

Asthma and Comorbidities

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Objective

- Goal of asthma management
- Impact & important of comorbidity
- Identify major comorbidities
- Appropriate evaluation for comorbidities

Goals of asthma management

Asthma control

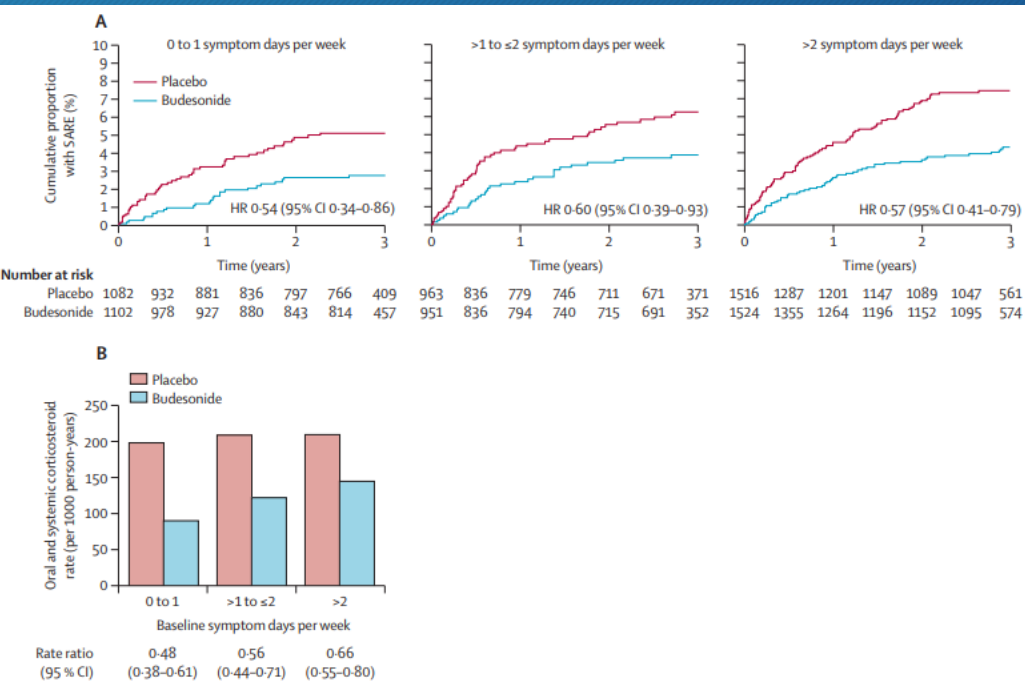
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graph TD; A[Asthma control] --> B[Achieve good control symptom and maintain normal activity level (symptom control)]; A --> C[Minimize risk asthma-related mortality, exacerbations, persistent airflow limitation and side-effects (future risks of adverse outcome)];
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Achieve good control symptom and maintain normal activity level
(symptom control)

Minimize risk asthma-related mortality, exacerbations, persistent airflow limitation and side-effects
(future risks of adverse outcome)

Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne



	Budesonide (symptom days a week)			Placebo (symptom days a week)		
	0 to 1 (n=1102)	>1 to ≤2 (n=951)	>2 (n=1524)	0 to 1 (n=1082)	>1 to ≤2 (n=963)	>2 (n=1516)
Time to first SARE* (%) (hospital admission or emergency treatment)						
Cumulative incidence 1 year	1%	2%	3%	3%	4%	5%
Cumulative incidence 2 years	3%	3%	4%	5%	6%	7%
Cumulative incidence 3 years	3%	4%	4%	5%	6%	7%
Rate of SAREs						
Rate per 1000 patient-years	15.4	17.5	20.2	23.5	26.2	40
Postbronchodilator FEV₁ (% predicted)						
1 year mean change from baseline (95% CI)	-1.40 (-1.98 to -0.81)	-0.77 (-1.38 to -0.15)	-0.75 (-1.24 to -0.25)	-2.95 (-3.54 to -2.36)	-2.35 (-2.96 to -1.73)	-2.22 (-2.72 to -1.72)
3 year mean change from baseline (95% CI)	-2.51 (-3.16 to -1.87)	-2.33 (-3.01 to -1.65)	-2.30 (-2.85 to -1.75)	-3.96 (-4.61 to -3.30)	-2.89 (-3.57 to -2.22)	-3.06 (-3.62 to -2.51)
Prebronchodilator FEV₁ (% predicted)						
1 year mean change from baseline (95% CI)	3.54 (2.74-4.33)	4.52 (3.69-5.36)	3.69 (3.02-4.36)	0.82 (0.01-1.62)	2.04 (1.21-2.88)	1.78 (1.09-2.47)
3 year mean change from baseline (95% CI)	2.67 (1.85-3.49)	2.41 (1.54-3.27)	3.16 (2.46-3.86)	0.33 (-0.5-1.16)	1.00 (0.13-1.87)	1.63 (0.92-2.34)
Time to first inhaled corticosteroid (%)						
Cumulative incidence 1 year	12%	12%	17%	18%	24%	32%
Cumulative incidence 2 years	18%	20%	25%	26%	33%	41%
Cumulative incidence 3 years	22%	23%	30%	31%	38%	46%
Time to first oral or systemic corticosteroid (%)						
Cumulative incidence 1 year	8%	9%	11%	16%	17%	17%
Cumulative incidence 2 years	13%	15%	17%	23%	23%	24%
Cumulative incidence 3 years	15%	17%	19%	26%	27%	27%
Rate of oral or systemic corticosteroid						
Rate per 1000 patient-years	90.1	122.1	145.1	198.6	208.9	209.5
Asthma symptoms in the past 2 weeks						
Mean proportion (%)	18%	24%	32%	25%	33%	38%
Restriction in normal activities in the past 2 weeks						
Mean proportion (%)	4%	5%	7%	6%	7%	10%
Sleeping problems in the past 2 weeks (%)						
Mean proportion (%)	5%	7%	10%	9%	12%	14%
Symptom-free days in the past 2 weeks (%)						
Mean (SD)	94% (8)	91% (12)	86% (16)	91% (12)	87% (14)	82% (19)

