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Case-Based Interactive ARS on Difficult to Control Asthma

Focus on Confounders & Adherence

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Disclosure

- **Lecture honorarium:** Astra Zeneca, Boehringer Ingelheim
- **Advisory Board Member:** Astra Zeneca, Boehringer Ingelheim, GSK

Case 1

- A 15-year-old female referred from GP for uncontrolled asthma
- She was diagnosed asthma for 2 years
- She had several emergency visits despite being treated with salmeterol/fluticasone evohaler (25/125) 2 puff bid, theophylline (200) bid and salbutamol 2 puff prn

Physical Examination

- HEENT: swelling of turbinate, mucopurulent nasal discharge
- Chest: rhonchi both lung

Diagnosis

- Difficult asthma

Difficult asthma (severe/refractory asthma)

- Failure to achieve control when the maximal recommended dose are prescribed

Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998;12:1209-18.

Which is the least likely cause of difficult asthma?

A. Wrong diagnosis
B. Poor compliance
C. Unidentified aggravating factors
D. Psychosocial factors
E. Severe asthma

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A. Wrong diagnosis
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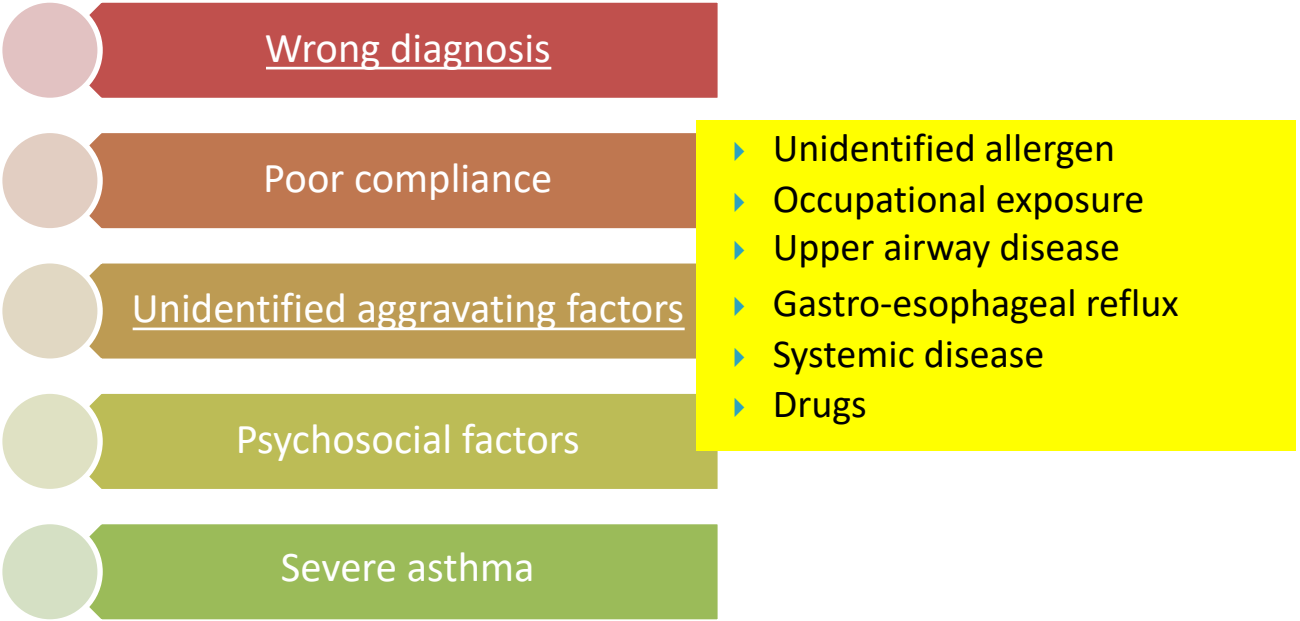
Difficult asthma

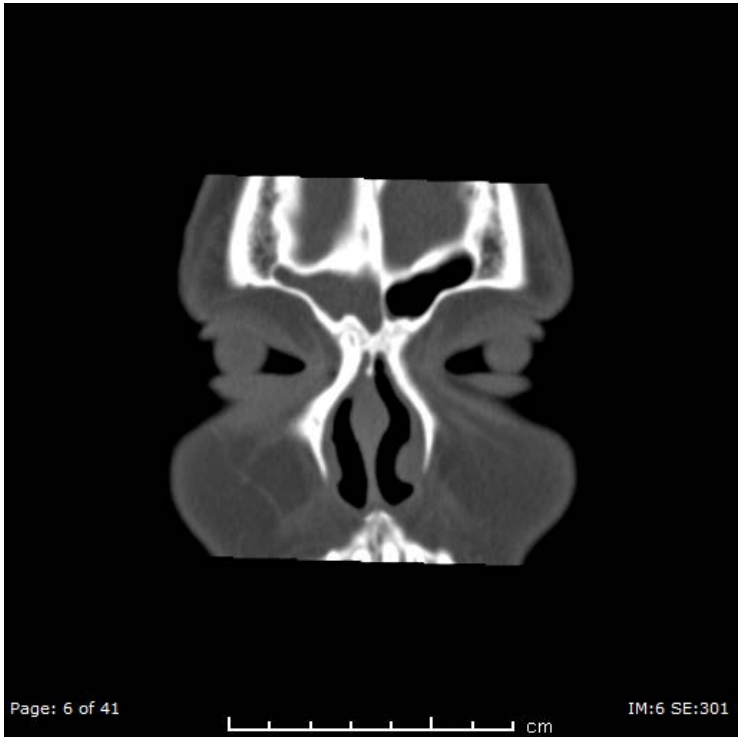
- COPD
- CHF
- Upper airway obstruction
- Localized airway obstruction
- Vocal cord dysfunction

