Νέες οδηγίες για το σοβαρό άσθμα

Μίνα Γκάγκα MD, PhD, FERS, FCCP
ΝΝΘΑ, WHO-GARD

Dr. Batty's

For Your Health

ASTHMA CIGARETTES

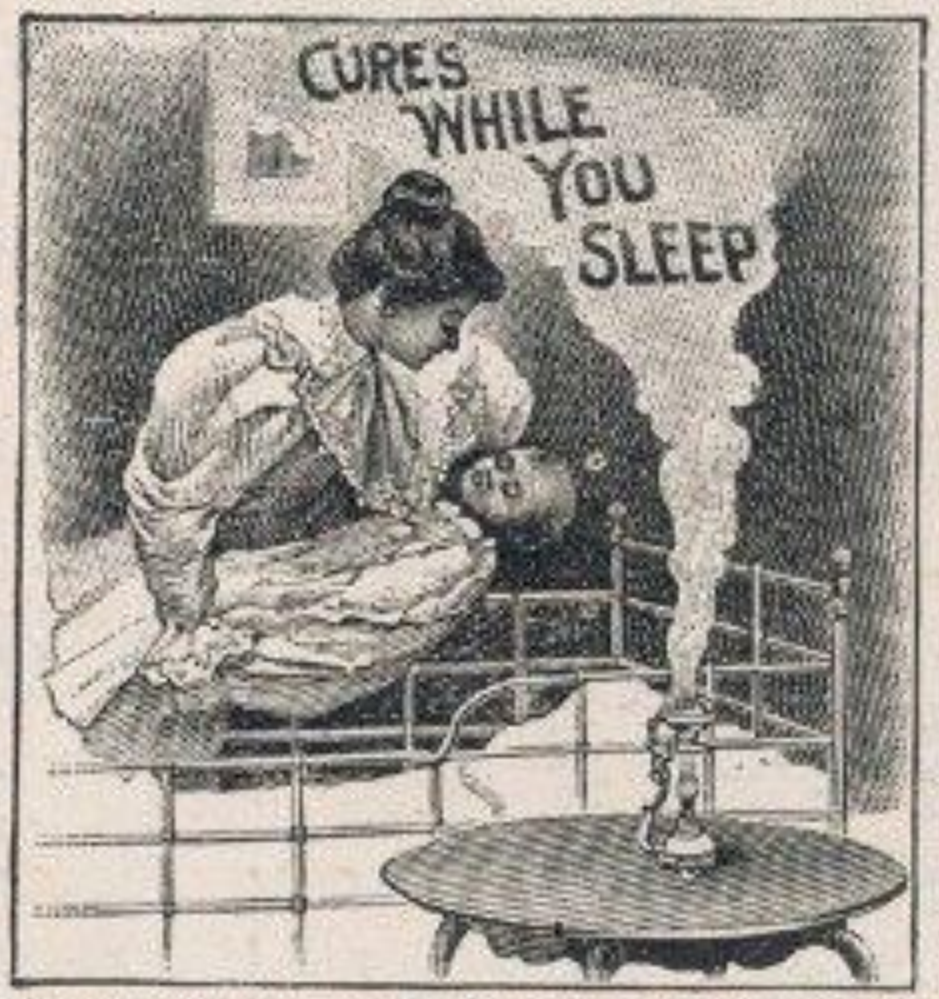
SINCE 1002

For the temporary relief of paroxysms of asthma

EFFECTIVLY TREATS:

ASTHMA, HAY FEVER, FOUL BREATH
ALL DISEASES OF THE THROAT,
HEAD COLDS, CANKER SOURS
BRONCHIAL IRRITATIONS

NOT RECOMMENDED FOR CHILDREN UNDER 6.



Vapo-Cresolene

Whooping Cough, Croup, Asthma, Catarrh, Colds,

Items from physicians' statements in our Descriptive Booklet. Send for it.

"Have found it of such great value in Whooping Cough, Croup and other spasmodic coughs, that I have instructed every family under my direction to secure one." "It is of great value in Diphtheria." "It gives relief in Asthma. The apparatus is simple and inexpensive." Sold by all chemists, &c.

Wholesale Agents: ALLEN & HANBURYS, Ltd.,
37, Lombard St., London.


ONE
ADRENALIN VAPORIZER
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To the Medical Profession
Adrenalin Vaporizer
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EFFICIENT • CONVENIENT
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Adrenalin (Epinephrine) 1 Gm.
Chloretone (Chlorobutanol-hydrate) 0.5 Gm.
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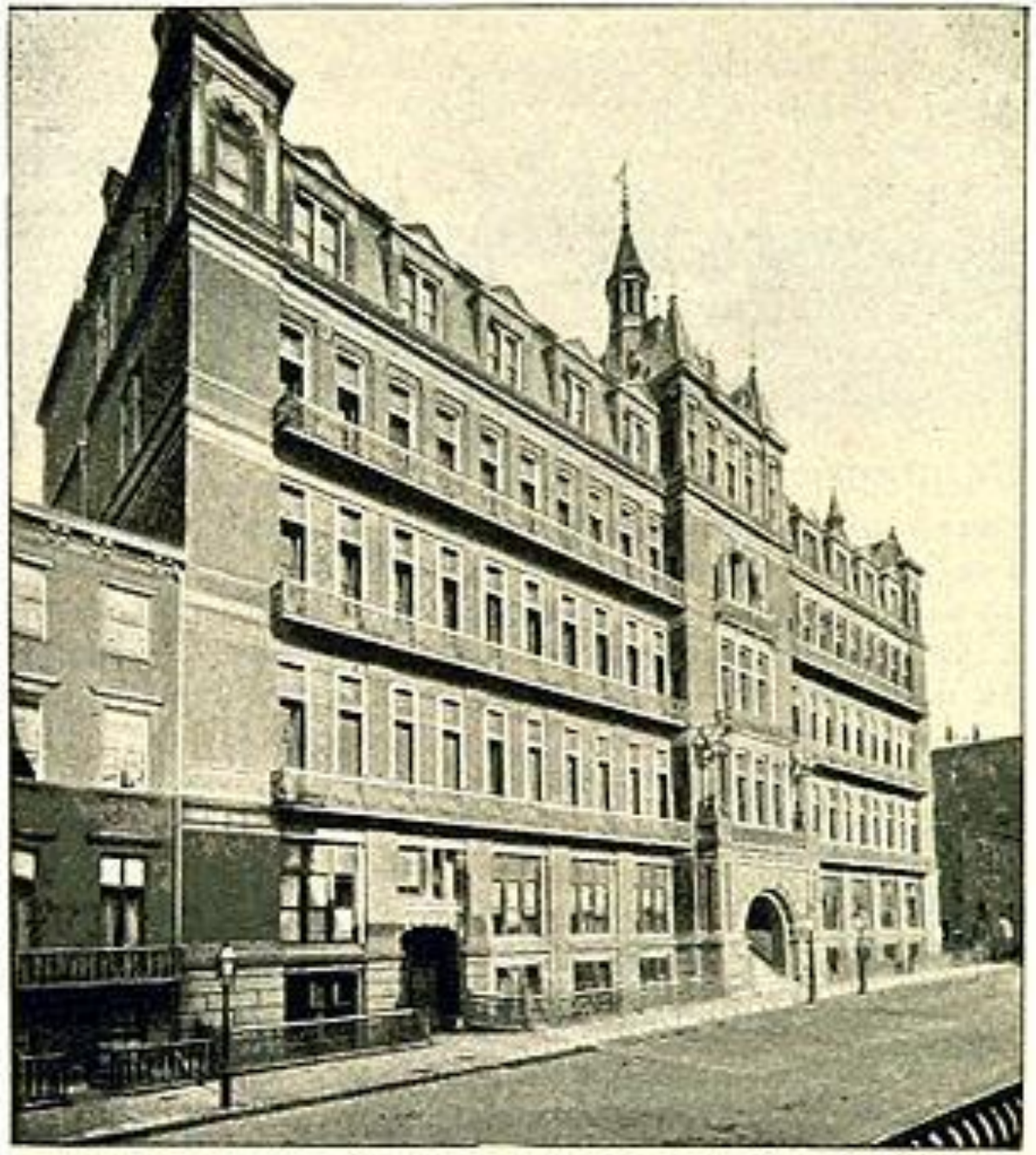
Sodium Bisulfite (not more than) 0.1%
8 CC. SOLUTION
ADRENALIN CHLORIDE
(P. D. & CO.) 1:100
FOR INHALATION ONLY. BY MOUTH.
NOT ADAPTED TO HYPODERMIC USE
PARKE, DAVIS & CO.
To the Medical Profession
ADRENALIN CHLORIDE
SOLUTION 1:100



