Asthma control in the US: have we made progress and if so how?

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Disclosures

Consultant/Advisor: Glaxo Smith Kline, Astra Zeneca, Regeneron, Sanofi Genzyme, Amgen, Teva, Genentech, Merck, Takeda

Clinical trial PI/Research Grants: Glaxo Smith Kline, Astra Zeneca, Amgen, Teva, Genentech, RAPT

Case 1: Circa 2009

Patient with asthma and history of nasal polyps

Patient history[1]

- 48-year-old female referred after a recent hospitalization for asthma
  - She developed asthma at age 35 years - initially well controlled, then developed CRSwNP
  - Failed medical therapy and required nasal polypectomy x2
- Asthma exacerbations requiring OCS 2-4 times/year for asthma and/or sinusitis. She uses albuterol daily for symptoms
- awakens at night 2x/week
- No history of allergies (SPT in the past)
- Was an avid runner until recently
- Works in healthcare administration
- Never smoker
- Identical twin has mild asthma not as severe, no nasal polyps – yoga instructor

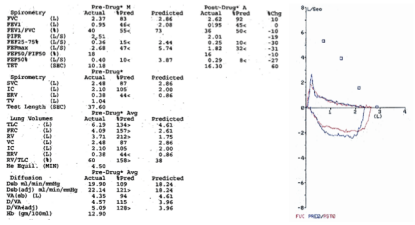
Medications:
- Fluticasone/salmeterol diskus 500/50 µg BID, tiotropium bromide, budesonide nasal washes, albuterol MDI/nebulisers, montelukast, prednisone 10 mg/day 7 months of the year

Physical exam:
- VSS; ACT score 13 (ACQ of 2.5)
- Erythematous, boggy nasal passages, bilateral polyps
- Lung exam: diffuse insp/exp wheezing, good air entry

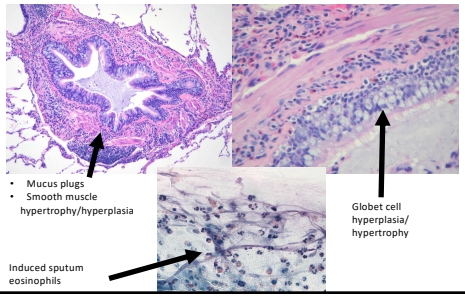
Patient with asthma and history of nasal polyps

Laboratory data[1]

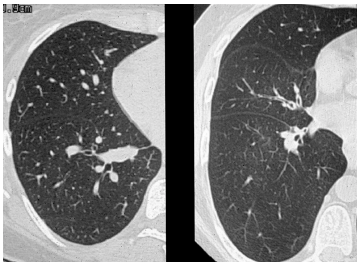
- FeNO 55 ppb
- IgE 500 IU/mL
- SPT/Immunocap negative for 22 aeroallergens
- BEC 500 cells/µL
- A1AT, CFTR, sweat test neg
- Nasal EM negative for PCD
- ANCA negative



Pathologic Features of Severe Asthma



Radiographic Features of Airway Remodeling



Normal

Refractory Asthma

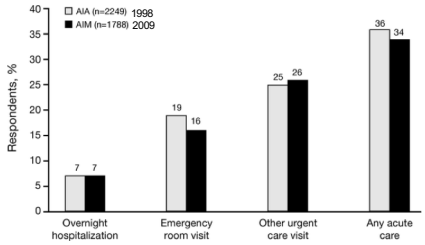
ATS/ERS Task Force Criteria for Severe Asthma

ERS/ATS Definition of Severe Asthma	ERS/ATS Definition of Uncontrolled Asthma
Use of high-dose ICS plus an additional controller to maintain asthma control *or* Use of systemic corticosteroids for ≥50% of the previous year to maintain asthma control *or* Asthma that remains uncontrolled despite these therapies	Meet the criteria for ≥1 of the following: • Poor symptom control: ACQ ≥1.5 or ACT <20 • Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (≥3 days each) in previous year • Serious exacerbations: ≥1 hospitalization, ICU stay, or mechanical ventilation in previous year • Airflow limitation: FEV_1 <80% predicted after appropriate bronchodilator withheld

