

MTT Továbbképző Fórum, 2016.

Az asthma aktualitásai



Dr. Horváth Ildikó

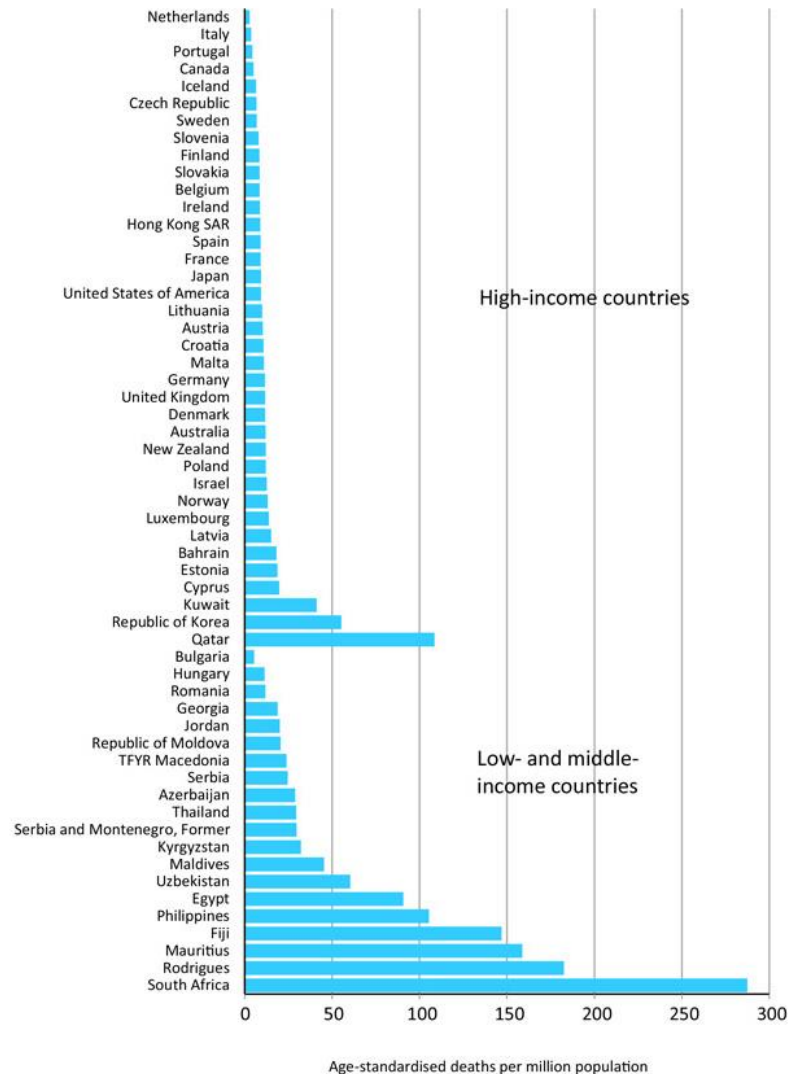
Országos Korányi Tbc és Pulmonológiai Intézet

Asthma

- népegészségügyi jelentősége
- Ellátórrendszer működésével kapcsolatos terhe
- Gyógyszerelési lehetőségek, problémák
- Újdonságok a fenotipizálásban, gyógyszerelésben
- Kutatási újdonságok

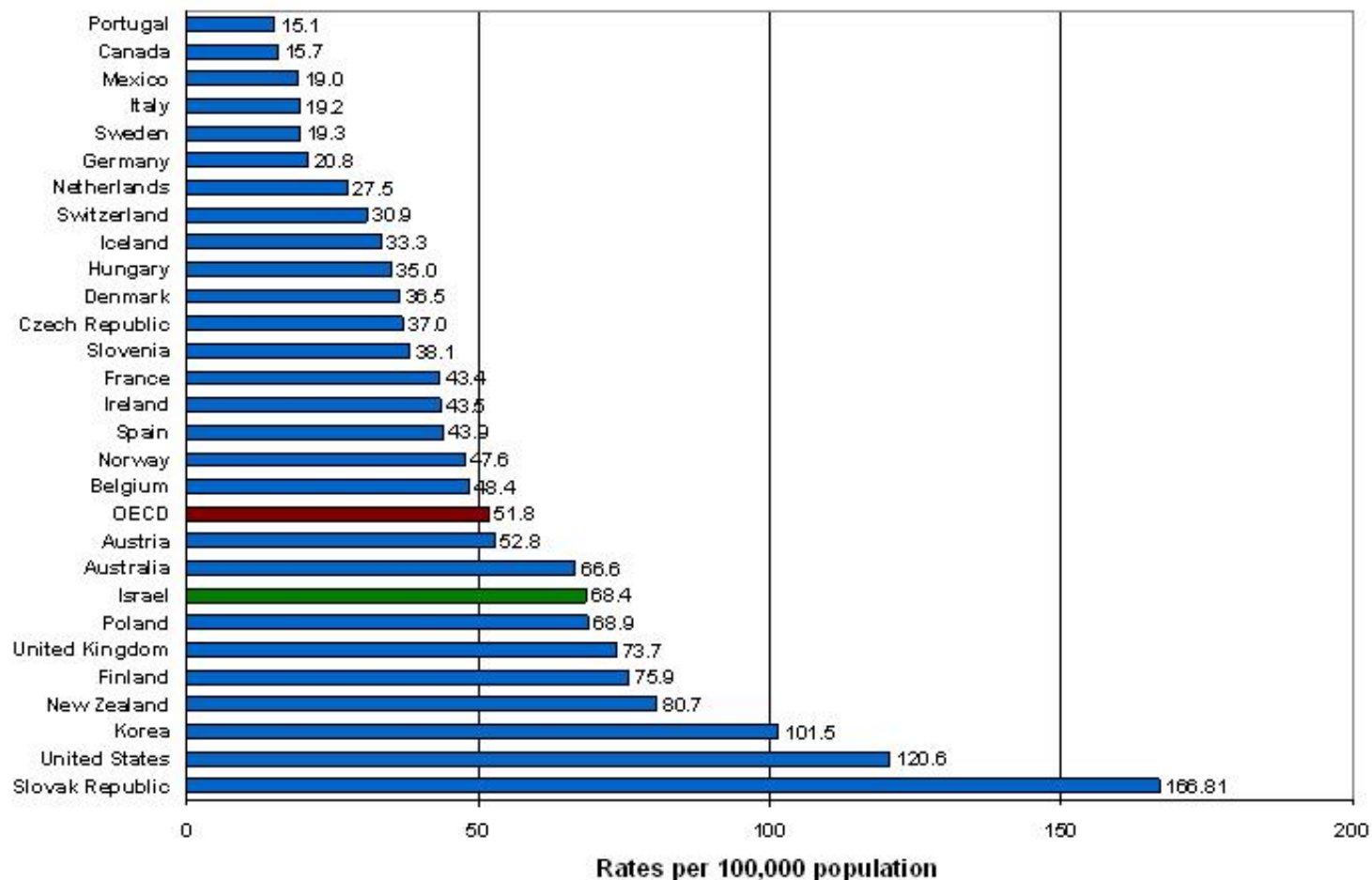
Az asztma mortalitása jelentős és összefügg az országok GDP-jével

