Asthma Immunopathogenesis and Management

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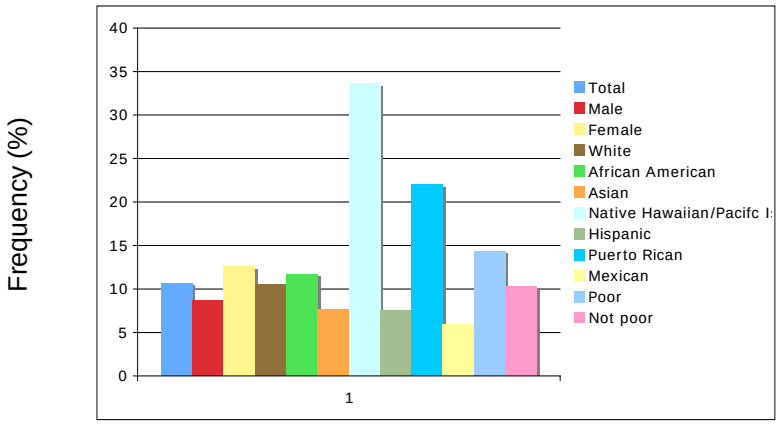
Ever asthma diagnosis, US, 2005, adults*

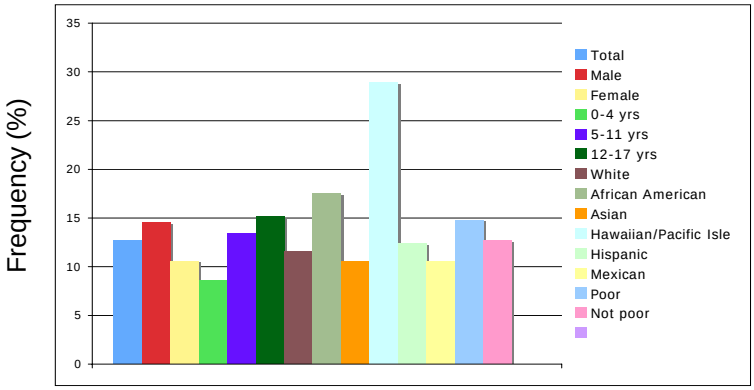


*23 million adults lifetime asthma diagnosis

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Ever asthma diagnosis, US, 2005, children*

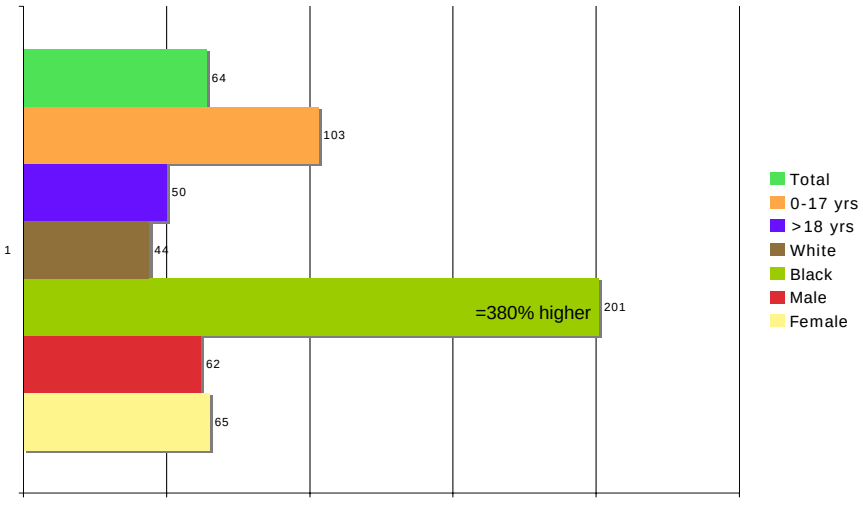


*9 million children lifetime asthma diagnosis

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Asthma ER visits, U.S., 2004