Patient has cycled through GINA, NAEPP steps and by ATS/ERS has severe uncontrolled asthma

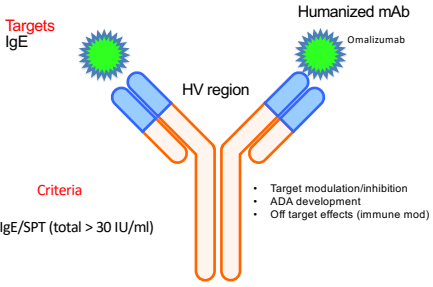
Chung et all ERJ 2014

Asthma Outcomes 1998-2009- survey based



Nathan et al. Allergy and Asthma Proceedings 2011;33:65

2009 omalizumab for severe asthma



Criteria

+ Specific IgE/SPT (total > 30 IU/ml)

- Target modulation/inhibition
- ADA development
- Off target effects (immune mod)

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page[1], Cheri Swenson[2], Isidore Faiferman[3], John Matthews[3], Michael Williams[3], Lesley Brannick[3], Douglas Robinson[4], Sally Wenzel[5], William Busse[2], Trevor T. Hansel[4], and Neil C. Barnes[6], on behalf of the International Mepolizumab Study Group[4]

- 362 patients: FEV1 50-80% with reversibility, on ICS
- Randomized, double-blind, placebo-controlled.
- Mepolizumab 250 mg or 750 mg i.v. Q month x 3.
- End-points:
  - 1° Change from baseline PEF week 12-20.
  - 2° FEV1, symptoms, exacerbations

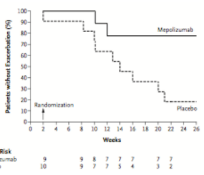
Results

- Minimal improvement in PEFR in 250 mg group (13.5L/min)
- No significant improvement in FEV1
- Minimal improvement in Symptom Score in 250 mg group
- Non-significant reduction in exacerbations (P=0.065): control (16%), 250 mg (18%), 750 mg (10%)
- Significant reduction in blood and sputum eosinophils

Am J Respir Crit Care Med Vol 176. pp 1062-1071, 2007

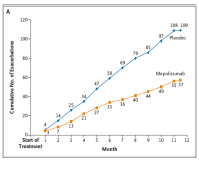
Mepolizumab reduced asthma exacerbations in refractory Eosinophilic Refractory Asthma (750mg IV qmonth)

N=20
Refractory Asthma
3% of Center population
>3% sputum eos on max meds



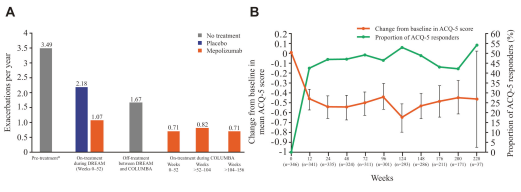
Nair et al. NEJM 2009;360:116

N=61
Refractory asthma
sputum eos > 3%
≥ 2 exacerbations/year



Haldar et al. NEJM 2009;360:10

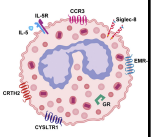
Dream and Columba Trials



Pavord et al. NEJM 2012

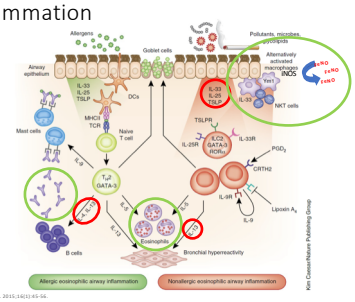
Severe Eosinophilic Asthma

- ~85 % of patients with severe asthma have blood Eos ≥ 150 cells/ul
- This is the definition of a new subtype of asthma: Eosinophilic asthma (severe asthma and blood eos ≥ 150 cells/ul).
- These patients are more commonly
  - *Adult onset*
  - *50% are non-atopic*
  - *have CRSwNP (~25%)*
  - *OCS dependent/responsive*
  - *Have a low FEV1*
- The workup of patients with severe uncontrolled asthma now requires immunophenotyping that includes:
  - CBC with diff to check for Eosinophils
  - Total IgE- to screen for asthma variants
  - SPT or Immunocap/RAST testing-identify IgE mediated inflammation
  - PFTs
  - FeNO- to identify IL-13/eosinophilic mediated airway inflammation