B. Risk factors for poor asthma outcomes

Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.

Measure FEV₁ at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.

a. Risk factors for exacerbations

Uncontrolled asthma symptoms

Having uncontrolled asthma symptoms is an important risk factor for exacerbations.⁹⁸

Factors that increase the risk of exacerbations even if the patient has few asthma symptoms†

Medications High SABA use (≥3 x 200-dose canisters/year associated with increased risk of exacerbations, increased mortality particularly if ≥1 canister per month)^{74,75,99,100}

Inadequate ICS: not prescribed ICS, poor adherence,¹⁰¹ or incorrect inhaler technique¹⁰²

Other medical conditions Obesity,^{103,104} chronic rhinosinusitis,¹⁰⁴ GERD,¹⁰⁴ confirmed food allergy,¹⁰⁵ pregnancy¹⁰⁶

Exposures Smoking,¹⁰⁷ e-cigarettes,¹⁰⁸ allergen exposure if sensitized,¹⁰⁷ air pollution¹⁰⁹⁻¹¹²

Psychosocial Major psychological or socioeconomic problems^{113,114}

Lung function Low FEV₁ (especially <60% predicted),^{107,115} high bronchodilator responsiveness^{104,116,117}

Type 2 inflammatory markers Higher blood eosinophils,^{104,118,119} elevated FeNO (in adults with allergic asthma taking ICS)¹²⁰

Exacerbation history Ever intubated or in intensive care unit for asthma,¹²¹ ≥1 severe exacerbation in last 12 months^{122,123}

b. Risk factors for developing persistent airflow limitation

History Preterm birth, low birth weight and greater infant weight gain,¹²⁴ chronic mucus hypersecretion^{125,126}

Medications Lack of ICS treatment in patient with history of severe exacerbation¹²⁷

Exposures Tobacco smoke,¹²⁵ noxious chemicals; occupational or domestic exposures⁴⁹

Investigation findings Low initial FEV₁,¹²⁶ sputum or blood eosinophilia¹²⁶

c. Risk factors for medication side-effects

Systemic Frequent OCS, long-term, high-dose and/or potent ICS, P450 inhibitors¹²⁸

Local High-dose or potent ICS,^{128,129} poor inhaler technique¹³⁰

Comorbidity

Comorbidity

- Diseases that develop coincidentally
- 2 illnesses that impact one another

- “Coexisting conditions”
- “Conditions with causal connection”
- “Multimorbidity”

Impact and Important of asthma

- Complicate diagnosis and management
- Associated poor asthma control
- Decrement quality of life (QoL)
- Lead to polypharmacy
- Increased healthcare use