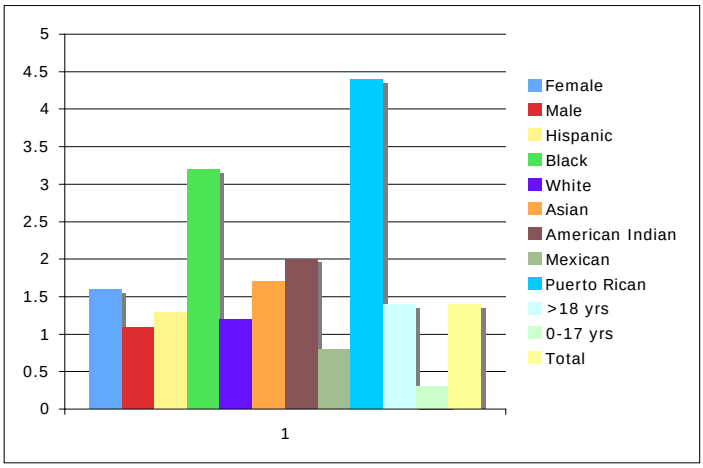


Per 10,000 Population

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Asthma deaths, 2003*



Per 100,000 Population

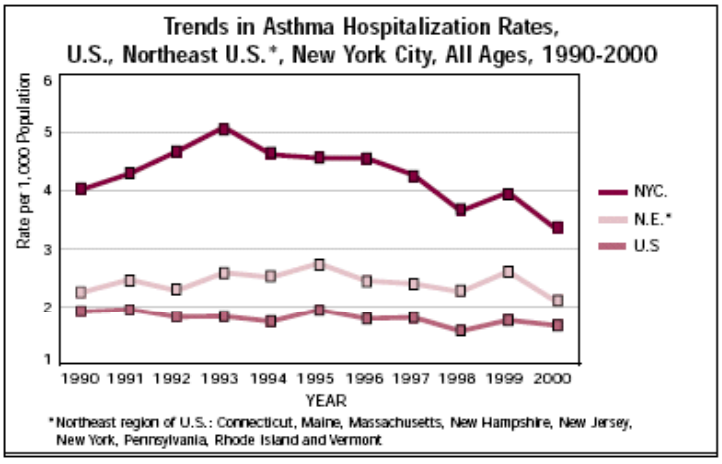
*3780 asthma deaths 2004, or 1.3/100,000, or > 10 people/day

Age-adjusted based on 2000 census

Source: CDC/NCHS/National Health Interview Survey

Between 1990-2000, asthma hospitalization decreased by 17% in NYC*, by 13% in US

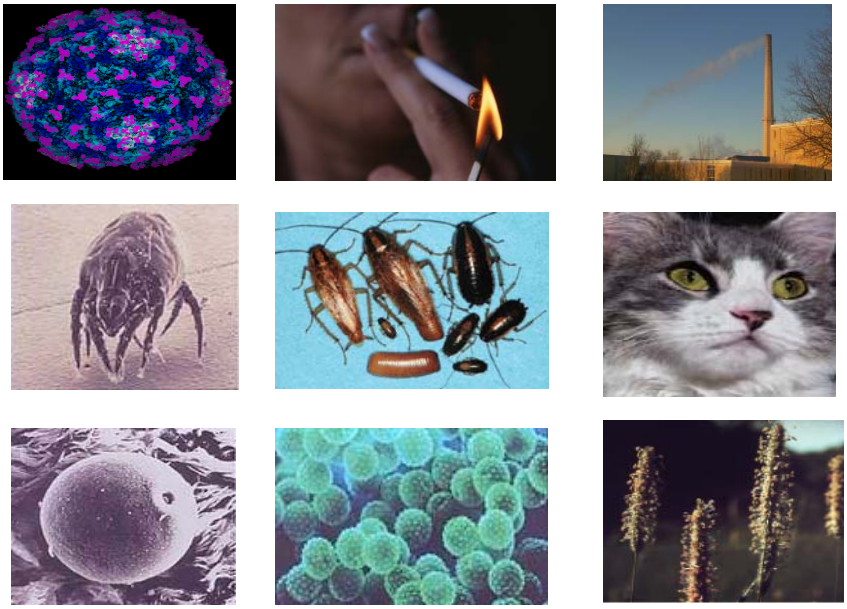
FIGURE 3



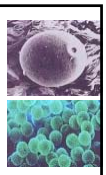
*35% decrease in pediatric admissions btw 1997-2000