Buhl et al ERJ 2017 49: 1700634

Evolving Paradigm of Adaptive and Innate Mediators of Airway Inflammation



Lambrecht BN, Hammad H. Nat Immunol. 2015;16(1):45-56.

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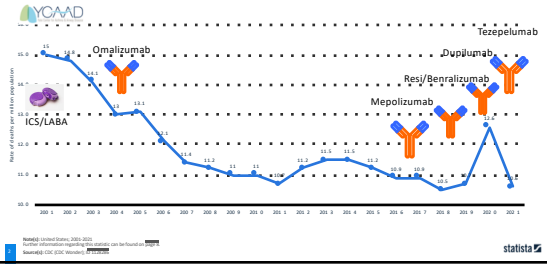
Rate of deaths due to asthma in the United States from 2001 to 2021 (per million population)

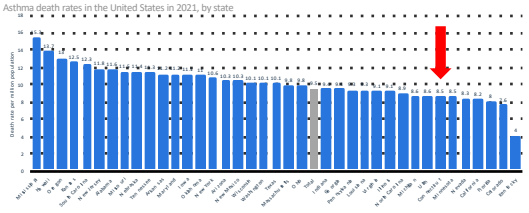
Asthma mortality rate in the United States from 2001 to 2021



statista

Death rates from asthma in the United States in 2021, by state. NH/Maine/VT did not make the list

Asthma death rates in the United States in 2021, by state



statista

Case History #2

- HPI: 68 yo male (retired MD) referred for an opinion regarding severe asthma. Developed allergies and asthma at age 18 when he lived in California. Asthma was relatively mild during his adult life with occasional flares and intermittent use of controller medications.
- 2-3 years ago noticed very slow onset of increasing SOB, trouble exercising. No frank flares. He increased his use of ICS/LABA. Tried a course of prednisone. Cardiac workup negative.
- Fluticasone/Salmeterol 500/50, montelukast, Spiriva, Albuterol
- Allergies to dogs and cats, ragweed, dust mites, pollen
- Asthma, Eczema, and allergies but not tested in years
- Denies GERD symptoms or chronic sinus problems.
- Never smoker, lives in a single-family home with no pets, HVAC, area rugs

Case #2: PE/Labs

- PE: Good air entry. Clear with no wheezing. ACT score 20
- Bloodwork: IgE 169 IU/ml, Eos 480 cells/ul. ANCA negative
- Allergy tests: Dog,cat, trees, dust mite
- Radiology: PA/Lat CXR and unremarkable

	FVC	FEV1	FEV1/FVC	FENO	TLC	RV	DLco
01/31/17	91(%)	54(%)	0.45	100ppb	95 (%)	90(%)	100(%)

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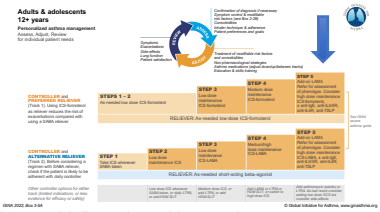
- Allergic and eosinophilic severe asthma patient on max dose ICS/LABA/LAMA/LTRA. SOB with exertion, low lung function, some OCS but not alot.
- What would you do?



