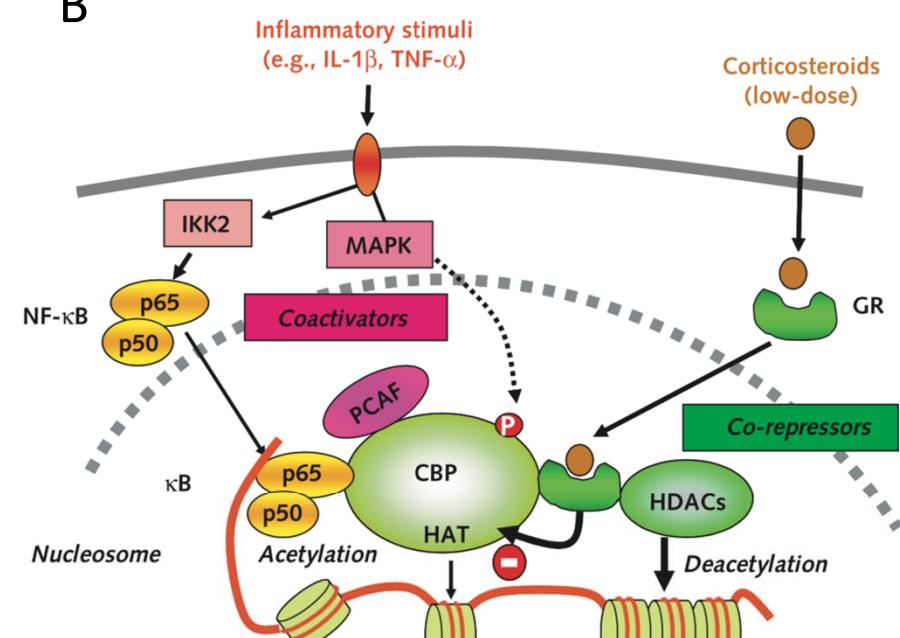
# How Do Corticosteroids Work in Asthma?

Peter J. Barnes, DM, DSc, and Ian M. Adcock, PhD

A



B



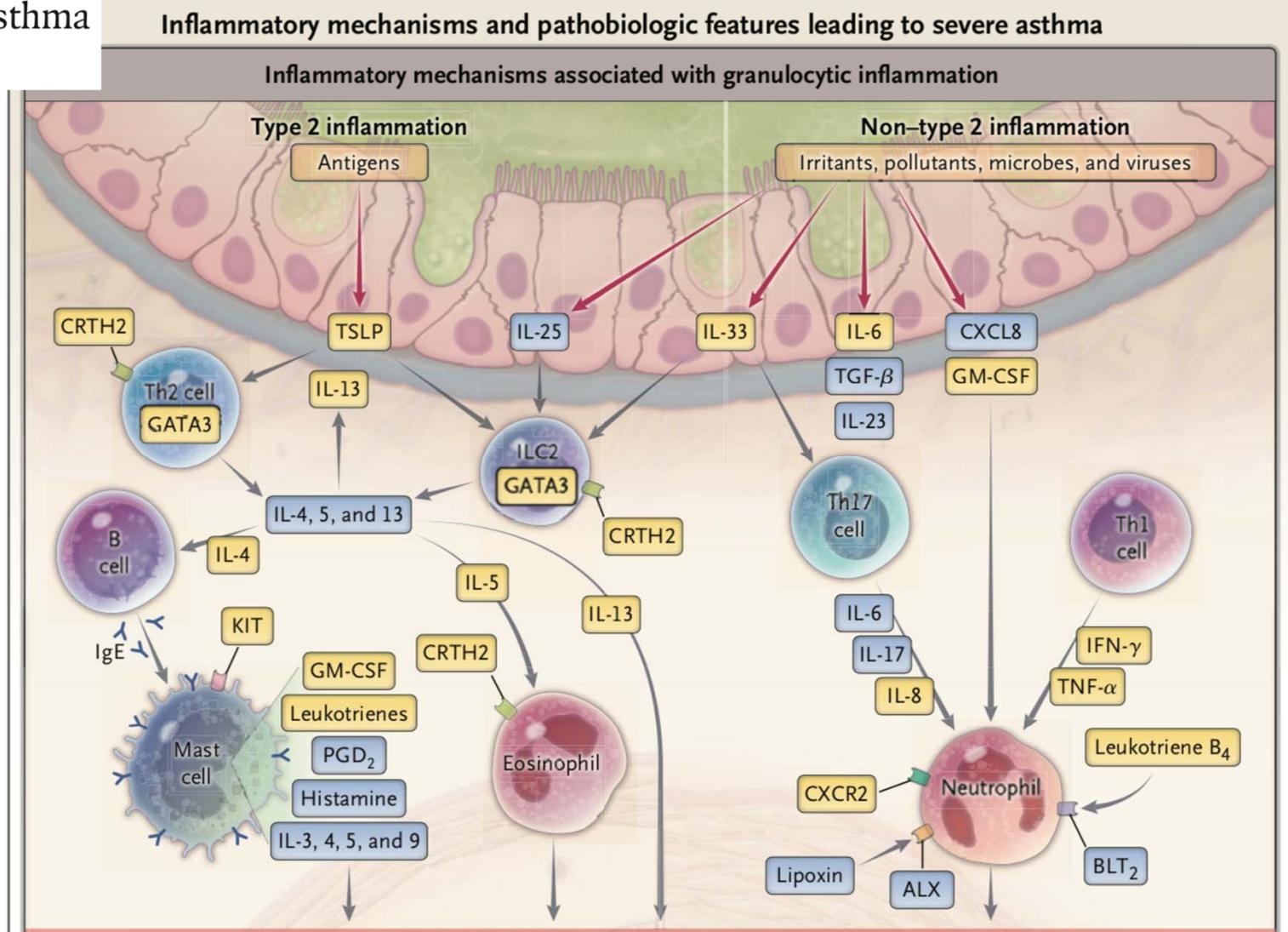
*L'attività antiinfiammatoria degli OCS è la chiave della loro efficacia nell'asma*

A- How corticosteroids switch on anti-inflammatory gene expression.

B- Processes by which corticosteroids switch off inflammatory genes.