NYC Childhood Asthma Initiative,
NYC Dpmt of Health and Mental Hygiene, 2003

Asthma triggers

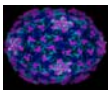


Allergens

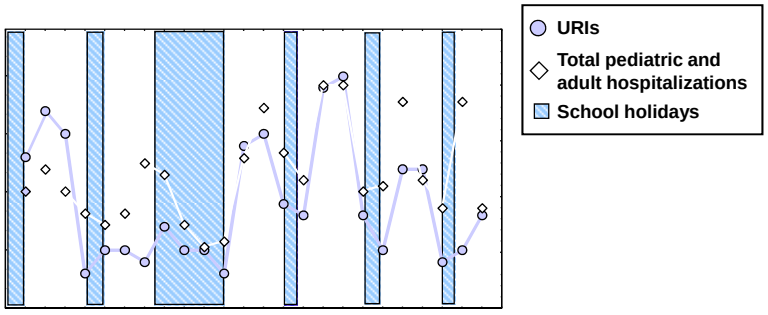


- Small proteins (2-60 microns)
- Highly soluble
- Inhaled in dessicated particles (pollen grains, mite feces)
  - easily elute from the particle
  - diffuse into respiratory mucosa
- Enzymatically active (eg. proteases)
- Low dose favors activation of IL-4 producing CD4 T cells
- Seasonal patterns of pollination:
  - Spring-trees
  - Summer-grass
  - Fall-ragweed