Figure 1: Age-standardised mortality rates for asthma, all ages 2001-2010



Source: WHO Detailed Mortality Database, February 2014 update

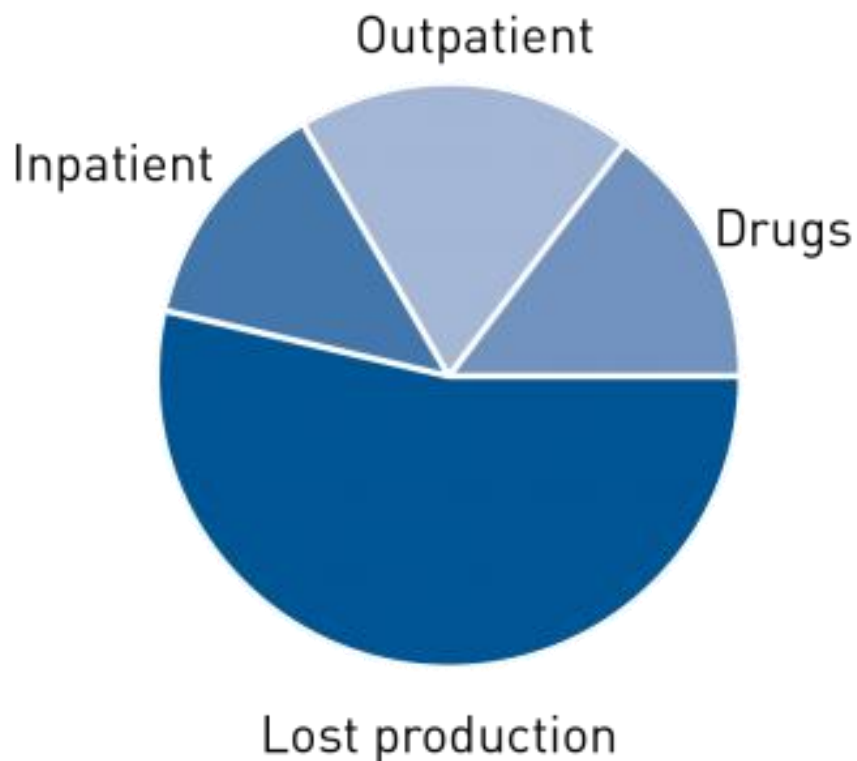
A kórházi ápolások asztma miatt jelentős mértékűek



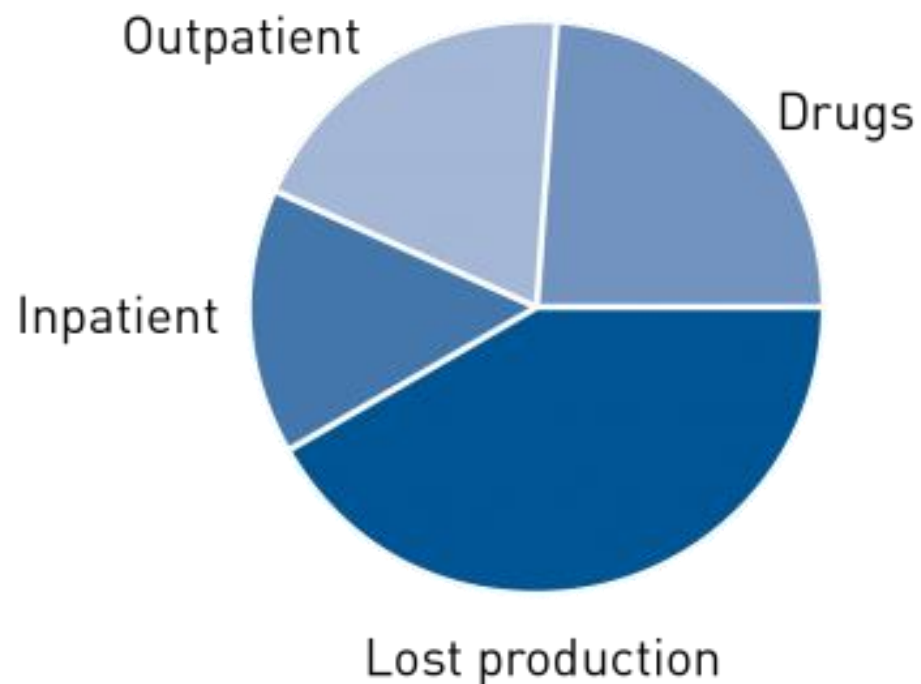
OECD, 2011 Asthma miatti kórházi ápolások 100,000 lakosra

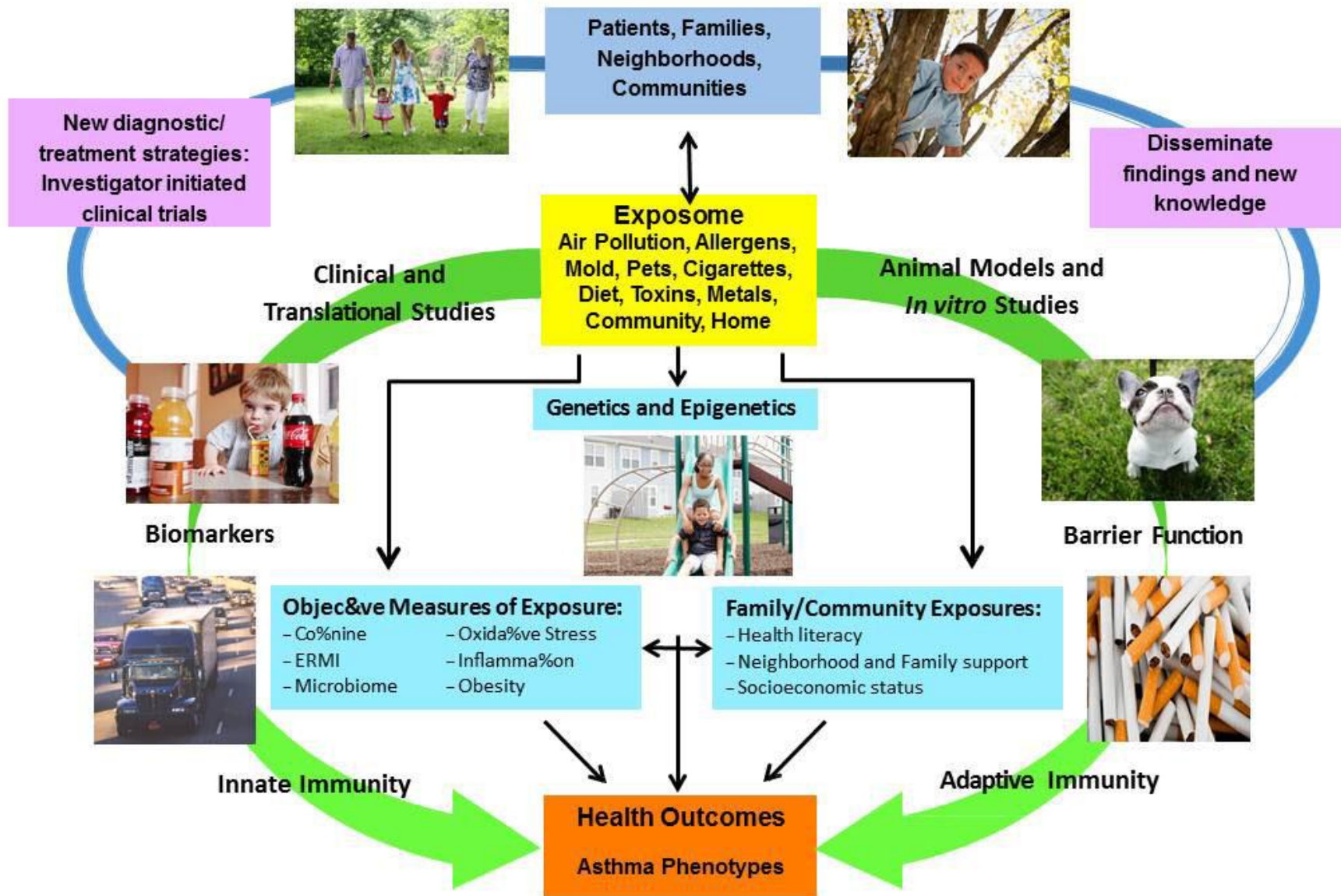
Az asztma miatti társadalmi teher részei