Phenotype- Adult allergic and eosinophilic severe asthma
High FeNO, Eos, + allergy tests

Limitations of GINA/NAEPP/ATS/ERS Guidelines: a case for phenotyping all patients

- Contribute to the dogma that all asthma is steroid responsive
- Do not embrace the heterogeneity of disease within and across the STEP levels
- Assume that all patients (at least partially) respond to a STEP treatment, so piling on treatments is the primary approach
- There is poor alignment between GINA and NAEPP which leads to confusions for providers and patients
- Phenotyping is only recommended if a patient is "difficult to control"

Case: Response to Mepolizumab

- Patient started dupilumab
- Exercise tolerance and lung function significantly improved in 6 months
- Stopped using controller medication- uses Symbicort PRN

	FVC	FEV1	FEV1/FVC	FENO	TLC	RV	DLco
01/31/17	91	54	0.45	100ppb	95 (%)	90(%)	100(%)
05/31/17	112	82	0.56				
08/11/20	112	87	0.59	37ppb			
10/31/23	119	94	0.60	54ppb			

Case illustrates 2 important advances in asthma control

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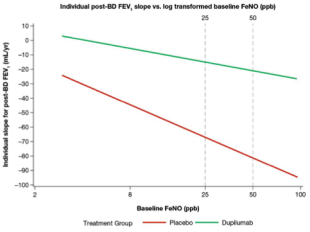
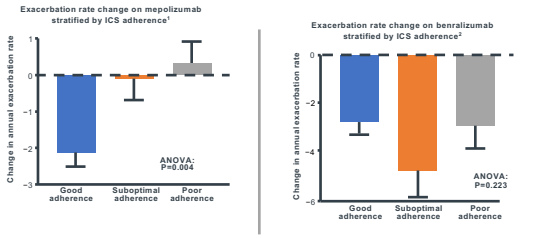
Rate of lung function in Phase 3 Dupilumab Trial (Quest)



Treatment	Subgroup	Post-BD FEV_1 change (mL/year)* Blood eosinophils (cells/μL) <150	≥150	≥300
Placebo	FeNO <25	−49 (SE=26) (N=104)	−56 (SE=19) (N=187)	−71 (SE=27) (N=90)
Dupilumab	FeNO <25	−12 (SE=17) (N=253)	−17 (SE=14) (N=363)	−35 (SE=20) (N=173)
Placebo	FeNO ≥25	−116 (SE=37) (N=53)	−47 (SE=20) (N=253)	−59 (SE=24) (N=181)
Dupilumab	FeNO ≥25	4 (SE=29) (N=99)	−23 (SE=15) (N=475)	−30 (SE=18) (N=334)
Placebo	FeNO ≥50	−102 (SE=70) (N=20)	−122 (SE=36) (N=109)	−149 (SE=41) (N=85)
Dupilumab	FeNO ≥50	43 (SE=61) (N=27)	−41 (SE=27) (N=199)	−50 (SE=32) (N=152)

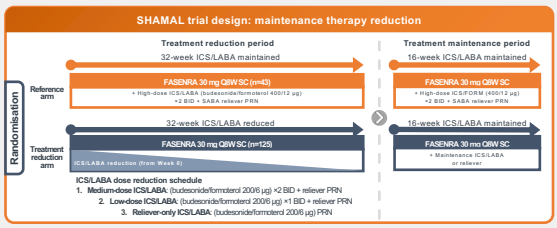
Pavord et al. AJRCCM 2024

Do patients become less adherent to their inhaled steroids following initiation of biologic therapy? If so, does it matter?