Viruses

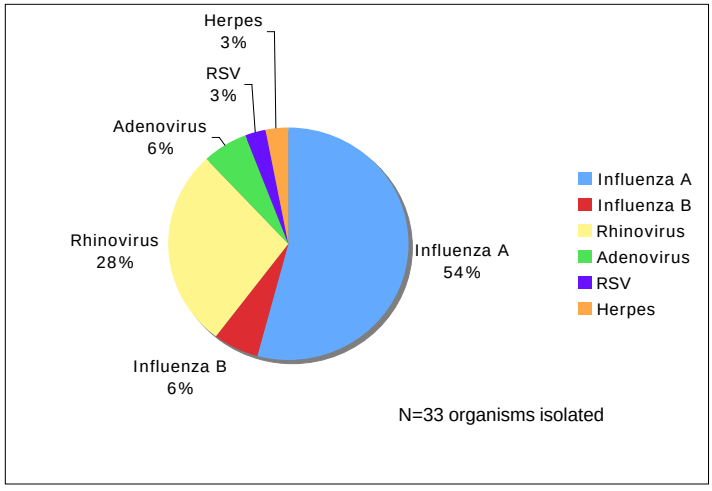


Hospital admissions correlate with virus isolation peaks and school terms



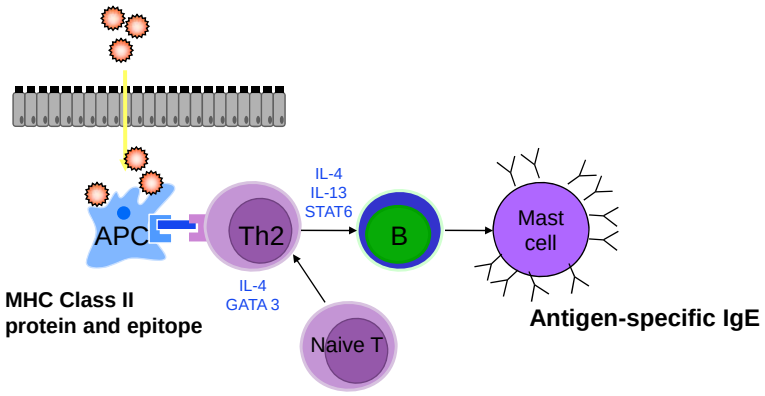
Johnston et al. *AJRCCM.* 154:654, 1996

Viruses detected in adults hospitalized with asthma



Teichtahl H et al. *Chest.*112:591, 1997

Immunological mechanisms: Allergic sensitization



Immunological mechanisms: Allergic sensitization

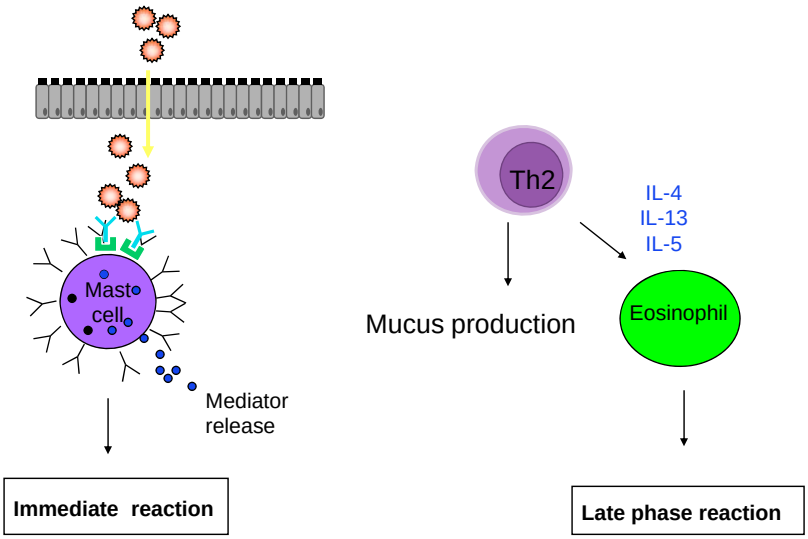
There are two main components of the immune response leading to IgE production. The first consists of the signals that favor the differentiation of naive TH0 cells to a TH2 phenotype. The second comprises the action of cytokines and co-stimulatory signals from TH2 cells that stimulate B cells to switch to producing IgE antibodies. Class switching of B cells to IgE production is induced by two separate signals, both of which can be provided by TH2 cells. The first of these signals is provided by the cytokines IL-4 or IL-13, interacting with receptors on the B-cell surface. These transduce their signal by activation of the Janus family tyrosine kinases JAK1 and JAK3 which ultimately lead to phosphorylation of the transcriptional regulator STAT6.

The second signal for IgE class switching is a co-stimulatory interaction between CD40 ligand on the T-cell surface with CD40 on the B-cell surface. This interaction is essential for all antibody class switching

The IgE response, once initiated, can be further amplified by basophils, mast cells, and eosinophils, which can also drive IgE production . All three cell types express FcRI, although eosinophils only express it when activated.

Then IgE secreted by plasma cells binds to a high affinity Fc receptor FCeR1 on mast cells.

Immunological mechanisms: Reexposure



Immunological mechanisms: Reexposure

When surface bound IgE is cross-linked by antigen, these cells express CD40L and secrete IL-4, which in turn binds to IL-4R on the activated B cell, stimulating isotype switching by the B cells and the production of more IgE.

IgE-dependent release of inflammatory mediators

- Immediate: Granule contents
  - Histamine
  - TNF-α
  - Proteases
  - Heparin
- Over minutes: Lipid mediators
  - Prostaglandins
  - Leukotrienes
- Over hours: Cytokine production
  - IL-4
  - IL-13

Mediating risk

- Genetic predisposition
  - FCεR1, HLA, IL-4, CD14, B2AR
- Environment
  - allergic sensitization, fewer sibs, excessive hygiene, prenatal antibiotic exposure, vaccination, farm
- Prenatal exposures
  - parent of origin effect for IgE, asthma; maternal atopy, maternal parity, ETS
- Prenatal diet
  - increased methyl donors; reduced zinc, vitamin E, vitamin D, zinc; Mediterranean diet

Chung, Miller, et.al. *Arch. Dis. in Child. Fetal Neonatal Ed*. 92: 68-73, 2007.

Hygiene hypothesis

Increased cleanliness in 20th century Western Society has led to greater number of allergic (Th2 skewed) individuals.