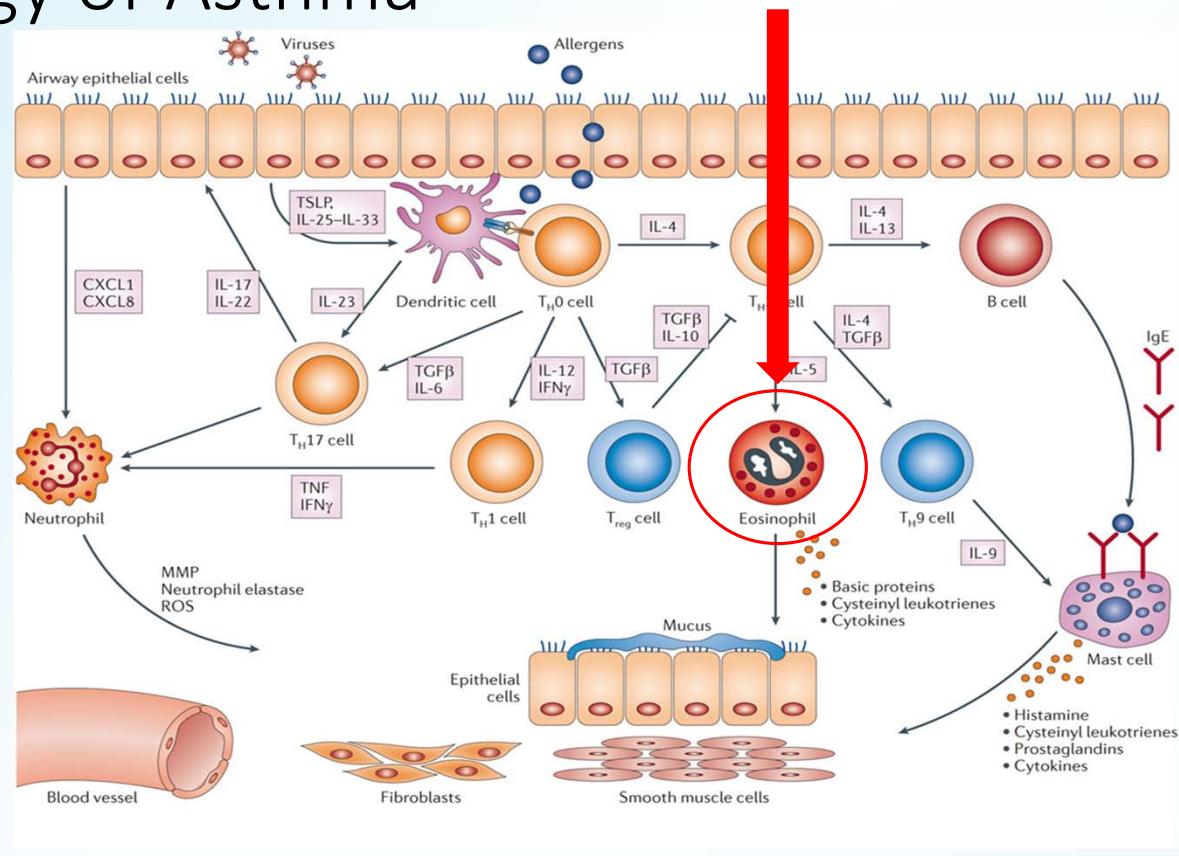
Ann Intern Med. 2003

# Severe and Difficult-to-Treat Asthma in Adults



E Israel, and H K. Reddel *N Engl J Med* 2017

# Immunobiology of Asthma



Pelaia G, et al. *Nature Rev Drug Discov.* 2012;11(12): 958–972.



# GINA Recommends Considering AEs When Including Add-On Low-Dose OCS at Step 5<sup>1,2</sup>

## Step 5: Consider AEs when using add-on low-dose OCS therapy

PREFERRED  
CONTROLLER  
to prevent  
exacerbations and  
control symptoms

### STEP 1

As-needed  
low-dose ICS  
+formoterol\*

Other  
controller  
options

Low-dose  
ICS taken  
whenever  
SABA taken†

### PREFERRED

### STEP 2

Daily low-dose inhaled corticosteroid (ICS),  
or as-needed low-dose ICS-formoterol\*

Leukotriene receptor antagonist (LTRA),  
or low-dose ICS taken whenever SABA taken†

### PREFERRED

As-needed low-dose ICS-formoterol\*

### STEP 3

Low-dose  
ICS-LABA

Medium-dose  
ICS, or  
low-dose  
ICS+LTRA†

### STEP 4

Medium-dose  
ICS-LABA

High-dose ICS,  
add-on  
tiotropium,  
or add-on LTRA†

### STEP 5

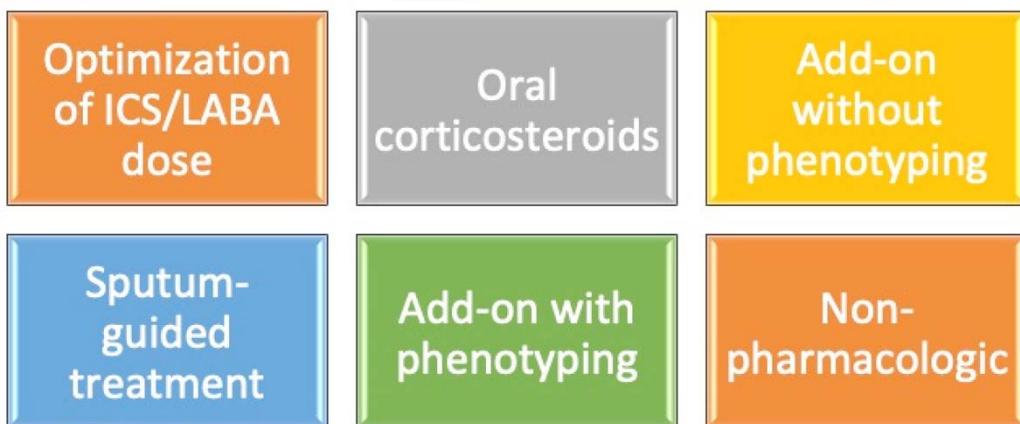
High-dose  
ICS-LABA

Refer for  
phenotypic  
assessment ±  
add-on therapy,  
eg,  
tiotropium,  
anti-IgE,  
anti-IL5/5R,  
anti-IL4R

Add low-dose  
OCS, but  
consider  
side effects

- ©2019 Global Initiative for Asthma, all rights reserved. Use is by express license from the owner.  
\*Off-label; data only with budesonide-formoterol (bud-form). †Off-label; separate or combination ICS and SABA inhalers. ‡Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV<sub>1</sub>>70% predicted. §Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy.
- 1. Global Initiative for Asthma (GINA). Asthma management and prevention for adults and children older than 5 years: a pocket guide for health professionals.  
Updated 2019. <https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention>. Accessed September 12, 2019. 2. Global Initiative for Asthma (GINA).  
What's new in GINA 2019? <https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/>. Accessed September 12, 2019.