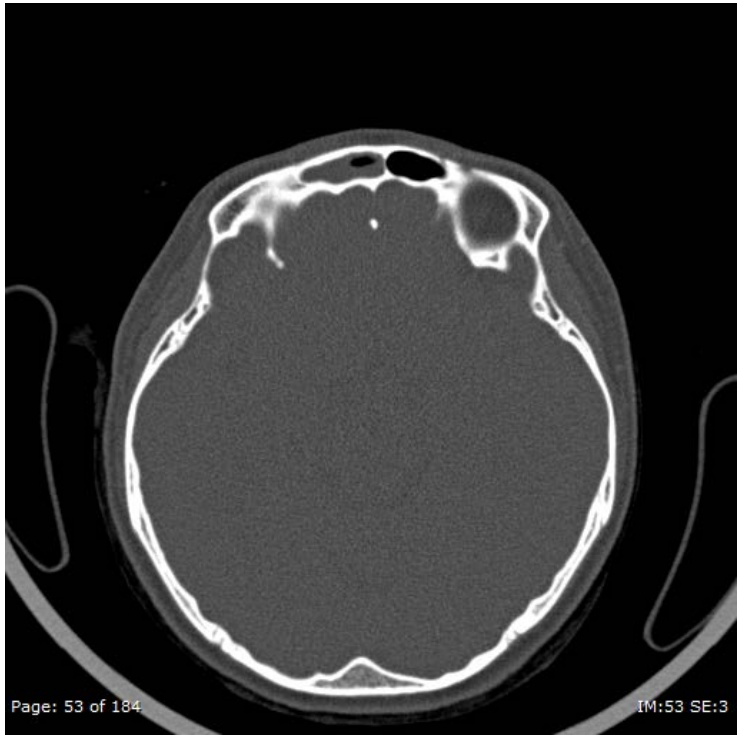


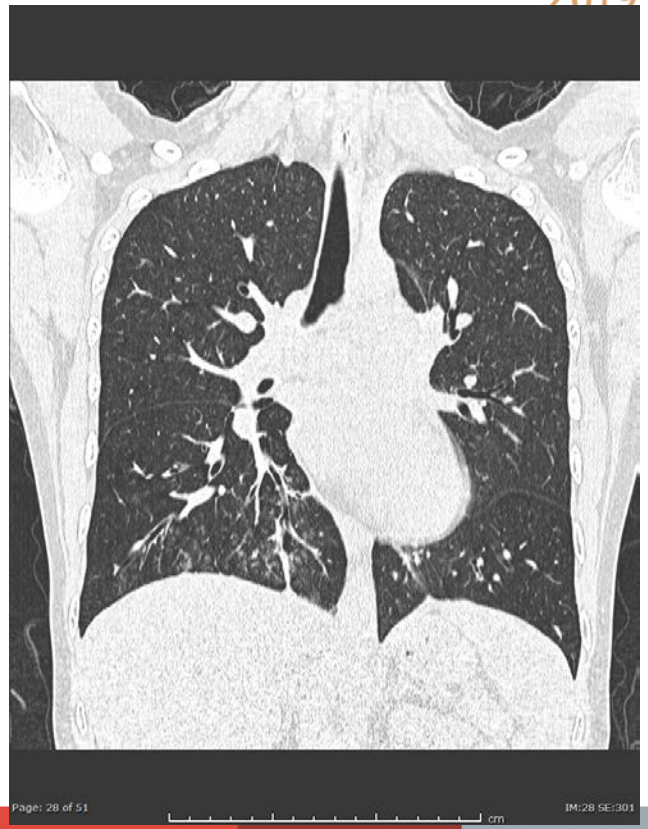
Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998;12:1209-18.

15F – left inferior turbinate hypertrophy with nasal septum deviation to the right

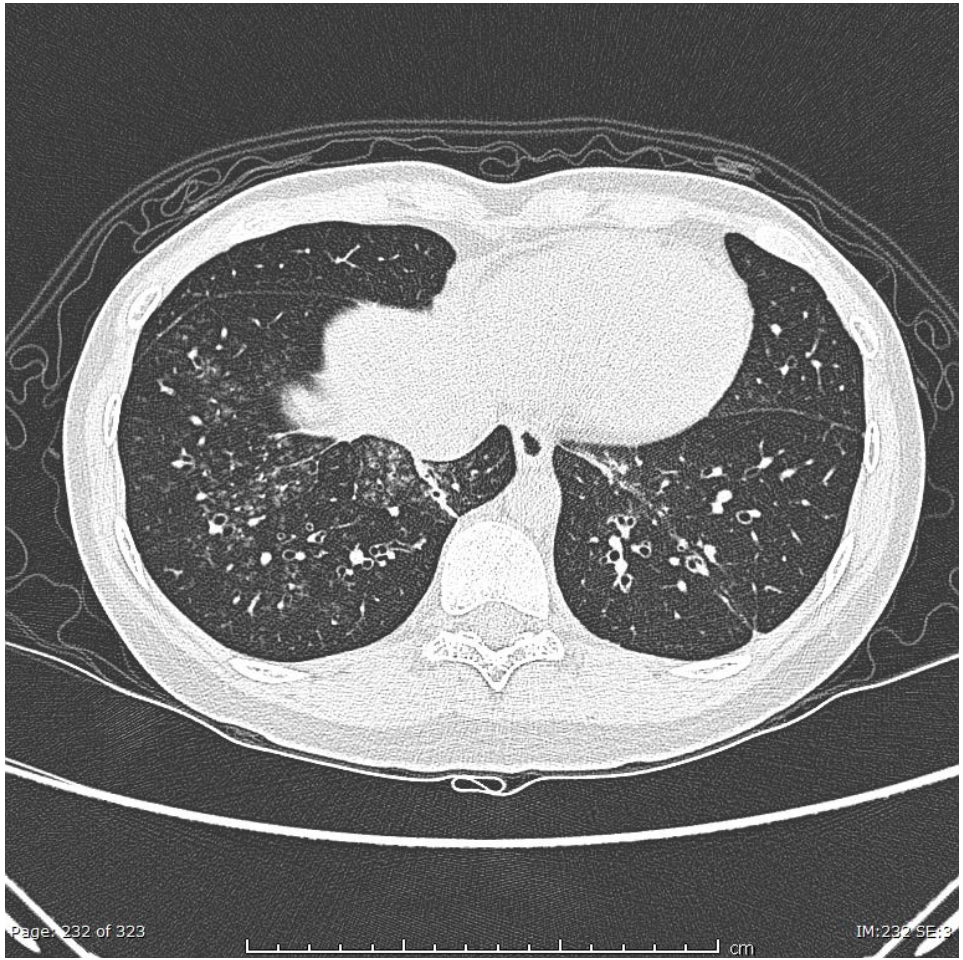
15F – Right frontal sinusitis







15F



15F – Random distribution of centrilobular nodular infiltration at RLL

Sinobronchial syndrome

- NSS nasal irrigation
- Pseudo epredine 1x3
- AMK 1X2
- Erythomycin (250) 1x4
- Avamys 2puff OD.
- Salmeterol/fluticasone (50/250) 1x2

Abo M, et al. Journal of thoracic disease 2018;10:E727-E9.