Protective exposures offered as evidence of the 'Hygiene hypothesis'

- Older siblings — Strachan, BMJ 1989
- Lack of vaccination — Shirakawa, Science 1997
- Early life respiratory infections — von Mutius, E Resp J 1999
- Parasitic infection — Yazdanbaksh, Lancet 2000, Science 2004
- Day care attendance — Ball, NEJM 2000
- Gut microflora — Kalliomaki, Lancet 2001
- Animal exposure — Platts-Mills, Lancet 2001
- Consumption of unpasteurized milk — Riedler, Lancet 2001
- Exposure to a barn in the 1st year of life — Riedler, Lancet 2001
- Bacterial endotoxin — Braun Fahrlander, NEJM 2002

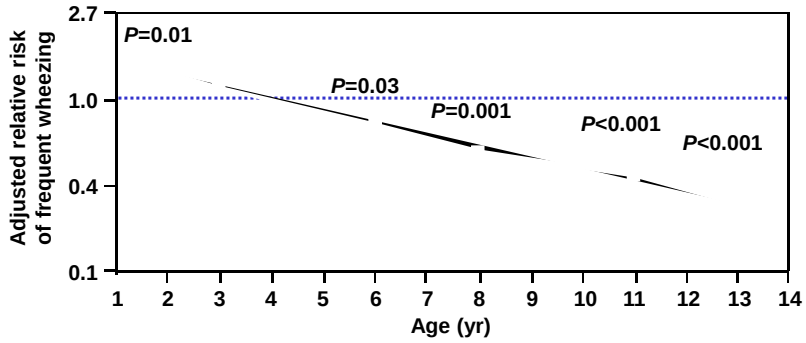
Protective effect of respiratory infections in infancy

- ≥2 episodes of "common cold" before age 1 yr decrease risk of asthma by age 7 by ~50%
- Other viral infections also protective
  - herpes
  - varicella
  - measles
- LRI with wheeze in the first 3 years of life increases risk of asthma

Illi S et al. *BMJ*. 322:390, 2001

Protective effect of early day care and older siblings

Children who had ≥2 older siblings or attended day care during first 6 mo of life had increased risk of wheeze early in life but decreased risk later.



Special groups

Occupational asthma

- "Variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors or fumes"
- Causes worsening in up to 15% of asthmatics
- Causes 2-5% of de novo asthma cases in U.S.
- Failure to diagnose and manage promptly can lead to long-term, irreversible sequelae

Two types

1. Production of specific IgE directed a'g:

– HMW natural allergens-flour, latex
– Allergens covalently bound to LMW chemicals
– Eg: diisocyanates, red cedar wood

2. Irritant-induced (RADS):

– Injury to respiratory epithelium following toxic exposure exposes vagal receptors or C fibers, resulting in increased AR.
– Eg: sulfur dioxide

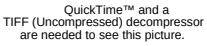
Features

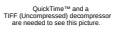
- Latent period of immunologic sensitization
- Low levels cause symptoms
- Sensitivity increases with continued exposure
- If IgE mediated, correlation with skin tests, in vivo tests
- Usually only in minority of workers

Exercise-induced asthma

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Olympic gold medalists with asthma





And the entire 1988 U.S. water-polo team

DT, JJK, AS, TD

Exercise-induced asthma (EIA): Defn

- Self-limited syndrome of cough and/or wheezing, chest pain or chest tightness developing within 30 minutes of 2-8 minutes of continuous exercise.
- Often reflection of the underlying asthma condition

Frequency

	Frequency (%)
General population	3-13
Asthmatics	90
Army recruits	7
Competitive athletes	10
Elite swimmers	21
Elite winter sports athletes	50

Storms, WW. *Medical Science and Sports Exercise* S33-8.1999
Milgrom, H., et al. *Pediatrics* 104:e38.1999
Sonna, LA, et al. *Chest* 1676-84.2001
Weiler, J.M. *JACI* 106:267-271.2000

Pathogenesis

- Thermal hypothesis
  - cold air → ↑ blood flow to bronchial circulation → airway obstruction
- Osmotic hypothesis
  - cold dry air → in loss of fluid from the airway → hyperosmotic state → mast cell degranulation
    → releases bronchoconstrictive mediators
    → increases bronchovascular permeability

McFadden, ER. *Allergy Principals and Practice* (66):953-962. 1998
Anderson, SD. *JACI* 105:453-9.2000

Sports specific factors

- Skaters: Ice resurfacing machines-emit PM's
- Swimmers: inhaled chlorine (that produces nitrogen trichloride) can cause airway inflammation and lung epithelial hyperpermeability

Rundell. *Inhal Toxicol* 15(3): 237-50, 2003.