# Management of Severe Asthma



## Optimization of ICS/LABA dose

- Some may respond to higher doses of ICS than routinely used; risk of systemic side effects
- Step down slow at 3-6 month intervals

## Oral corticosteroids

- Some may benefit from low-dose, maintenance OCS
- Monitor for osteoporosis
- If  $\geq 3$  months → lifestyle counseling, Rx for preventing osteoporosis

## Add-on without phenotyping

- Selected patients with uncontrolled symptoms and persistent airflow limitation despite moderate-/high-dose ICS and LABA
- Consider add-on tiotropium; alternatively, theophylline or LTRA

Global Initiative for Asthma. <https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed September 5, 2018.

# Come si confrontano le linee guida sull'uso dei corticosteroidi orali per i pazienti con asma grave?

## NHLBI

- L'OCS cronico dovrebbe essere considerato solo per l'asma più grave e difficile da trattare
- È preferibile ridurre al minimo la dose di OCS e massimizzare altre modalità di terapia

## Linee guida ERS / ATS2, se è giustificata la terapia OCS continua:

- Monitora il peso, la pressione sanguigna, la glicemia, gli occhi e la densità ossea
- Utilizzare misure profilattiche per prevenire la perdita di densità ossea

## GINA

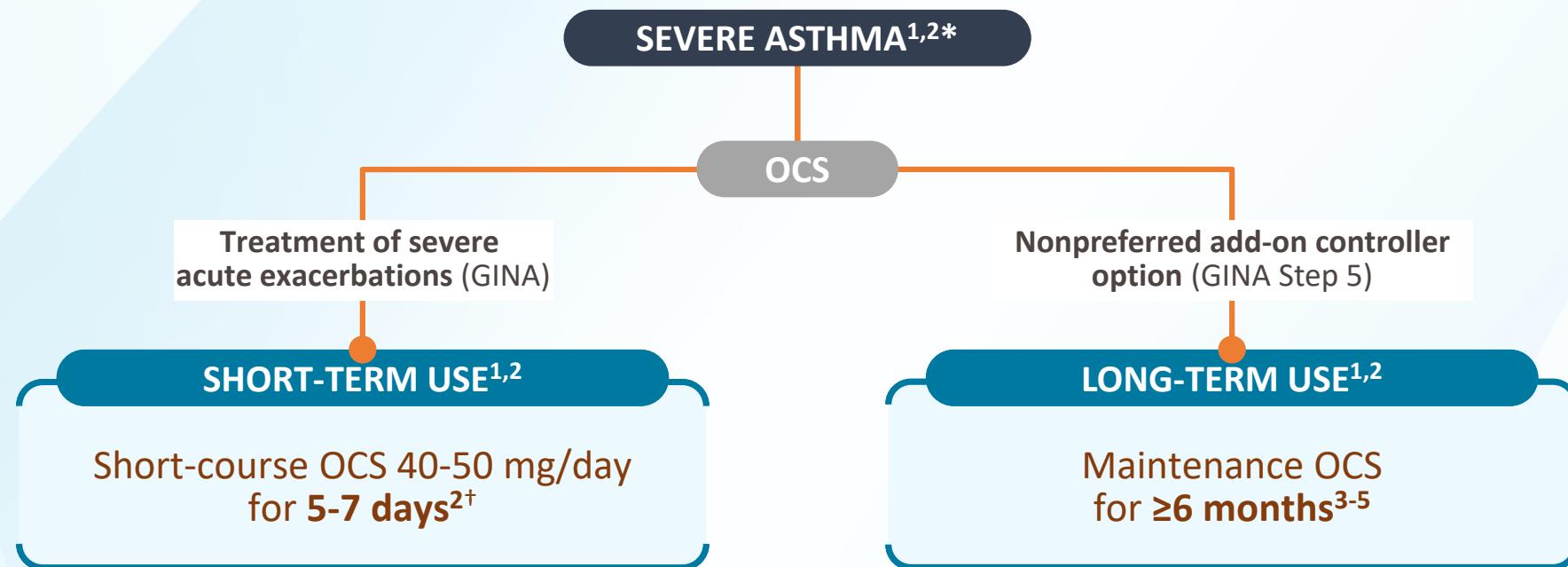
- Alcuni pazienti possono trarre beneficio da OCS di mantenimento a basso dosaggio, ma deve essere considerato il rapporto rischio / beneficio a lungo termine
- Monitorare i pazienti per prevenire la perdita ossea
- Incoraggiare il riferimento a cure specialistiche se  $\geq 2$  corsi di OCS / anno

1. National Heart, Lung, and Blood Institute. [https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthgdn\\_1.pdf](https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthgdn_1.pdf). Accessed August 15, 2018.

2. Chung KF, et al. *Eur Respir J*. 2014;43:343-373.

3. Global Initiative for Asthma. <https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed September 5, 2018.

# Management of Patients With Severe Asthma May Include Short- or Long-term OCS Use



\*GINA defines severe asthma as asthma that remains uncontrolled despite adherence with maximal optimized Step 4 or 5 therapy and treatment of contributory factors or that worsens when high-dose treatment is decreased.<sup>1</sup>

- <sup>†</sup>Recommended dose and duration for prednisone or prednisolone in patients ≥12 years of age.
- 1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. <https://ginasthma.org/severeasthma/>. Accessed May 23, 2019. 2. Global Initiative for Asthma (GINA). Asthma management and prevention for adults and children older than 5 years: a pocket guide for health professionals. Updated 2019. [https://5.Nair P, et al. N Engl J Med. 2017;376\(25\):2448-2458.](https://5.Nair P, et al. N Engl J Med. 2017;376(25):2448-2458.)