Case 2

- A 65 year old man was diagnosed asthma for one year.
- He was treated with salmeterol/fluticasone acuhaler (50/250) bid, salbutamol 2 puff prn and for 3 months but he still have asthma symptoms.
- He never smoke
- CXR= normal

- PE: HEENT normal, Chest Clear

Spirometry

	predicted	PRE-RX	%pred	POST-RX	%pred	%CHG
FVC (L)	4.12	3.25	79	3.50	85	8
FEV1(L)	3.13	2.15	60	2.60	83	20
FEV1/FVC		68		74		

Diagnosis

- Difficult asthma

What should we do next?

A. Change salmeterol/fluticasone 50/250 to salmeterol/fluticasone 50/500 bid
B. Add montelucast
C. Add triotropium respimat
D. Check inhaler technic

What should we do next?

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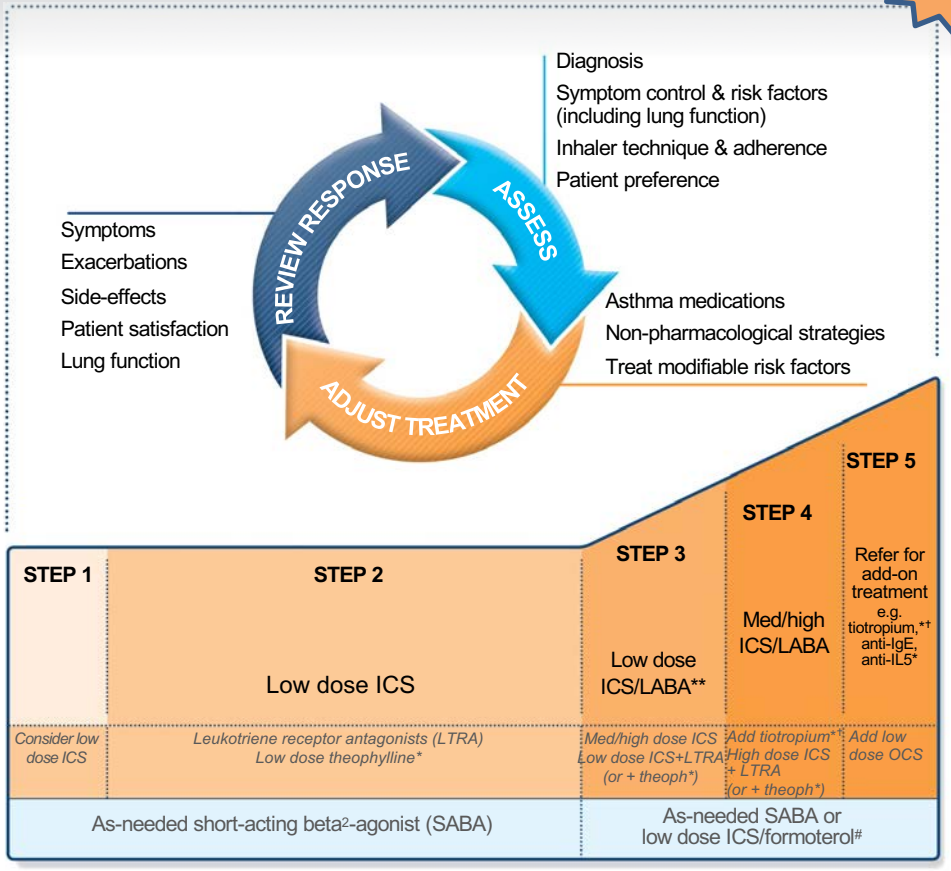
D. Check inhaler technic

Stepwise management - pharmacotherapy

UPDATED 2017



*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Provide hands-on inhaler skills training

Choose

- Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills and cost. For ICS by pMDI, prescribe a spacer
- Avoid multiple different inhaler types if possible

Check

- Check technique at every opportunity – "*Can you show me how you use your inhaler at present?*"
- Identify errors with a device-specific checklist

Correct

- Give a physical demonstration to show how to use the inhaler correctly
- Check again (up to 2-3 times)
- Re-check inhaler technique frequently, as errors often recur within 4-6 weeks

Confirm

- Can you demonstrate correct technique for the inhalers you prescribe?
- Brief inhaler technique training improves asthma control

Case-Based Interactive ARS on Difficult to Control Asthma

Focus on Comorbidities and Triggers

Sandy Khurana, MD, FCCP
Director, Mary Parkes Asthma Center
University of Rochester, NY

UNIVERSITY of ROCHESTER

Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices

Objectives

- Review systematic and multi-disciplinary approach to management of ‘difficult to treat’ asthma
- Discuss common challenges when caring for such patients with focus on role of environmental triggers and contribution from comorbidities.

Case 1

A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

Based on this information, all that can be said is that this patient has:

A. Uncontrolled Asthma
B. Difficult Asthma
C. Severe Refractory Asthma
D. Do not have enough information to answer

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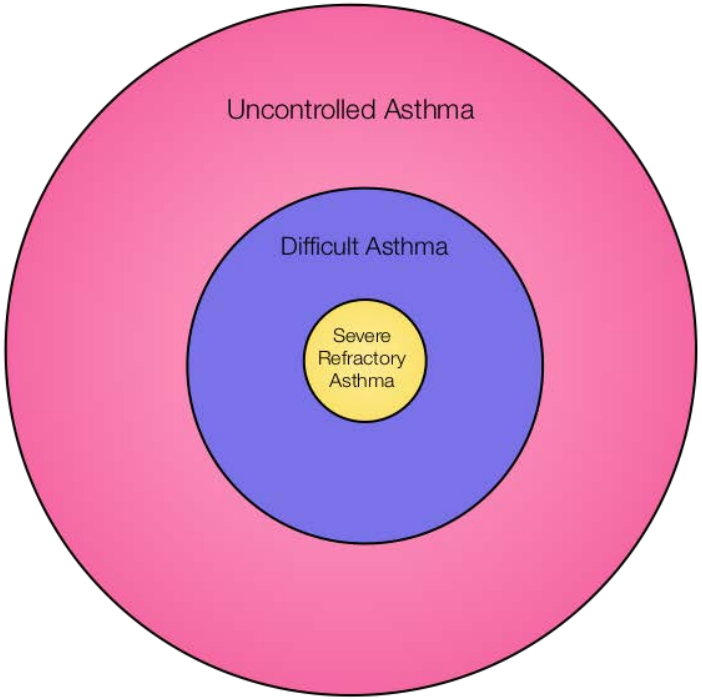
Severe Asthma - Definition