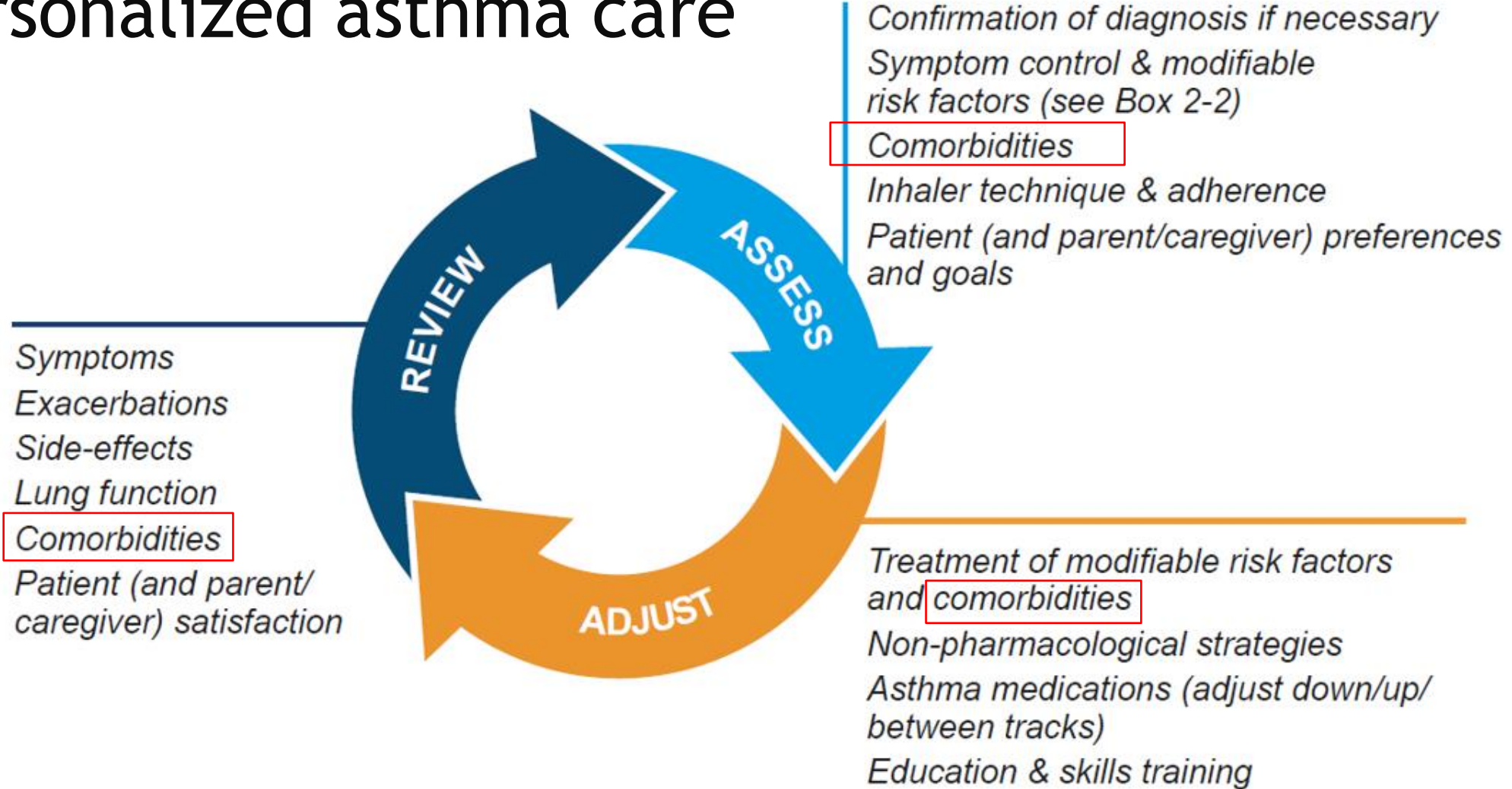
Table 3. Weighted prevalences of symptom episodes, functional impairment, and emergency department visits among adults with asthma (N = 2,873) with and without comorbidity

Asthma Symptoms and Functional Impairment	Asthma Only (n = 1,180)	Asthma and Comorbidity (n = 1,693)	P Value
Asthma symptom episodes in the last 12 mo	42.2 (38.7–45.8) [‡]	49.4 (46.4–52.4)	0.003
Asthma symptom episodes	5.1 (4.6–5.5)	5.9 (5.5–6.6)	0.01
Sleep disturbances	9.2 (7.2–11.1)	14.4 (12.6–16.2)	<0.001
Activity limitation	17.9 (15.5–20.4)	26.7 (24.3–29.0)	<0.001
Emergency department visit in the last 12 mo	4.0 (3.6–6.2)	8.6 (7.1–10.2)	<0.001

[‡]Data are percentage or mean with 95% confidence interval in parentheses.

Source: NHANES 2003–2010 data.

Personalized asthma care



Multi(co)morbidity

Upper airway and pulmonary

- Allergic & Non-Allergic Rhinitis
- Chronic Rhinosinusitis
- Dysfunctional Breathing
- Vocal Cord Dysfunction
- Chronic Obstructive Pulmonary Disease
- Bronchiectasis
- Obstructive Sleep Apnea

Extrapulmonary

- Obesity
- Anxiety & Depression
- Gastro-esophageal Reflux Disease (GERD)
- Osteoporosis
- Cardiovascular Disease & Metabolic Disease

Allergic & Non-Allergic Rhinitis

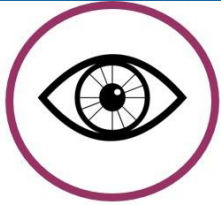
- Prevalence:
 - Allergic rhinitis 55% severe asthma and 60% non severe asthma
 - Nonallergic rhinitis 15% severe asthma and 11% of non severe asthma
- Mechanism: united airway, bidirectional crosstalk occurs between the upper and lower airways
- Influence: poorer symptom control and quality of life, but not greater exacerbation frequency

Allergic & Non-Allergic Rhinitis



Nasal Symptoms

Nasal itching
Sneezing
Rhinorrhoea
Nasal obstruction
(Hyposmia)



Ocular Symptoms

Eye itching
Red eyes
(Conjunctival injections)
Swollen eyes



Oral Allergy Symptoms*

*In pollen-induced allergic rhinitis after contact with source
Oral and pharyngeal itch (rarely angioedema of the lips, mucosa, soft palate, or pharynx)



Other Symptoms

Sleep disorders and emotion problems (e.g. fatigue and low mood).
Symptoms can also extend to ears, sinuses and lungs



