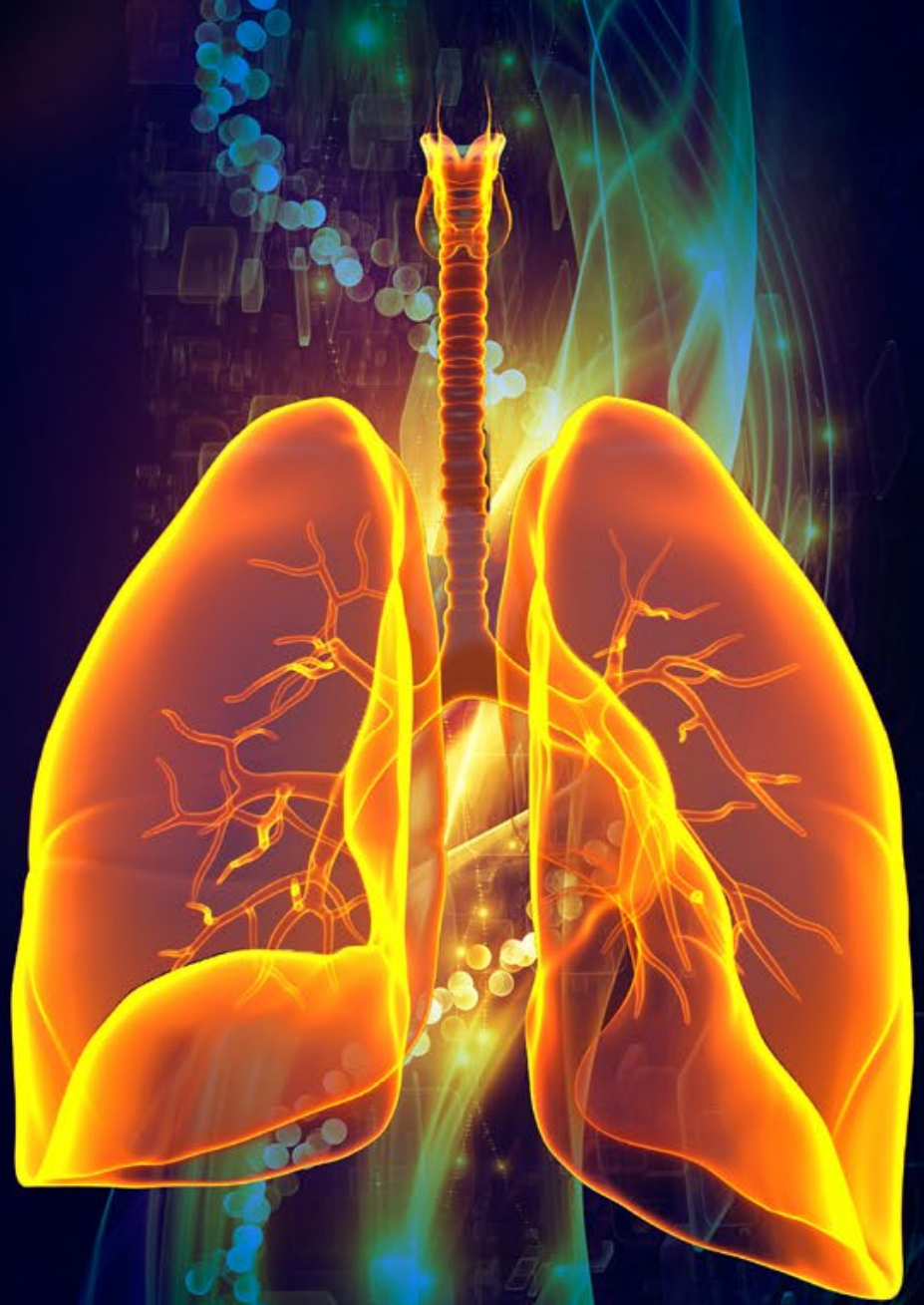

Overview of Asthma

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Breathing Science is Life.®

What is Asthma?

Asthma is a chronic inflammatory disease of the airway with

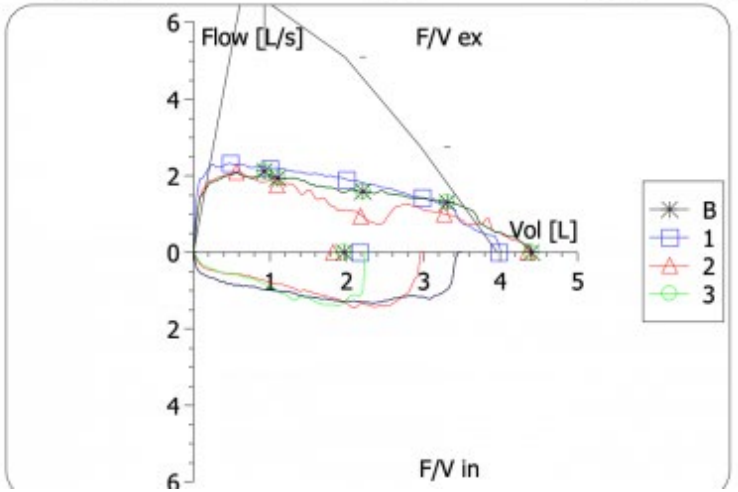
- Airway obstruction that may or may not be reversible, either spontaneously or with medication
- Airway inflammation caused by many cellular components
- Increased airway hyperresponsiveness

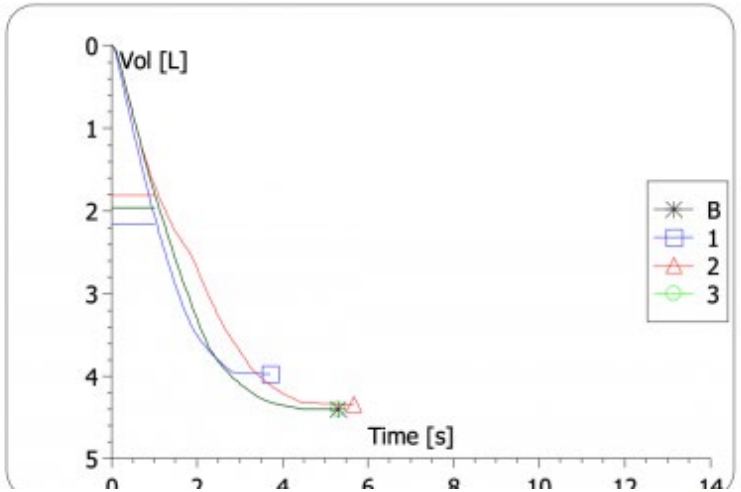
Differential Dx Of Wheezing

- “Asthma”
- VCD
- ABPA
- Chronic Eosinophilic Pneumonia
- Airway Tumors
- Bronchostenosis/TBM/DAC
- CHF
- Infection
- TB
- Tonsils
- Foreign body
- Goiter
- Post polio syndrome
- COPD
- PE
- Fixed lesions

Spiro

	LLN	Pred	Best	%Pred	Act1	Act2	Act3	Act4	Act5	Act6	Act7	Act8	Act9	Act10
FVC	3.23	3.95	4.40	111.5	3.97	4.35	4.40							
FEV 1	2.83	3.44	1.96	57.1	2.16	1.82	1.96							
FEV1/F	77	86	45		54	42	45							
PEF	5.27	7.06	2.10	29.7	2.31	2.09	2.10							
F25/75	2.51	3.80	1.62	42.6	1.86	1.17	1.62							
PIF		4.30	1.34	31.1	1.34	1.45	1.41							
FE/FIF		124	130	104.7	157	90	149							
FET			5.21		3.66	5.60	5.21							
VBe/FV			1.63		0.87	1.28	1.63							





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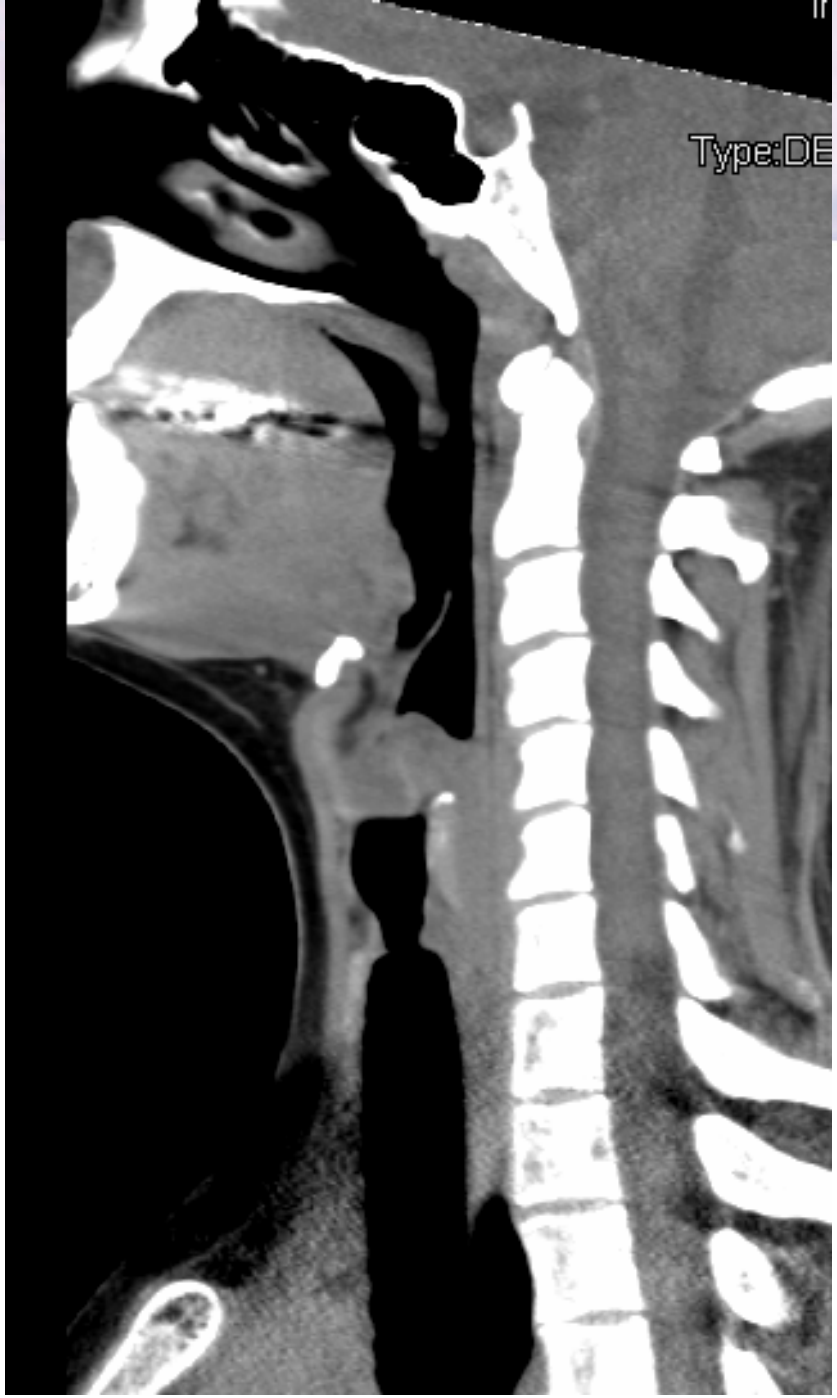
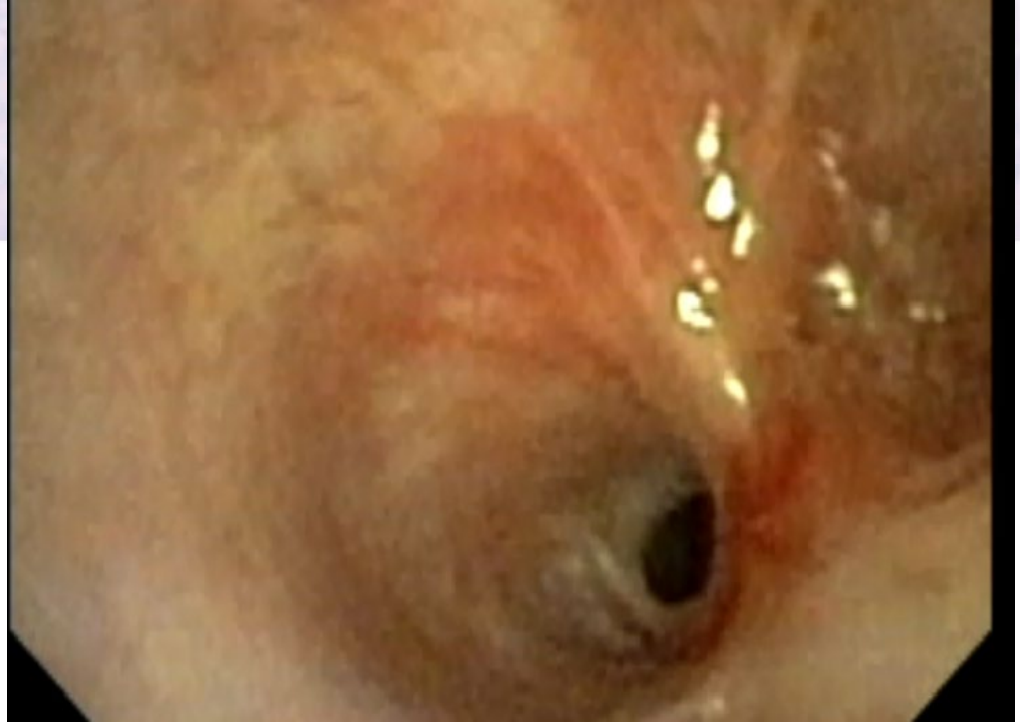
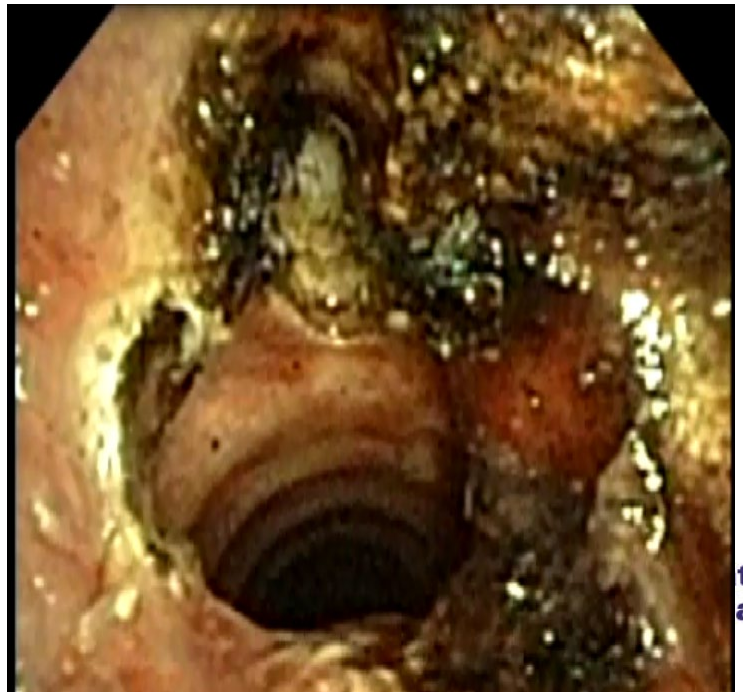
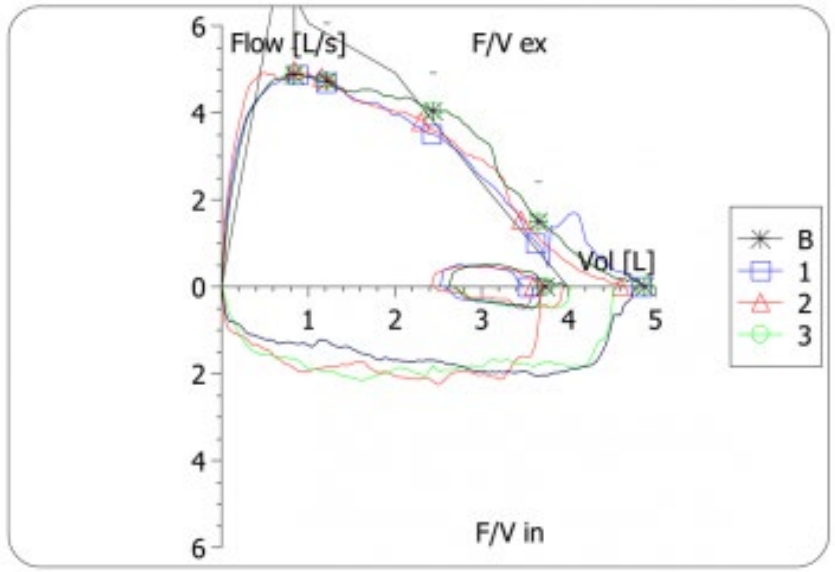
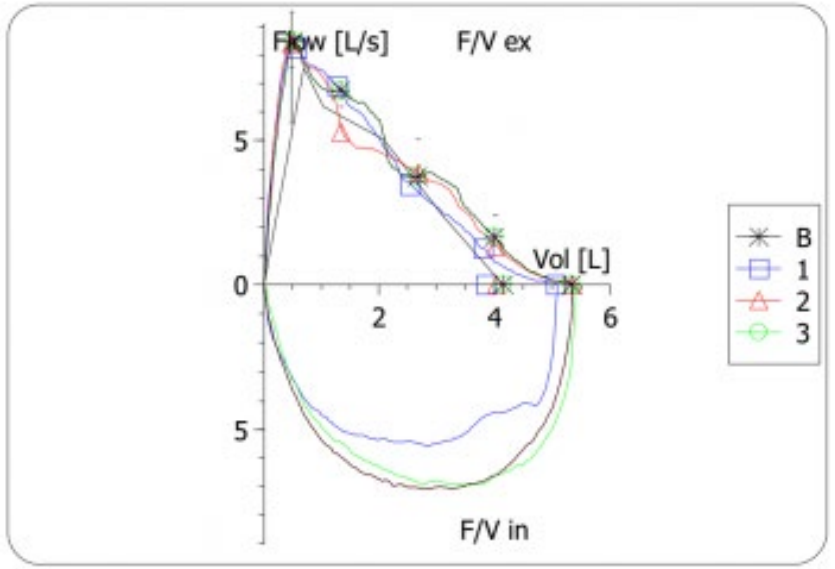