NEW-YORK HOSPITAL, WEST 15TH STREET, NEAR FIFTH AVENUE.

EVALUATION OF THE STEROID TREATMENT OF ASTHMA SINCE 1950

Horace S. Baldwin, M.D., Murray Dworetzky, M.D.,** and Norman J. Isaacs, M.D.,****
New York, N. Y.

THE USE of the corticosteroids in asthma presents problems that are unique to the disease and peculiarly related to current questions as to the dangers of steroid therapy. In the first place, asthma in a high percentage of patients is reversible when the sum total of stimuli to the asthmatic state are studied and treated. Also, in intractable cases, chronic infection in the respiratory tract is so common that steroid treatment carries with it the dangerous possibility of lowering the patient's resistance to infection[1] and masking the development of acute intercurrent infection, especially pneumonitis. Therefore the physician, when starting an asthmatic patient on steroid therapy, should be sure of the thoroughness of his analysis of the patient's asthmatic factors so that if steroid therapy is instituted the dosage will be at the minimum effective amount. At all times the hazards of steroid therapy should be kept in mind but with the added precaution to be alert to the problems of respiratory infections that are so common in the asthmatic patient. The present paper is based on a study of forty-eight patients with continuous intractable asthma and thirty-nine patients with intermittent severe asthma in whom corticosteroids have been used. The investigation began in 1950 when cortisone was first used in The New York Hospital as an adjunct in the treatment of asthma and includes experience with the various steroid compounds, prednisone, 6 methyl prednisolone, triamcinolone, and dexamethasone.[2-5] The study presents data on the general conditions of patients in the Continuous and Intermittent groups, the duration and dosage of steroids used, side effects and complications, mortality, and analysis of cases where steroid therapy was unsuccessful, the management of interval surgery, hospitalization before and after steroid treatment, and a summary of ancillary medical treatment with particular emphasis on management of chronic and acute infection.

From the New York Hospital-Cornell Medical Center, Department of Medicine, New York, N. Y.