Dennie-Morgan lines



Normal turbinate



Pale (allergic) turbinate



Allergic salute →

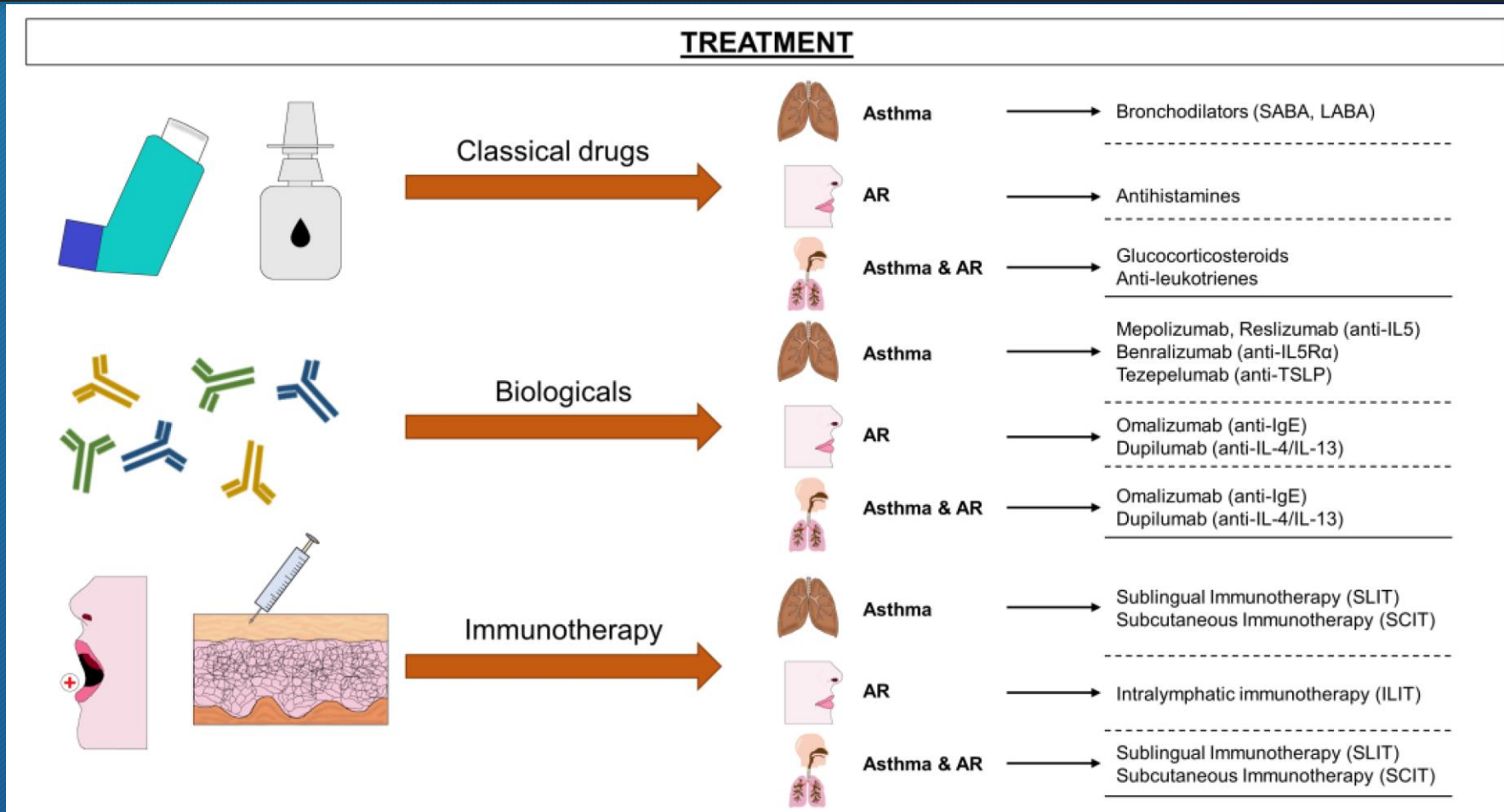


Nasal crease



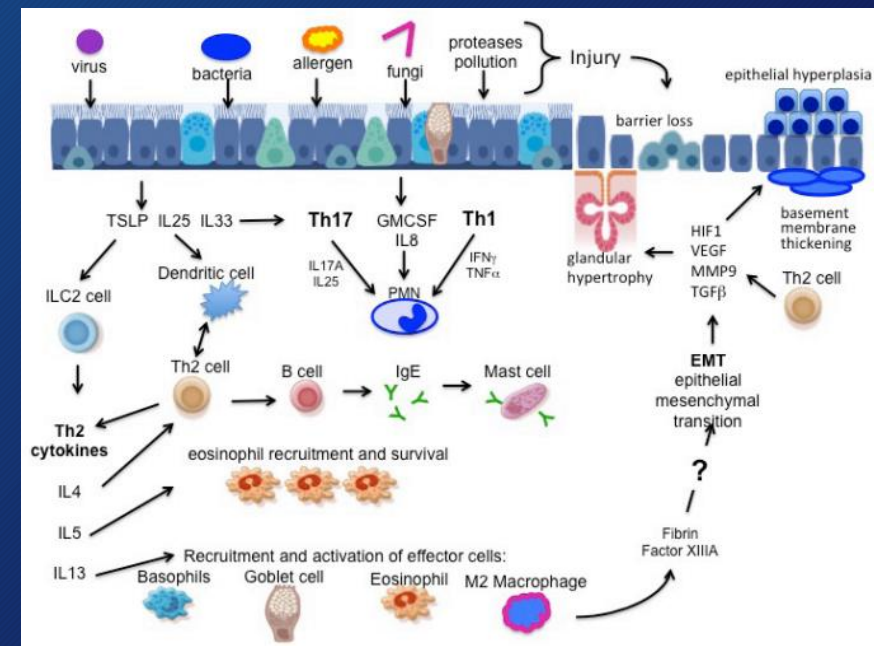
Allergic shiners

Allergic & Non-Allergic Rhinitis



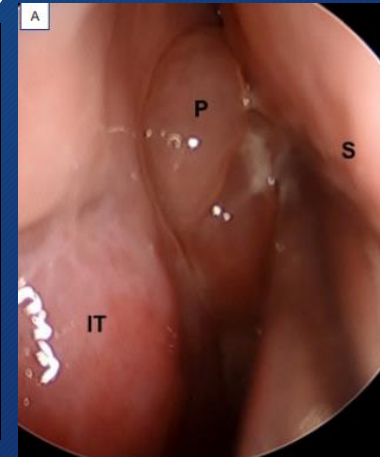
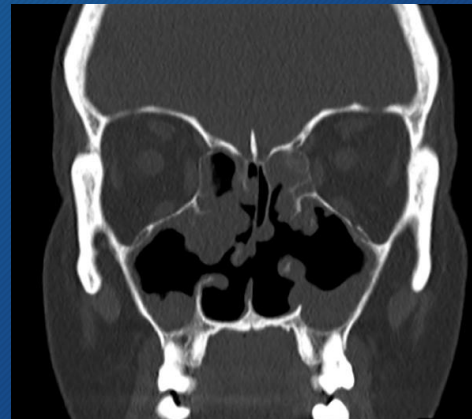
Chronic Rhinosinusitis

- Prevalence: 22% to 42% and higher in severe asthma, also nasal polyposis increases with asthma severity
- Influence: more asthma symptoms, more frequent exacerbations and poorer quality of life
- Mechanism:
 - Epithelial damage and basement membrane thickening
 - Type 2 high and type 2 low inflammatory phenotypes
 - Pattern of inflammation within the upper and lower airways



Chronic Rhinosinusitis

- Diagnosis (3 months of ≥ 2 of the following symptoms)
 - Nasal obstruction
 - Nasal discharge
 - Facial pain/pressure
 - Anosmia (loss of sense of smell)
- Treatment:
 - Intranasal steroid spray
 - Saline lavage