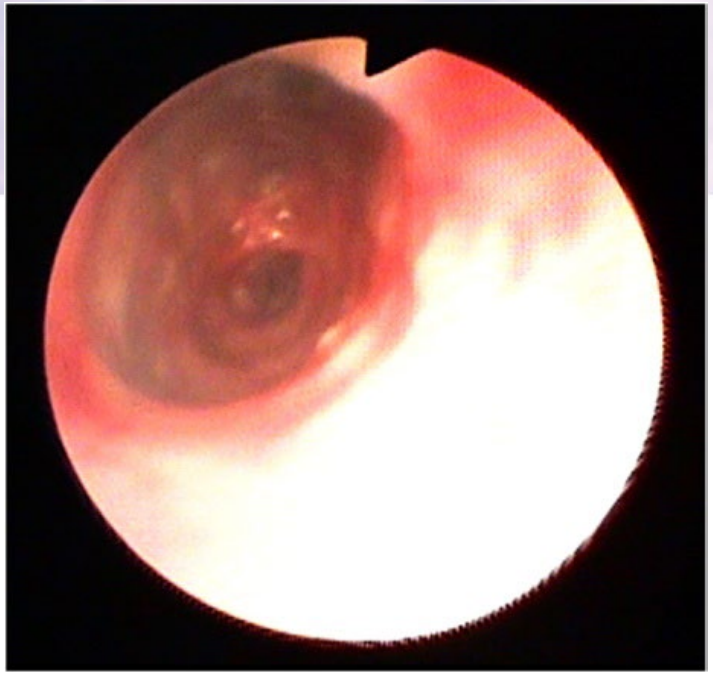


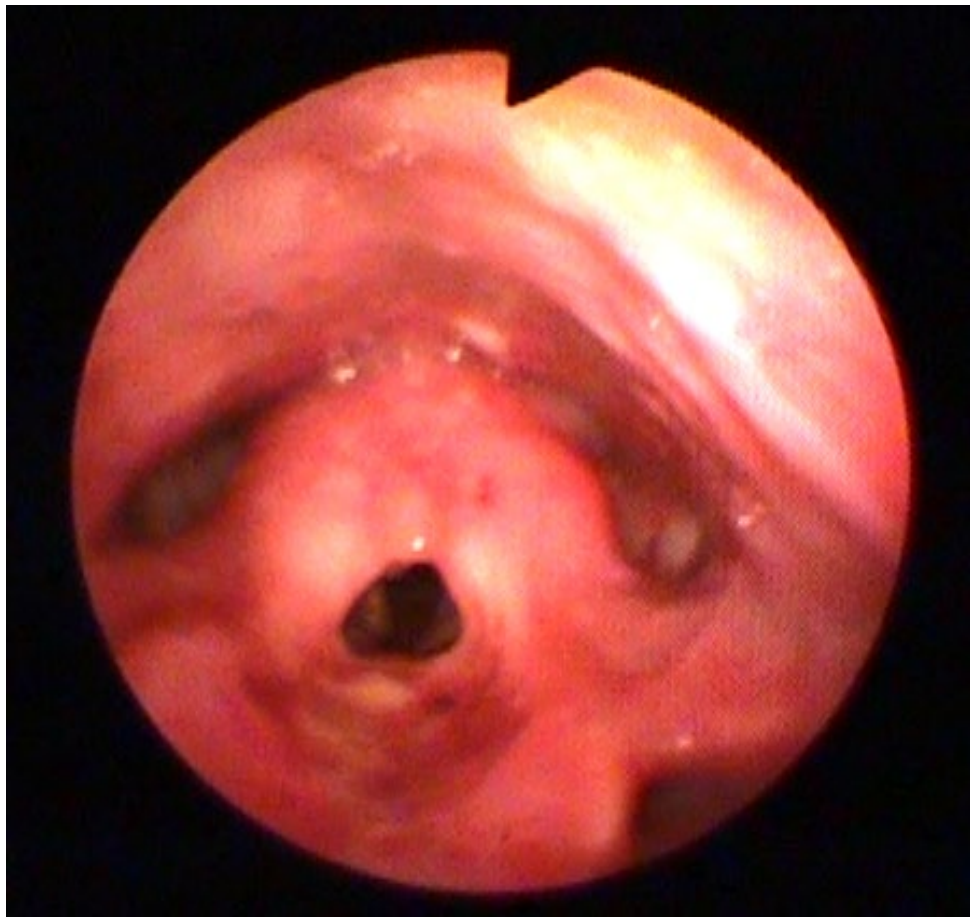


5/2012 (pre-dilation)



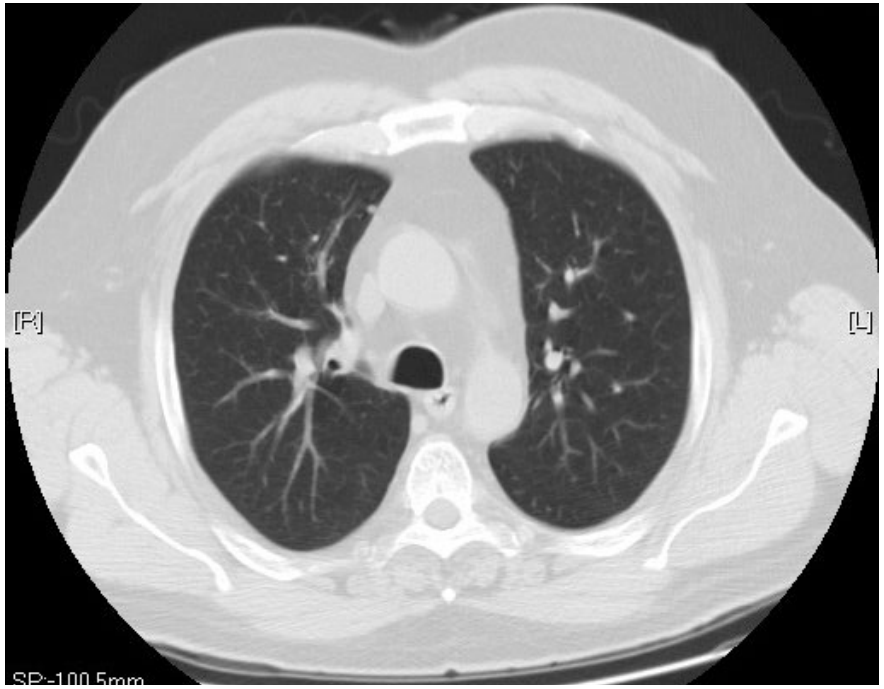
9/2012 (post-dilation)

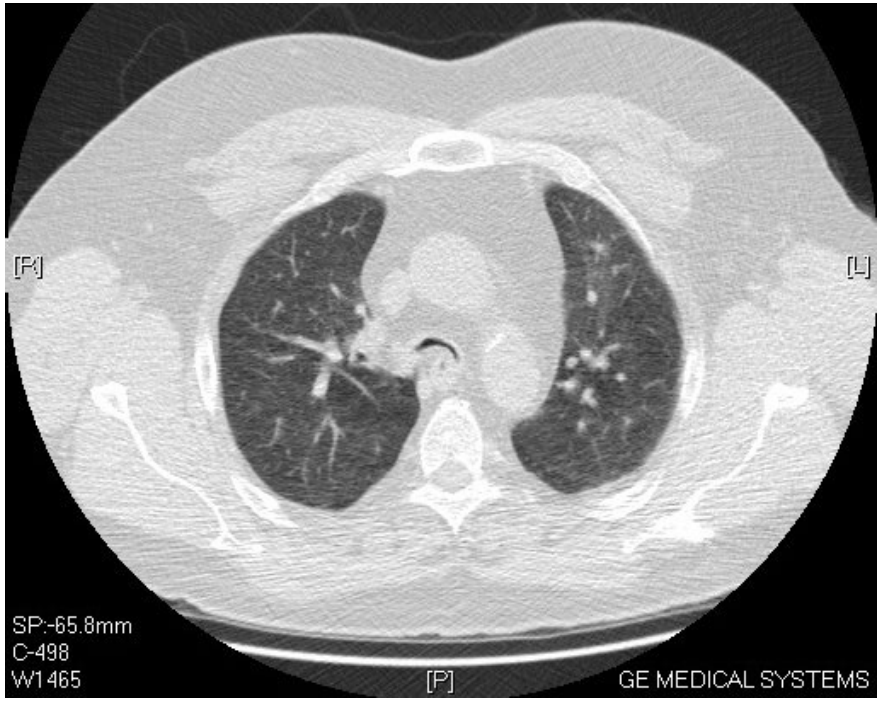




Cicatricial Pemphigoid

Dyspnea at Rest and with Exertion/ “Severe Asthma”