# GINA riconosce la necessità di ridurre al minimo l'uso di OCS nei pazienti con asma grave a causa di eventi avversi associati

## Short-term OCS use

Mood changes  
Sleep disturbances

GERD

Thromboembolism

Hyperglycemia

Fractures

Increased risk of infection

## Long-term OCS use

Anxiety  
Depression

Cataracts  
Glaucoma

Hypertension

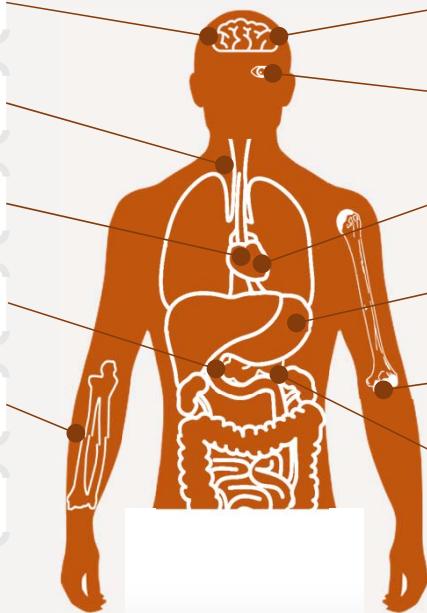
GI bleeds  
Ulcers

Osteoporosis

Type 2 diabetes  
Adrenal suppression

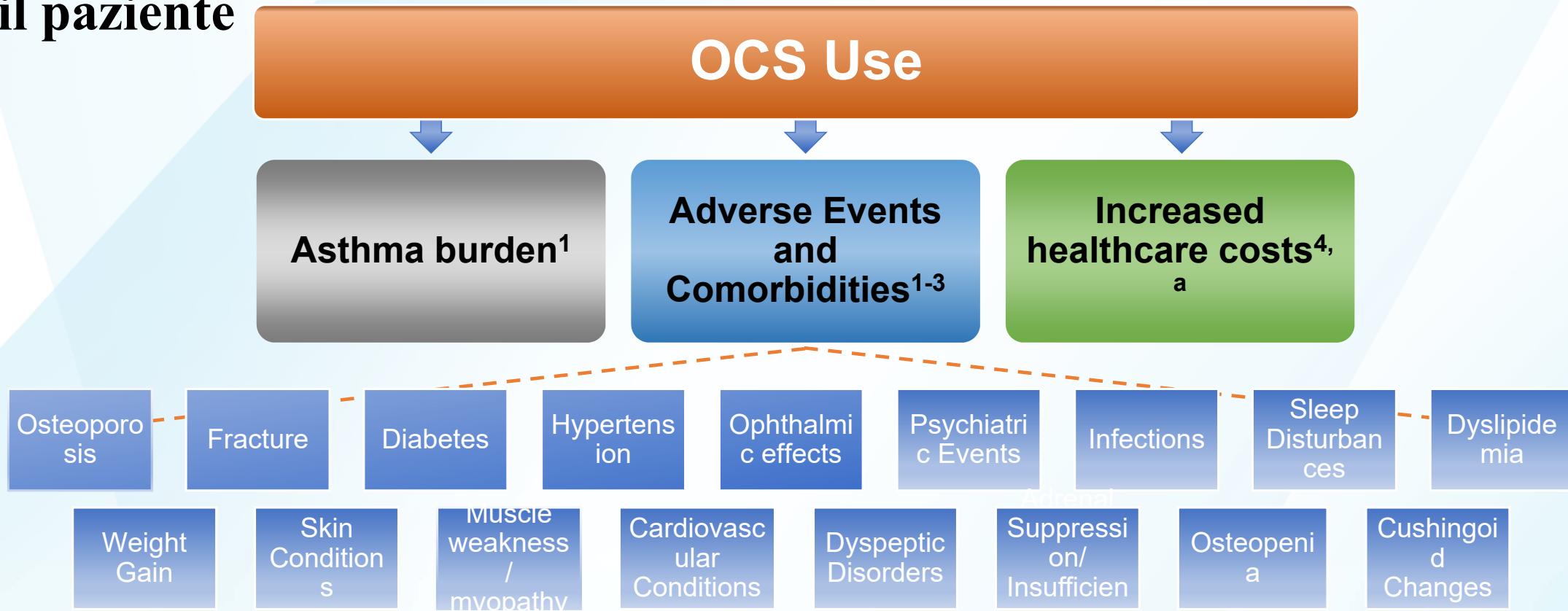
Dyslipidemia

Obesity/weight gain



1. Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. A GINA pocket guide for health professionals, V2.0 April 2019. <https://ginasthma.org/severeasthma/>. Accessed May 23, 2019. 2. Sullivan PW, et al. *J Allergy Clin Immunol*. 2018;141(1):110-116. 3. Bleecker ER, et al. *Am J Respir Crit Care Med*. 2019. doi:10.1164/rccm.201904-0903SO.