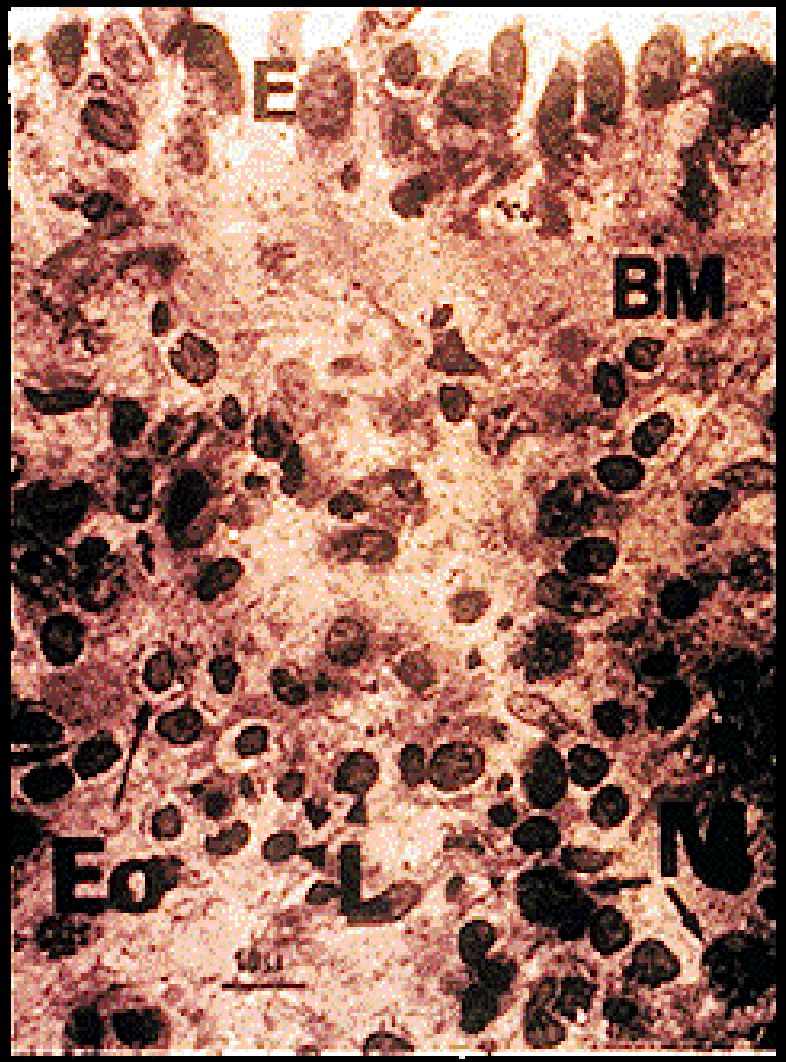
. P.H MARCH 14, 1962

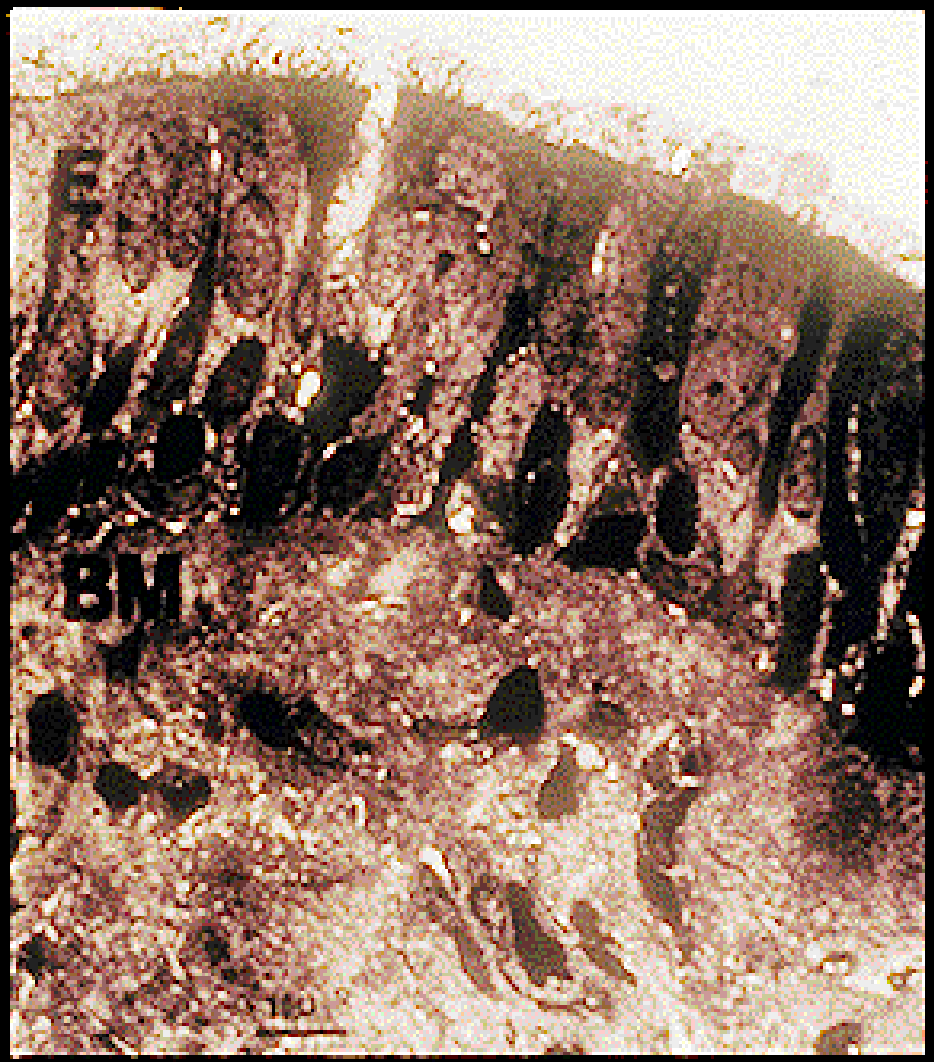
Asthma, one of the mystery diseases

EACH year more than 400 people in Australia die from asthma — more than half the number killed by chronic heart disease, and almost as many as those who die from all forms of T.B.

Doctors estimate break of coping with

The revolution in asthma understanding and treatment





Laitinen LA et al, J Allergy Clin Immunol 1992

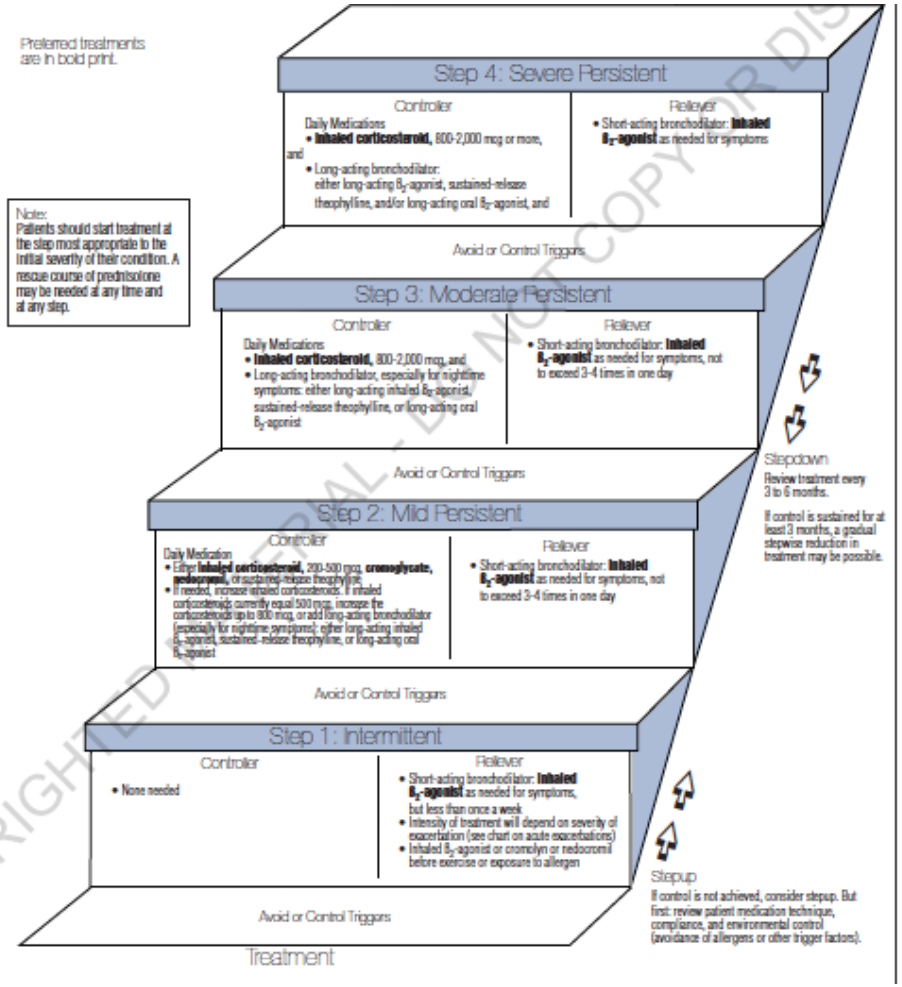
Σταθμοί στο άσθμα

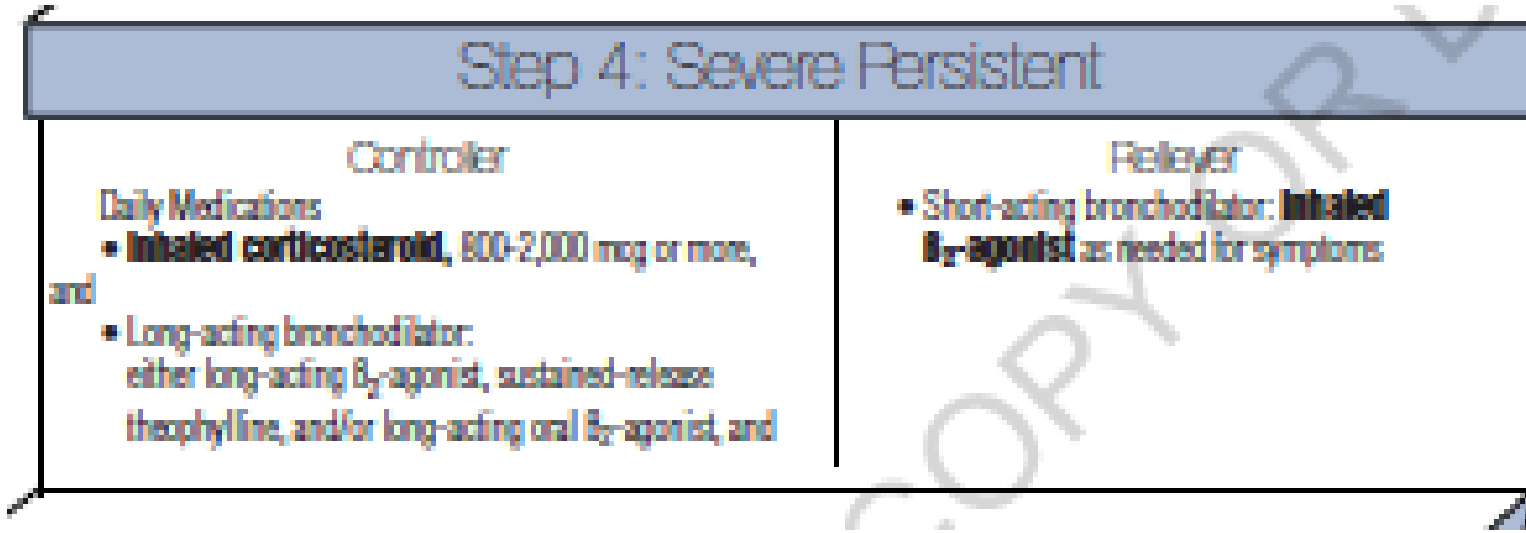
- SABAs- salbutamol
- ICS- Beclomethasone
- Κατανόηση των μηχανισμών
- Νεώτερα ICS
- LABAs