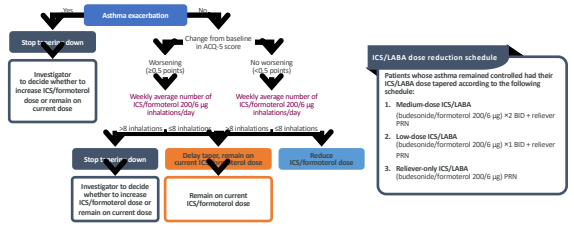


d'Ancona G, et al. Eur Respir J 2020;55:1902259 and Allergy 2021;76:2238–2241

ICS reduction: evidence from the SHAMAL trial

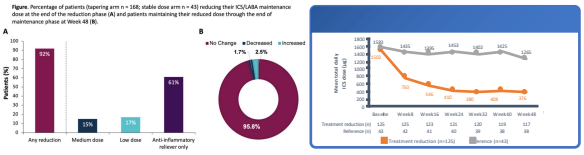


Shamal algorithm for stepping up or down inhaled therapy



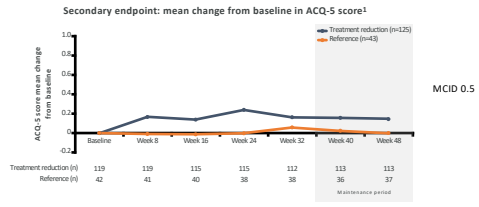
Jackson et al. Eur Respir J 2023;62:RCT798

Tapering of ICS/LABA maintenance in patients controlled on biologics: SHAMAL



Jackson et al. Eur Respir J 2023;62:RCT798

Slight increase in symptoms as measured by ACQ-5[1]

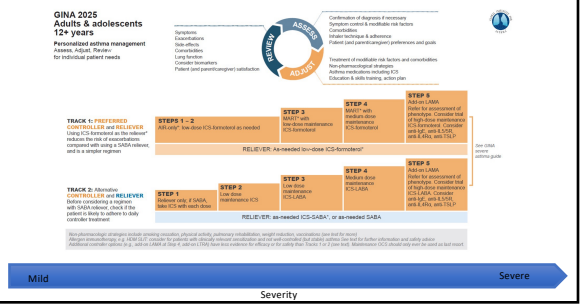


MCID 0.5

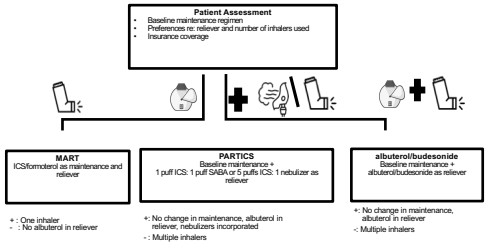
Some increase in exacerbations in tapering arm

Jackson et al. Eur Respir J 2023;62:RCT798

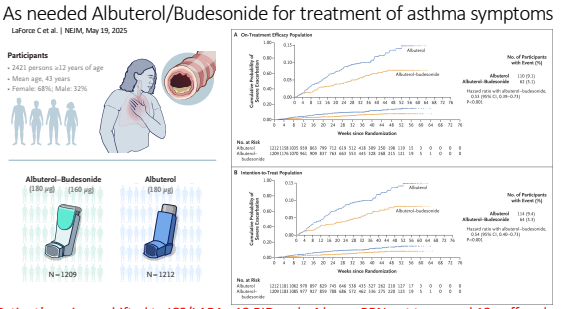
Guideline based management– the addition of AIRS



Anti-inflammatory Reliever Therapies for Moderate to Severe Asthma



As needed Albuterol/Budesonide for treatment of asthma symptoms



Patient's regimen shifted to ICS/LABA q12 BID and q4 hours PRN not to exceed 12 puffs a day

These studies are promising but we need better biomarkers/predictors of response and outcome

Leveraging Pharmacogenomics in Asthma for Prediction, Mechanism and Endotyping

NHLBI

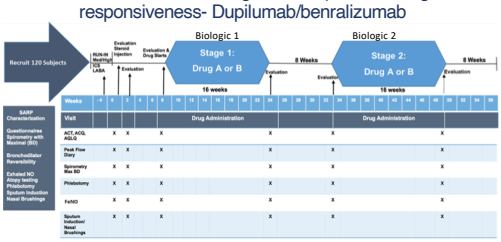
Epiphany Study

Multi-Center Collaboration

Hypothesis: Translational, "omics", and system medicine approaches will define biomarkers and responsiveness to biologic therapies and better characterize disease heterogeneity