COPD



Asthma

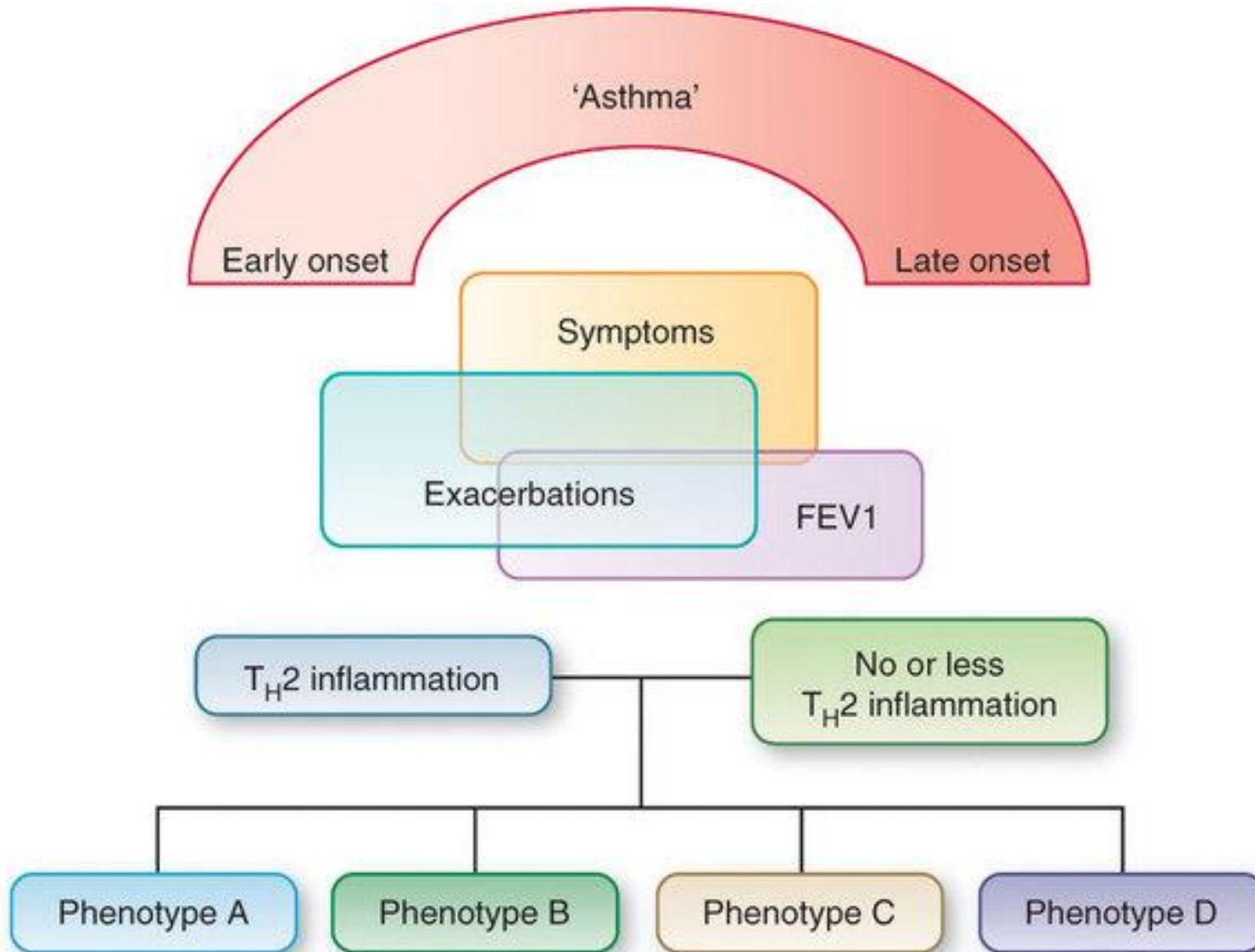




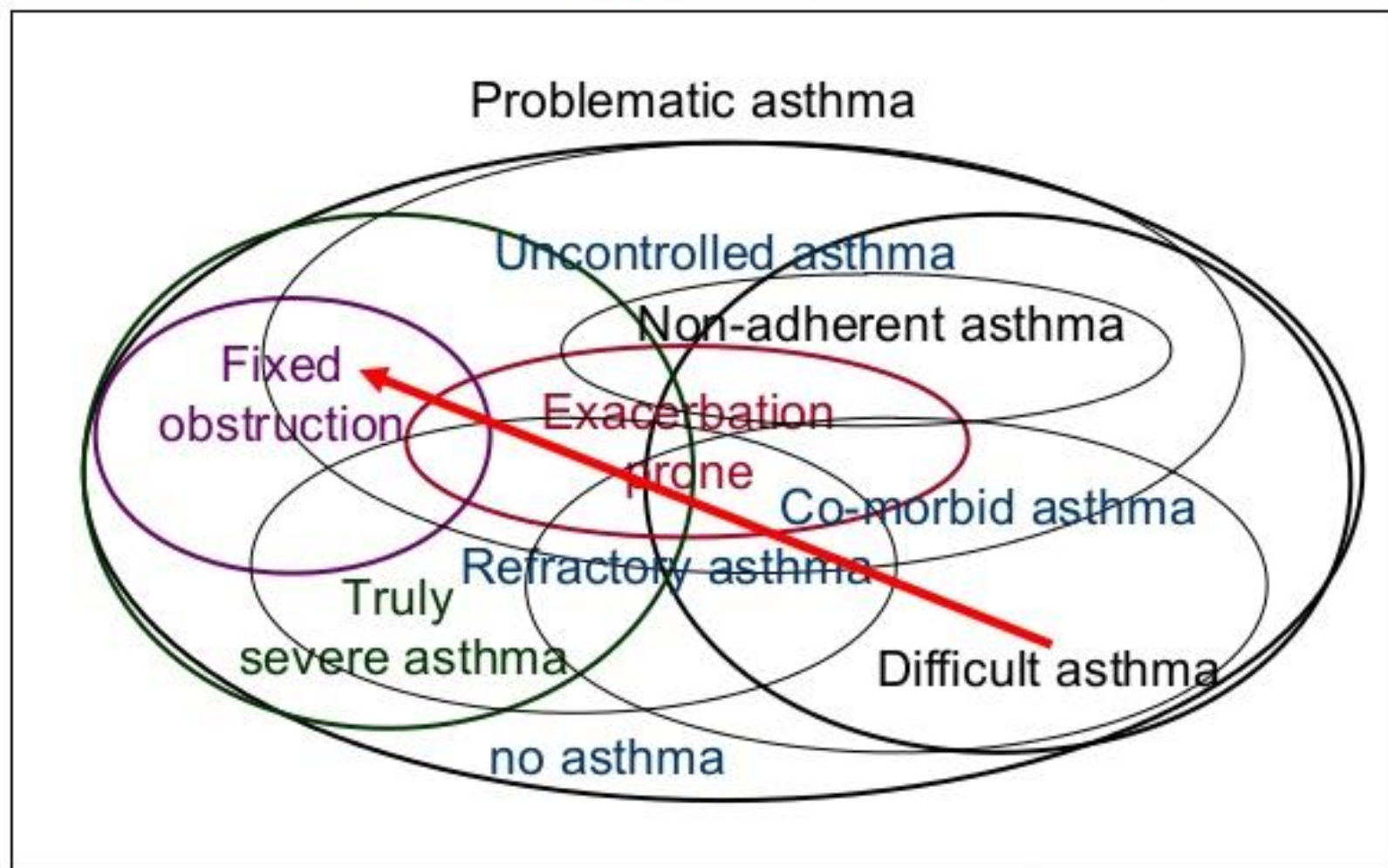
Paradigmaváltás a házikedvencekkel kapcsolatosan



Az asztma fenotipizálás evolúciója



Clinical phenotypes of severe asthma



NAEPP 1997, ERS 1999, GINA 2002, ATS & SARP 2002, ENFUMOSA 2003, BIOAIR 2005