End-Inspiratory

Dynamic Expiratory

Dynamic Expiratory CT Severe Tracheomalacia

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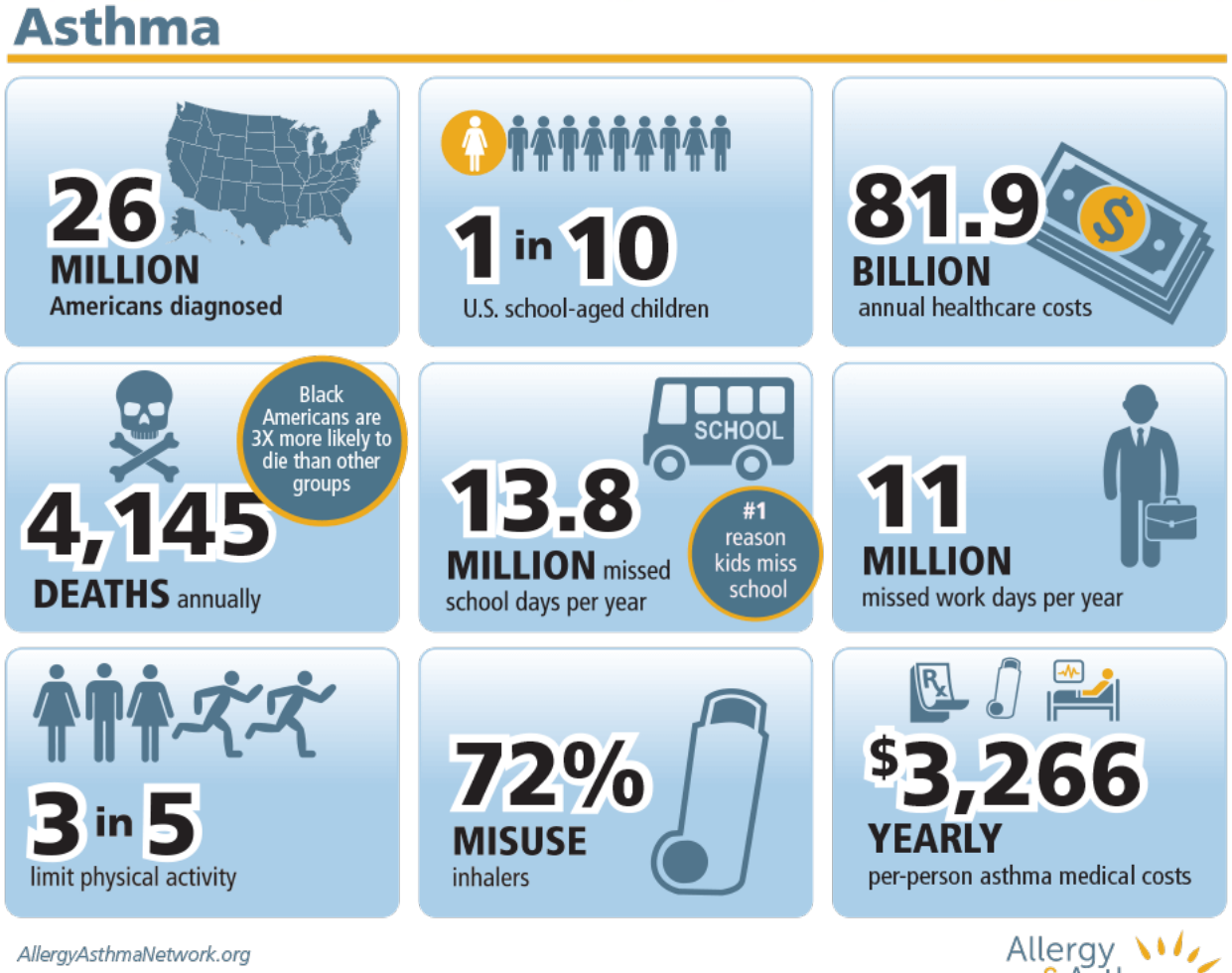
Severe Asthma as a Multi-Faceted Disease with High Morbidity

- 1.7 M ED visits in 2015 (986K in 2020)
- 11 M physician office visits in 2014
- 9.8 M asthma attacks in 2021
- 10.6 deaths per million in 2021
- Annual economic cost $82 B (2013)



https://www.cdc.gov/asthma, accessed 8Sep2024

Nurmagambetov T, Kuwahara R, Garbe P. Annals ATS 2018;15(3):348-56

Allergy & Asthma NETWORK

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How should an accurate diagnosis of severe uncontrolled asthma be made?

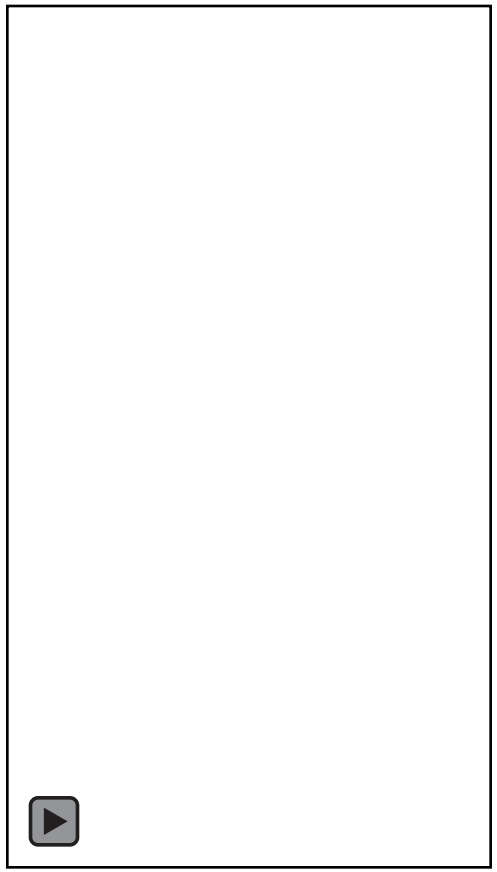
Check adherence/ inhaler technique

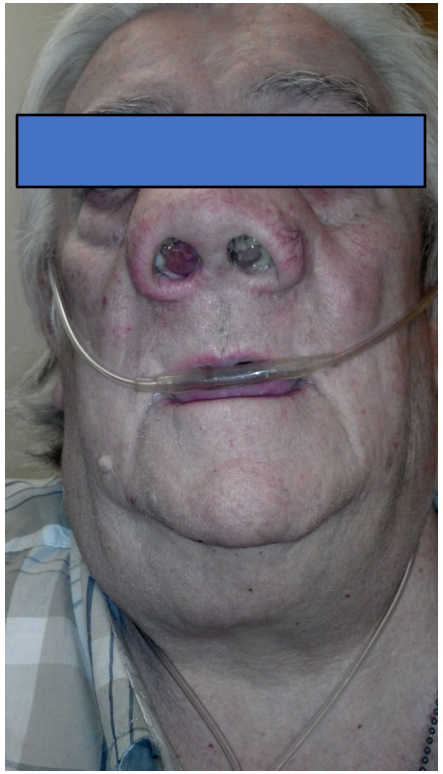
Screen for comorbidities

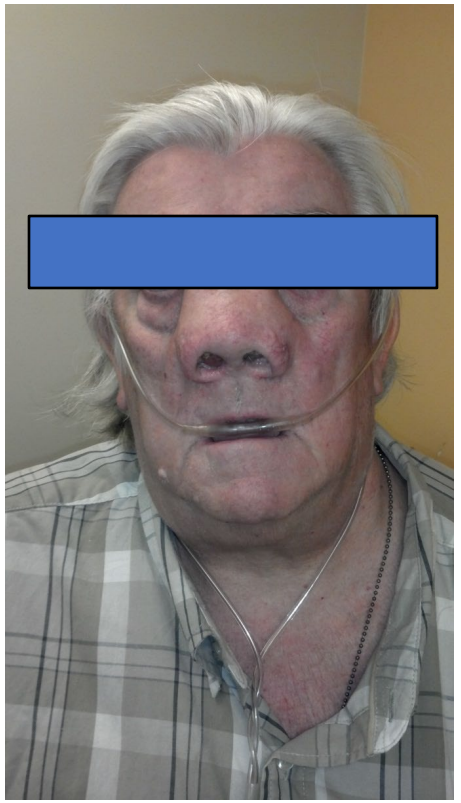
Rule out other potential diagnoses

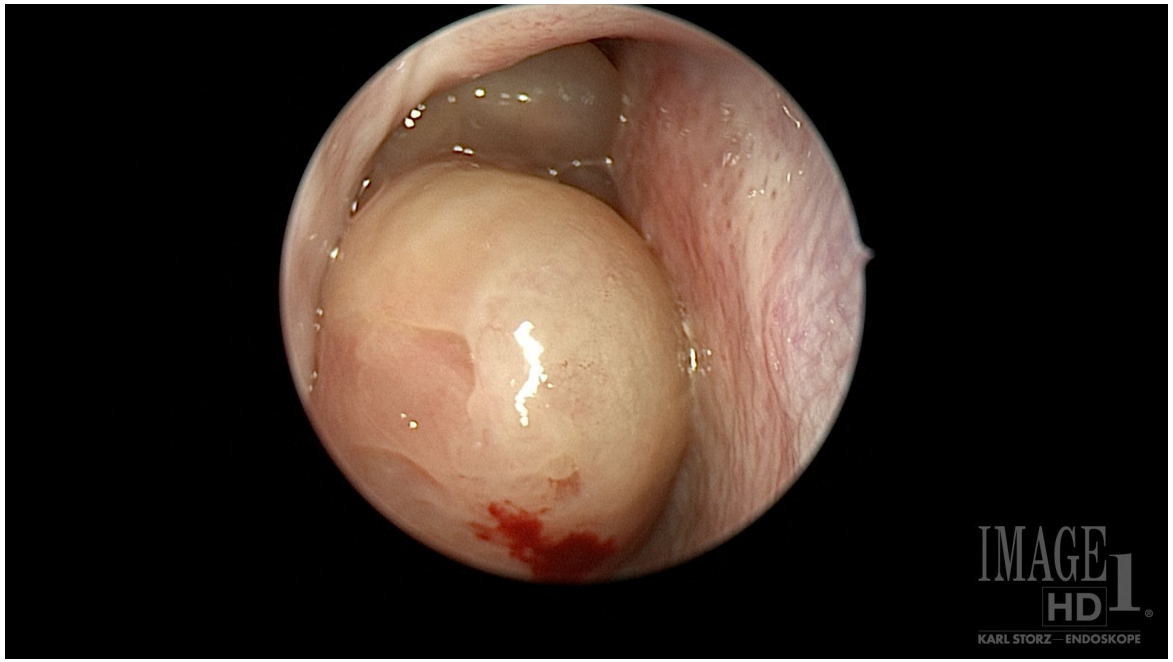
Check for triggers/irritants

Assess asthma control

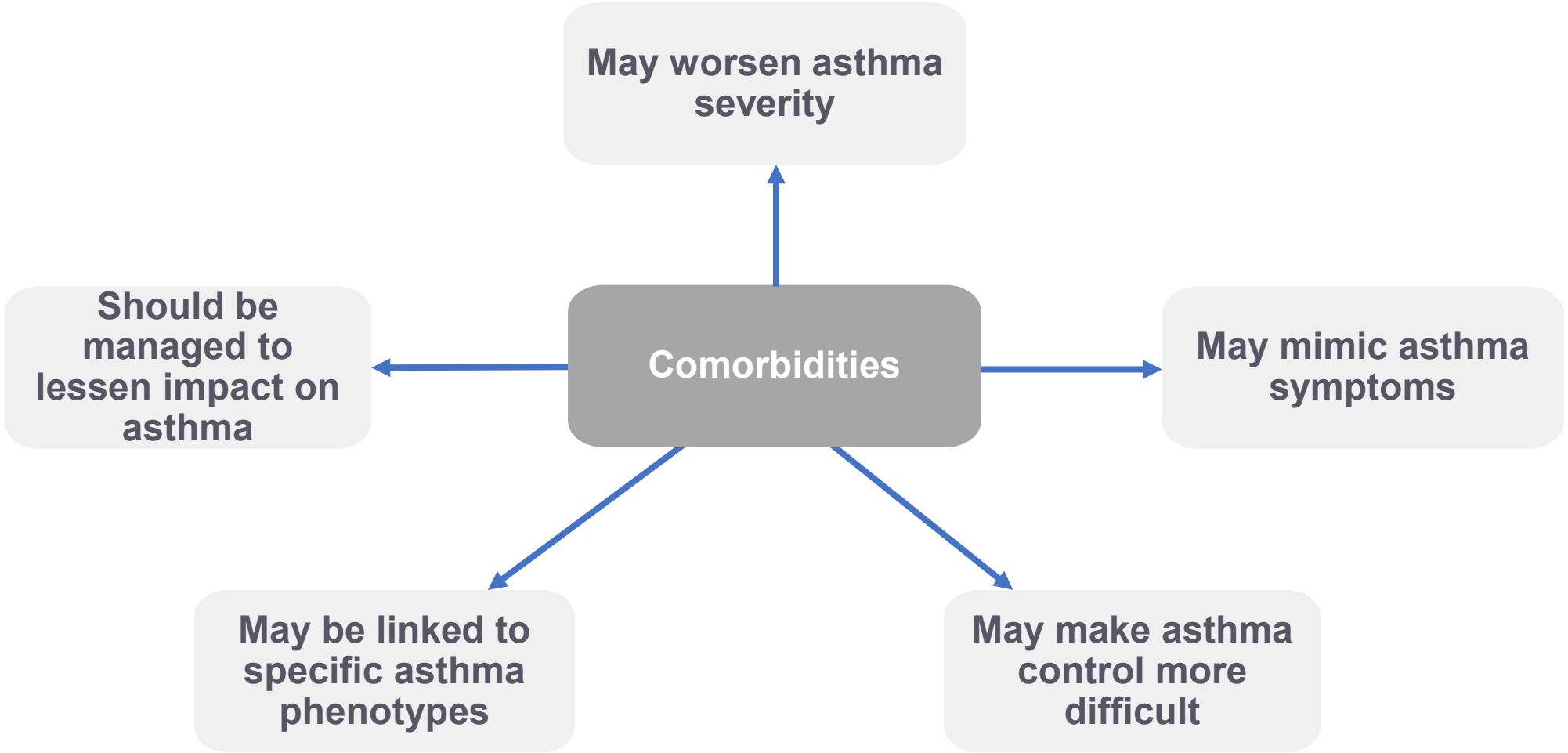








Comorbidities Have Significant Implications For Evaluation/ Assessment Of Asthma Control And Medication Needs



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Boulet LP. *Eur Respir J.* 2009;33:897-906.