Breathing Pattern Disorder (BPD) / Dysfunctional Breathing

WHAT IS BPD / DYSFUNCTIONAL BREATHING?

A GROUP OF DISORDERS WHERE THERE ARE CHRONIC CHANGES IN BREATHING PATTERN



RESULTING IN:

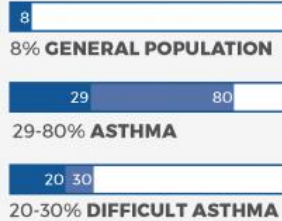
- Dyspnoea
- Chest tightness
- Chest pain
- Deep sighing
- Exercise-induced dyspnoea
- Frequent yawning
- Hyperventilation

HOW DOES IT RELATE TO ASTHMA?

SYMPTOMS ARE OFTEN SIMILAR:

- Under-recognised in asthma population
- Causes symptoms disproportionate to lung disease severity

PREVALENCE:



DIAGNOSIS & ASSESSMENT:

- Nijmegen questionnaire
- Clinical observation
- Oximetry
- End tidal CO₂
- Breath hold test (<30s)
- Ventilatory response
- Arterial blood gas
- Plethysmography

TREATMENT OPTIONS:

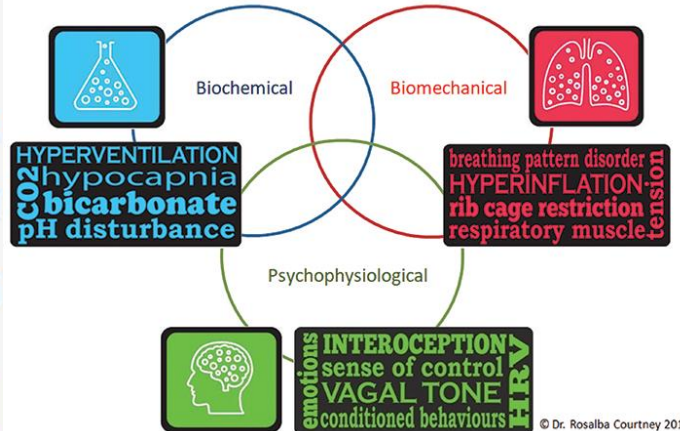
NOTE: BPD DOES NOT RESPOND TO ASTHMA TREATMENTS

- Breathing retraining by a qualified professional (e.g. physiotherapist) is recommended
- Having patients differentiate symptoms of BPD and asthma is an important goal