Asthma that requires treatment at GINA steps 4–5 or systemic CS for ≥50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or remains ‘‘uncontrolled‘‘ despite this therapy

Or

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Chung et al. Eur Respir J 2014; 43: 343–373



Incorrect Diagnosis
Poor Adherence
Uncontrolled comorbidities
Persistent Triggers

Guidelines based stepped controller Rx

Severe Refractory Asthma

Prevalence 50% <10%

Case continued

A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Never smoker
- No atopic disease or family history of asthma
- Frequent dyspnea, cough and wheeze, limiting physical activity
- Constant fear of a severe asthma attack

Case continued

A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Frequent GERD symptoms with nocturnal awakening
- Other symptoms – rapid onset of asthma symptoms, recent hoarse voice
- Asthma triggers – exercise, cold air, cigarette smoke, strong perfume, cleaning chemicals
- Medications – Budesonide/formoterol, montelukast, as needed albuterol

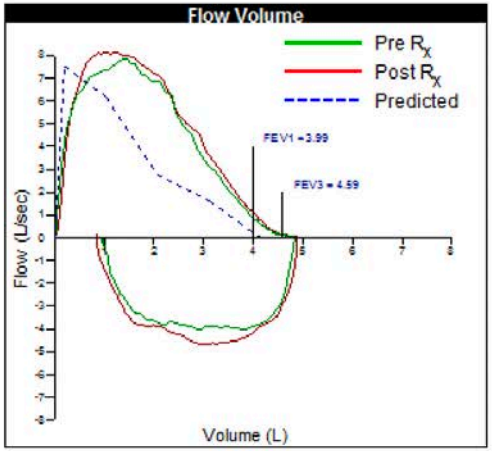
Case continued

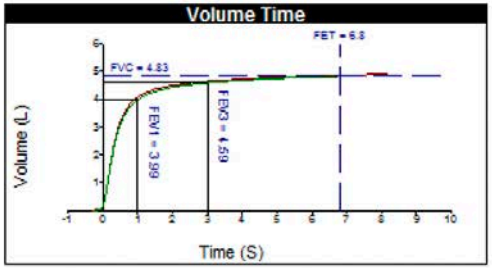
A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Occupation – automobile mechanic
- On exam: Normal vital signs. BMI 34. Inflamed nasal turbinate. Mild end-expiratory wheeze.
- Chest x-ray unremarkable
- Blood eosinophil count 300 cells/mm^3. IgE 78 kU/L. Negative allergen specific IgE panel.
- Medication adherence and inhaler technique confirmed

Spirometry

Legend	N = Normal	A = Abnormal								
Spirometry at BTPS		ATS ✔	Pre Bronchodilator					✔	Post Bronchodilator	
		Actual	Predicted	% Pred	CI Range			Actual	% Pred	% Chg
FEV_1	L	3.99	3.32	120	2.66	3.98	A	4.09	123	3
FVC	L	4.83	4.15	116	3.36	4.93	N	4.88	118	1
FEV_1 / FVC	%	83	81	102	71	91	N	84	104	1
FEF_{25-75} [ISO]	L/s	4.46	3.19	140	1.79	4.60		4.83	151	8
PEFR	L/s	7.84	7.53	104	5.59	9.47		8.16	108	4
FIF50	L/s	3.99	----	----	----	----		4.62	----	16
MVV	L/m	----	108.5	----	57.5	159.5		----	----	--





Which of the following statements is correct?

A. Patient has **severe** eosinophilic asthma and treatment with anti-IL5 therapy should be initiated immediately

B. The next step in management of this patient should be aggressive treatment of GERD

C. Omalizumab therapy is indicated next as patient's IgE level is in the treatment range

D. Patient does not have asthma as spirometry is normal with no bronchodilator response

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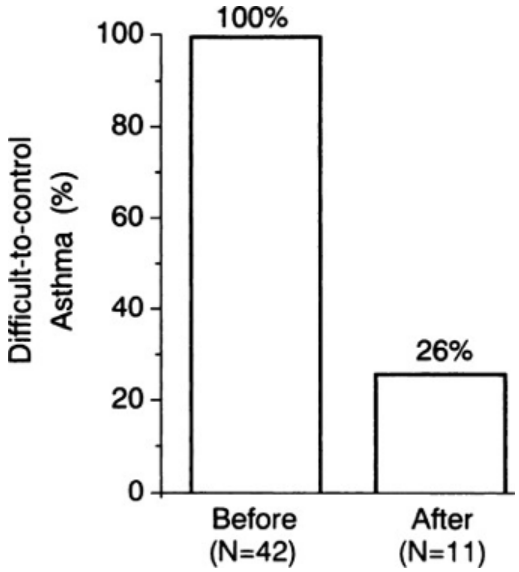
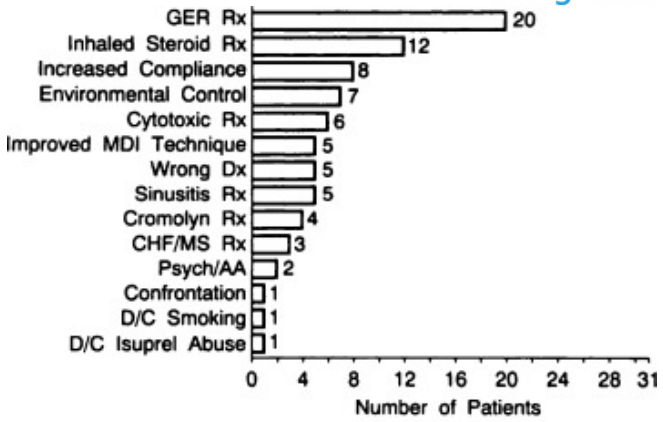
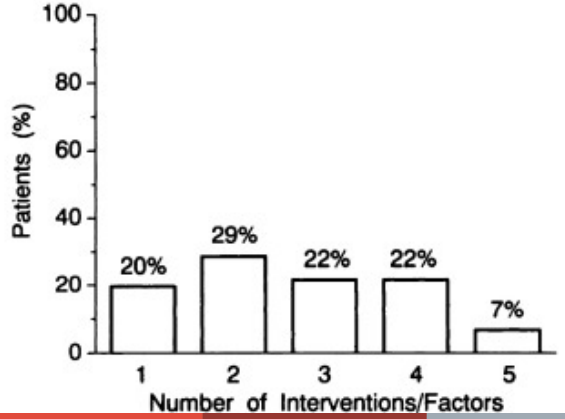
Difficult vs. Severe asthma