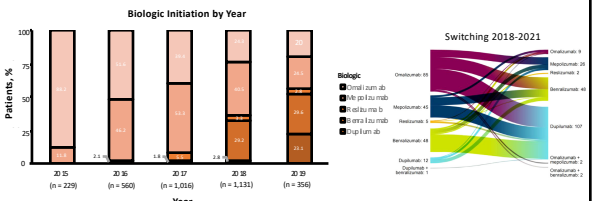
UC San Diego School of Medicine | The University of Arizona College of Medicine | Yale University School of Medicine | Harvard Medical School, Brigham and Women's Hospital

Towards a blood based signature to predict biologic responsiveness- Dupilumab/benralizumab



Asthma Questionnaires to be used: ACT (Asthma Control Test), ACQ (Asthma Control Questionnaire)
Peak Flow diary – AM peak flow and diurnal peak flow variability
Spirometry with Maximal Bronchodilation – 6 hour withhold of short-acting bronchodilators, 12-24 hour withhold of long acting bronchodilators, 4 puffs albuterol used
Phlebotomy for CBC with differential count, absolute eosinophils and neutrophils, DNA isolation, RNA (from PBMCs) for gene expression, serum and plasma for proteomics
Sputum for inflammatory cell counts, supernatant for proteomics, and cell pellet for RNA isolation and gene expression
Nasal Brushing for epithelial cell genomics

Real-World Biologic Use and Switch Patterns: Data From the International Severe Asthma Registry and the US CHRONICLE Study



- 79% of patients continued their first biologic
- 10.2% stopped
- 10.8% switched

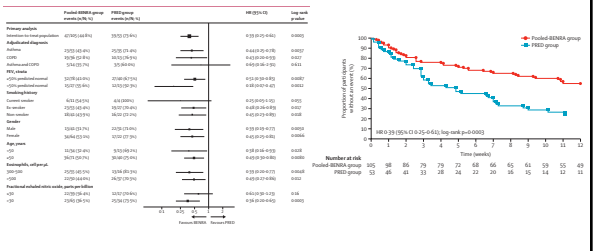
R.A. Panettieri et al. / Ann Allergy Asthma Immunol 129 (2022) 467–474

Case #3

- 20 yo female, h/o childhood asthma- multiple hospital admissions as a child and prednisone tapers, never intubated. Moved from Pennsylvania to CT 5 months ago with her newborn (9 months old) to live with her mother
- 3 Stepdown admissions in the last year. Seen in YCAAD a month ago and started on Benralizumab
- Increasing asthma symptoms started 5 days ago. Wheezing, cough, mucus production and SOB. Seen in the ER yesterday for asthma, discharged after treatment with albuterol nebs, prednisone. Acutely worsened today- came to ER
- Has only albuterol inhaler/nebs at home, using excessively for last 6 weeks
- Smokes cannabis daily often in the form of blunts
- Known triggers weather humidity, cats, exercise

	FVC	FEV1	FEV1/FVC	TLC	ERV	RV/TLC	DLCO	FeNO
7/8/22	3.28 (90%) -> 3.48 (96%)	2.58 (81%) -> 2.79 (87%)	0.79 -> 0.80	4.13 (88%)	0.74 (63%)	25%	18.87 (88%)	99 ppb

ABRA study- anti-IL5 treatment for exacerbations of Asthma and COPD



Ramakrishnan et al. Lancet Respir Med 2025; 13: 59–68

Asthma control in the United States

Relationships between short-acting β_2-agonist and systemic corticosteroid use

Geoffrey Chupp, MD*; Kevin R. Murphy, MD†; Hitesh N. Gandhi, MBBS, MHA, MAS‡; Ileen Gilbert, MD‡; Eugene R. Bleecker, MD§

* Department of Pulmonary, Critical Care, and Sleep Medicine, Yale University, New Haven, Connecticut
† Boys Town National Research Hospital, Boys Town, Nebraska
‡ BioPharmaceuticals Medical, AstraZeneca, Wilmington, Delaware
§ Department of Medicine, The Mayo Clinic, Phoenix, Arizona

Data Source

IQVIA Longitudinal Access Database (2015-2018)