Dysfunctional Breathing

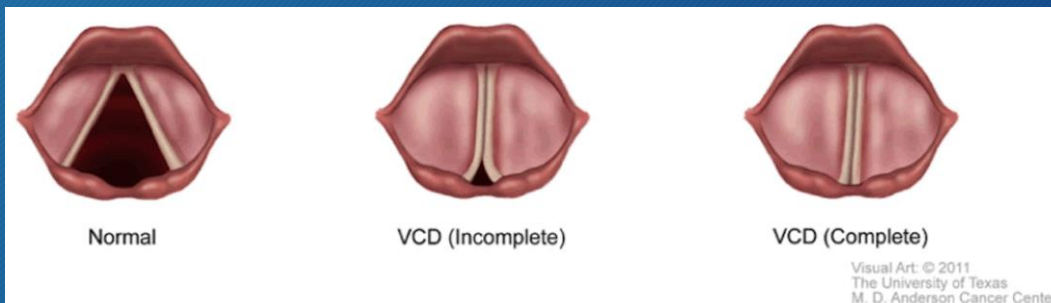
Dimensions of Dysfunctional Breathing



	Asthma episode	Dysfunctional breathing
Asthma Medication	Will respond	Will not respond
PEF	Will drop	Will not change (may effect technique)
Symptom	Expiratory wheeze	Unable to take a deep breath
Aetiology	Bronchospasm	Inappropriate breathing
Cause	Inflamed airways	Low CO ₂ & Altered breathing pattern
Spirometry	Reduced FEV ₁	Can be normal
Diagnosis	Spirometry with reversibility test – 3 challenge methods	Nijmegen questionnaire Breathing pattern

Vocal Cord Dysfunction (Inducible laryngeal obstruction)

- Episodic upper airway obstruction secondary to inappropriate narrowing of the true vocal fold and/or the supraglottic structures
- Primary inducers: exercise, irritants, and emotional stress
- Prevalence (adults): 19% to 32%
- Dyspnea with an identifiable start and end, may stridor as a prominent sign, typically not prevented or resolved with β -agonists
- Influence: misdiagnosed, higher medication use and healthcare utilization



Vocal Cord Dysfunction (Inducible laryngeal obstruction)

- Gold standard for diagnosis: continuous laryngoscopy during the evoked challenge
- Treatment:
 - Speech retraining (mainstay)
 - Psychotherapy
 - Botulinum toxin injection

	Asthma episode	Vocal cord dysfunction
Asthma Medication	Will respond	Will not respond
PEF	Will drop	Can be erratic
Symptom	Expiratory wheeze	Inspiratory stridor
Aetiology	Bronchospasm	Apical breathing
Cause	Inflamed airways	Adduction of vocal folds
Spirometry	Reduced FEV1	Flattened inspiratory loop
Diagnosis	Spirometry with reversibility test – 3 challenge methods	Laryngoscopy

Obstructive Sleep Apnea

- Characterized by repetitive collapse of the upper airway
- Symptom: snoring, gasping, choking, snorting during sleep, daytime hypersomnolence, morning headaches
- Gold standard for diagnosis: polysomnography
- Influence: increased asthma exacerbations and decreased quality of life and asthma control
- Mechanism: alters oxidative balance in the airways through repeated hypoxia and reoxygenation
- Treatment: continuous positive airway pressure (CPAP)

Obesity

- Excess body fat
- Indirectly measured by body mass index (BMI)
 - Overweight ≥ 23 kg/ m²
 - Obese ≥ 25 kg/ m²
- Mechanisms:
 - Altered pulmonary mechanics (lung restriction, premature airway closure),
 - Production of adipokines and pro-inflammatory cytokines by adipose tissue
 - Systemic inflammatory response (non-T₂, lower levels of FeNO and normal blood eosinophils)

Obesity

- Influence: misdiagnosis, poorer asthma control, more frequent exacerbations, poorer quality of life
- Treatment:
 - Weight loss improve asthma control, lung function, health status and reduce medication needs