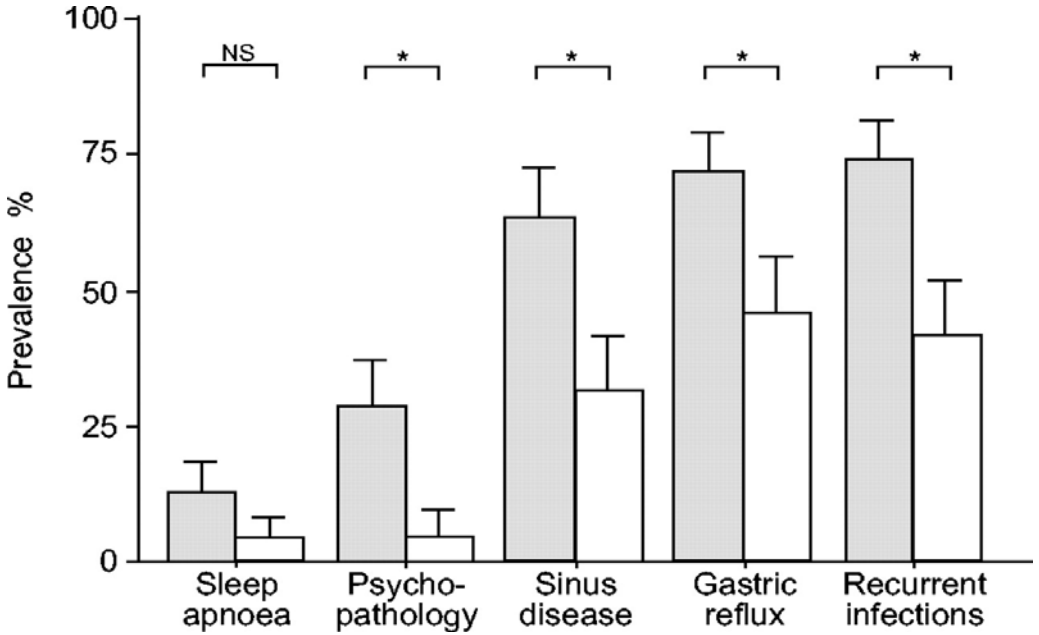






Irwin et al. Chest 1993; 103:1662-69

Comorbid Factors Associated with Severe Asthma Exacerbations



1 exacerbation/year
N=24

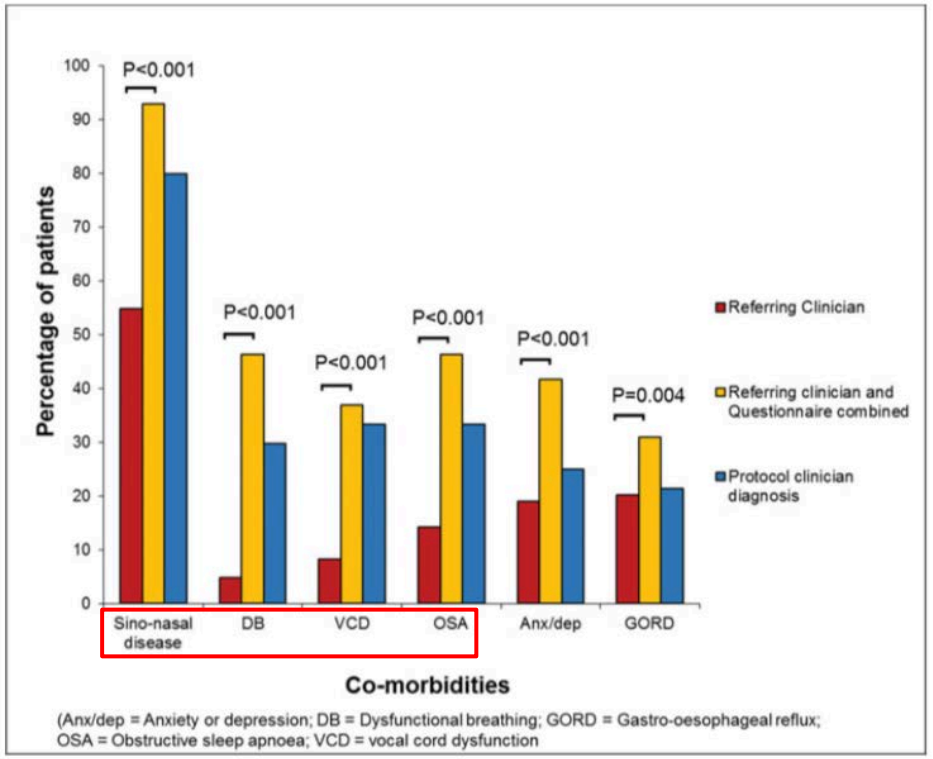
>3 exacerbations/year
N=39

ten Brinke et al. Eur Respir J 2005;26:812

Validated questionnaires can improve detection of comorbidities in difficult asthma. N=86

Questionnaires	Comorbidity	Items	Sensitivity (%)	Specificity (%)
SNQ [32,33]	Sino-nasal disease	5	90	94
SFAR [34]	AR	8	74	83
NIJMEGEN [3,5,26]	DB	16	91	95
PVCDI [37]	VCD	4	83	95
BERLIN [38,39]	OSA	10	86	77
HADS [40]	Anx/Dep	14	80	80
GERD-Q [41,42]	GORD	6	65	71

The average time for questionnaire administration was approximately **40 minutes.**



Radhakrishna N. Journal of Asthma. 2016

Association, prevalence and treatment outcomes of comorbidities in difficult asthma

Comorbidity	Associated with asthma?	Prevalence in asthma	Does treatment improve asthma?
Sino-nasal disease AR	Yes	80% #	Yes
Sino-nasal disease CRS	Yes	70-74% *	Yes
GERD	Yes	59% #	Inconsistent
OSA	Yes	75-95% *	Yes
VCD	Yes	75% *	Inconsistent
DB	Yes	29% #	Yes
Anx/Dep	Yes	49% *	Yes