Effect of pregnancy on asthma

- 1/3 improve; 1/3 unchanged; 1/3 deteriorate
- Pattern repeats in successive pregnancies
- 10-20 % have asthma Sxs during L & D
- Usually return to their pre-pregnancy asthma status by 3 months postpartum

Pregnancy (like asthma) Th2 state?

- Postulated: skewing away from the production of Th1 cytokines and towards the production of Th2 may help the survival of the fetus and reduce the risk for preeclampsia

Th1 chemokine ratio (IP10/eotaxin) declines during pregnancy; eotaxin rises

	Mother			Newborn
	Pregnancy	Peripartum	Postpartum	
IFN-γ	4.03 ±0.85 (n=36)	2.34 ±0.43 (n=44)	2.14 ±0.57 (n=20)	1.98 ±0.71 (n=28)
IL-4	0.35±0.11 (n=36)	0.84±0.38 (n=48)	0.49 ±0.19 (n=19)	0.38 ±0.17 (n=32)
IP-10	90.3 ±9.1 (n=45)	79.9 ±7.04 (n=49)	124 ±17.3 (n=15)	274.9 ±182.5 (n=26)
eotaxin	58±5.16 (n=47)	66.7 ±4.8 (n=47)	129 ±18.1 (n=15)	116 ±18.7 (n=26)
IFN-γ/IL-4	95.5 ± 31.9	62.3±21.2	29.2 ±9.3	25.7 ±8.3
IP10/eotaxin	3.3 ±1.3	1.4 ±0.2	1.1 ±0.73	2.8 ±1.5

D Rastogi, C Wang, C Lendor, PB Rothman, RL Miller. *CEA*, 36 (7), 8920-898, 2006

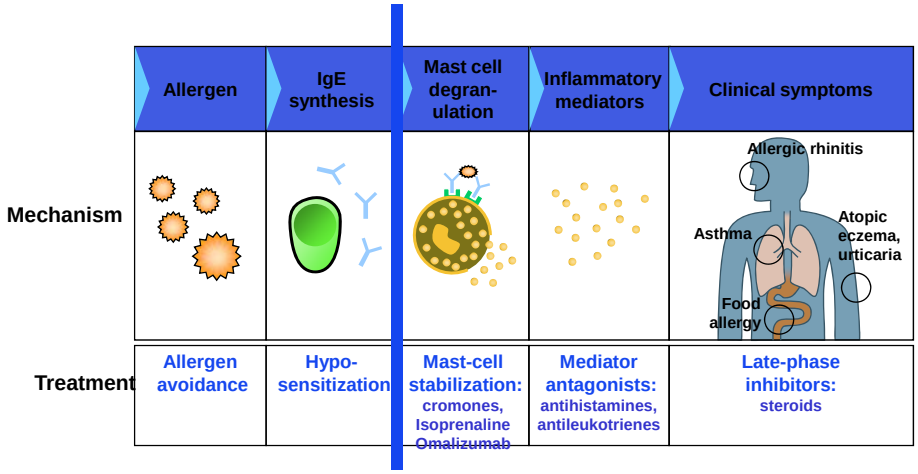
Steroid insensitive asthma

- 10% of asthmatics have severe asthma
- 0.1 to 1% of all asthmatics have steroid insensitive asthma
- NOT a major subgroup

Immunopathogenesis?

- Extension of mild/mod asthma with ongoing Th2 inflammation?
- “Different” inflammatory process featuring neutrophils?
- Structurally remodeled airways leading to fixed/irreversible obstruction?
- Altered distribution of inflammation and/or structural abnormalities?

Targeted treatment of asthma



Adapted from Roitt J. Essential Immunology. 1994.