Defining Inflammatory Diseases of the Upper Airway in Severe Asthma

- **Chronic rhinosinusitis with nasal polyps (CRSwNP)**
  - 20%-60% of patients with asthma have CRSwNP
  - Associated with eosinophilia and T2-high asthma phenotype
  - Associated with more severe asthma, lower FEV_1, and more frequent exacerbations

- **Chronic rhinosinusitis without nasal polyps (CRSsNP)**
  - 30%-40% of patients with asthma have CRSsNP
  - Less often associated with T2-high inflammation
  - More commonly associated with T2-low asthma phenotype

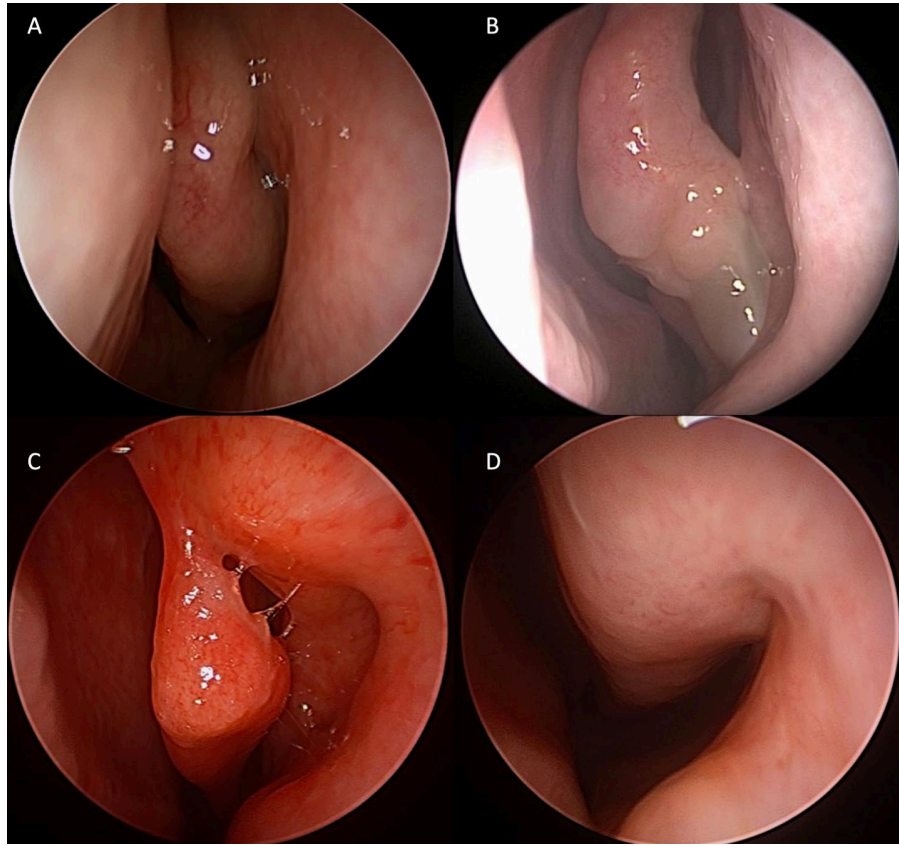

Photo Credit: Osie G et al, Rhinology 2022; 60(5):335-46

Features of inhalant allergy on nasal endoscopy: a systematic review and meta-analysis
G. Osie - K. Wegrecki - R. Alvarado - R.G. Campbell - L. Kalish - J. Rimmer - R. Sacks - R.J. Harvey, *Rhinology 60-5: 335-346, 2022*

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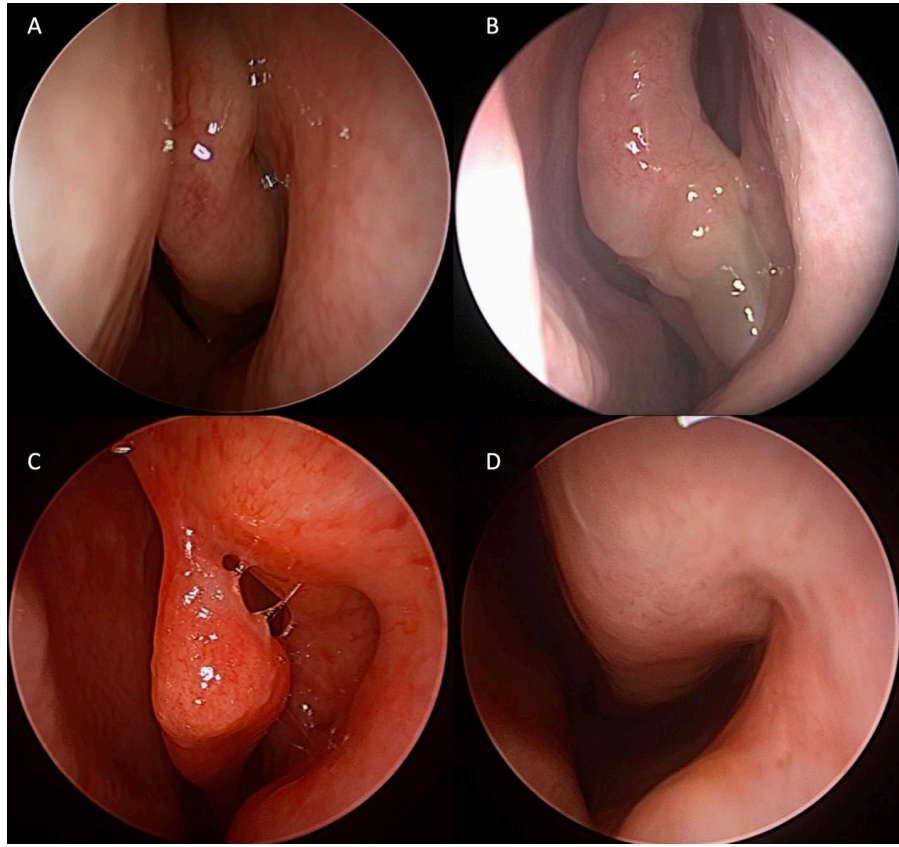
Defining Inflammatory Diseases of the Upper Airway in Severe Asthma

- **Aspirin-exacerbated respiratory disease (AERD)**
  - Samter's Triad: asthma, nasal polyps, and aspirin sensitivity
  - Strong association with T2-high asthma
  - 7% of asthma, but 14% of severe asthma
  - More ED visits, hospitalizations, and exacerbations

- **Allergic rhinitis (AR)**
  - 80%-100% of individuals with asthma have AR
  - AR and asthma share common pathophysiology
  - AR is a risk factor for the onset and severity of asthma
  - Treatment of AR can improve asthma control

Key Point: upper airway inflammation is common and can exacerbate or complicate asthma management



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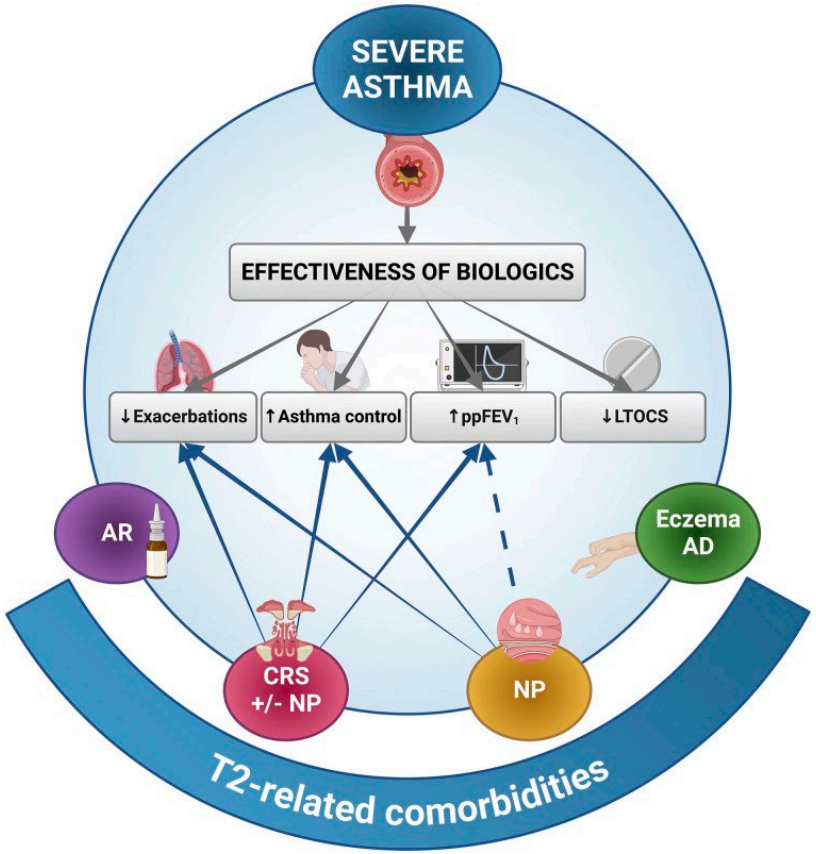
Comorbidities Can Impact Degree of Asthma Improvement with Biologics



- International Severe Asthma Registry (ISAR)
- 1765 patients started on biologics, most on anti-IL-5 therapy
- Compared to those without, those with co-morbid CRS with or without NPs:
  - 23% fewer exacerbations per year
  - 59% higher odds of better asthma control after starting biologics
  - Additional FEV1% predicted improvement of 3.2%
  - No difference in weaning OCS doses
- No effect of co-morbid AR or AD
- Corroborates findings of individual biologic agents in sub-analysis studies of RTCs & real-world trials

Pelaia C, et al. In Do Comorbidities Influence the Response to Biologics in Severe Asthma? Am J Respir Crit Care Med. 2024;209(3):233-235 doi:10.1164/rccm.202311-2103ED.

Wechsler ME, et al. Respir Crit Care Med. 2024;209(3):262-272.

Differential Diagnoses for Eosinophilia and Pulmonary Symptoms

Other Forms of ANCA-Associated Vasculitis

- AAV is a group of 3 separate diseases: MPA, GPA, and EGPA[1]
- **GPA and MPA are more likely to have kidney involvement and to be ANCA positive**, and less likely to be associated with asthma

Hypereosinophilic Syndrome

- Distinction between EGPA and HES is challenging as both conditions are characterized by **eosinophilia and widespread organ involvement**[2,4]
- Patients with HES usually do not have asthma or vasculitic complications and are ANCA negative[4]

Infection and Other Exposures

- Stool culture could be considered, particularly in patients with GI symptoms, to exclude **helminthic infections**[2]
- Eosinophilia and respiratory symptoms are major features of **allergic bronchopulmonary aspergillosis and eosinophilic pneumonia**[2]
- Eosinophilia can also be caused by **drug reactions and malignancies**, such as leukemia, lymphoma, and solid tumors[5]

Jennette JC, et al. *Arthritis Rheum.* 2013;65(1):1-11. 2. Trivioli G, et al. *Rheumatology (Oxford).* 2020;59(suppl 3):iii84-iii94.
3. Yates M, et al. *Clin Med (Lond).* 2017;17(1):60-64. 4. Gioffredi A, et al. *Front Immunol.* 2014;5:549. 5. Bloom JL, et al. *Rheum Dis Clin North Am.* 2023;49(3):563-584.

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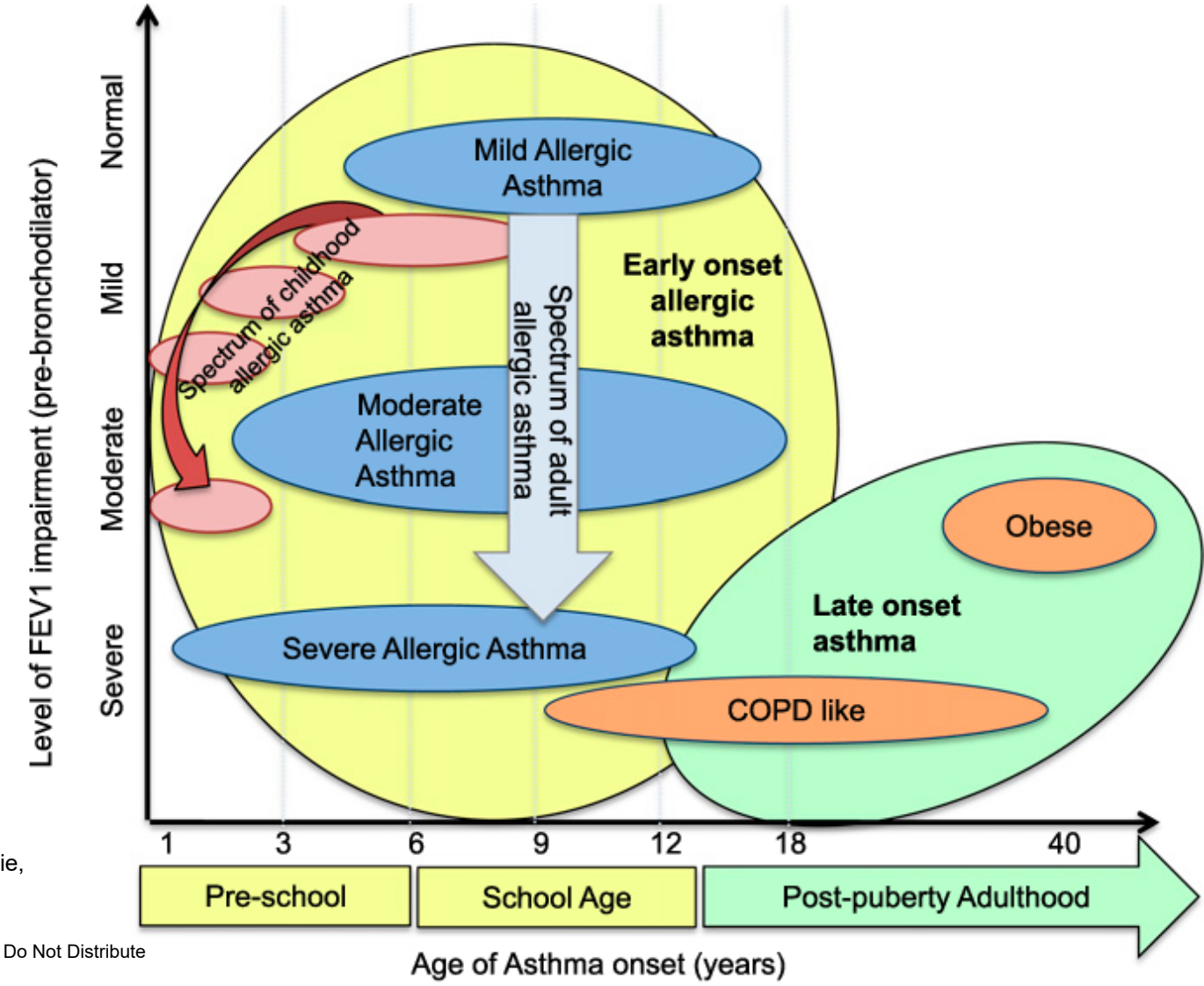
Heterogeneity of Severe Asthma