TENOR 2004, Paris 2007, ERS 2008, PSACI 2008, WHO 2009, **U-BIOPRED 2011**

Az asztma fenotipizálása komplex

Genes

Gene
expression

Airway
histology

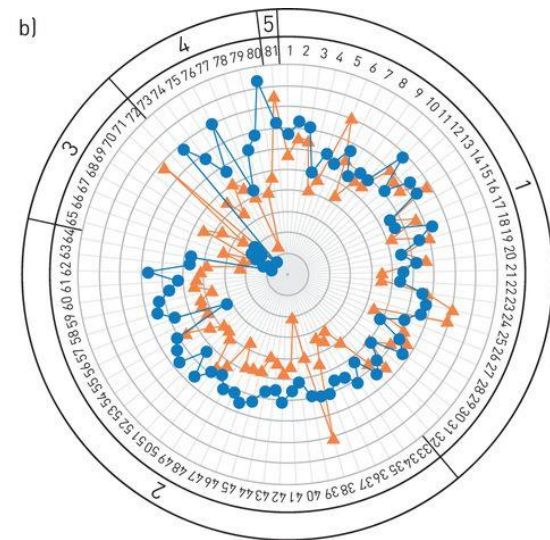
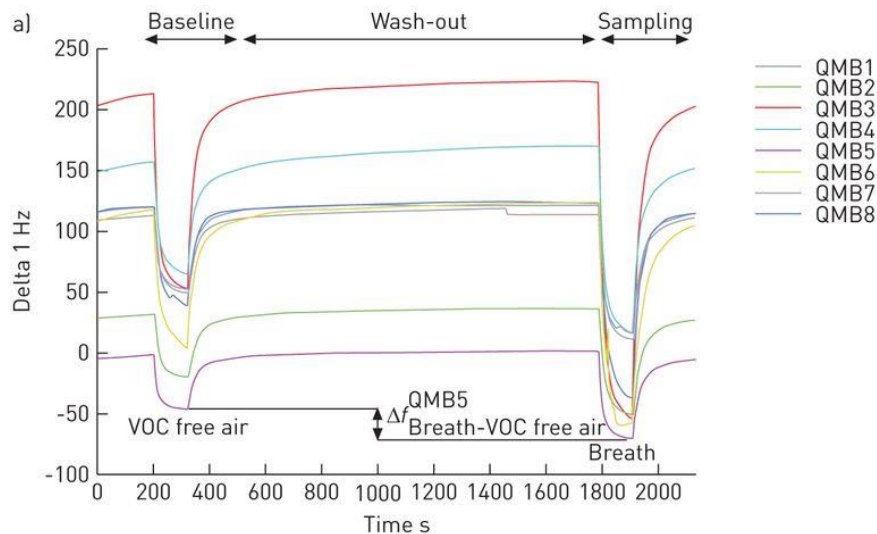
Lung
function