- FACET study - ICS/LABA

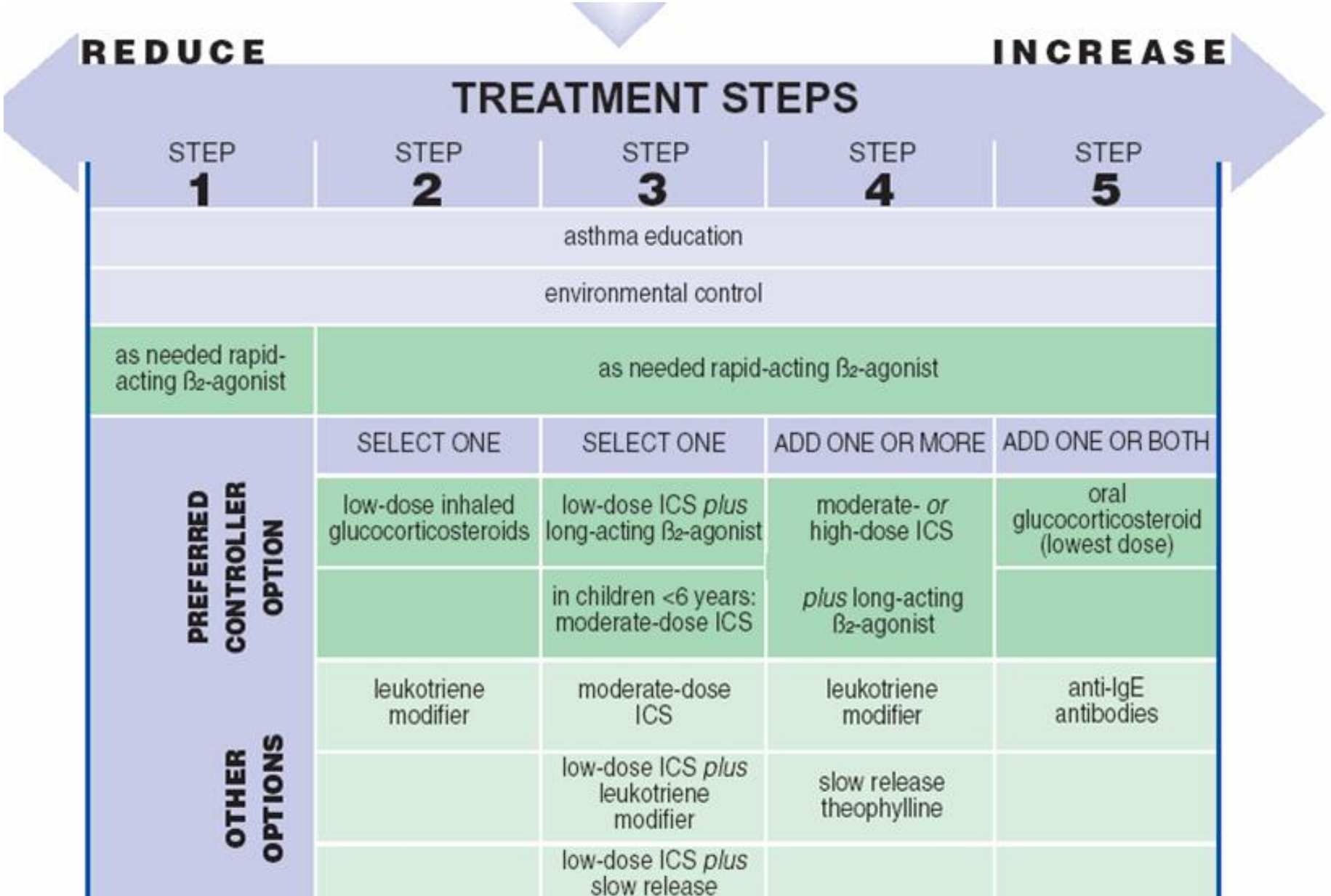
- Μονοκλωνικά Abs- στοχευμένη θεραπεία

GINA 1995- WHO-NHLBI





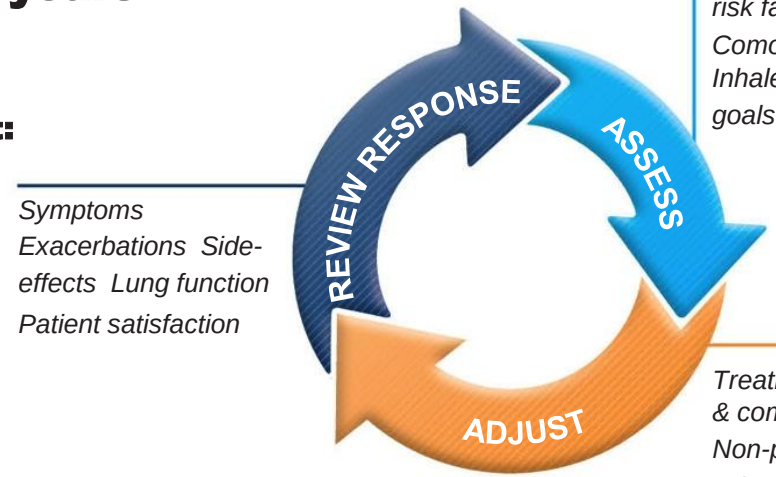
Stepwise Approach to Asthma Therapy - GINA 2006



Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence Patient goals

Symptoms
Exacerbations Side-effects Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ERS 1999, ATS 2000, ……..
ERS/ATS 2014
SEPAR 2019, SPLF 2019
GINA 2019, ERS/ATS 2019