# L'uso di corticosteroidi orali porta a maggiori oneri e costi per il paziente



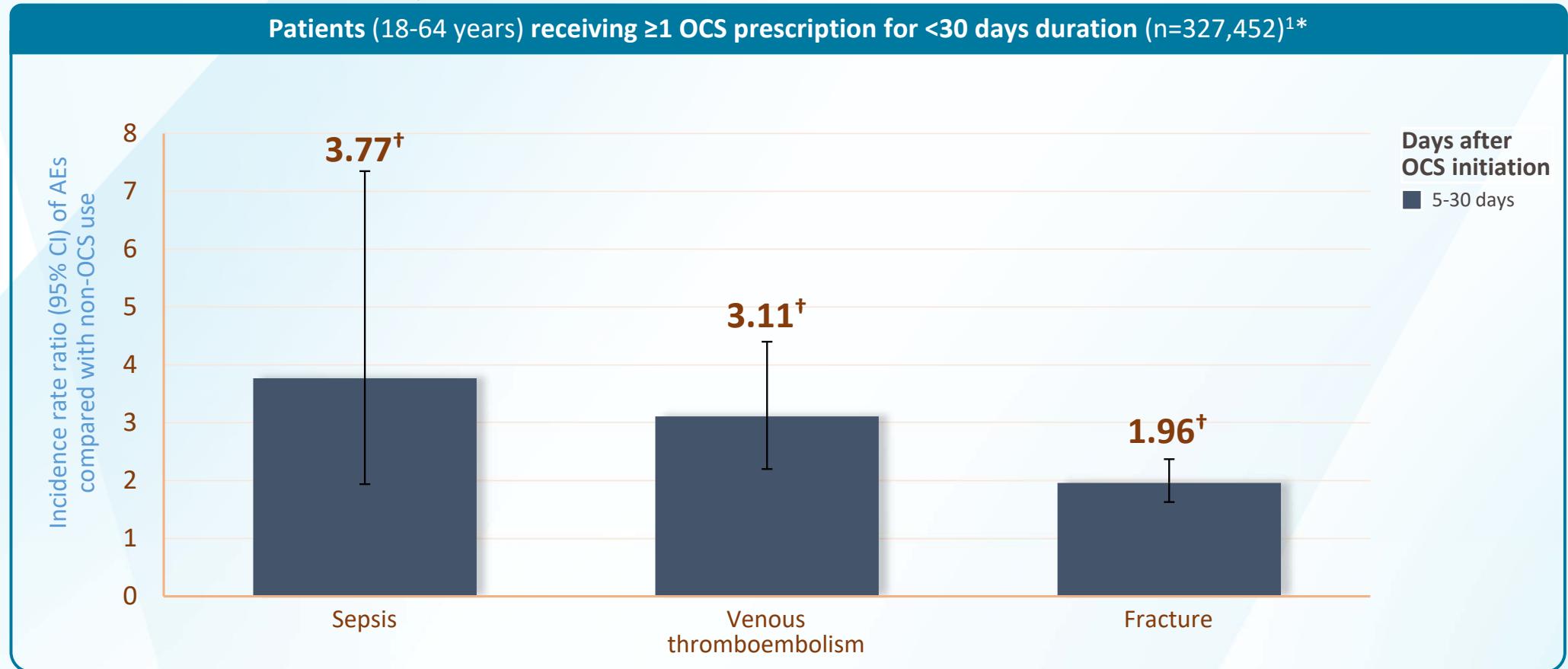
<sup>a</sup>Based on UK data.

OCS=oral corticosteroids.

1. Zeiger RS et al. *J Allergy Clin Immunol Pract.* 2017;5:1050-1060; 2. Sullivan PW et al. *J Allergy Clin Immunol.* 2018;141:110-116; 3. Sweeney J et al. *Thorax.* 2016;71:339-346; 4. Kerkhof M et al. *Thorax.* 2018;73:116-124.

# Short-term OCS Use Can Result in AEs Within 30 Days of OCS Prescription

Patients (18-64 years) receiving  $\geq 1$  OCS prescription for <30 days duration (n=327,452)<sup>1\*</sup>

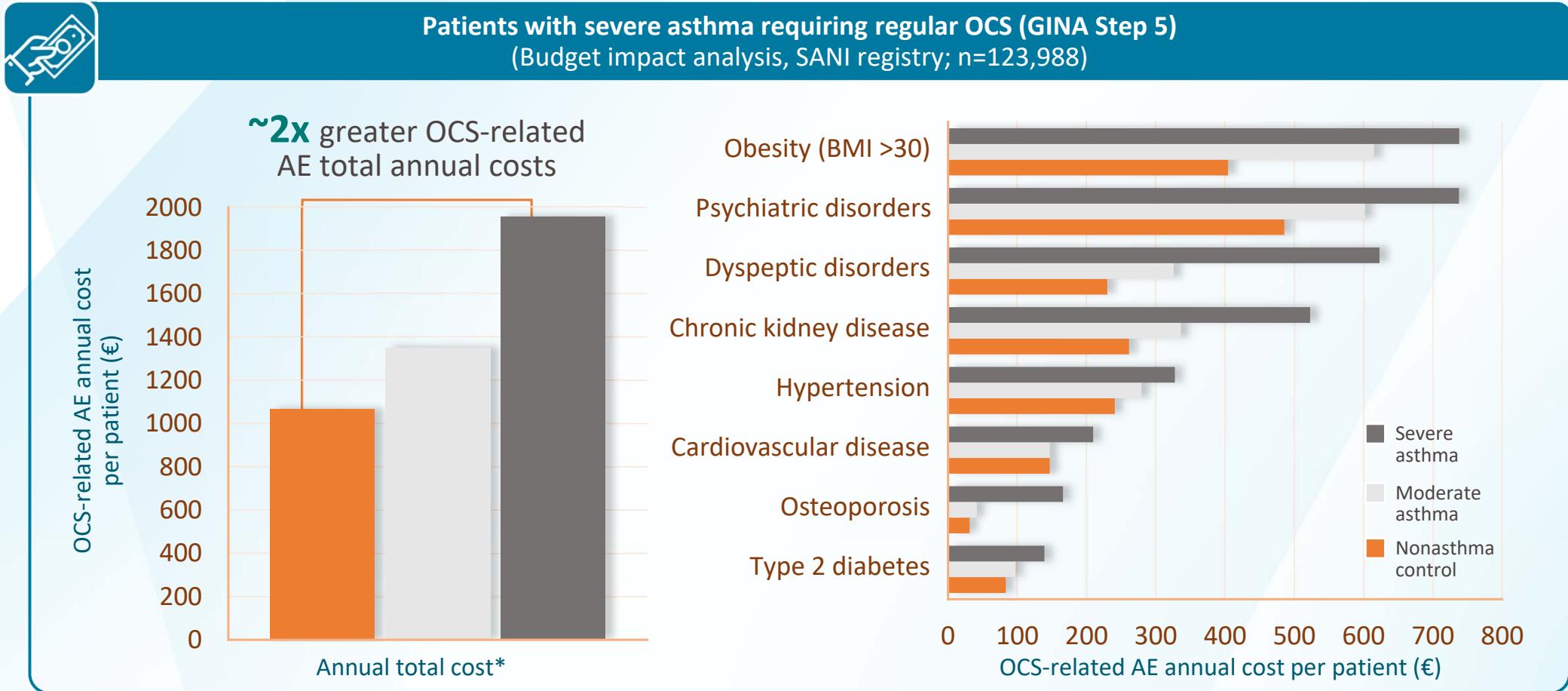


- \*Upper respiratory tract infection, allergy, bronchitis, lower or upper respiratory tract disorder, or asthma.