- 1.5 billion medical claims
- 92% retail pharmacy coverage
- 72% mail-order coverage

Inclusion Criteria

ICD-9/10 asthma diagnosis + ≥1 maintenance therapy claim during 2016

Excluded: COPD comorbidity

4.5M	2,935	56%	30%
Total Patients	US Counties	Female	Children ≤11
Analyzed across all ages and severities	Geographic analysis conducted	Gender distribution	Pediatric representation

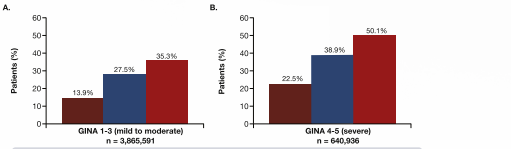
G. Chupp et al. / Ann Allergy Asthma Immunol 133 (2024) 302–309

Asthma Control in the United States

15%
≥2 annual SCS claims (exacerbation risk)

29%
≥3 annual SABA fills (symptom impairment)

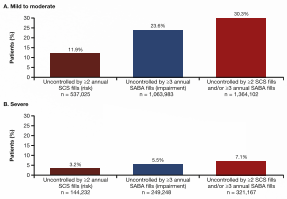
37% of all the patients were uncontrolled



Critical Finding: 1.7 million patients with uncontrolled asthma—equivalent to the population of Philadelphia

Made with GRAMMA

Breakdown by Severity



81%

of uncontrolled patients had **mild to moderate** asthma

1.36 million patients treated as mild-moderate had uncontrolled disease

The majority of uncontrolled asthma burden exists in patients not classified as severe

G. Chupp et al. / Ann Allergy Asthma Immunol 133 (2024) 302–309

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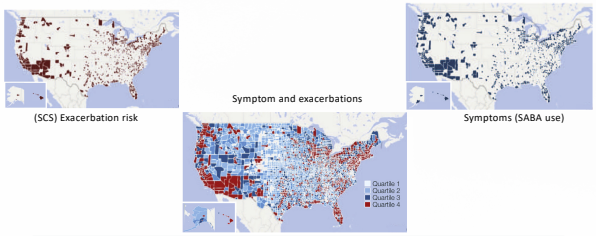
Geographic Variability Reveals Hotspots

High-resolution county-level mapping identified significant geographic disparities in uncontrolled asthma burden



Clinical Implication: Geographic mapping can direct resources and interventions to areas with greatest disease burden

G. Chupp et al. / Ann Allergy Asthma Immunol 133 (2024) 302–309

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Conclusions

- Large scale analyses of claims databases using OCS/SABA prescriptions to define uncontrolled suggest that a large percentage of patients (35-50%) remain uncontrolled in 2025.
- However, asthma mortality has plummeted over the last 20 years which correlates with the advent novel therapies/approaches particularly targeted biologic therapies
- Biologic therapies have also allowed patients to optimal control and reduce the use of both OCS and ICS (SHAMAL)
- Biologic therapies also may also be effective in patients with asthma or COPD and elevated eosinophils at the time of exacerbations (ABRA)
- ICS/SABA for all GINA treatment steps if implemented will lead to further improvements in asthma control. Strategies are in development to improve implementation

EDITORIAL

New Biologics for Asthma

Jeffrey M. Drazen, M.D., and David Harrington, Ph.D.

- Four new biologics —mepolizumab, reslizumab, benralizumab, and dupilumab directed vs. type 2 inflammation
- (While not in editorial, other anti-type 2 agents are approved or in phase III development, including targeting of IL-33 and TSLP)
- **None has eliminated exacerbations in all patients and normalized the physiological changes that are the core of the asthmatic diathesis**
- **Some subjects are "asthma free" and some have no effects from targeted biologic therapy**
- **"We need to go beyond blood eosinophil counts, nitric oxide, and the presence of viral infections. There are other markers, yet to be discovered and validated, that will guide more effective treatment of severe asthma; let's commit to finding them."**

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