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

2019

Task Force Report

Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline

Fernando Holguin, Juan Carlos Cardet, Kian Fan Chung, Sarah Diver, Diogenes S. Ferreira, Anne Fitzpatrick, Mina Gaga, Liz Kellermeyer, Sandhya Khurana, Shandra Knight, Vanessa M. McDonald, Rebecca L. Morgan, Victor E. Ortega, David Rigau, Padmaja Subbarao, Thomy Tonia, Ian M. Adcock, Eugene R. Bleecker, Chris Brightling, Louis-Philippe Boulet, Michael Cabana, Mario Castro, Pascal Chanez, Adnan Custovic, Ratko Djukanovic, Urs Frey, Betty Frankemolle, Peter Gibson, Dominique Hamerlijnck, Nizar Jarjour, Satoshi Konno, Huahao Shen, Cathy Vitary, Andy Bush

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

2014

Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

GINA Pocket Guide
Difficult to treat and severe asthma in adults and adolescents

V2.0 April 2019

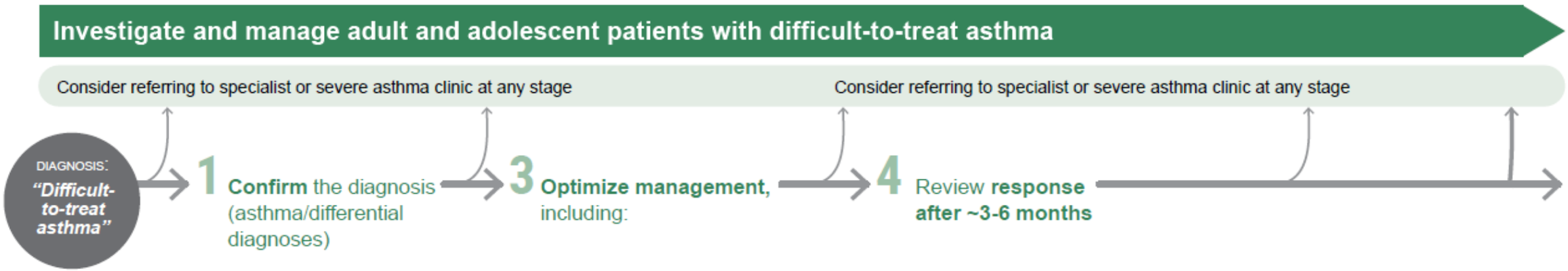
Guidelines vs Statements and Consensus reports

- Guidelines- μεθοδολογία GRADE
- Statement- Δεν μπορούν να περιέχουν οδηγίες
- Consensus reports- expert opinion

About the GINA strategy

- The GINA report is not a guideline, but an integrated evidence-based strategy focusing on translation into clinical practice
- Recommendations are framed, not as answers to isolated PICOT questions, but as part of an integrated strategy, in relation to:
  - The GINA goals of preventing asthma deaths and exacerbations, as well as improving symptom control
  - Current understanding of underlying disease processes
  - Human behavior (of health professionals and patients/carers)
  - Implementation in clinical practice
  - Global variation in populations, health systems and medication access
- GINA provides practical resources for clinicians
  - Figures and tables about implementation in clinical practice: not just ‘what’, but ‘how to’
  - A survey of GINA Assembly members in 2017 strongly encouraged development of a practical resource about severe asthma

GP OR SPECIALIST CARE



SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

6a Consider ***non-biologic*** treatments

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider ***add-on biologic Type 2*** targeted treatments

SPECIALIST AND PRIMARY CARE IN COLLABORATION

Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review **response** → 8 Continue to **optimize management**

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline

Fernando Holguin, Juan Carlos Cardet, Kian Fan Chung, Sarah Diver, Diogenes S. Ferreira, Anne Fitzpatrick, Mina Gaga, Liz Kellermeyer, Sandhya Khurana, Shandra Knight, Vanessa M. McDonald, Rebecca L. Morgan, Victor E. Ortega, David Rigau, Padmaja Subbarao, Thomy Tonia, Ian M. Adcock, Eugene R. Bleecker, Chris Brightling, Louis-Philippe Boulet, Michael Cabana, Mario Castro, Pascal Chanez, Adnan Custovic, Ratko Djukanovic, Urs Frey, Betty Frankemolle, Peter Gibson, Dominique Hamerlijnck, Nizar Jarjour, Satoshi Konno, Huahao Shen, Cathy Vitary, Andy Bush

ERJ 2019

Ερωτήσεις PICO
Σε παιδιά και ενήλικες με ΣΑ

- Να χρησιμοποιήσουμε αγωγή με anti-IL5;
- Να χρησιμοποιήσουμε κάποιο βιοδείκτη για την έναρξη θεραπείας με anti-IL5 ή IL5Rα; (eNO, ηωσινόφιλα, περιοστίνη)
- Πέραν του τίτλου IgE , να χρησιμοποιήσουμε κάποιο βιοδείκτη για την έναρξη θεραπείας με anti-IgE; (eNO, ηωσινόφιλα, περιοοστίνη)
- Να χρησιμοποιήσουμε LAMA;
- Να χρησιμοποιήσουμε μακρολίδη (i.e., azithromycin, clarithromycin);
- Να χρησιμοποιήσουμε anti-IL4/13 ;

Recommendation 1

Should an anti-interleukin 5 strategy versus no anti-interleukin 5 strategy be used for adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma
INTERVENTION:	Anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)
COMPARISON:	No anti-interleukin 5 strategy
MAIN OUTCOMES:	Rate of exacerbations Time to first asthma exacerbation Asthma exacerbations requiring ER visits or hospitalization Lung function Asthma control Maintenance corticosteroid dose reduction Adverse events Serious adverse events Quality of life

BACKGROUND:

By definition, patients with severe asthma have disease that is either unresponsive to traditional therapies with inhaled corticosteroids and bronchodilators or require these therapies to maintain adequate control. To address this unmet need for improved therapies, several biologic therapies have been designed to target the inflammatory signature typical of most patients with asthma. Interleukin 5 (IL5) is the principal cytokine driving eosinophilic inflammation in most of these patients. Monoclonal antibodies that target the IL5 cytokine or its receptor have been found to be efficacious in randomized controlled trials in improving asthma-related outcomes. These three drugs in this category are mepolizumab, reslizumab, and benralizumab, and will henceforth be referred to as the anti-IL5 strategy. This systematic review and meta-analysis synthetizes the data from randomized controlled trials and meta-analyses investigating the anti-IL5 strategy and provides treatment recommendations based on the results

- How substantial are the desirable and the undesirable anticipated effects?
- What is the overall certainty of the evidence of effects?
- How much people value the main outcomes?
- Does the balance between desirable and undesirable effects favor the intervention or the comparison?
- Does the cost-effectiveness of the ;intervention favor the intervention or the comparison?
- What is the certainty of the evidence of resource requirements (costs)?
- What would be the impact on health equity?
- Is the intervention acceptable to key stakeholders?
- Is the intervention feasible to implement?