<sup>†</sup>Statistically significant compared with patients who did not receive corticosteroids ( $P<0.001$ ).

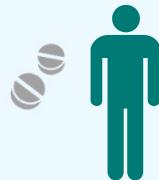
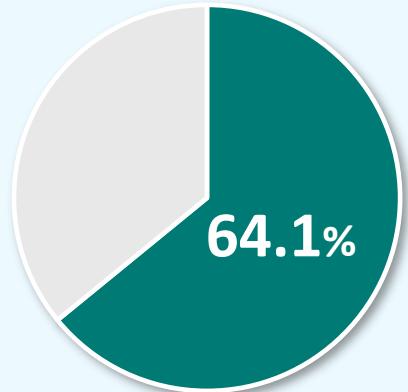
- 1. Waljee AK, et al. *BMJ*. 2017;357:j1415.

# OCS-Related AEs in Severe Asthma Can Result in 2x Greater Total Annual Healthcare Costs<sup>1</sup>



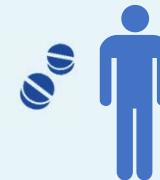
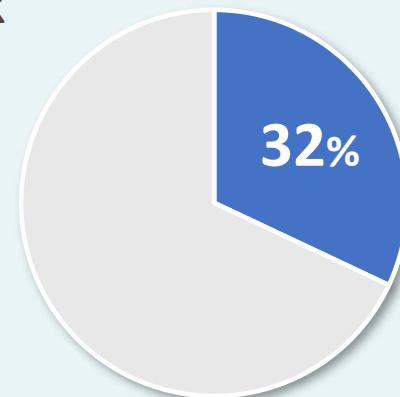
# Patients With Severe Asthma Are Treated With Chronic OCS Despite Established AEs

Severe Asthma Network in Italy  
(n=437)<sup>1\*</sup>



**Chronic OCS=Treatment with OCS for  
≥6 months in the previous year**

Severe Asthma Research Program  
in US and UK  
(n=204)<sup>2†</sup>



**Chronic OCS=Treatment with continuous or  
near continuous (≥50% of the year) OCS**

- \*Diagnosis of severe asthma according to ERS/ATS criteria. †Diagnosis of severe asthma according to ATS criteria.
- 1. Heffler E, et al. *J Allergy Clin Immunol Pract*. 2019;7(5):1462-1468. 2. Moore WC, et al. *J Allergy Clin Immunol*. 2007;119(2):405-413.



# How can we minimise the use of regular oral corticosteroids in asthma?

Maintenance with OCS  
OR repeated bursts  
cumulative dose  $\geq 1 \text{ g}\cdot\text{year}^{-1}$

Assess OCS overuse:  
Poor adhesion to predicted maintenance therapy  
Persistent exposure to triggers (particularly allergens)  
Poor inhalation technique  
Untreated comorbidities  
Misdiagnosis and interpretation of symptoms not necessarily caused by asthma/consider justification of each burst by an external adviser  
Insufficient patient education  
Assess OCS-related side-effects and OCS worsened comorbidities  
Screen for EGPA, ABPA, or other OCS-sensitive cormorbid diseases

## Initiate OCS-tapering

Optimise inhaled therapies:  
Therapeutic education  
Optimise ICS dose  
Consider intranasal CS  
Consider adding a LAMA  
Consider SMART strategy  
Psychological support  
Screen for adrenal insufficiency  
Assess eligibility for biologic repeatedly  
T2 biomarkers every other week  
Nasal polyps

## Initiate OCS-sparing therapy

OCS-sparing biologicals (prefer drugs with evidence):  
IL-5 targeting drugs  
IL-4Ra-targeting drugs  
Consider anti-IgE on a case-by-case basis  
Establish anticipated stopping/switching rules  
If not eligible, consider: macrolides, thermoplasty, RCT

## Assess the response

If OCS weaning is not achieved:  
Consider adrenal insufficiency  
Consider switching of OCS-sparing therapy  
Consider a directly observed weaning  
Screen again for EGPA, ABPA, or other OCS-sensitive cormorbid diseases

## Potential barriers to reduce OCS exposure in severe asthma

### Patient Barriers

- OCS familiarity, easy accessibility and low cost
- Fear of exacerbation or clinical deterioration