- Asthma is not a single disease; there are many phenotypes
- There is significant overlap among phenotypes
- T2-High vs. T2-Low
- Need for precision medicine due to differential treatment responses
- Phenotypic overlap with other inflammatory conditions



Treatment Complexity, Challenges, and Barriers

- Misdiagnosis
- Lack of recognition of uncontrolled and severe asthma
- Confounders and co-morbidities
- Medication access and cost
- Access to subspecialty care
- Medication administration complexity
- Biologic therapies
- Glucocorticoid resistance

Up to half of patients do not achieve well-controlled status with guideline-based treatment

Asthma Guidelines: The Checklist

For ALL patients with asthma

- ❑ Asthma control
- ❑ Medication adherence
- ❑ Appropriate therapy
- ❑ Inhaler technique
- ❑ Environment (work, home)
- ❑ Psychological issues
- ❑ Spirometry
- ❑ Tobacco use
- ❑ Vaccinations

For patients with uncontrolled asthma, severe asthma, or exacerbations

- ❑ Asthma phenotyping (Type 1/2)
- ❑ Comorbidities: OSA, CRS, GERD, eczema, obesity
- ❑ Confounders: ILO/VCD, COPD, airway aspiration, bronchiectasis, infection, airway lesion, CHF
- ❑ Adjust maintenance therapy
- ❑ Add third agent
- ❑ Referral to asthma specialist
- ❑ Rescue therapy approach
- ❑ Respiratory biologic

Asthma Therapy Through the Ages

G. Cardano
- Diet
- Exercise
- Sleep
- No feathers

T. Willis
- Fetid gums
- Musk
- Vitriolic ether

J. Floyer
- Gill
- Hyssop
- Syrup of sulphur
- Bleeding

W. Osler
- Atropine
- Morphine
- Chloroform
- Lobelia

- Amyl nitrate
- Asthma cigarettes

Asthma Therapy – 1800s

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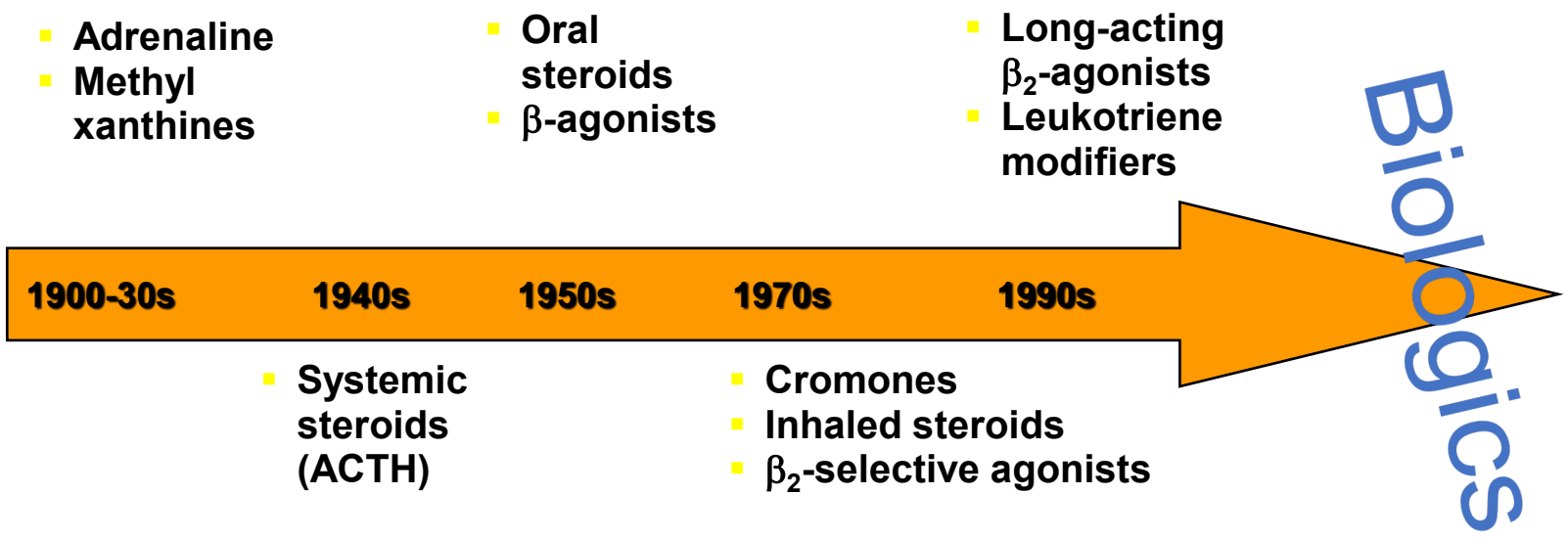
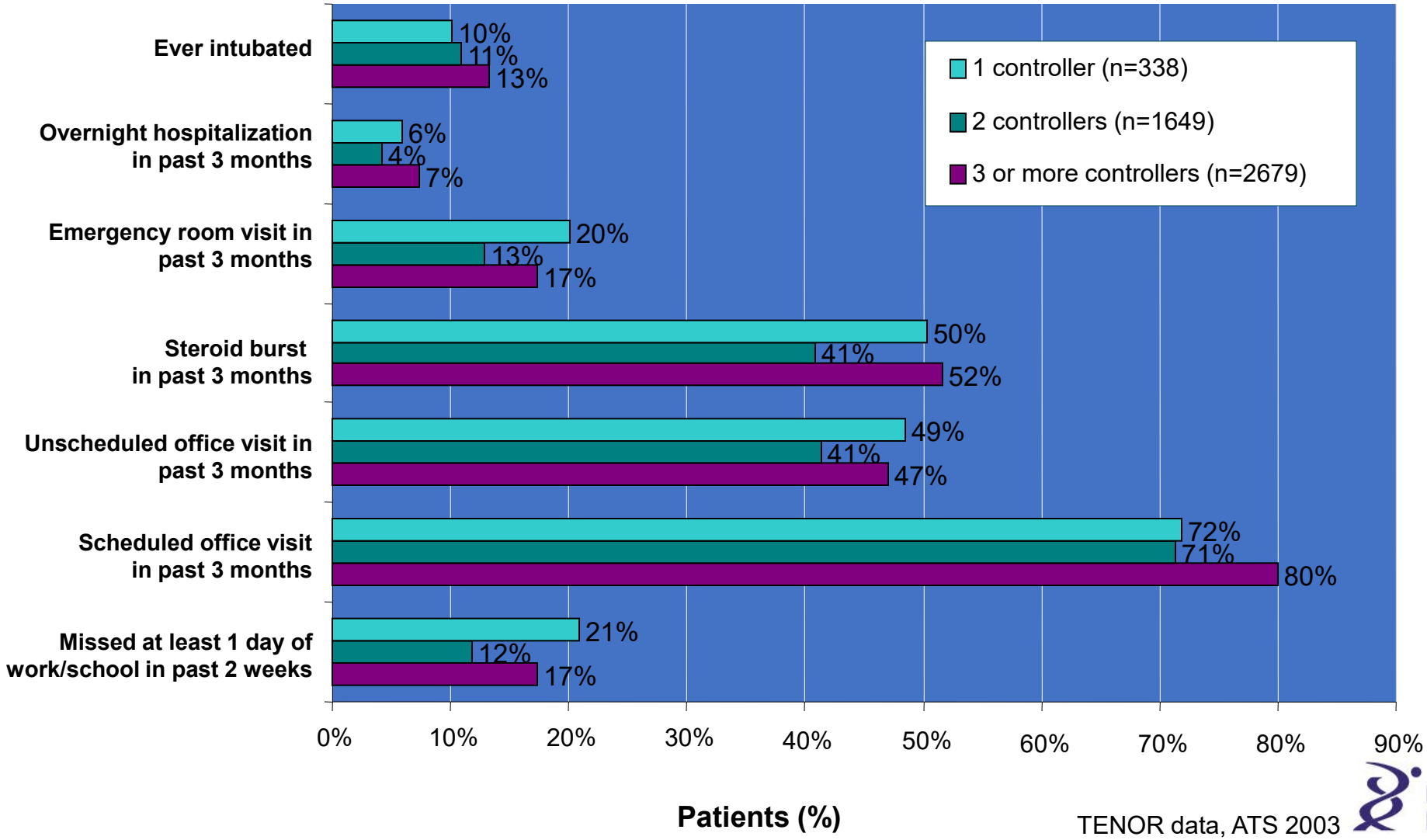
Asthma Therapy in the 1900s



Little evidence that using additional "standard" Rx helpful



TENOR data, ATS 2003

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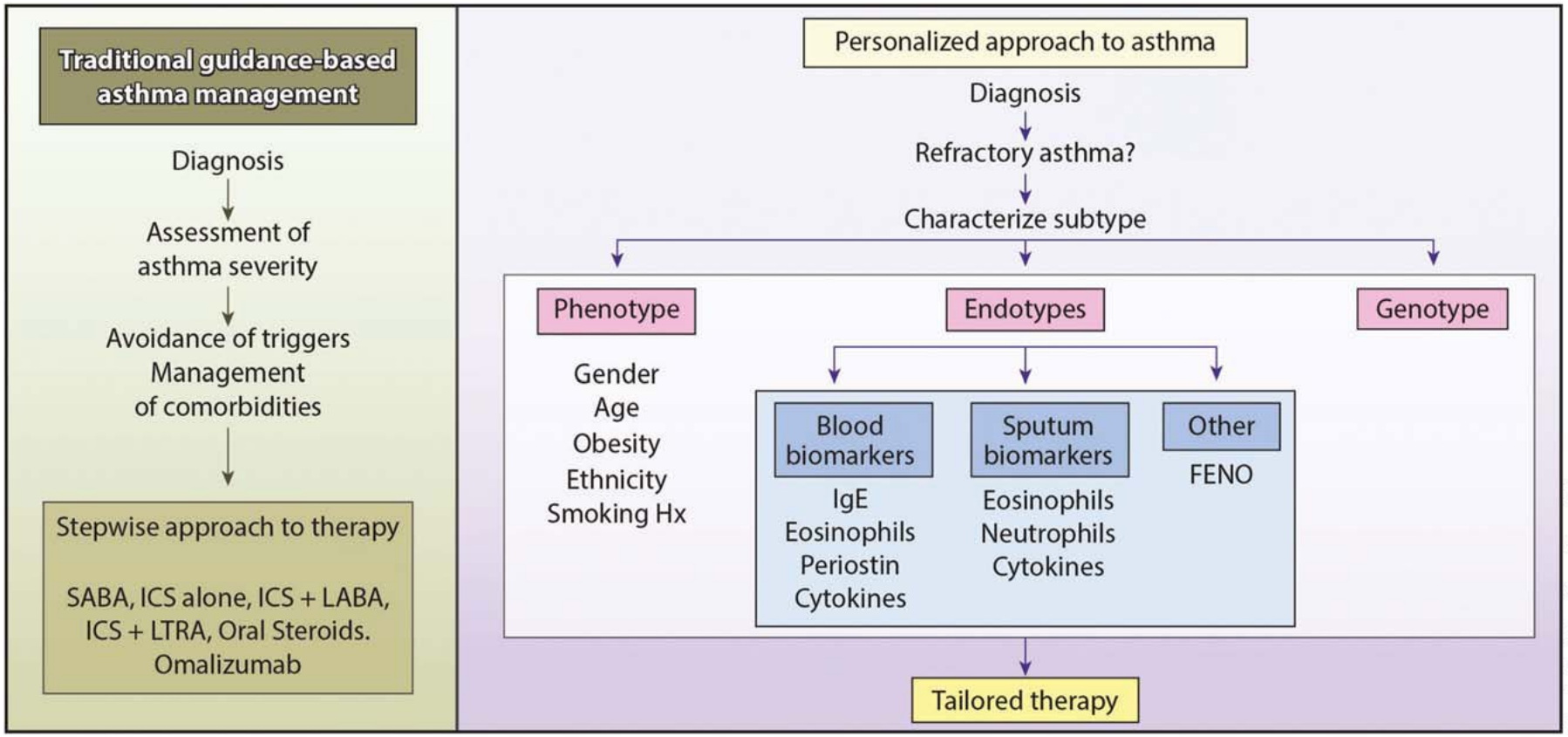
Traditional and Personalized Approach to Asthma Therapy



Dunn RM and Wechsler ME. Clinical Pharmacology and Therapeutics 2015; 97(1): 55-65

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Success of Therapy Based on Biomarkers: Anti-IL-5 Therapy in Patients with Elevated Eosinophils

Table 1—*Response to Anti-IL-5 and Eosinophil Phenotype*

Study/Year	Intervention	Sputum Eosinophil at Entry	Success
Flood-Page et al[18]/2007	Mepolizumab	5% of patients had >3% eos	X
Kips et al[19]/2003	Reslizumab	~30% of patients had >3% eos	X
Haldar et al[14]/2009	Mepolizumab	All patients had >3% eos on one occasion in 2 y	√
Castro et al[15]/2011	Reslizumab	All patients had >3% eos at randomization	√√
Nair et al[13]/2009	Mepolizumab	All patients had >3% eos on ≥3 occasions	√√√

√ = grade of success of intervention; eos = eosinophils; X = intervention unsuccessful.