*** Difficult asthma**
 # All asthma

Adapted from Radhakrishna N. Journal of Asthma. 2016

GERD & Asthma

- Prevalence 32-84% by esophageal pH-monitoring studies; about half are asymptomatic
  - Carefully review symptoms: Heartburn, Regurgitation, Water brash, Dysphagia, Sore throat, Choking, Hoarseness, Dental erosions, Chest pain, Cervical pain, Worsened asthma symptoms with Eating, Alcohol, Supine position, Theophylline
- Proposed mechanisms – 'Reflux' vs 'Reflex'
  - Likely a bi-directional relationship
- Studies demonstrate some benefit in <u>symptomatic GERD and uncontrolled asthma</u>
  - Improvement in peak flow, quality of life, exacerbations

AJRCCM 2006 May 15;173(10):1091-7
AJRCCM 2010 May 15;181(10):1042-8.
Chest 2005 Sep;128(3):1128-35
N Engl J Med 2009; 360:1487-1499

CRS & Asthma

- Symptomatic inflammation of the paranasal sinuses and the nasal cavity
  - Chronic Rhino-Sinusitis = lasting > 12 weeks
  - With or without nasal polyps (CRSwNP or CRSsNP)
- The unified airway model
  - Links the upper and lower airway as a single functional group
  - Shared systemic inflammatory pathways
- Prevalence of CRS
  - 10-12% general population
  - 23.4-74% in all asthma
  - 84% in severe asthma
- Associated with decreased lung function, QOL, severe exacerbations

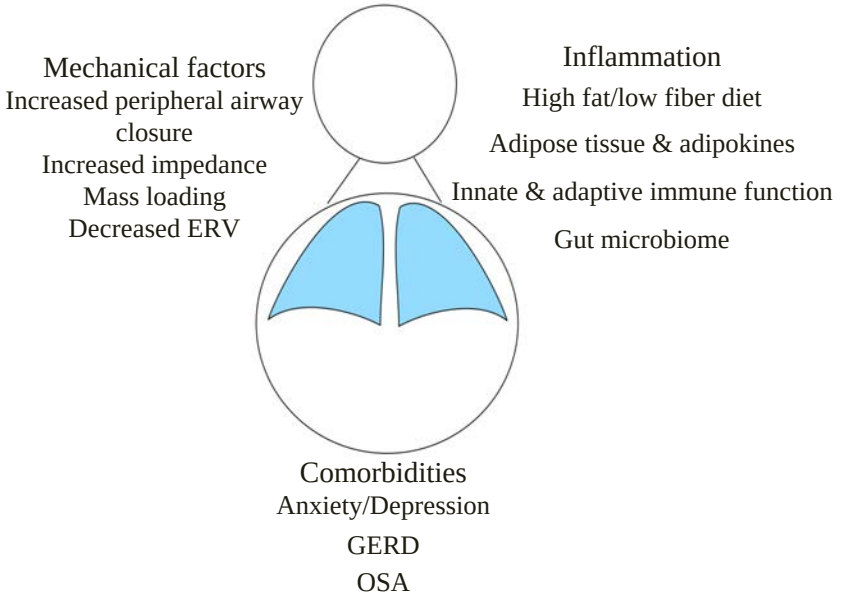
Ear Nose Throat J 2007; 86: 409. J Allergy Clin Immunol 2001;107:73.
J Allergy Clin Immunol 2002;109:621 . Otolaryngol Head Neck Surg. 2007;136:S75-S106.
Otolaryngol Clin N Am. 2008;48:297-309. 2015 NHIS data.

CRS: Treatment options

- Nasal steroids: first line
  - Technique
- Oral steroids:
  - CRSsNP: No evidence for benefit
  - CRSwNP: Benefit
- Antibiotics:
  - CRSsNP: No placebo controlled study for short courses of antibiotics
  - CRSwNP: 1 study showing doxycycline has limited benefit
- Nasal saline irrigation: Improves symptoms
- Surgery: For medical management failures
- Biologics: In clinical trials

Obesity & Asthma

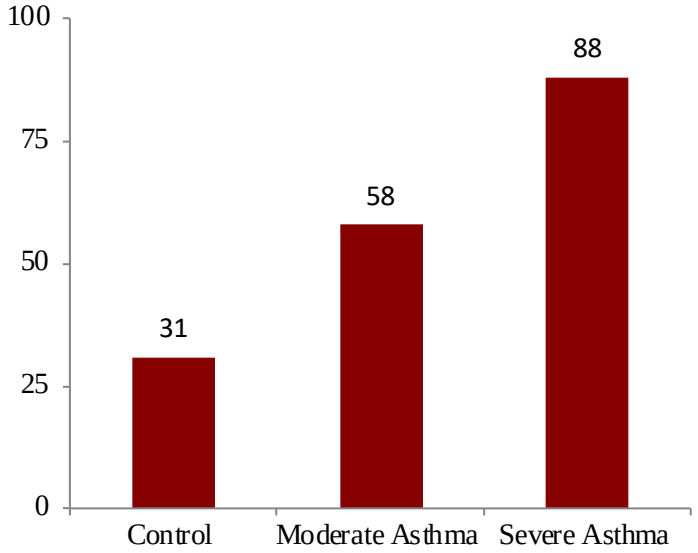
- Obesity is associated with
  - Worse asthma control
  - Higher health care utilization
  - Poor response to standard controller therapy
- Weight loss – dietary or surgical – is effective
- Recent studies support a role for exercise
- Diet quality – high protein/low glycemic index, plant-based, Mediterranean



OSA & Asthma

- Mechanisms
  - Mechanical stress, intermittent hypoxemia activate proinflammatory pathways
  - Apneas may trigger activation of muscarinic receptors
  - Negative intrathoracic pressure during Muller maneuver
    - Edema of airway wall ~ decreased airway diameter

- Treatment of OSA
  - Improves nocturnal asthma control and PEFR
  - Reduces bronchial reactivity
  - Improves asthma quality of life
  - Improves asthma night-time symptom scores