Updated NAEPP guidelines: 6 steps

- Step 1 - short acting inhaled beta agonist prn
- Step 2 - Low dose inhaled corticosteroid (ICS), or leukotriene antagonist, or cromolyn, or theophylline
- Step 3 - Medium dose ICS or low dose ICS plus inhaled long acting beta agonist (LABA)
- Step 4 - Medium dose ICS plus LABA
- Step 5 - High dose ICS plus LABA - consider omalizumab (anti-IgE) therapy
- Step 6 - Oral corticosteroid

NAEPP guidelines: pregnancy*

- Monthly objective measures of lung fn; spirometry at 1st visit
- Avoidance of triggers-continue, but don't begin IT
- Patient education-recognizing signs, importance of pharmacological Rx
- Pharmacological Rx*

•Minimal human data on leukotriene antagonists; reassuring animal data submitted to FDA; alternate recommend for mod asthma

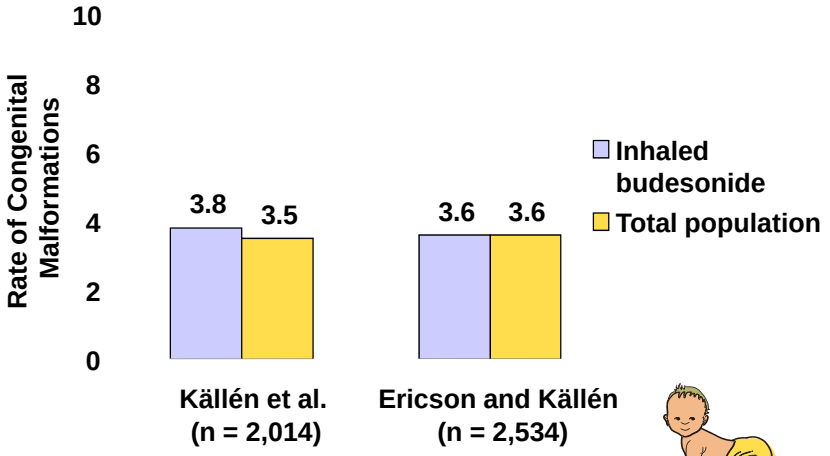
Updated NAEPP 2004

NAEPP guidelines: pregnancy*

- Treat asthma as aggressively in pregnant women as in nonpregnant women
  - Pregnant women with persistent asthma need daily controller medication.
  - ICS (budesonide) is first-line therapy for persistent asthma.
- Adequately controlled asthma does not increase the risk of perinatal mortality, morbidity.

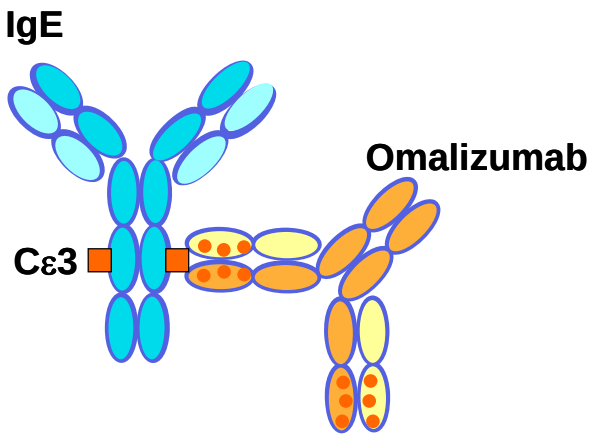
Updated NAEPP 2004

Inhaled budesonide does not increase rate of congenital malformations

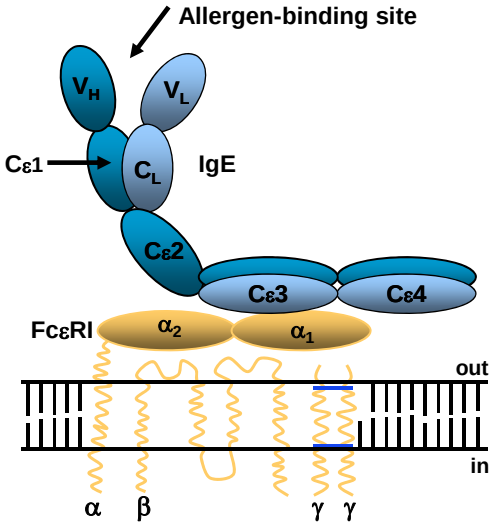


Källén et al. *Obstet Gynecol* 1999;93:392-5
Ericson and Källén. *Information from the Swedish Medical Products Agency* 1999;1:8-11.