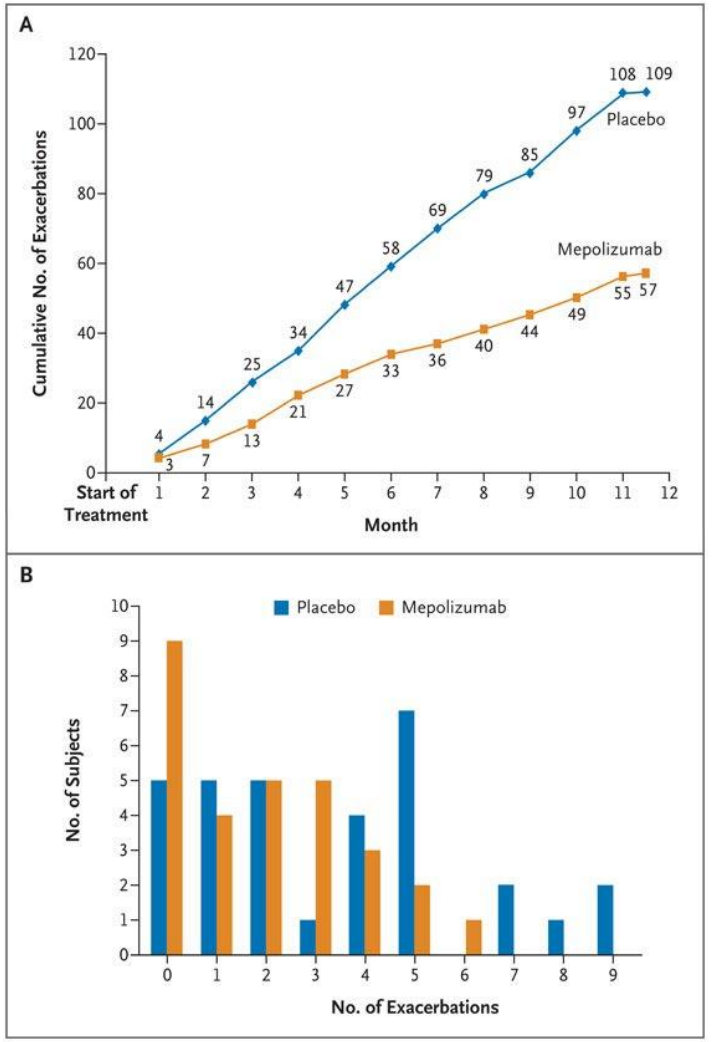
Q1.Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?
1. Mepolizumab

3 placebo-controlled RCTs

(patients with severe eosinophilic asthma (blood eosinophil count >300 cells/mm3in the 12 months prior to screening or >150 cells/mm$^{3)}$

- 50% reduction in the rate of any exacerbation
- 64% reduction in severe exacerbations
- 50% reduction in the dose of maintenance OCS
- No effect on FEV_1

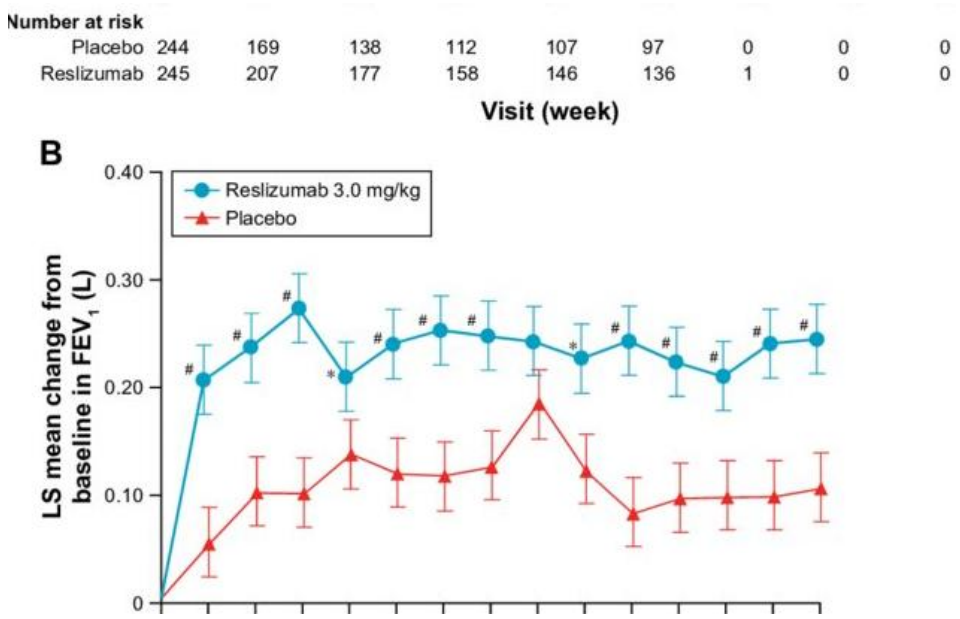
Bel EH,. N Engl J Med. 2014, Ortega HG, N Engl J Med. 2014, Chupp. Lancet Respir Med. 2017



Q1. Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?
2. Reslizumab

4 studies, 3 used blood eosinophils >400 cells/mm^3 and one RCT used sputum eosinophil >3%.

- 54% reduction in the rate of any exacerbation
- 33% reduction in severe exacerbations
- Improved AQLQ and ACQ –Not MCID
- No effect on FEV_1

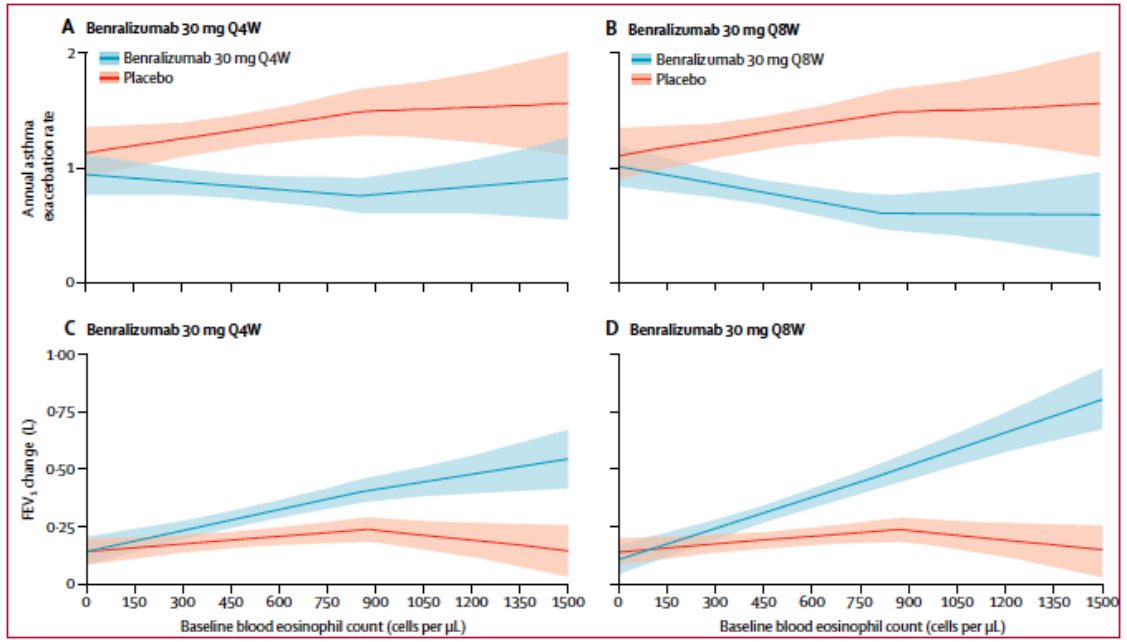


Bjermer, Chest 2016, Castro, Am J Respir Crit Care Med., Castro, Lancet Respir Med 2015, Corren, Chest 2016

Q1.Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?
3. Benralizumab

5 studies, 3 used blood eosinophils >400 cells/mm^3 and one RCT used sputum eosinophil >3%.