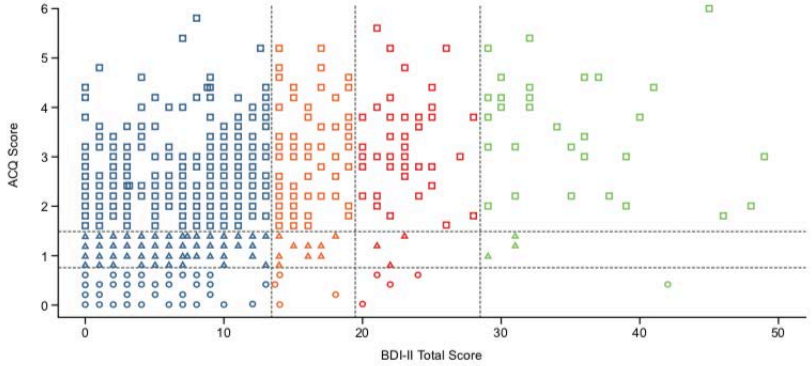


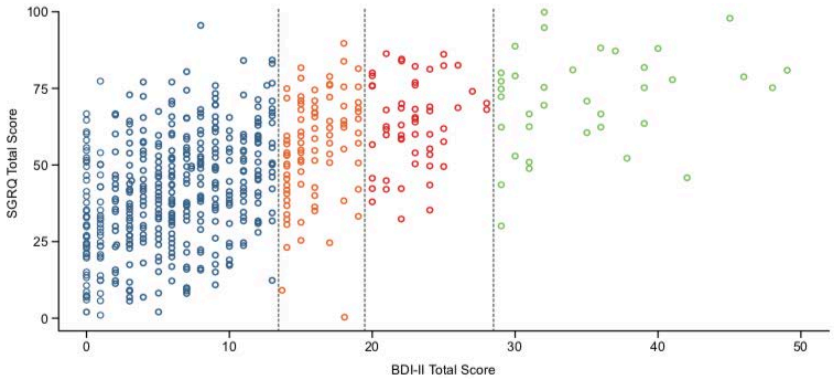
N=26 in each group
OSA diagnosed by HST

Julien JY. J Allergy Clin Immunol. 2009;124(2):371–6

Psychopathologies & Asthma

- Pooled data from MENSA and SIRIUS trials of mepolizumab in severe eosinophilic asthma (N=681)
- Higher depressive symptoms scores (BDI-II) were associated with worse asthma control, QOL,





Khurana et al (submitted)

Case continued

- Treatment with omeprazole 20 mg daily initiated
- OSA diagnosed and started CPAP therapy
- Improved GERD and nocturnal asthma symptoms

- Continues to experience frequent cough, wheeze and shortness of breath
- Symptoms most notable at work and with certain chemical smells

What would you recommend next?

A. Removal from work place as this patient has occupational asthma
B. Evaluation for suspected paradoxical vocal fold motion (PVFM)
C. Consideration of allergen immunotherapy
D. Referral for bronchial thermoplasty

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PVFM & Asthma

- VCD/ILO/PVFM
- Laryngeal hypersensitivity
- Occurs commonly as asthma mimic and comorbidity
- Prevalence
  - 19% in all asthma
  - 32% in difficult asthma
- Clinical suspicion and detailed history
  - Triggers, rapid onset/offset, phase of respiration affected, other laryngeal symptoms
- Objective confirmation often elusive - Questionnaire screening, Laryngoscopy, Challenge tests.
- Respiratory retraining

Case continued

- Evaluated by laryngologist and Speech Pathologist colleagues
- Laryngoscopy revealed LPRD and PVFM
- Increased PPI dose. Added H2 blocker. Anti-reflux diet. Started respiratory retraining.

- Follow-up visit: much improved asthma symptoms but continues to have increased rescue inhaler use at work.
- Asthma better on weekends and on vacation

- Next step? Focus on triggers' evaluation

Relevant triggers in difficult asthma

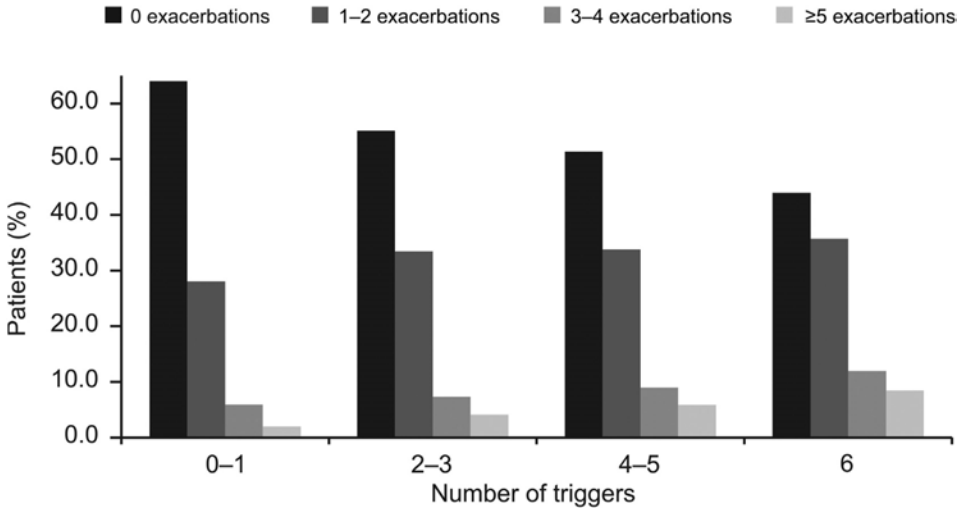
- Allergic Triggers
  - Indoor: HDM, pets, pests, mold
  - Outdoor: Pollen, mold

- Non-allergic triggers
  - Irritants: Air pollution, active/passive smoking
  - Viral infections
  - Stress
  - Drugs/Food

- <u>Occupational triggers are especially important</u>
  - Can account for up to 25% of adult onset asthma
  - Immunologic or irritant
  - For immunologic triggers, prompt and complete avoidance is necessary

Triggers negatively impact asthma control and QoL

- TENOR 3-yr observational study
- Difficult asthma; N 2675
- Age >12 years
- Increasing number of triggers associated with worse QoL and higher frequency of exacerbations