The
patient

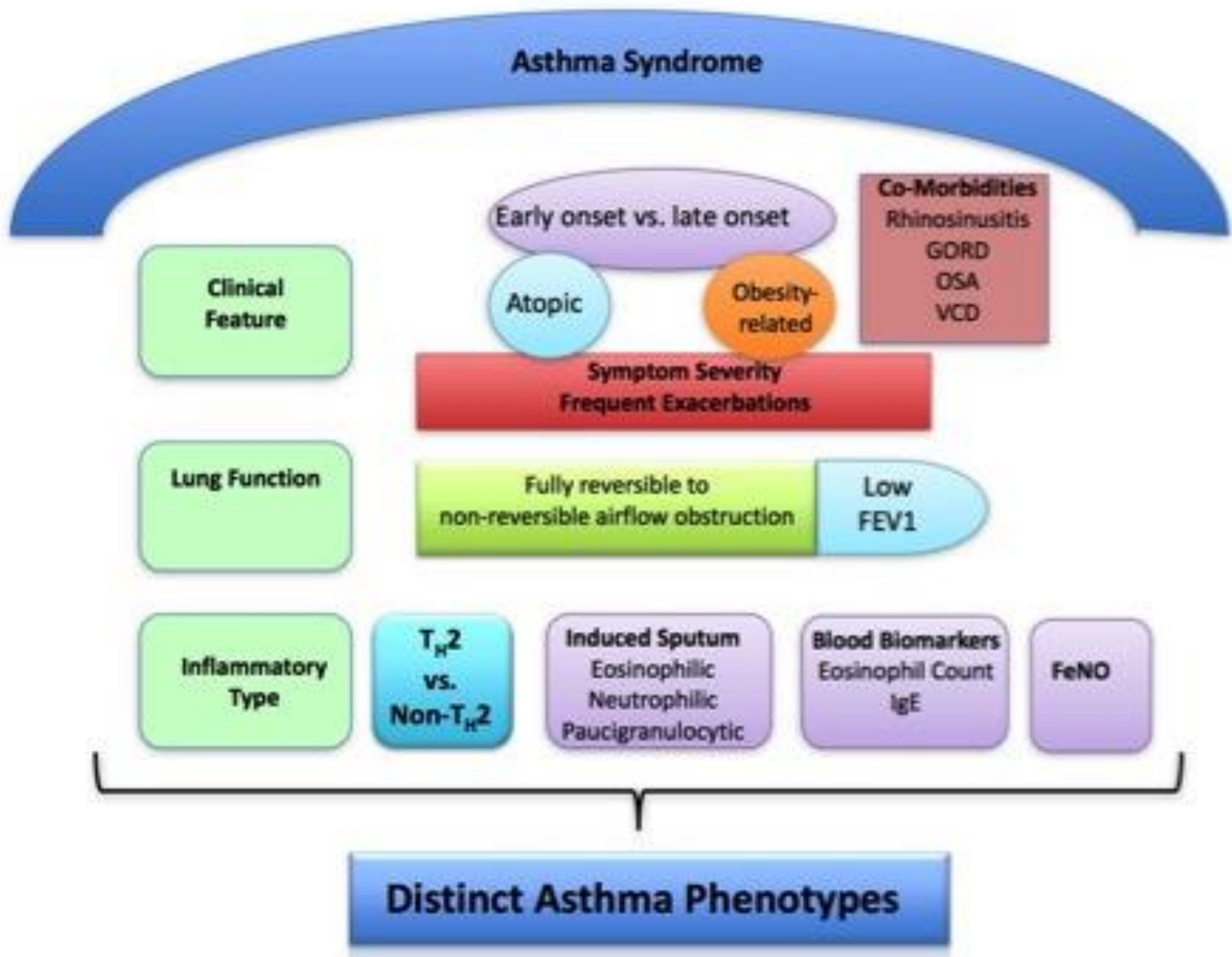
respiratory disease phenotyping

Genetics
Epigenetics
Transcriptome
Proteome
Metabolome
Microbiome
Immunity
Inflammation
Remodeling
BHR
Obstruction
Symptoms
Co-morbidity
Quality of life

Ezért nagy az elvárás a komplex információkat adó, „omika” megközelítésekkel szemben

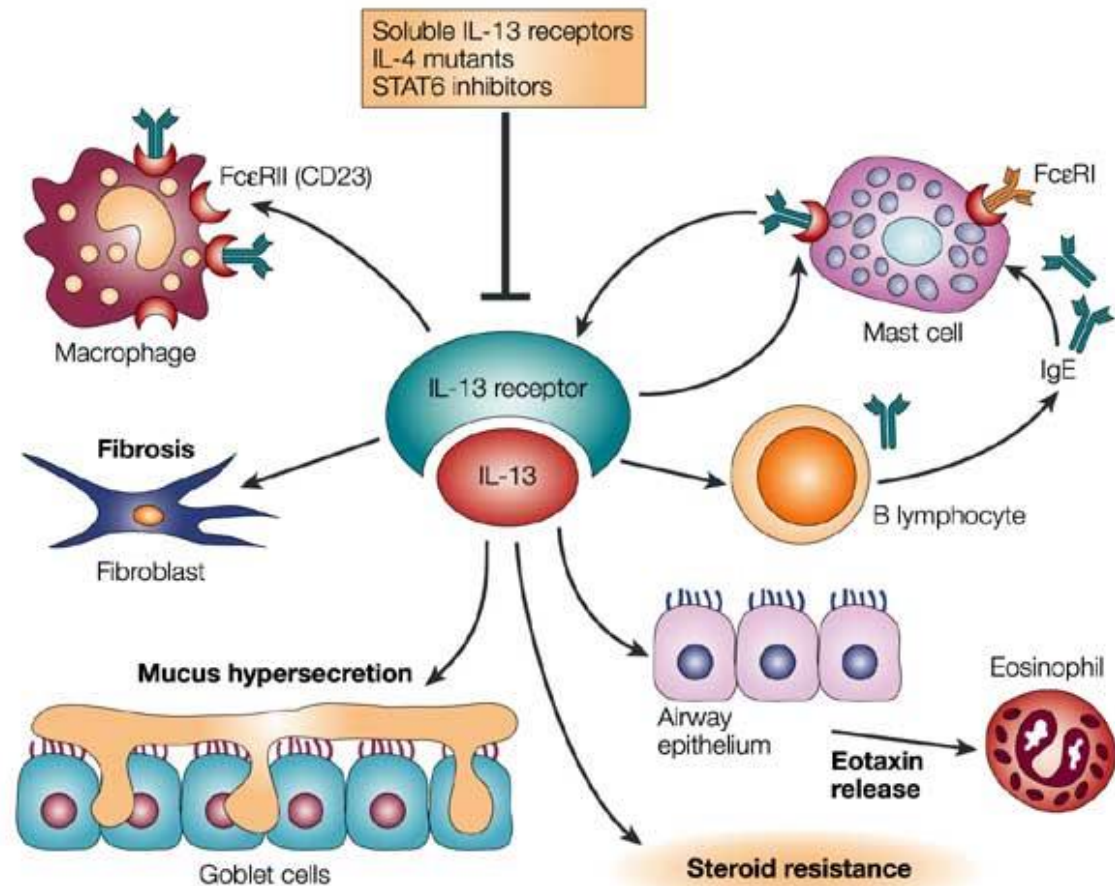


Craig E. Wheelock és mtsai **Application of 'omics technologies to biomarker discovery in inflammatory lung diseases** Eur Respir J 2013