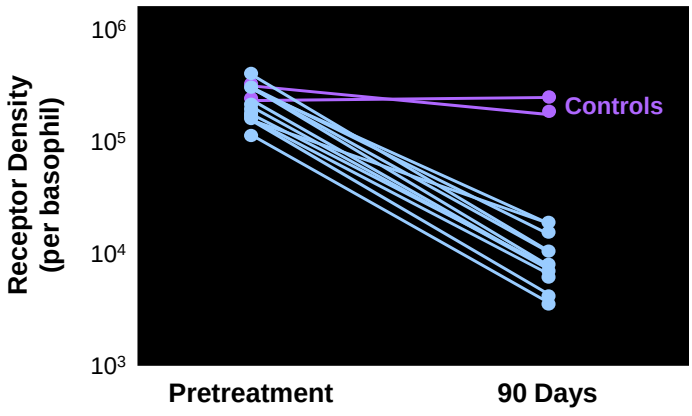
Omalizumab complexes bind free IgE and interrupts allergic cascade



Binding of IgE to high-affinity (FceRI) receptor



IgE receptors downregulated



MacGlashan D, et al. J Immunol. 1997.

High-risk patients

- Significant add-on therapy
  - Halves the number of asthma exacerbations
  - Reduces the likelihood of re-hospitalization
- Consistent reduction in exacerbation rates across all FEV_1 severity groups
- Greater improvements in lung function, asthma symptoms, and asthma-specific quality of life

Refractory Asthma: Types

- Severe despite appropriate therapy, vs
- Under-treated because of adherence or other problems
- "brittle" vs. nonbrittle

Refractory asthma: workshop consensus for typical clinical features*

Major Characteristics

In order to achieve control to a level of mild-moderate persistent asthma:

1. Treatment with continuous or near continuous (50% of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids:

Drug	Dose (*µg/d*)	Dose (*puffs/d*)
a. Beclomethasone dipropionate	> 1,260	> 40 puffs (42 µg/inhalation; > 20 puffs (84 µg/inhalation
b. Budesonide	> 1,200	> 6 puffs
c. Flunisolide	> 2,000	> 8 puffs
d. Fluticasone propionate	> 880	> 8 puffs (110 µg), > 4 puffs (220 µg)
e. Triamcinolone acetonide	> 2,000	> 20 puffs

Minor Characteristics

1. Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, e.g., long-acting -agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring short-acting -agonist use on a daily or near daily basis
3. Persistent airway obstruction (FEV_1 < 80% predicted; diurnal PEF variability > 20%)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid "bursts" per year
6. Prompt deterioration with 25% reduction in oral or inhaled corticosteroid dose
7. Near fatal asthma event in the past

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* Requires that other conditions have been excluded, exacerbating factors treated, and patient felt to be generally adherent.

Definition of refractory asthma requires one or both major criteria and two minor criteria.

Refractory asthma: differential diagnosis

- Mild asthma with another functional breathing problem
- Stridor
- Persistent isolated cough
- Prolonged wheezing from bronchiolitis (infants)
- COPD
- LV Dysfunction
- VC Dysfunction (32% coexistent asthma)

Is it ONLY refractory asthma? exacerbating factors

- GER (34-80%)
- Upper airway disease, nasal polyposis
- Psychosocial factors
  - Meds prescribed for depression, conflict, psychiatric illness assoc with incr risk of asthma death
    (Campbell et al. Thorax, 50: 254, 1995)
- Poor adherence
  - Reported compliance with ICS 30 (adolescents)-55% (Garcia et al Allergy 58:114, 2003)
- Sleep apnea

Compliance

- Prescriptions collected?
  - 1/6 parents filled all asthma prescriptions
  - 72% women, 68% men possess prescribed ICS
  - 30% women and 24% men possess peak flow meters
- Prescriptions used?
  - 50% women, 58% men use prescribed ICS daily
- Parents supervising?

Warner, *BMJ:* 311:663, 1995
\Krishnan et al, 2001, 161:1660

PO steroids

- If pt does not respond to prednisone/ methylprednisolone 20 mg qod, consider:
  - incomplete steroid absorption
  - failure to convert to active form (prednisolone), or
  - rapid elimination
- Drug interactions
  - rifampin, phenytoin, carbamazepine, phenobarbital

Conclusion

- Asthma markedly heterogeneous disease in terms of:
  - Natural history
  - Phenotype
  - Pathogenesis
- Such heterogeneity relevant to its clinical management