Luskin et al. J Allergy Clin Immunol Pract 2014

Common Environmental Triggers

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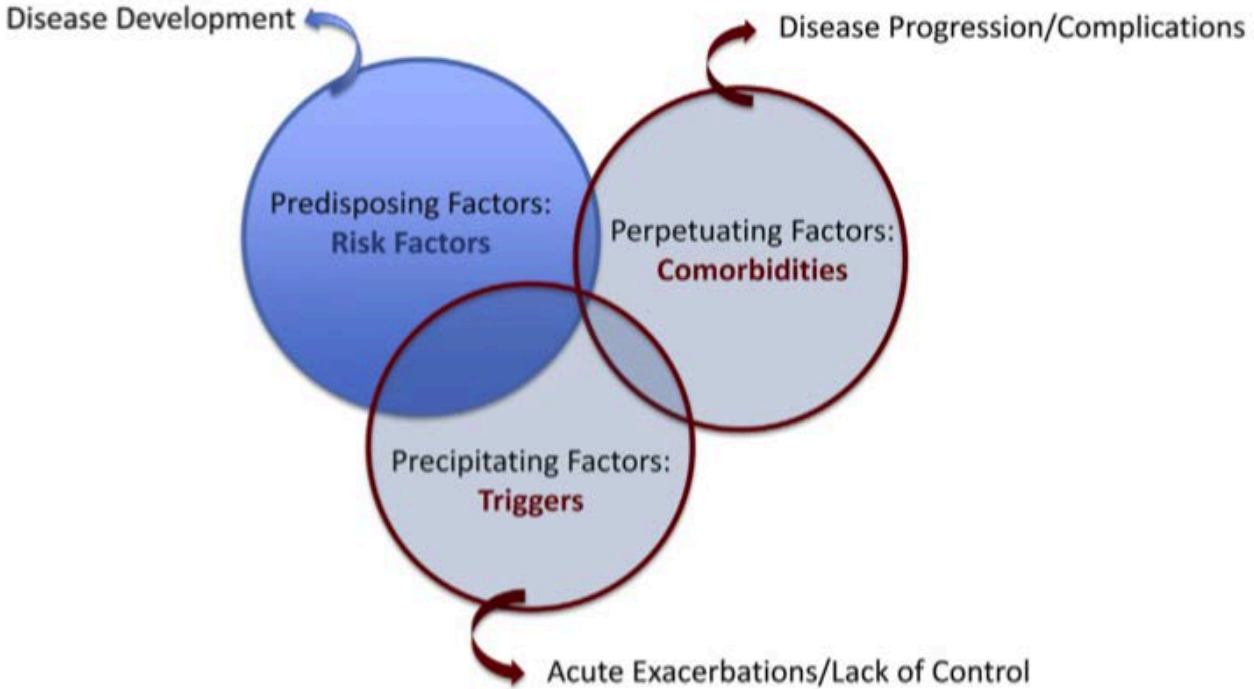
Indoor Triggers					Work-place Triggers	
House Dust -Mite	Furry pets	Pests (roaches, rodents)	Indoor Mold	Air pollutants Tobacco smoke	Immunologic triggers High or Low MW	Irritant triggers
Keep relative humidity in home at 35-50%. Wash bedding weekly. Regular vacuuming. HEPA filters. Allergen-proof encasings.	Removal of pet from the home. At least limit access to the bedroom. Frequently vacuum. Remove carpets.	Mitigate factors that facilitate infestation. Access to food/water, paths of ingress. Integrated pest management program by a professional	Remove visible mold. Eliminate dampness. Repair leaks. Improve ventilation. Avoid use of organic building materials	Eliminate indoor smoking and other pollutant sources. Exhaust fans and HEPA filters. Replace gas stoves with electric stoves	Prompt and complete exposure avoidance. Exposure reduction is a significantly less satisfactory.	Respiratory protective devices. Minimize all exposure.

Khurana & Jarjour. Clin Chest Med 40 (2019) 59-70

Trigger control & challenges

- Data on effectiveness of trigger mitigation show variable effectiveness
- Most studies focus on occupational, indoor environmental allergens, pediatric population, inner city environment
- Significant heterogeneity in methods and outcomes
- Allergen reduction does not always translate to improved clinical outcomes
- More studies are needed to identify interventions that are effective, cost efficient and practical

The 3P Framework

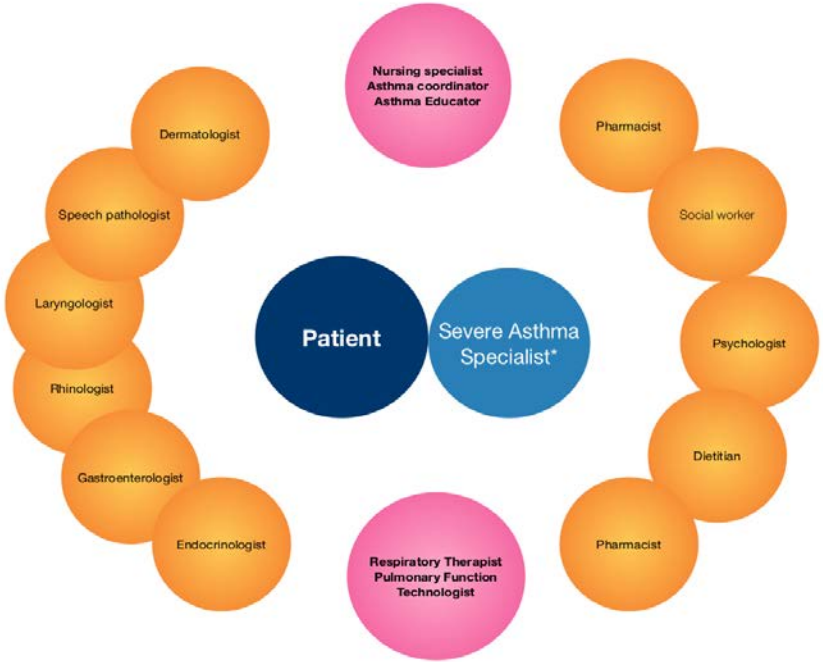


Ioachimescu & Desai. Clinics in Chest Medicine 40 (2019)

Summary

- True prevalence of severe refractory asthma is low
- Many factors other than intrinsic severity of asthma make it ‘difficult’ to treat
- A successful management plan for asthma needs to include a structured multi-faceted assessment of confounders, adherence, comorbidities and triggers
- Identification and mitigation of these factors will
  - Improve asthma outcomes
  - Ensure appropriate utilization of novel and expensive therapies
  - Limit unnecessary drug exposure by allowing step-down in asthma therapy

It takes a village



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