Anxiety & Depression

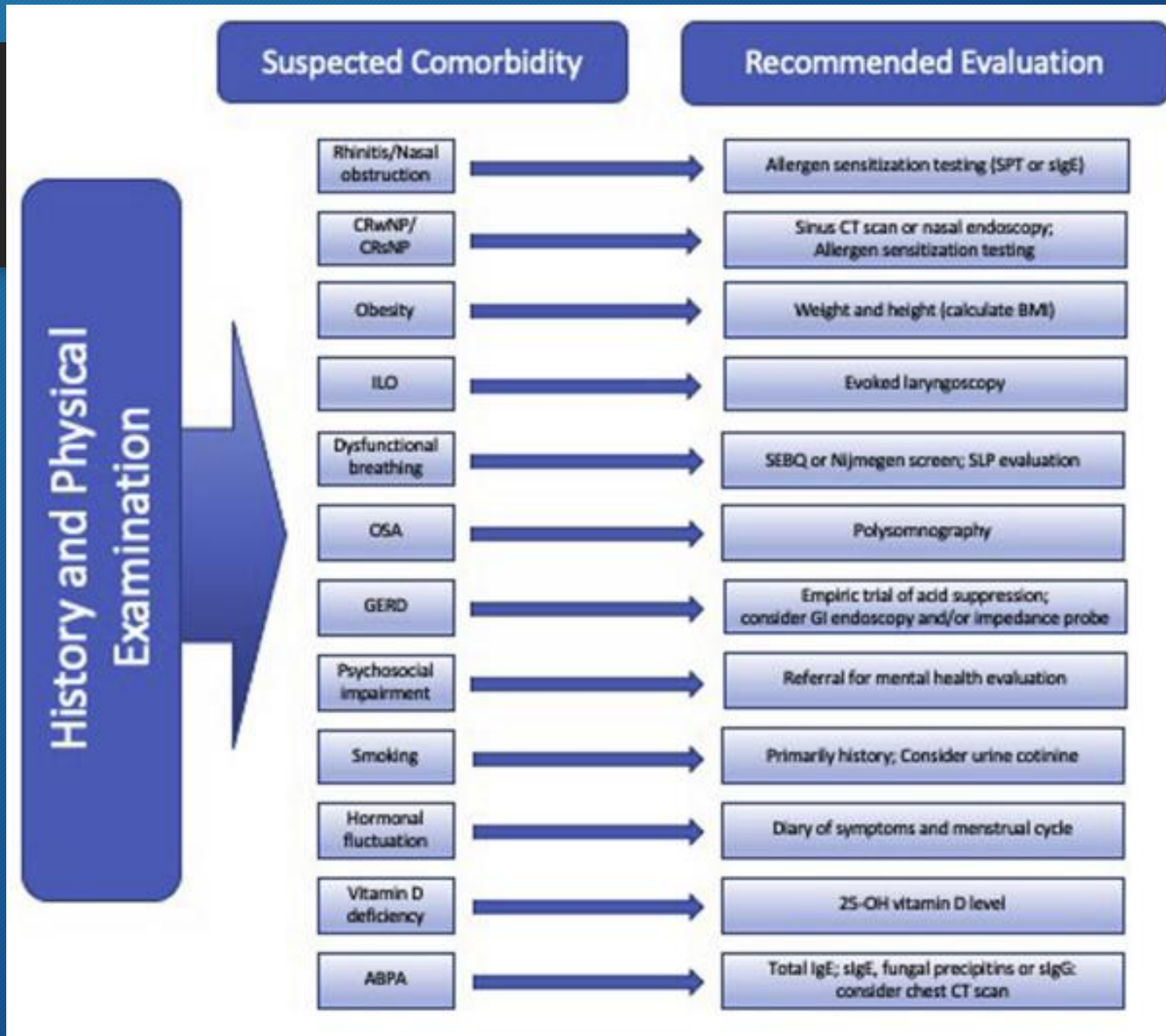
- Prevalence: Up to 18% depression, 11%-37% anxiety
- Impact: poor asthma control, impaired quality of life, reduced lung function, impaired functional outcomes, increased healthcare utilization
- Mechanisms: impairing self-care and triggering hyperventilation
- Treatment:
 - Cognitive behavioral therapy
 - Antidepressive medication

Gastro-esophageal Reflux Disease (GERD)

- Symptoms or complications relating to reflux of stomach contents into the esophagus
- Prevalence: 40%-80% of asthmatics, most frequent among severe asthma patients
- Mechanisms: bidirectional
 - Esophageal irritation (acid, vagal) cause bronchoconstriction (worsened PEFR and airway resistance)
 - MCT (methacholine) increases GER and transient lower esophageal sphincter relaxation
- Influence: worse asthma symptoms and poorer quality of life