### Clinical Barriers

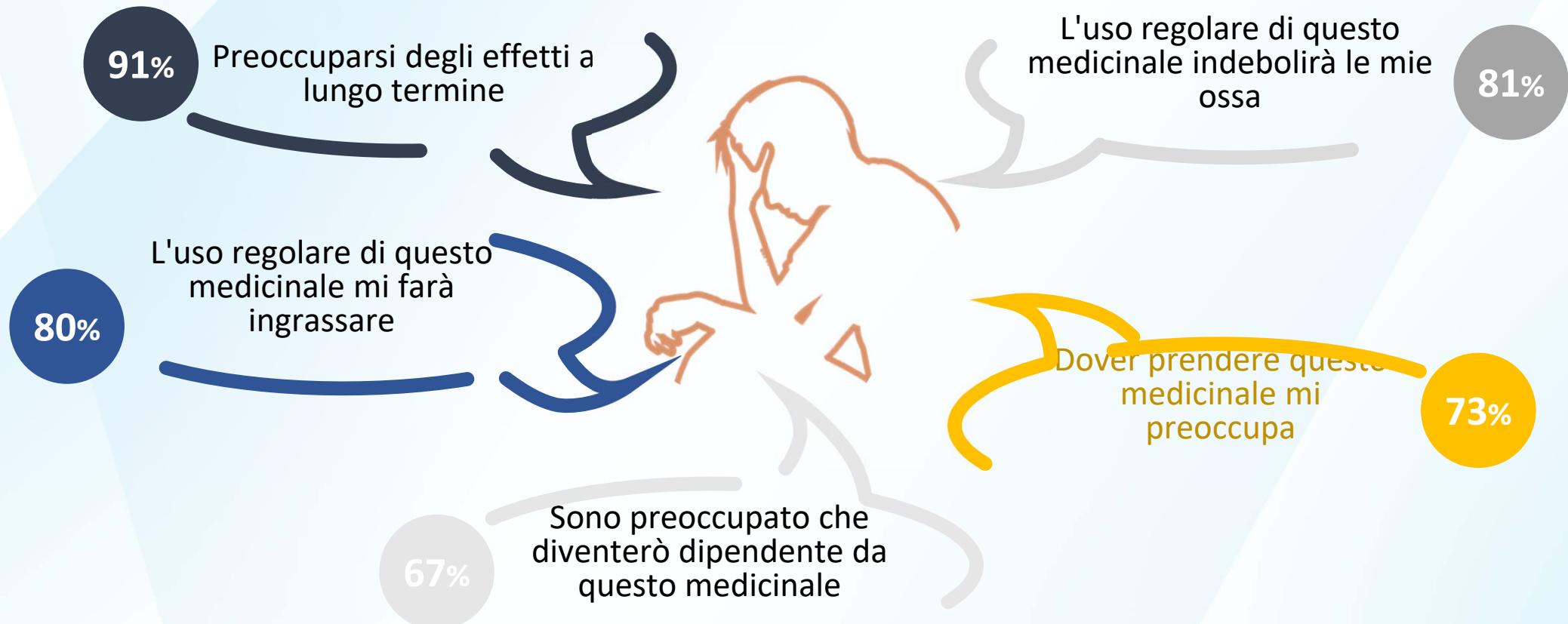
- Adrenal insufficiency
- Poor adherence to guideline inhaled therapies
- Under-recognition of cumulative OCS burden
- Lack of alternative treatment for asthma exacerbations
- No standardised approach to OCS weaning or systematic screening of OCS adverse effects

### System Barriers

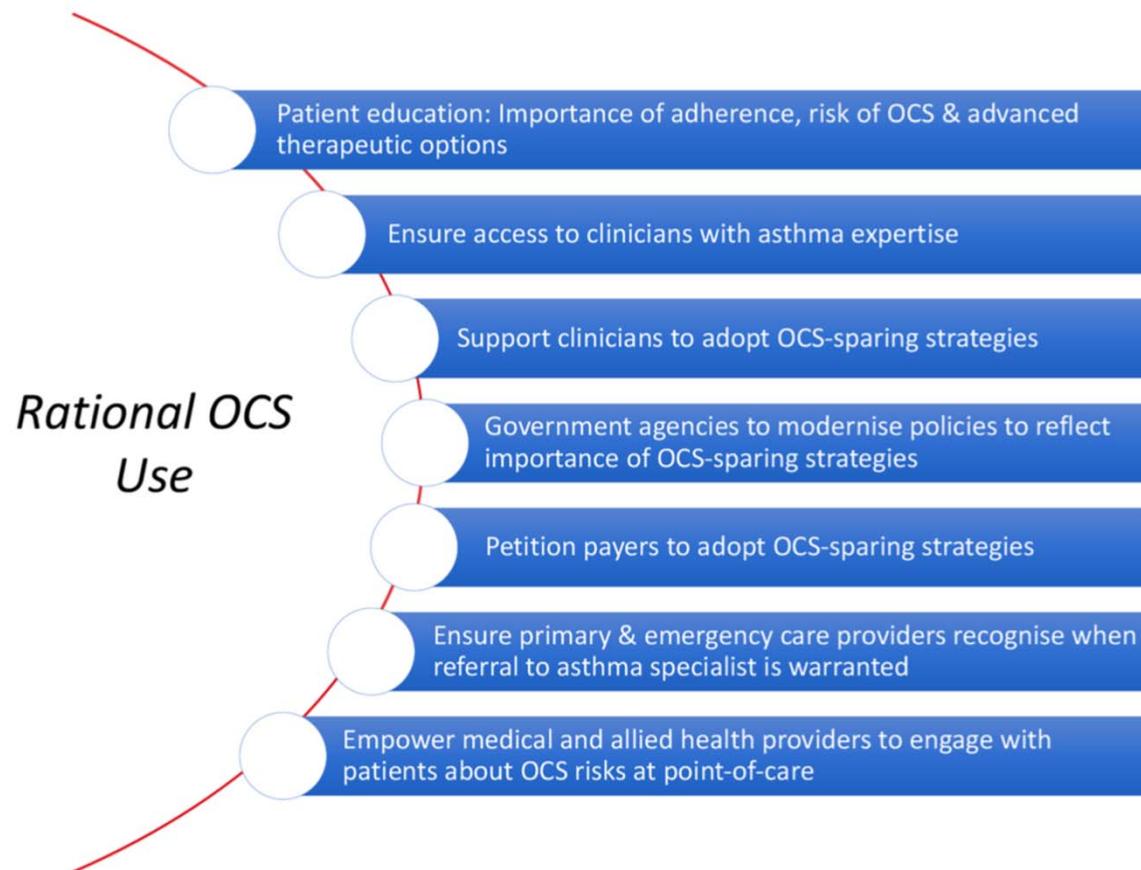
- Delayed referrals
- Limited access to multidisciplinary asthma services
- Restricted access to reimbursed biological therapies
- Lack of monitoring of OCS prescribing

# I pazienti che assumono OCS possono avere grandi preoccupazioni per la loro salute

- Percentuale di persone che hanno segnalato le 5 principali preoccupazioni sull'uso di OCS