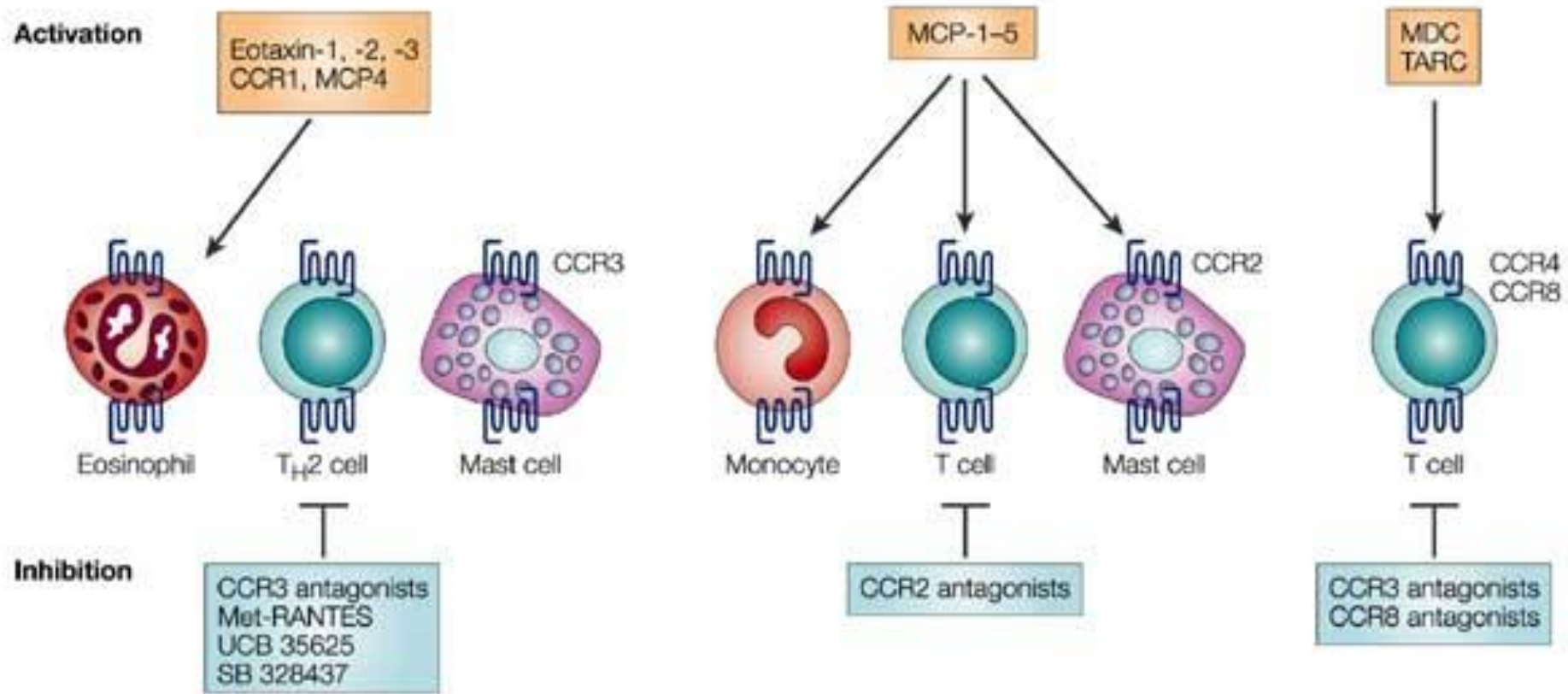


A fenotípus alapú kezelési megközelítésben az eozinofilsejtes gyulladás célzott kezelése meghatározó

- Steroids
- Anti -IL-5
- Anti-IL13



Egyéb gyulladási sejtek mint kezelési célpontok



Mediátor elleni gyógyszerek és kostimulánsok allergén kiváltott immunválaszt bontják

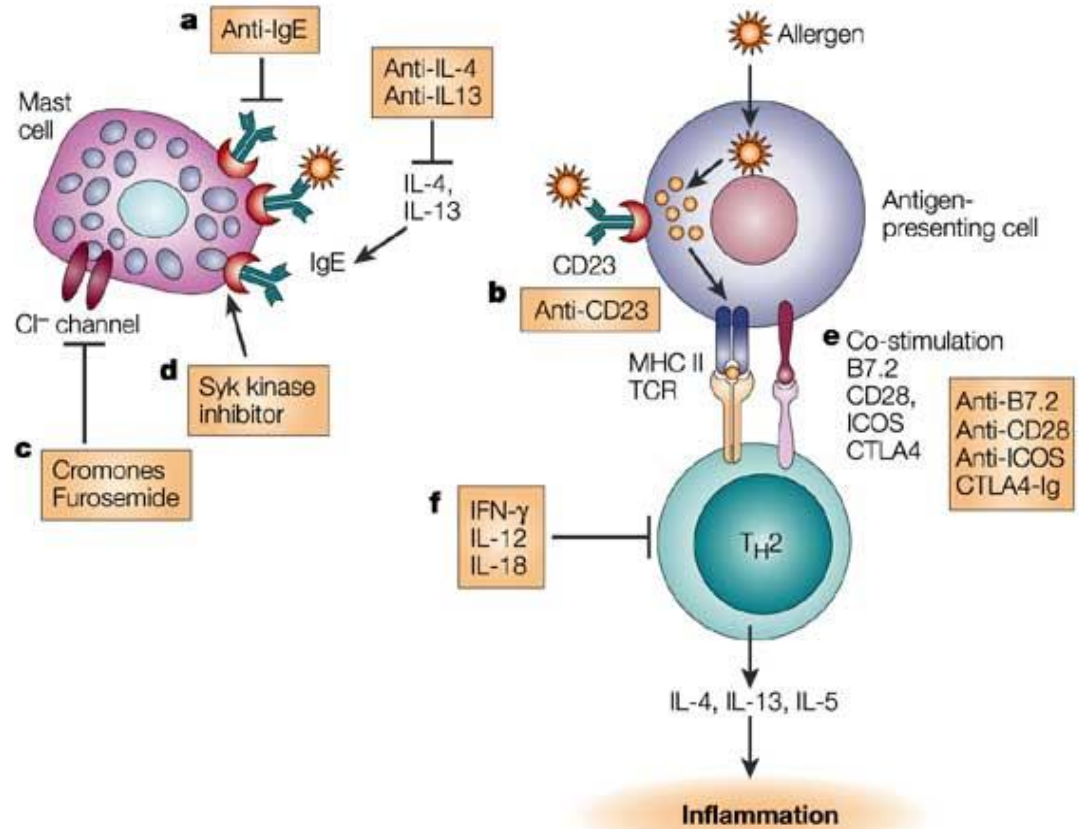
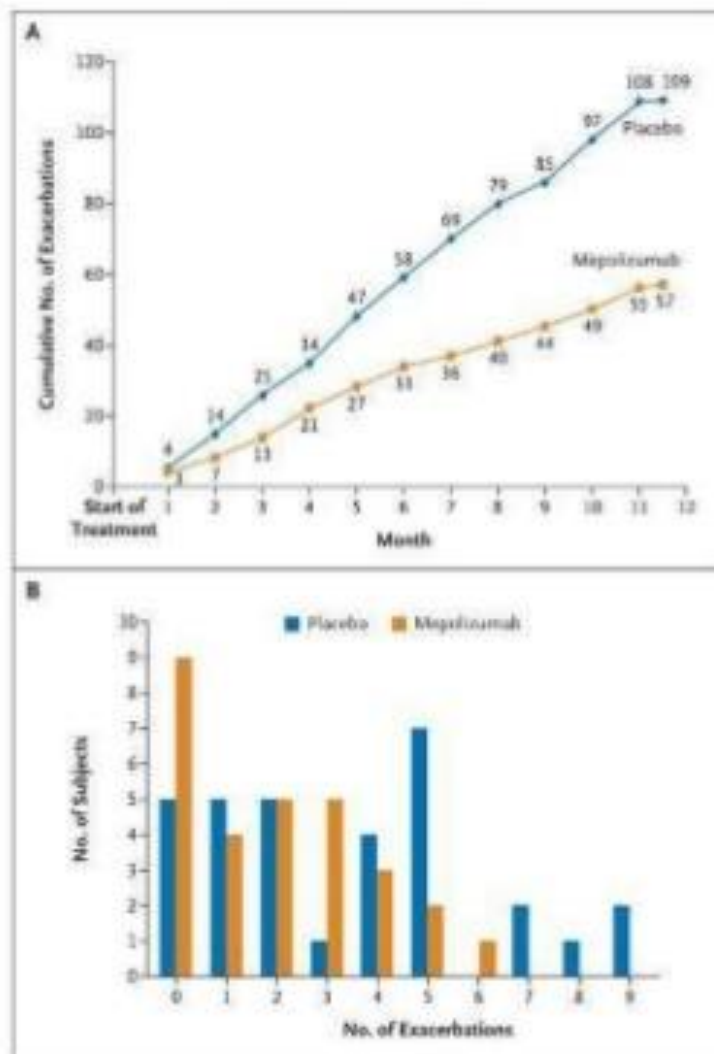