- Success in response to Anti-IL-5 Therapy is based on eosinophil phenotype
- In 2 of the 5 studies that measured sputum eosinophils and in the three RCTs, the greater the certainty that an increase in eosinophils was persistent, the greater the success of treatment

Mitigation of Unmet Need in Asthma

1980 → 1989 → 1995 → 2001 → 2004 → 2007 → 2010 → 2015 → 2016 → 2018 → 2020

1989: NAEPP established

1997 EPR-2 published;

1991 EPR-1 published; Guidelines for the Diagnosis and Management of Asthma

2002 EPR-2 All severity-based treatments dependent on symptoms, rescue, lung function

2004: EPR-2 updated

2004 ACT™ launched

2003 first approved anti-IgE antibody

2007 EPR-3 published; impairment* and risk** treatments based on initial severity and subsequent control+

2015 tiotropium bromide
2015: IL-5 antagonist (IgG1)

2016: IL-5 receptor antagonist(IgG4)

2012: GINA: Bronchial thermoplasty for uncontrolled asthma

2017 PRECISION heatmaps highlight geographic regions of unmet need

2018 EPR-4 LAMA as add-on therapy; (No update to biologics;

2018 OCS Stewardship & Patient Charter

2017: IL-5 antagonist (IgG1)

2018: IL-4 receptor antagonist

2019 GINA recommends:
1. Symptom-driven or daily dose ICS
2. As-needed ICS-formoterol at steps 1 & 2
3. Refer for phenotypic assessment if uncontrolled on high dose tx; add-on biologic therapy at step 5

2019 Positive results for ICS/LABA/LAMA trials in Asthma

- Guidelines
- Major Therapy Introduced
- PRECISION Program
- Other

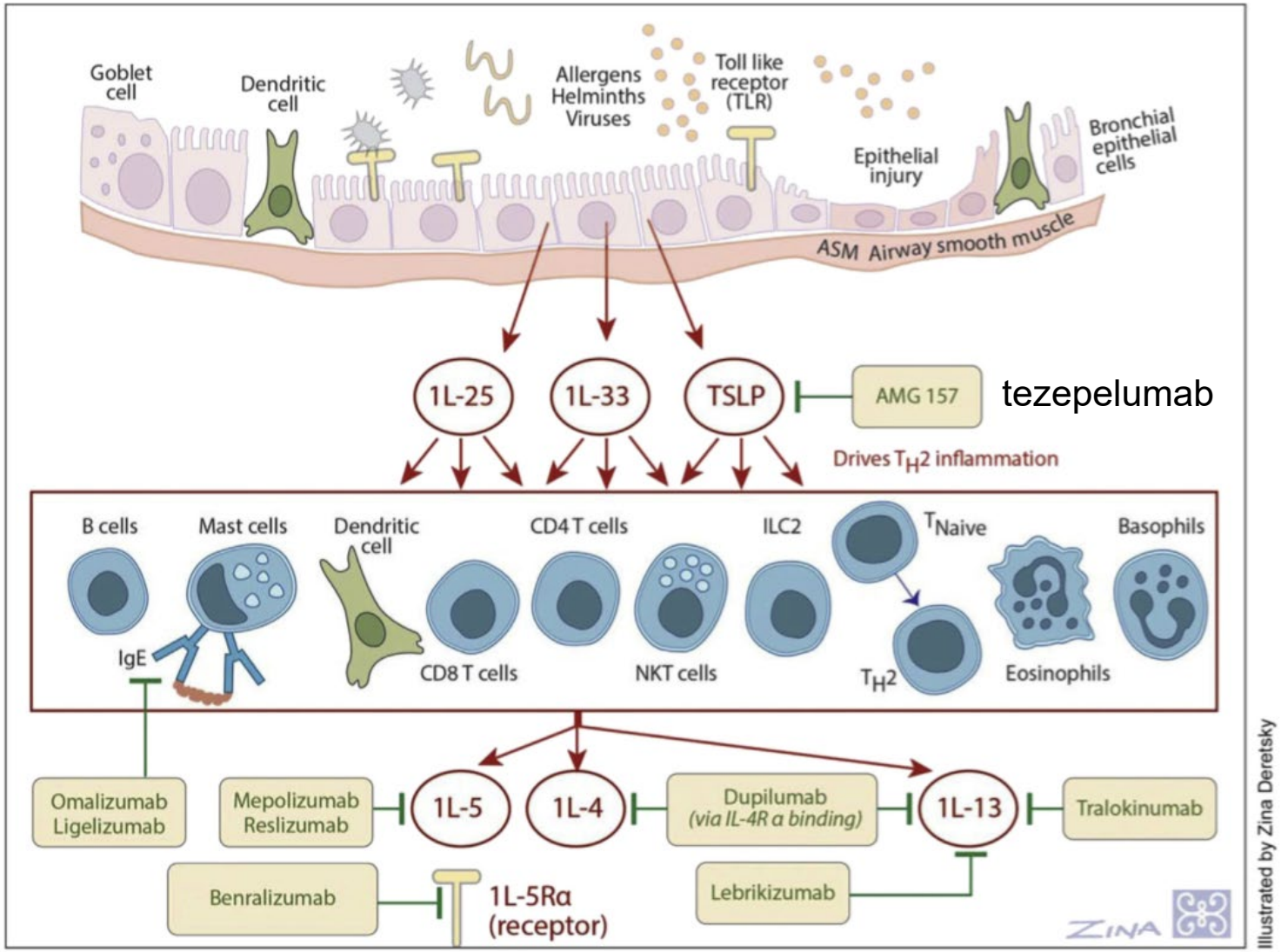
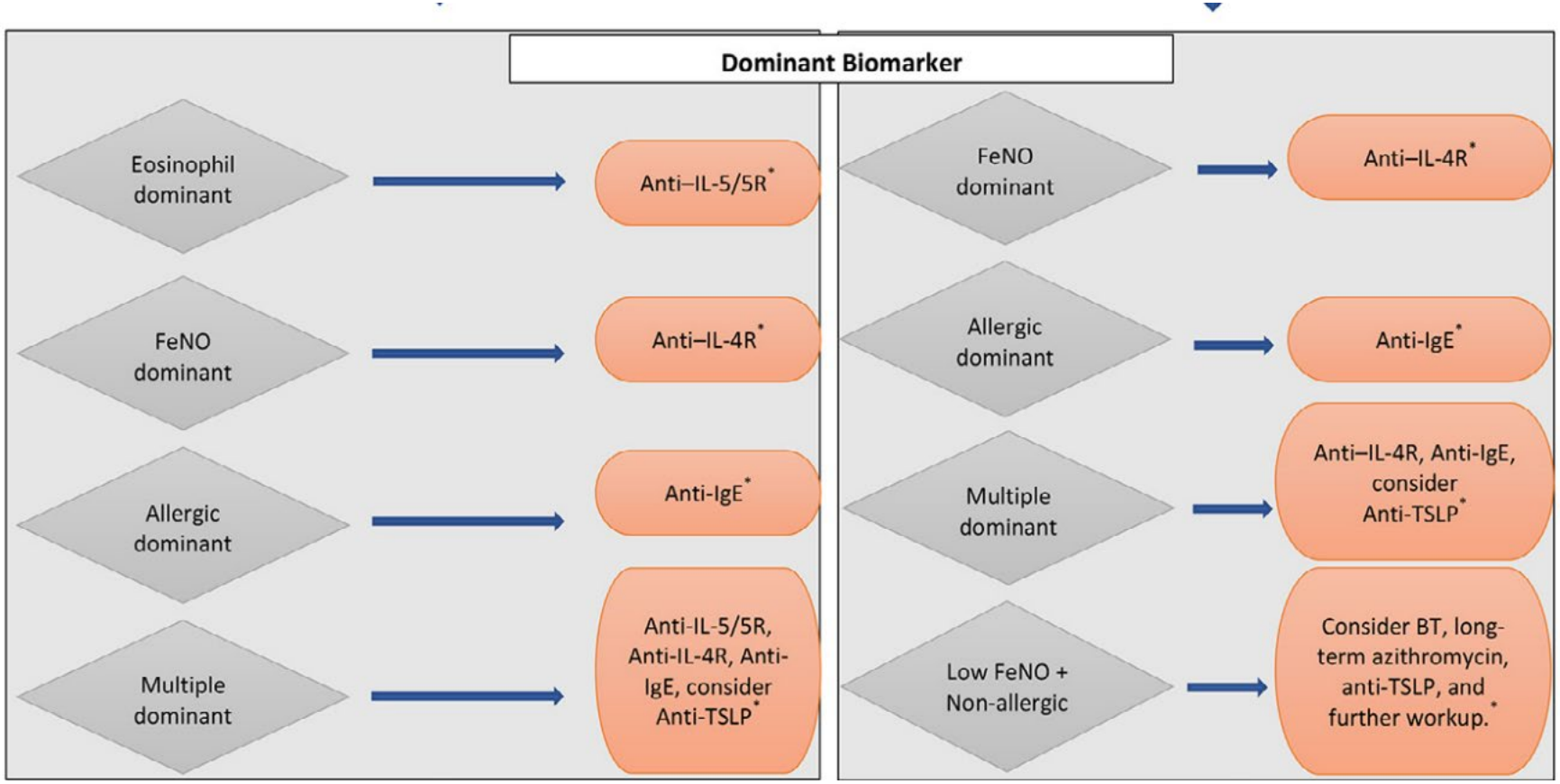


FIGURE 2. Important type 2-inflammation targets for biologic therapies. *TSLP,* Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al.[57]

Katial et al. JACI: In Practice 2017. 5(2): S1-S14.

Biomarkers Determining Use of Biologic



Wang E, Weschler M, Ann Allergy, Asthma Immunol 2022: 128:379

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Total IgE as a Biomarker of Response

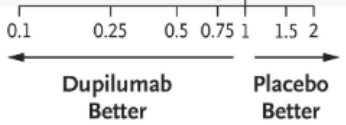
Allergen-specific IgE				
Omalizumab	Univariate analysis of INNOVATE[114]	Allergic[a]	Number of (severe) exacerbations[b]; responder analysis	Not predictive
Total IgE				
Omalizumab	Univariate analysis of 7 trials[115]	Allergic[c]	Number and rate of (severe) exacerbations[b]; AQLQ score; physician's overall assessment, FEV_1	Not predictive
Omalizumab	STELLAIR[50]	Severe allergic[c]	Physician's overall assessment; exacerbation[b] rate	≥75 IU/mL total IgE not predictive
Mepolizumab	Post hoc meta-analysis of MENSA and MUSCA[24]	Eosinophilic[d]	Exacerbation[e] rate; FEV_1; SGRQ; ACQ-5	Total IgE quartiles (≤ 30, >30-170, >170-450 and >450 UI/mL) not predictive
Benralizumab	Pooled data from SIROCCO and CALIMA[44]	Severe uncontrolled[f]	Exacerbation[e] rate	Total IgE quartiles (<62.0, ≥62.0-<176.2, ≥176.2-<453.4, ≥453.4 kU/L) not predictive
Dupilumab	Post hoc analysis of QUEST[15]	Severe uncontrolled[g]; allergic asthma[h] subgroup analysis	Exacerbation[d] rate; FEV_1; ACQ-5 score	Ø 700 IU/mL total IgE not predictive

Oppenheimer et al. / Ann Allergy Asthma Immunol 129 (2022) 169−180

Dupilumab Phase 3 Biomarker Data

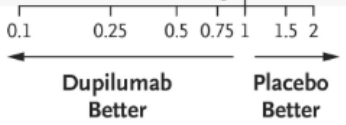
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
Fe_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Castro M, et al. NEJM 2018; 378:2486-2496.

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High Feno And High B-eos In Combination Associated With Significantly Increased Exacerbation Rates In Patients With Moderate to Severe Asthma

Estimated annualized severe exacerbation rates over 52 weeks by baseline FeNO and b-EOS level in placebo-treated patients from Dupilumab Phase III LIBERTY ASTHMA QUEST study

		FeNO (ppb)		
		<25	≥25 to <50	≥50
Blood Eosinophils (cells/µL)	≥300	0.84 (n=89)	1.24 (n=97)	1.78 (n=98)
	≥150 to <300	0.82 (n=96)	1.14 (n=53)	0.48 (n=25)
	<150	0.56 (n=106)	0.62 (n=35)	0.53 (n=21)

In patients with b-EOS ≥300, the risk of exacerbations increases with increases in FeNO, while for those with b-EOS <300 the rates are similar regardless of FeNO

FeNO=fraction exhaled nitric oxide; b-EOS-blood eosinophils; ppb=parts per billion

Busse WW et al. Poster presented at American Academy of Asthma, Allergy, and Immunology; 2020 Virtual Annual Meeting; Virtual Poster Hall. Poster 063.