- 42% reduction in the rate of any exacerbation
- 55% reduction in severe exacerbations
- Improved AQLQ and ACQ
- No effect on FEV_1



Bleeker, Lancet 2016, Castro, Lancet Respir Med. 2014,

FitzGerald, Lancet 2016, Nair, N Engl J Med. 2017 , Park, Int Arch Allergy Immunol. 2016

Q 1. Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?

Anti-IL5 strategy reduces exacerbations in severe eosinophilic asthma.
Mepolizumab and benralizumab are effective in reducing OCS dose in corticosteroid-dependent asthma.

The effects on asthma control, quality of life and FEV1 are modest for all drugs and did not meet the MCID threshold

GINA and NAEPP include anti-IL5 in their algorithms

ERS/ATS suggest using anti-IL5 as add-on treatment in adults with SEA

Conditional recommendation- cost effectiveness, equity, feasibility

Q 2. Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5Rα antibody in adults and children with severe asthma? (Exhaled NO, eosinophils, periostin)

12 RTCs

150/µL for mepolizumab, ≥300/µL for benralizumab and ≥400/µLfor reslizumab- Usually blood eos, one study used sputum

No evidence on FeNO or periostin

Most studies used fixed dose, one switch study of adjusted dose reslizumab

Q 2. Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5Rα antibody in adults and children with severe asthma?

GINA Anti-IL5 in patients with ≥300 /µLcan

ERS/ATS Recommendation

- **A blood eosinophil count cut-off point of ≥150 /µLcan be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations**

(conditional recommendation, low quality evidence).

Remarks

The TF placed a high value on reducing exacerbations and a greater feasibility of biomarker measurement and a lower value on cost

Q 3. Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma?

(exhaled NO, peripheral or sputum eosinophils, and periostin)

2RTCs, 1014 patients

Subgroup study 1. low (<300/µl) and high (≥300/µl) eosinophils.

Subgroup analysis 2. high and low subgroups as follows:

FeNO - low<19.5 ppb, high ≥19.5 ppb;

peripheral blood eosinophils - low<260/µl and high ≥260/µl

serum periostin levels – low <50 ng/ml and high ≥50 ng/ml.

Hanania, Am J Respir Crit Care Med. 2013, Busse, J Allergy Clin Immunol. 2013;

Q 3. Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (exhaled NO, peripheral or sputum eosinophils, and periostin)

2RTCs, 1014 patients

GINA A blood eosinophil level of ≥260/µl and FeNO ≥20 ppb are factors that may predict a good response to treatment

ERS/ATS Recommendation

Using a blood eosinophil cut-off of ≥ 260 /µl and a FeNO cut-off of ≥ 19.5 ppb may help to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment

(conditional recommendation, low quality evidence).

Hanania, Am J Respir Crit Care Med. 2013, Busse, J Allergy Clin Immunol. 2013;

Q 4.Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?

3RTCs adults and children, high dose ICS/LABA, 3rd controller

Benefits: Improve FEV1 and reduction loss of asthma control. In adults, treatment with tiotropium also improves asthma control and increases time to the first exacerbation

GINA recommend its use, NAEPP, do not include any reference

ERS/ATS conclusion A large benefit and trivial harm with the balance of effects clearly favoring tiotropium.

This recommendation also accounts for the feasibility of this inhaled therapy compared to the cost and burden of alternative add-on biologic therapies for severe asthma.

Kerstjens H, J Allergy Clin Immunol. 2011, Kerstjens H, N Engl J Med. 2012; Hamelman E, ERJ 2017

Q 5. Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

6RCTs

- Azithromycin reduced the number of combined moderate and severe exacerbations (1.07 vs. 1.86/year; RR=0.59; it did not, however, reduce th rate of severe exacerbations (25.3% vs. 34.6%; RR 0.77) in children or adults, during a follow up period ranging from 24 – 48 weeks
- No effect on QoL or AC
- No serious adverse events- diarrhea

GINA –Include macrolides

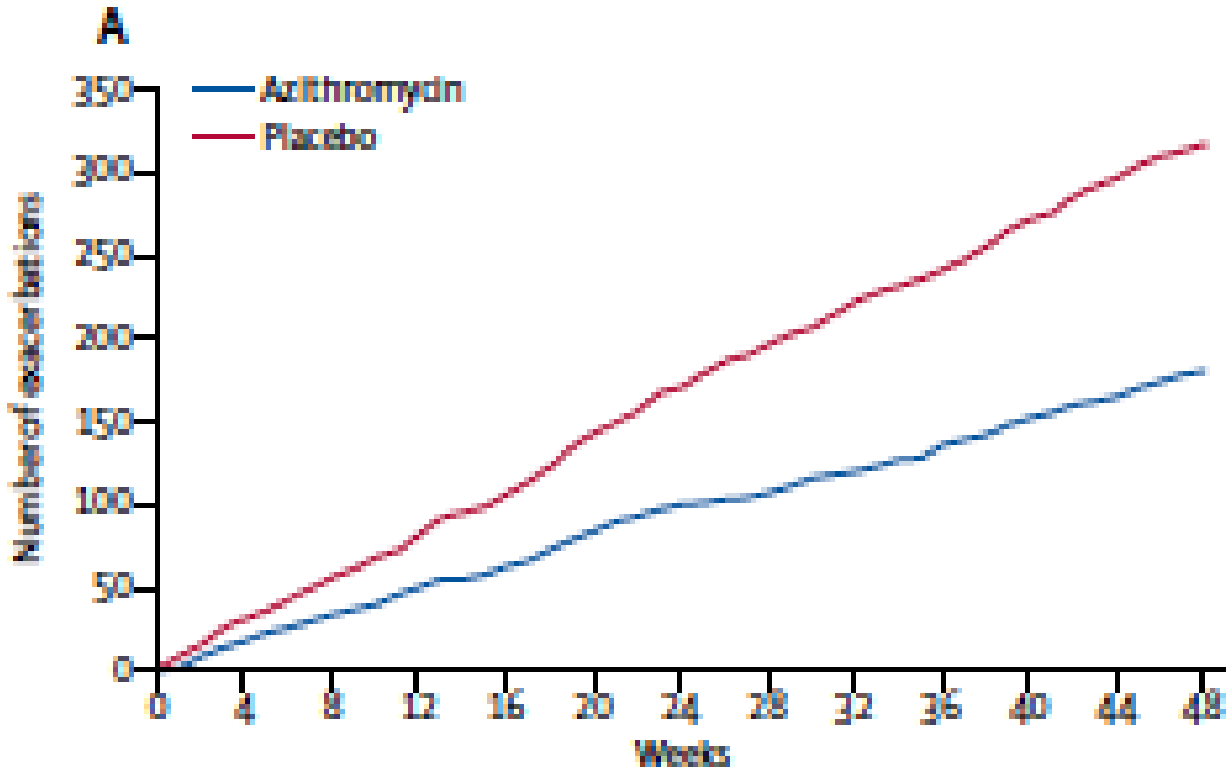
ERS/ATS recommendation use in adults, not adolescents nor children-