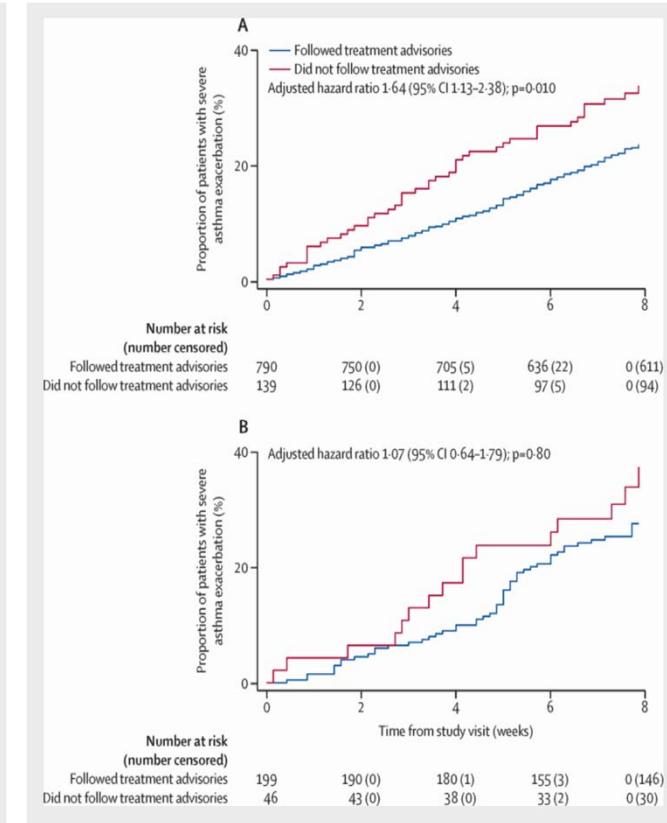
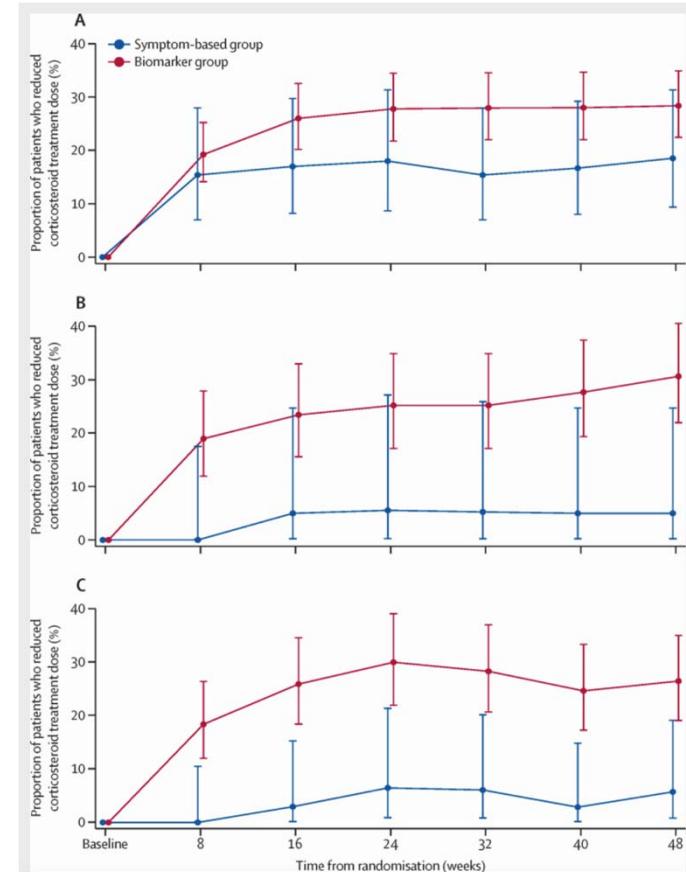
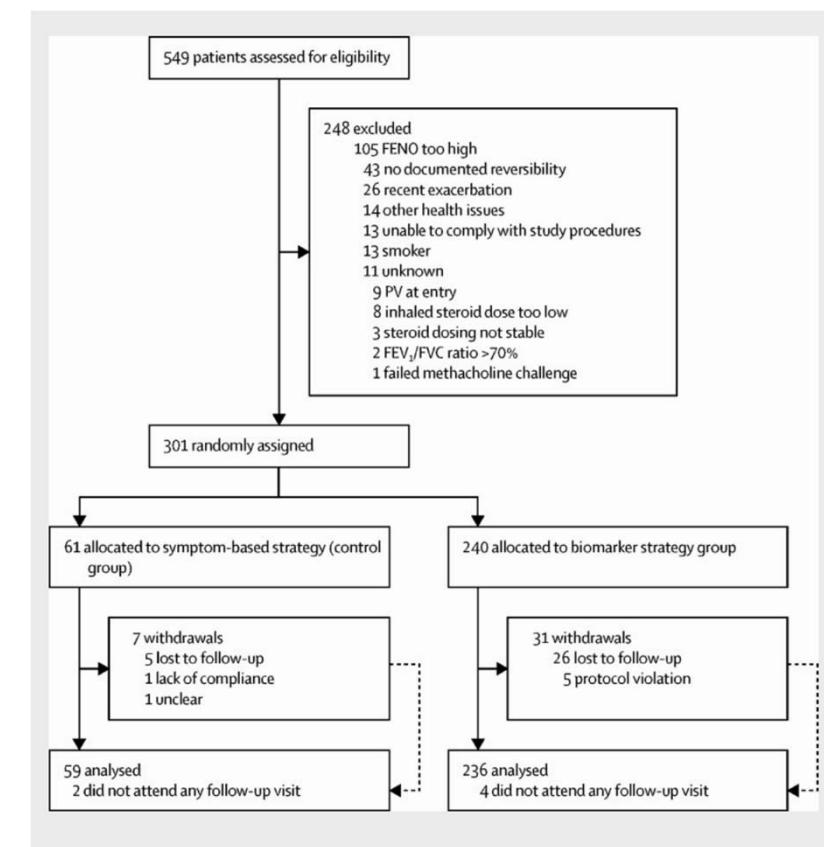


1. Cooper V, et al. *NPJ Prim Care Respir Med.* 2015;25:15026.



*Principi chiave della gestione dell'OCS per l'asma  
 (Adapted from the Asthma and Allergy Foundation of America)*

# Composite type-2 biomarker strategy versus a symptom–risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial



Heaney GL et al Lancet Resp Med 2021 Jan