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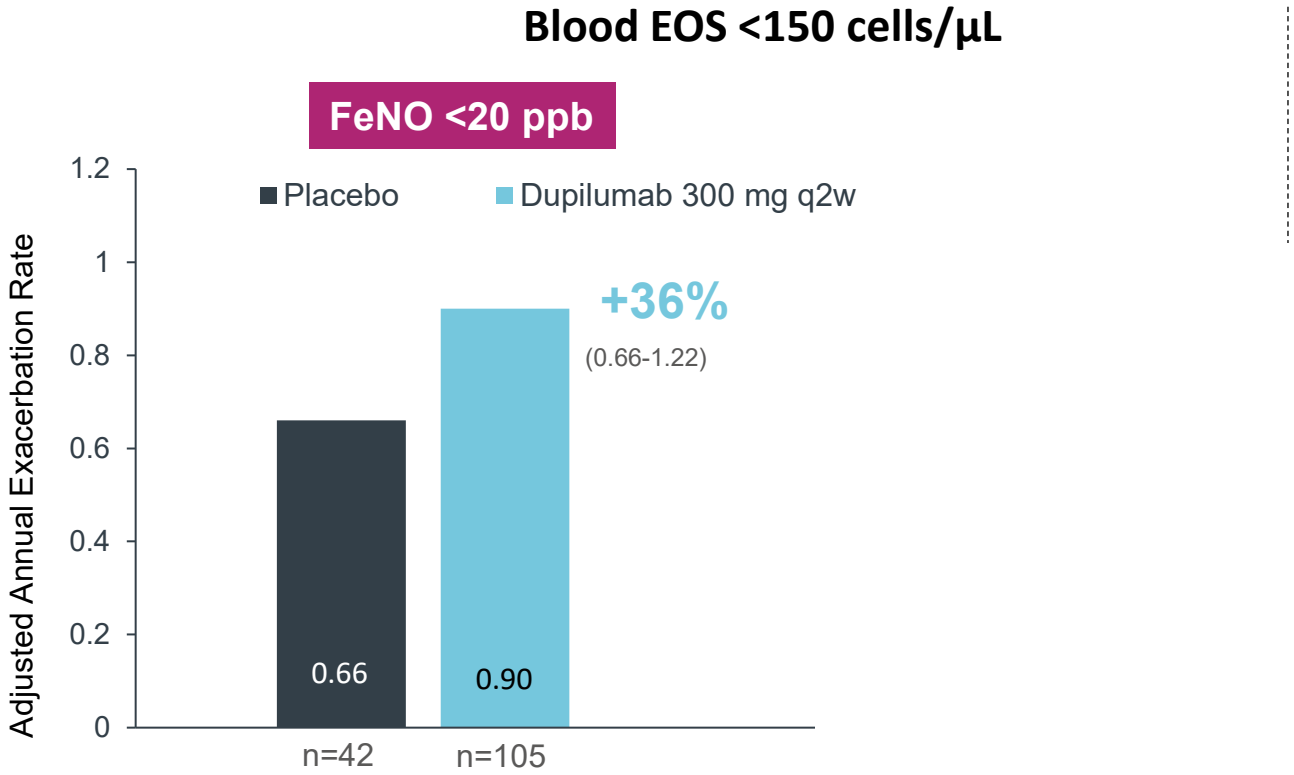
Combination of high b-EOS / high FeNO Predicts higher exacerbation risk



In high b-EOS/high FeNO group, baseline b-EOS increased along with FeNO

b-EOS=blood eosinophils; FeNO=fraction of exhaled nitric oxide; BL=baseline; ppb=parts per billion

*Baseline values are the combined values across both dupilumab dosing groups studied: dupilumab 200 mg q2w and dupilumab 300 mg q2w.

1. Pavord ID et al. Eur Resp J. 2019;54:suppl 63, OA3807. 2. Pavord ID et al. Presentation at: European Respiratory Society International Congress 2019; Madrid, Spain; Sept 28-Oct 2, 2019.

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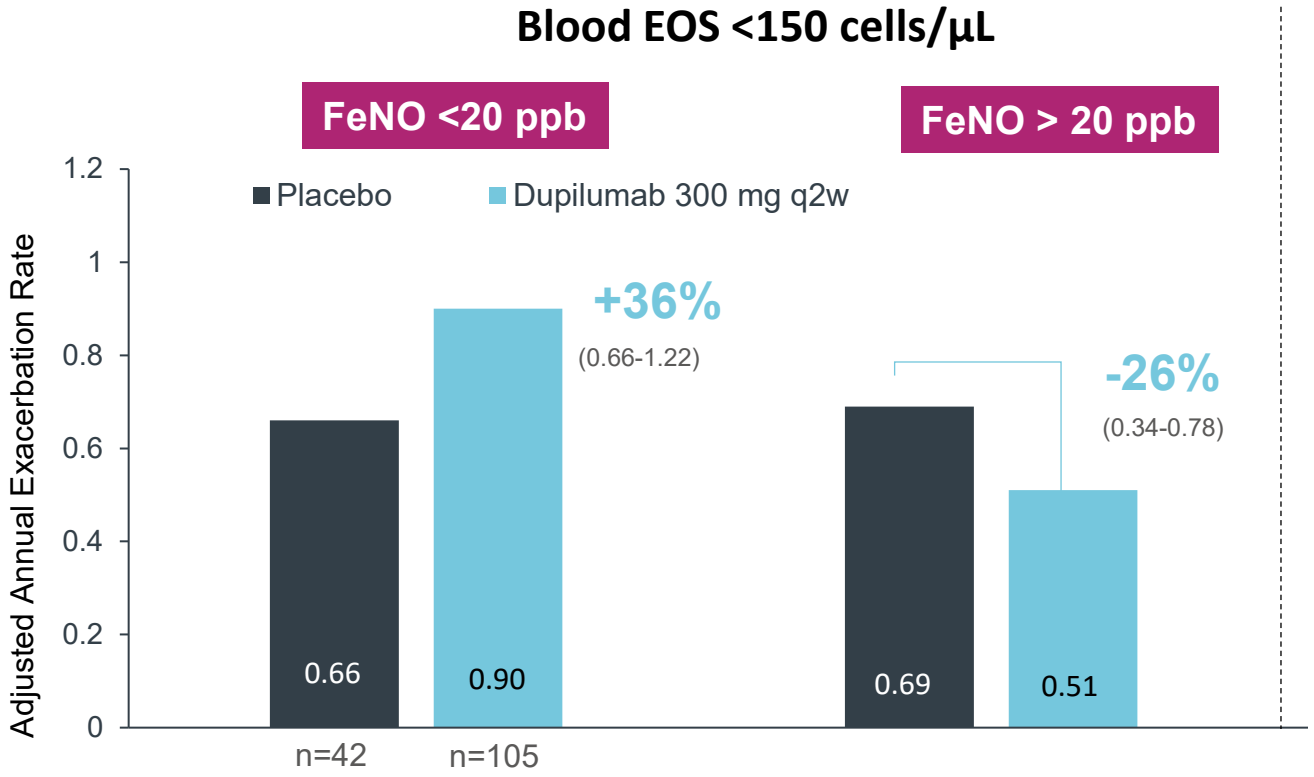

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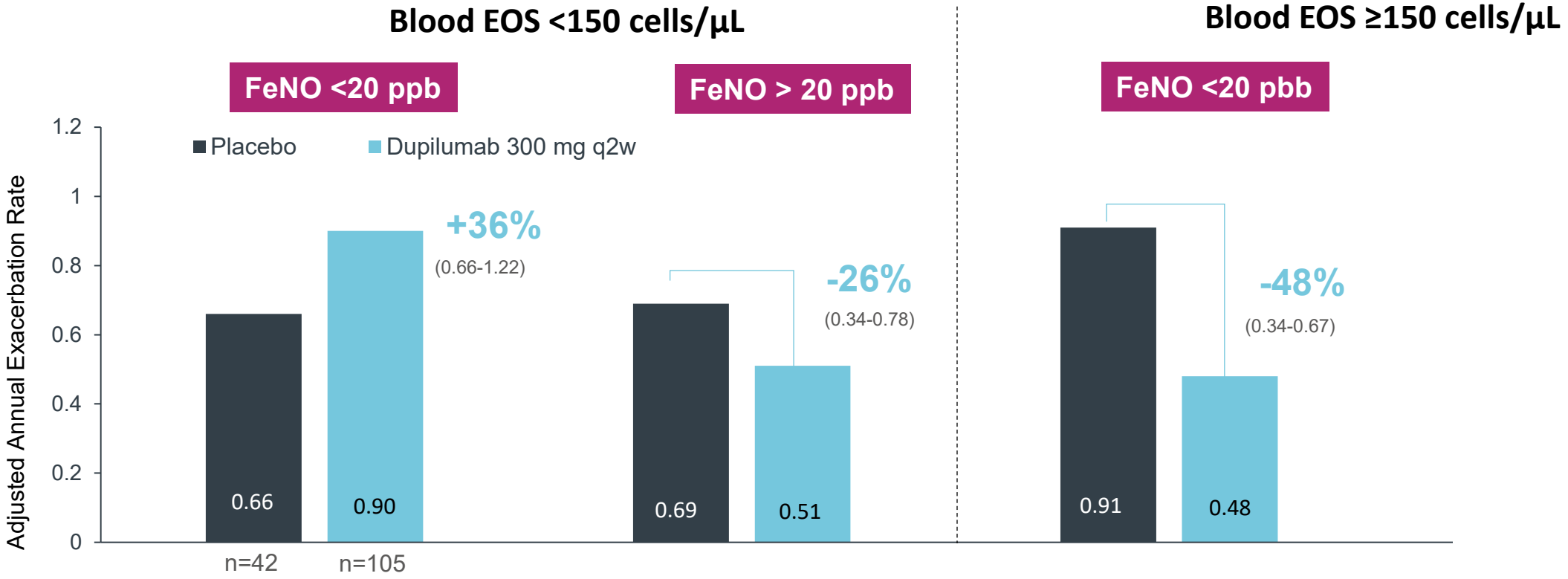

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Do Not Distribute

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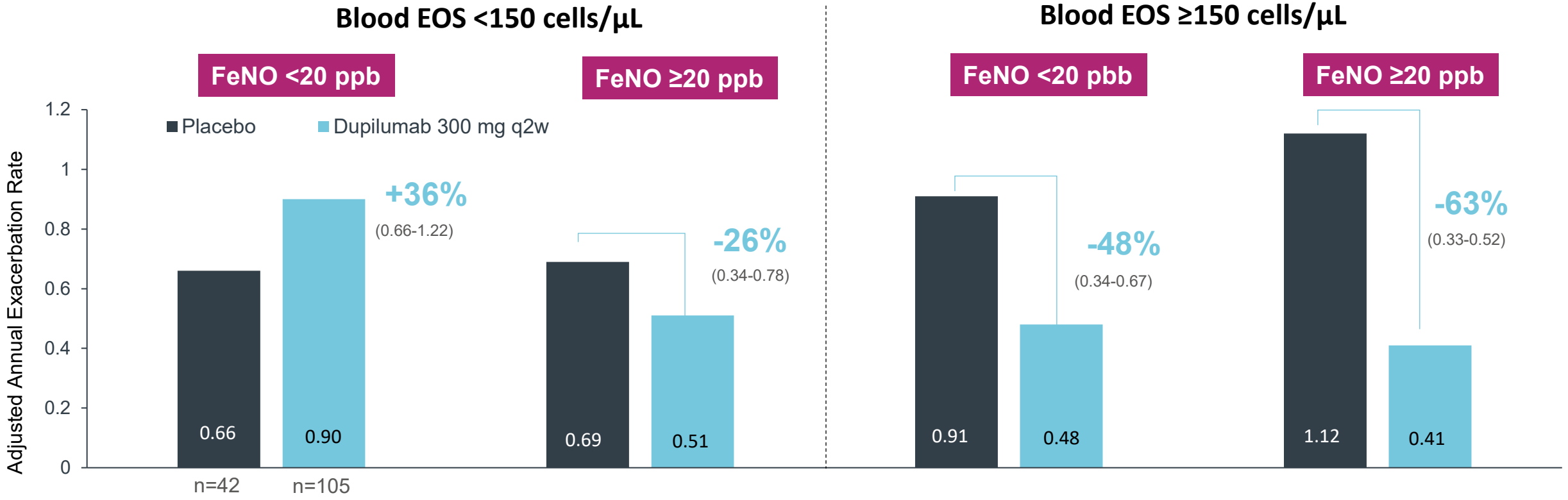

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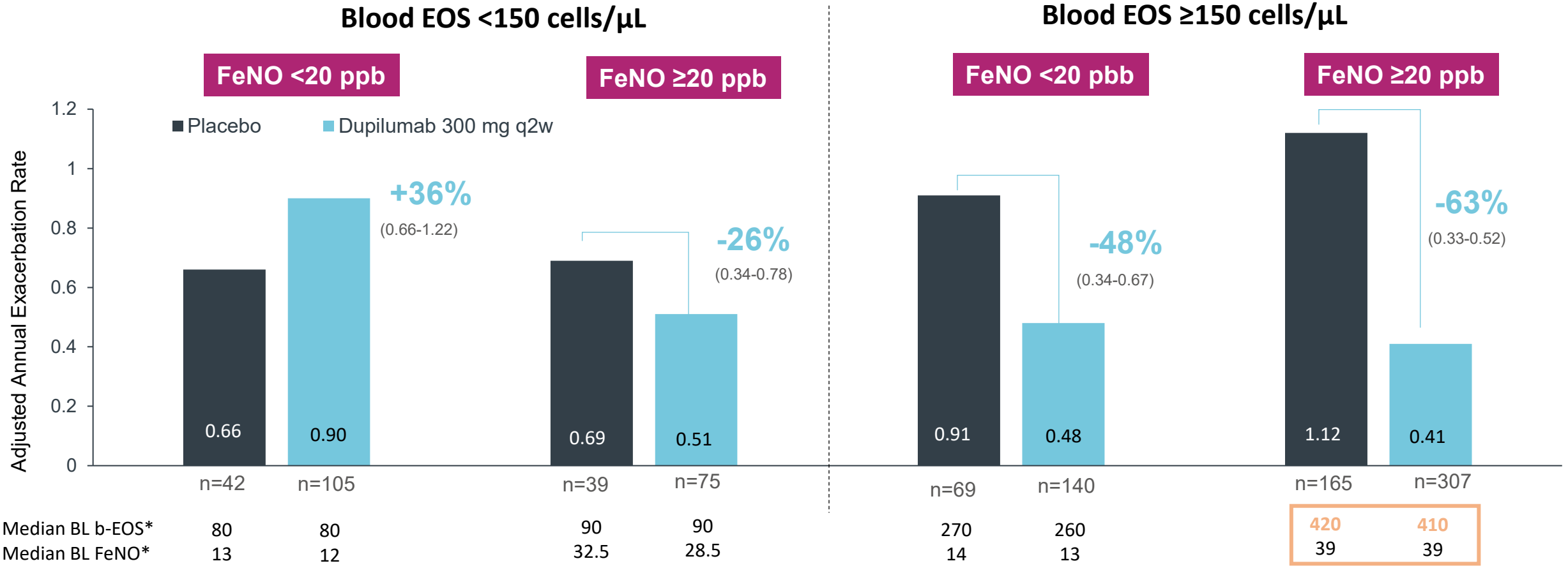