Table 2 | **New therapeutic strategies for asthma**

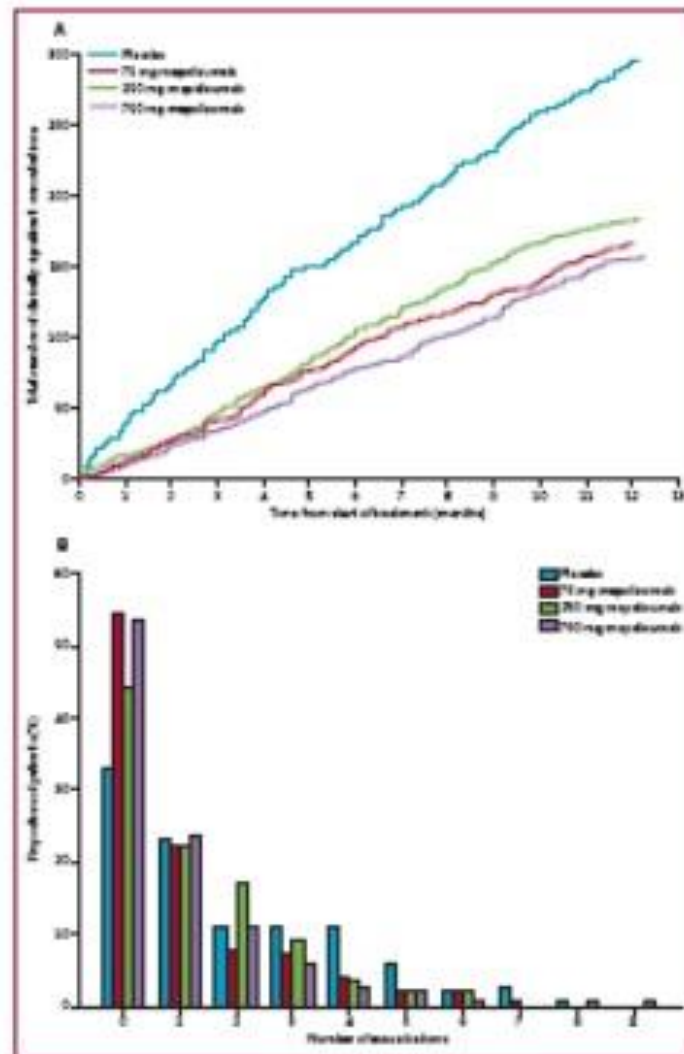
Class	Example
New glucocorticoids	Ciclesonide and dissociated steroids
Immunomodulators	Inhaled cyclosporin, tacrolimus, rapamycin and mycophenolate mofetil (CellCept; Roche)
Phosphodiesterase-4 inhibitors	Cilomilast and roflumilast
p38 MAP kinase inhibitors	CSAIDs, for example, SB203580, SB239063 and RWJ67657
Nuclear factor- κ B pathway inhibition	Inhibitor of nuclear factor- κ B kinase-2 (IKK-2) inhibitors
Adhesion molecule blockers	Inhibitors of very late antigen-4 and selectin
Cytokine inhibitors	Anti-interleukin (IL)-4, anti-IL-5, anti-IL-13, anti-IL-9 and anti-tumour-necrosis factor antibodies
Anti-inflammatory cytokines	Interferon- γ , IL-10, IL-12 and IL-18
Chemokine receptor (CCR) antagonists	CCR3, CCR2 and CCR4 antagonists
Anti-allergic drugs	Anti-immunoglobulin E, anti-CD23 antibodies and co-stimulatory molecule inhibitors
Peptides for immunotherapy	House dust-mite allergen
Vaccines	BCG inoculation

MAP, mitogen-activated protein.

Mepolizumab (anti-IL-5). Effect on severe exacerbations



Haldar et al. NEJM 2009;360:973-84



Pavord et al. Lancet 2012;380:651-9.

Ongoing

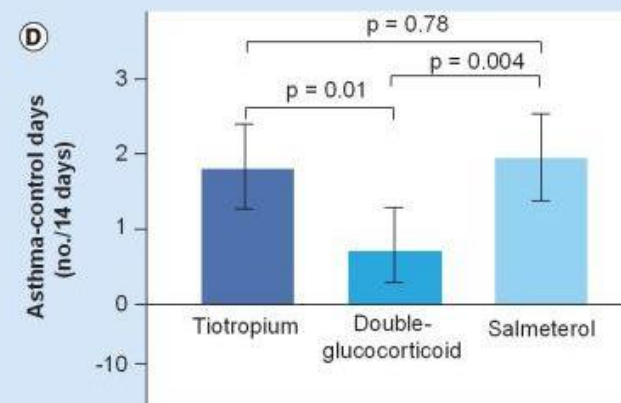
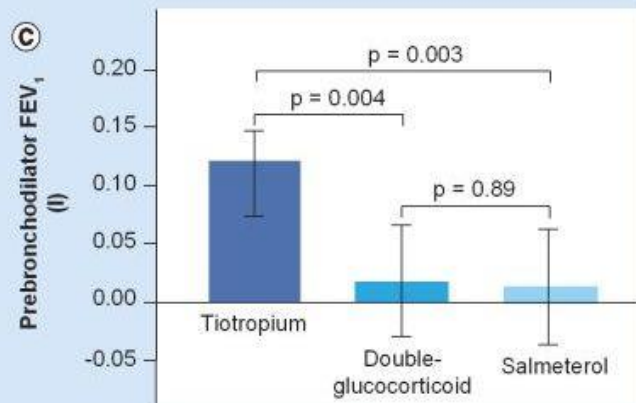
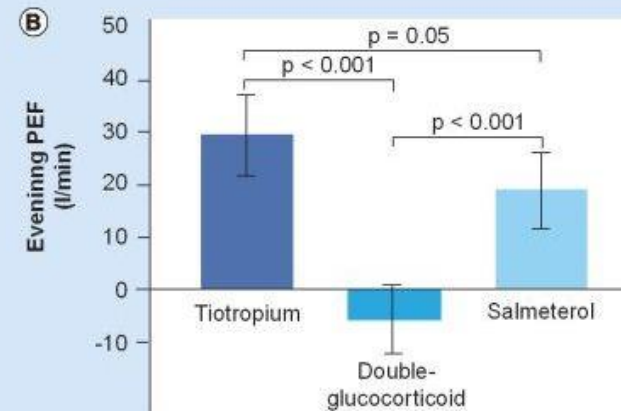
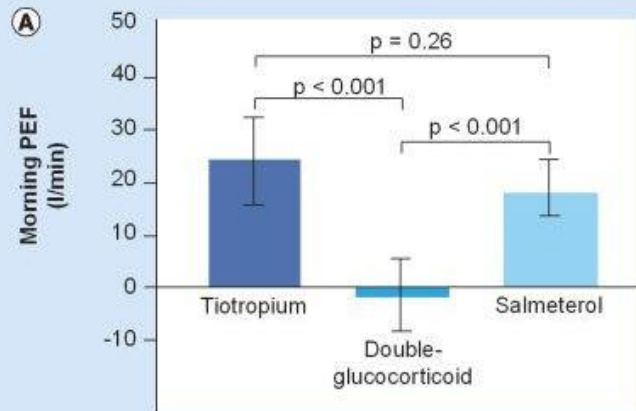
Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Status
Anti-IL-13 Ab (Lebrikizumab)	Roche/Genentech	-	+	phase III ongoing
Anti-IL-13Ab (Tralokinumab)	AstraZeneca/Medimmune	-	+	phase IIa finished
Anti-IL-13/IL-4 Ab (QBX258)	Novartis	-	+	phase II ongoing
Anti-IL-4R α Ab (Dupilumab)	Sanofi/Regeneron	+	+	phase II finished