Conditional recommendation, low quality evidence

Gibson, Lancet 2017; 390: 659–68, Strunk, J Allergy Clin Immunol. 2008, Hahn, Am J Respir Crit Care Med. 2008;177(2):148-55 Brusselle, Thorax. 2013;

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

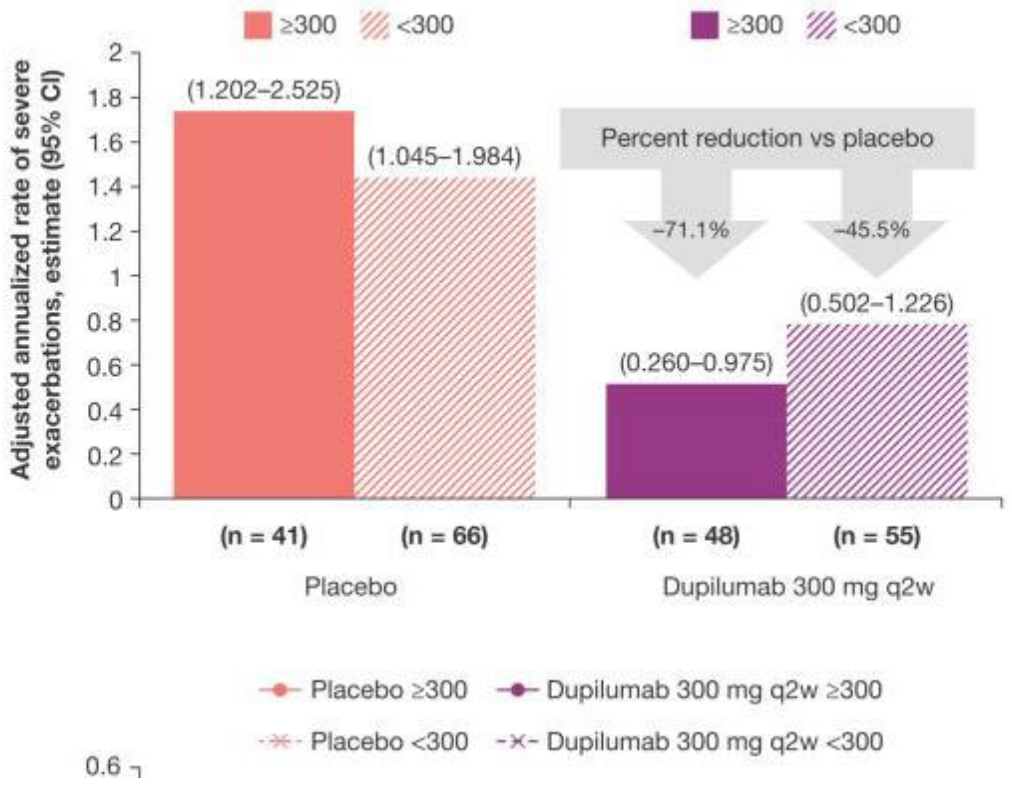


Q 6. Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

3RTCs 200-300mcg/2 weeks, adults and adolescents

- 46-70% reduction in the rate of any exacerbation
- Rate of exacerbations was significantly reduced in patients with more than 150 eos/mm^3
- >50% reduction/discontinuation OCS dose
- Improvements in FEV1, ACQ-5 and AQLQ were statistically significant but did not reach MCID.

ERS/ATS suggest dupilumab as add-on therapy for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (conditional recommendation



Wenzel, Lancet 2016, Castro, N Engl J Med 2018, Rabe, N Engl J Med 2018

Άλλα θέματα

- Πως μπορεί να αντιμετωπιστεί η μη-συμμόρφωση και να προληφθούν θάνατοι, ιδιαίτερα σε παιδιά, και αν μπορεί να δοθεί στοχευμένη θεραπεία – DOT
- Αν πρέπει η αποτελεσματικότητα μιας θεραπείας να ελέγχεται και σε παιδιά συγχρόνως με ενήλικες
- Ποιο σκεύασμα είναι αποτελεσματικότερο?
- Πρέπει να σταματήσει η στοχευμένη αγωγή μετά από κάποιο διάστημα? Ποιο?
- Το κόστος των φαρμάκων
- Θα πρέπει να μειώσουμε τα στεροειδή σε T2 low ασθενείς?

Long term oral steroids-some facts from short term studies

- BIOAIR: The highest sensitivity and specificity to predict more than 12% increase in FEV1 in SA after oral prednisolone was found for sputum eosinophils ≥3% and FeNO >45 ppb.
  - Kupczyk M Resp Med 2013
- SHARP: A total of 21% of adults with SA and 20% of children with SA achieved greater than or equal to 10% improvement after TA.
  - Phipatanakul W Am J Respir Crit Care Med. 2017
- In a paediatric severe asthma population, only 11% of SA children exhibited complete corticosteroid responsiveness
  - Bosley et al Eur Respir J 2009

Higher cumulative SCS doses are associated with increased mortality

TABLE 2 The Effects of Systemic CS Dose on Overall Mortality, ED visits, and Hospitalisations

	Mortality		Annual ED visits				Annual hospitalisations			
	All-cause		All-cause		Asthma-related		All-cause		Asthma-related	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All patients										
CS-independent asthma	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CS-dependent asthma										
Low dose	1.84	1.69-2.00	1.26	1.17-1.37	3.12	2.64-3.69	1.54	1.44-1.64	2.48	2.28-2.70
High dose	2.56	2.35-2.80	1.43	1.32-1.55	3.61	3.06-4.25	1.78	1.67-1.91	3.24	2.97-3.53
Overall	2.17	2.04-2.31	1.34	1.27-1.42	3.37	2.99-3.78	1.65	1.58-1.73	2.84	2.67-3.01

CS: corticosteroid; ED: emergency department; HR: hazard ratio; CI: confidence interval; Ref: reference.

Lee et al, ERJ, 2019

Oral steroids in asthma: a double-edged sword

Mina Gaga and Eleftherios Zervas

@ERSpublications
There is poor evidence on the benefits of long-term systemic steroid use in asthma while the risks of morbidity and mortality are high. Systemic steroids should be a last resort and should be withdrawn in non-responders. http://bit.ly/343fs3T

Table 2. Task Force recommendations for the management of severe asthma

Recommendation	Strength	Quality of evidence
We suggest anti-IL5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma	Conditional	Varied by treatment*
We suggest that a blood eosinophil cut-point of ≥ 150/μl can be used to guide anti-IL5 initiation in adult patients with severe asthma and prior exacerbations.	Conditional	Low
We suggest using a blood eosinophil cut-off of ≥ 260 /μl to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment	Conditional	Low
We suggest using a FeNO cut-off of ≥ 19.5 ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment	Conditional	Low
For children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies, we recommend the addition of tiotropium	Strong	Moderate
We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthmatics on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled. We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma	Conditional	Low
We suggest dupilumab for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels	Conditional	Low


Our goal, control of severe asthma