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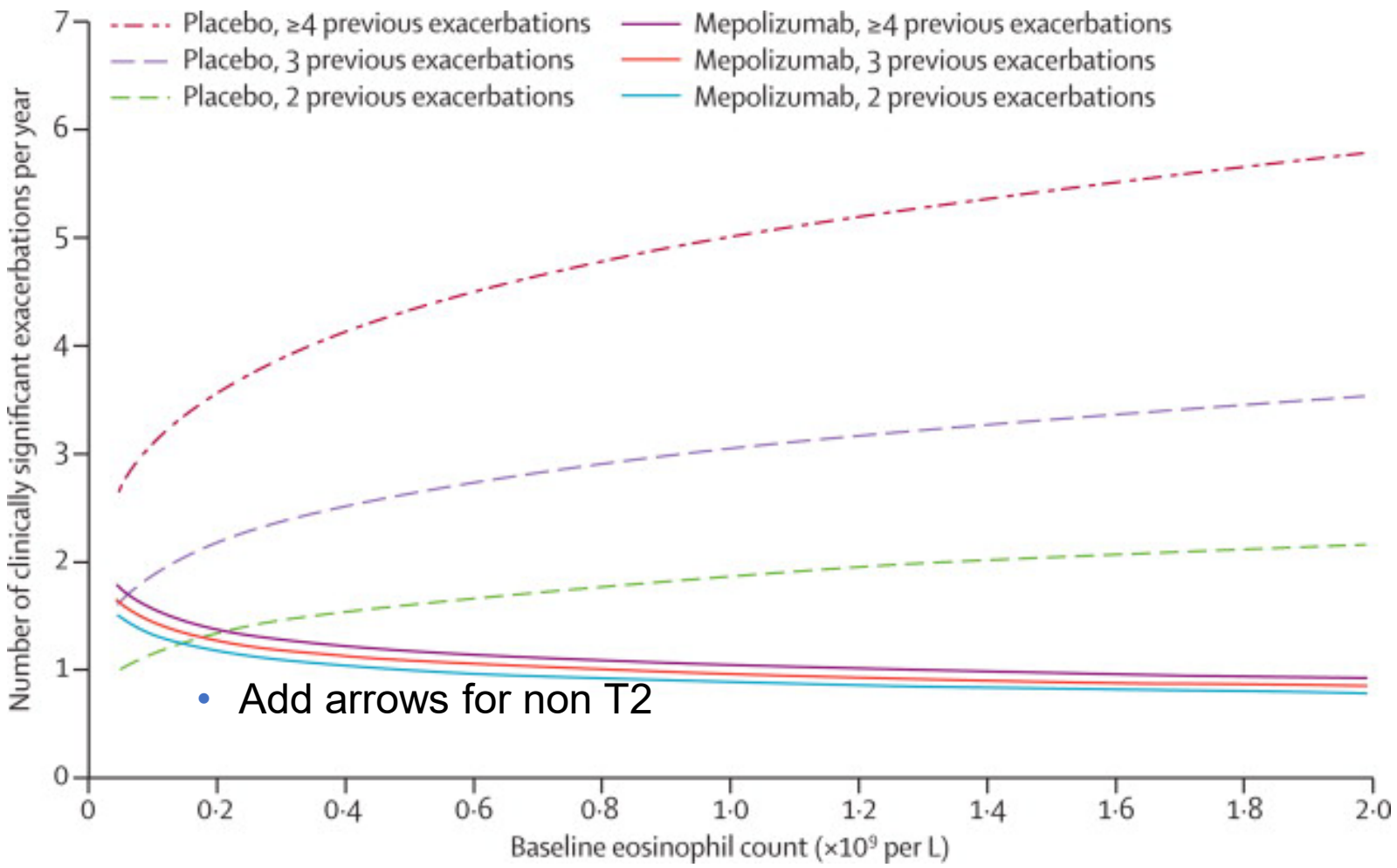
Blood eosinophil and number of exacerbations in the prior year



- Add arrows for non T2

Lancet 2012; 380: 651–59

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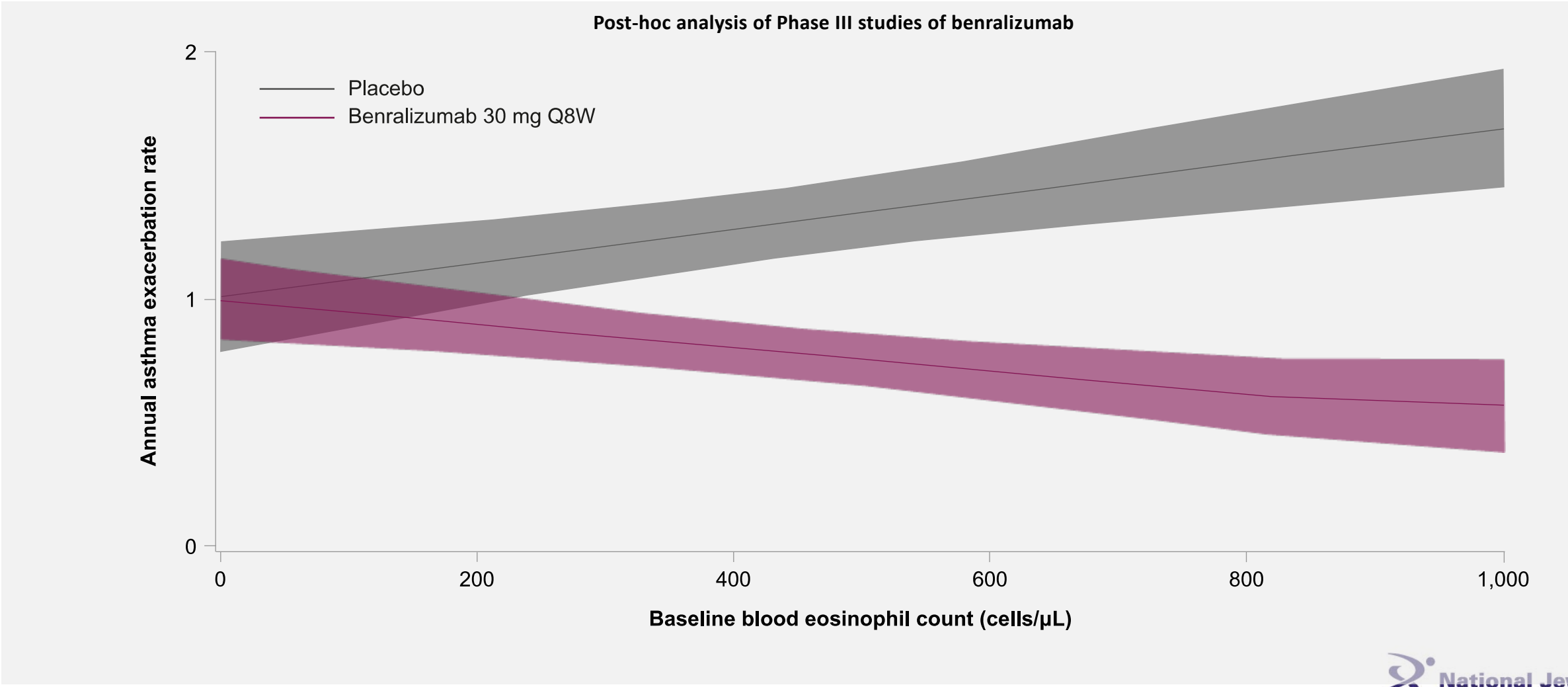
Increasing baseline blood eosinophil counts is associated with exacerbation frequency in severe asthma[1]



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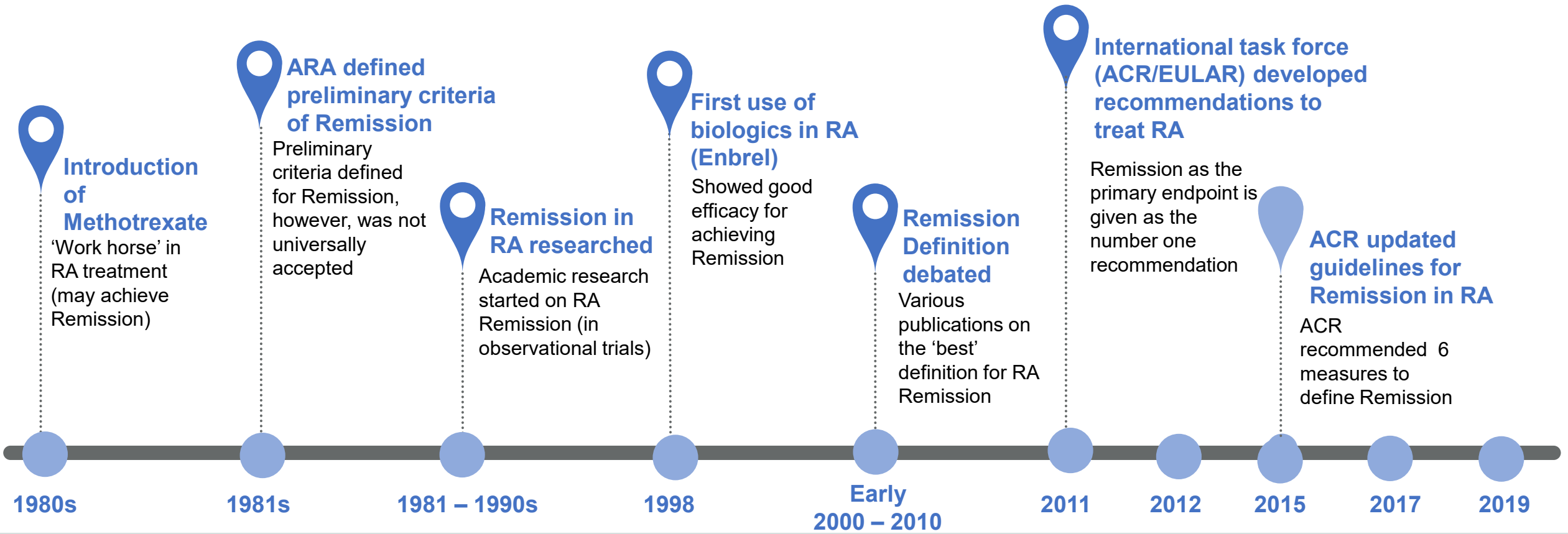
- Q8W: every eight weeks

1. Jackson DJ *et al*. Ability of serum IgE concentration to predict exacerbation risk and benralizumab efficacy for patients with severe eosinophilic asthma. *Advances in Therapy*. 2020; **37:** 718–29.

RA Remission Journey



Source for data: BMJ Journals, 2004 ;BMJ Journals, 2011; NCBI 2013; American college of Rheumatology, 2015

Can RA Be A Model For How To Achieve Remission In SA

Rheumatoid arthritis	Severe asthma
Incurable inflammatory condition[1]	✓ Incurable inflammatory condition[4]
Disease progression results in irreversible joint damage and visible disability[2]	✓ Disease progression results in irreversible lung function decline[5] and disability that is not visibly perceived; underestimated disease burden contributes to worse outcomes[6]
Multiple targeted treatments, including DMARDs available with a realistic goal of clinical remission[1,3]	? Multiple targeted treatments available[7]; whether remission can be achieved is currently being explored[8]

DMARD = disease modifying anti-rheumatic drug.

1. Girdler SJ, et al. *J Orthop.* 2019;17:17-21; 2. Brown PM, et al. *Clin Med (Lond).* 2014;14(Suppl 6):s50-55; 3. Felson DT, et al. *Arthritis Rheum.* 2011;63:573–586; 4. Busse WW, et al. *Eur Respir Rev.* 2022;31(163):210183; 5. Pascual, RM, Peters SP. *J Allergy Clin Immunol.* 2009;124(5):883-892; 6. Crespo-Lessmann A, et al. *BMJ Open Respir Res.* 2017;4:e000189; 7. Pelaia C, et al. *Front Immunol.* 2020;11:603312; 8. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765.

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What can be achieved with biologics?

	Dupilumab	Dupilumab	Benralizumab	Benralizumab	Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/CALIMA Phase 3	2022[4] ANDHI Phase 3b	2022[5] NAVIGATOR Phase 3	2022[6] REDES	2022[7] CHRONICLE	2022[8] Danish Registry
Absence of symptoms[a,b] and	ACQ-5 <1.5	ACQ-5 <1.5	ACQ-6 <1.5 or ≤0.75	ACQ-6 <1.5 or ≤0.75	ACQ-6 ≤0.75[a,b]	ACT ≥ 20	Majority≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function and	Post-BD FEV_1pp ≥80%	Post-BD FEV_1 ≥80% *OR* pre-BD FEV_1 ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1pp >80% *OR* Pre-BD FEV_1 >20% from baseline	Not included	Not included	Post-BD FEV_1pp ≥80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	14.5%	28.7%	12.7%	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated· ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 6. Ribas DC et al. Drugs 2021;81(15):1763-1774. 7. Chipps, B et al. JACI 2022;149:Suppl AB147 8. Hansen S et al ERJ 2022;60:3553

Novel Asthma Therapies

- Depemokimab - long acting anti I-L5
- Dexpramipexole - depletes eosinophils
- Anti IL-33 - itepekimab, astegolimab, tozorakimab
- OX40; OX40L
- JAKi; Oral and inhaled
- Anti IL-17
- Anti IL-6
- Anti M1
- Anti Gata3 DNAzyme
- TLR9 agonists
- CRTH2 antagonists
- Anti IL-13 lebrikizumab, tralokinumab - failed phase 3
- Antibiotics
- Vitamin D

Key Points Summary

- Asthma is a highly prevalent condition with a high disease burden
- Severe asthma accounts for disproportionate amount of asthma cost to society
- Several subtypes of asthma exist:
  - Type 2 or T2 High, characterized by eosinophilic and/or allergic inflammation
  - Non Type 2 or T2 Low, characterized by neutrophilic or paucigranulocytic inflammation
  - Mixed (eosinophilic and neutrophilic), with features of both
- Need better biomarkers for response to therapy
- Current biologics for T2 high disease with best data for Tezspire for T2 low

Questions?