Withdrawn

Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Final Evaluation
IL-4 mutein (Pitrakinra)	Bayer/AEROVANCE	+	+	phase IIa
Anti-IL-4R α Ab (AMG 317)	Amgen	+	+	phase II
Anti-IL-13 Ab (IMA-638)	Pfizer	-	+	phase II

LAMA az asztma terápiás lépcsőjén

Medscape



Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

Move up to improve control as needed

Move down to find and maintain lowest controlling step

Inhaled short-acting β_2 agonist as required

Add inhaled steroid

200–800 $\mu\text{g}/\text{day}^*$

400 $\mu\text{g}/\text{day}$ is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
 - Good response to LABA – continue LABA
 - Benefit from LABA but control still inadequate – continue LABA and increase inhaled steroid dose to 800 $\mu\text{g}/\text{day}^*$ (if not already on this dose)
 - No response to LABA
 - Stop LABA and increase inhaled steroid to 800 $\mu\text{g}/\text{day}^*$. If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

Consider trials of:

- Increasing inhaled steroid up to 2,000 $\mu\text{g}/\text{day}^*$
- Addition of a fourth drug eg, leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

Use daily steroid tablet in lowest dose providing adequate control

Maintain high-dose inhaled steroid at 2,000 $\mu\text{g}/\text{day}^*$

Consider other treatments to minimize the use of steroid tablets

Refer patient for specialist care

Step 1

Mild intermittent asthma

Step 2

Regular preventer therapy

Step 3

Initial add-on therapy

Step 4

Persistent poor control

Step 5

Continuous or frequent use of oral steroids

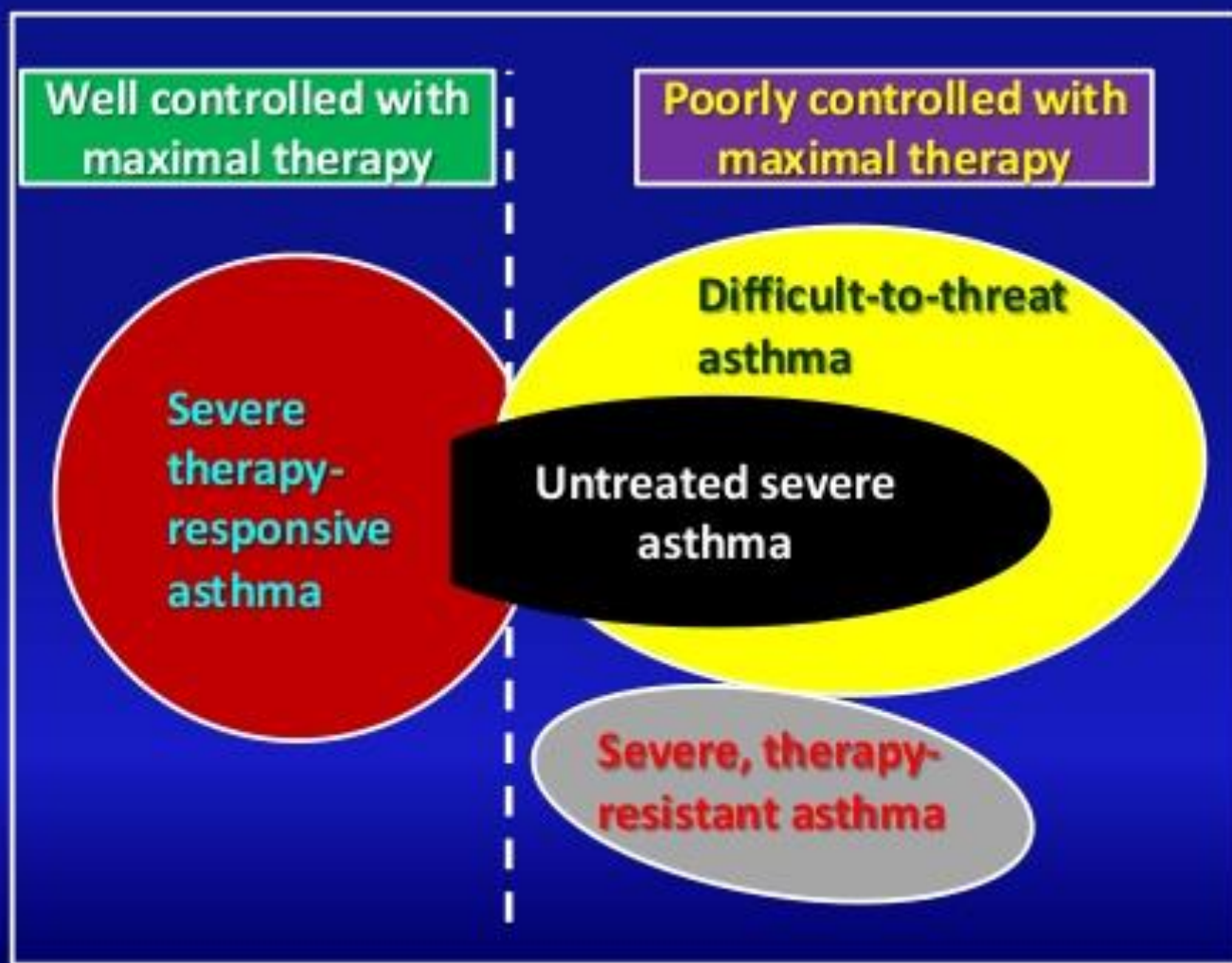
*BDP or equivalent

Symptoms

vs

Treatment

Severe Asthma Phenotypes in Childhood



The WHO definition of severe asthma

Összefoglalva

- Paradigmaváltás a megelőzés tekintetében
- Terhes asztmásokkal kapcsolatos új ismeretek
- Súlyos asztma kezelési lehetőségeinek bővülése
- Holisztikus megközelítés

Köszönöm

a súlyos asztma kutatás nemzetközi közösségének és munkatársaimnak:

Bikov András, Lázár Zsófia, Tárnoki Ádám és Dávid, Pákó Judit, Peter Barnes és Peter Sterk valamint az Országos Korányi Tbc és Pulmonológiai Intézetnek és a Semmelweis Egyetemenek

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