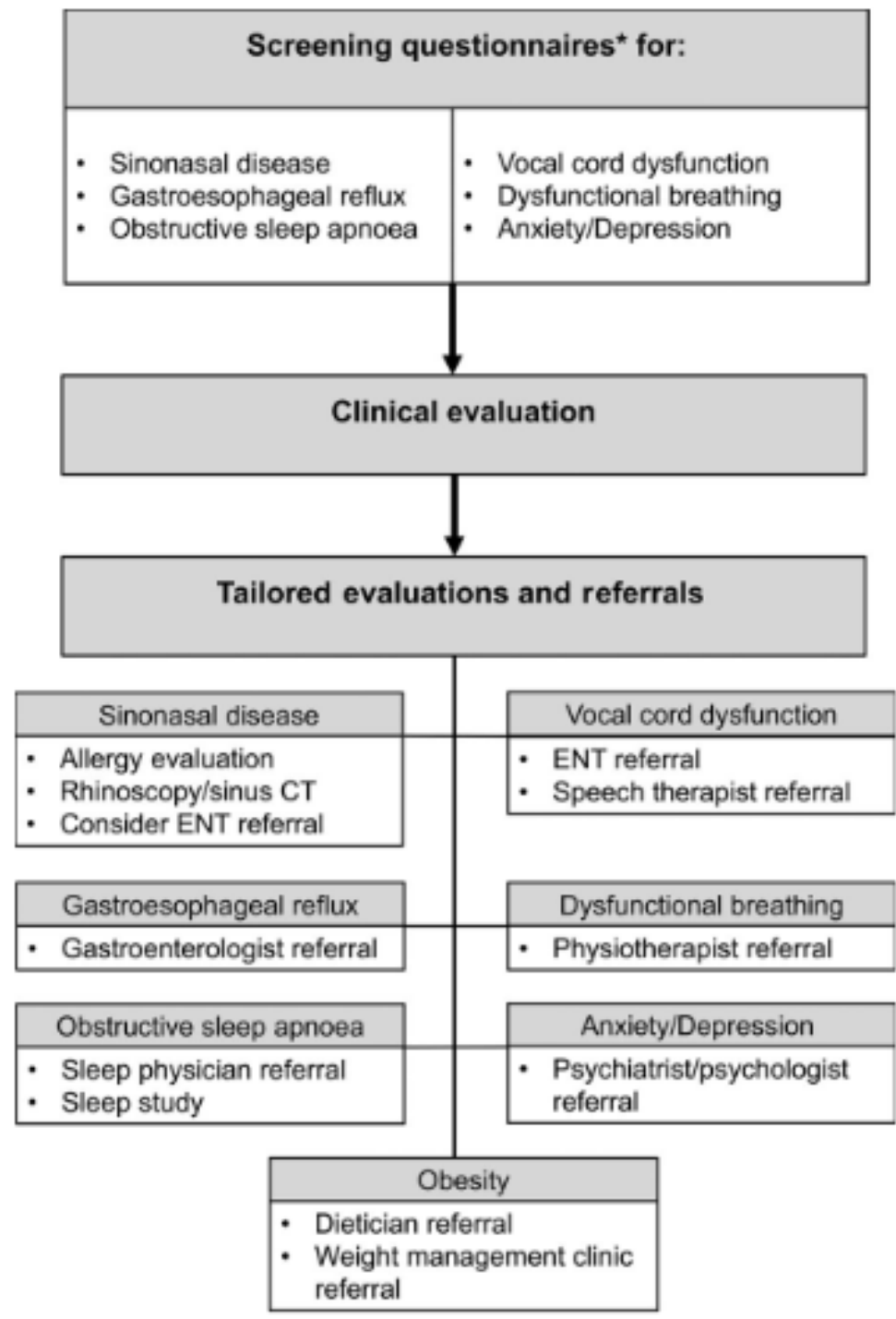
Comorbidity	Clinical clues	Suggested evaluation	Recommended intervention	Anticipated asthma benefit
Allergic rhinitis	Nasal symptoms	SPT or sIgE	INCS ± oral/nasal antihistamines, montelukast, nasal saline	Uncertain, possible fewer exacerbations
CRSwNP	Chronic congestion, sinus pressure, cough	Nasal examination, sinus CT, rhinoscopy; aspirin sensitivity In children: sweat test, ciliary bx/PCD genetics	Oral/intranasal steroids, antihistamines, nasal saline, antibiotics, sinus surgery; aspirin desensitization; anti-IgE, anti-IL5, anti-IL4R therapy	Improved symptoms, FEV ₁ , exacerbations
Obesity	Elevated BMI	BMI, metabolic syndrome	Diet, exercise program; bariatric surgery (adult)	Improved QOL, asthma control, FEV ₁
ILO	Stridor, discrete episodes, hyperventilation	Laryngoscopy with provocation	Speech pathology, stimulus avoidance, inhaled anticholinergics*; psychopharmacologic therapy, if indicated	Improved symptoms
Dysfunctional breathing	Hyperventilation, sighing, asynchronous thoracoabdominal breathing	SEBQ/Nijmegen Questionnaire	Breathing retraining	Improved symptoms, QOL
OSA	Snoring, daytime somnolence	PSG	Adenotonsillectomy (children); CPAP	Improved exacerbations, symptoms, QOL
GERD	Heartburn, regurgitation, chest pain, cough	GI endoscopy, impedance/pH probe	Gastric acid suppression, fundoplication	Possible improved FEV ₁ and rescue medication use
Anxiety/depression	Mood/behavioral cues	Screening tools (ie, GAD7, PHQ9, HADS); psychology referral	CBT, psychopharmacologic therapy	Possible improved symptoms, QOL
Vitamin D deficiency		25 OH vitamin D level (<30 ng/mL)	Vitamin D supplementation	Possible improved exacerbation rate in adults achieving normal vitamin D levels
ABPA/M	Uncontrolled asthma, bronchitis, mucus plugs	Skin test/sIgE to fungus, total IgE, Aspergillus precipitins or sIgG ⁺ ; CXR; chest CT	Systemic corticosteroids + antifungal agent; alternative: omalizumab	Symptoms, lung function
Smoking/SHS	History, observed odor of smoke	History, urinary cotinine	Smoking cessation counseling, medical management	Symptoms, lung function, exacerbations
COPD	Dyspnea, chronic cough, sputum production	History, pre- and post-spirometry	Smoking cessation; asthma pharmacotherapy; LAMA-LABA-ICS therapy	Symptoms, lung function, exacerbations

Approach



Stratified approach

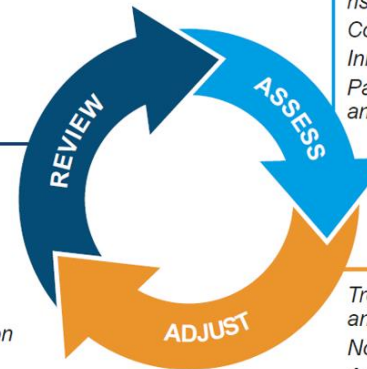
- Sinonasal Questionnaire (SNQ) for sino-nasal disease
- Score for Allergic Rhinitis (SFAR) for allergic rhinitis
- Nijmegen Questionnaire for dysfunctional breathing
- Pittsburgh Vocal Cord Dysfunction Index (PVCDI) for vocal cord dysfunction
- Berlin Questionnaire for obstructive sleep apnea
- Hospital Anxiety and Depression Scale (HADS) for anxiety & depression
- Gastroesophageal Reflux Disease Questionnaire (GERD-Q) for gastro-esophageal reflux disease



Conclusion

Comorbidity	Adult/pediatric	Level of evidence	Affected asthma domain		
			Patient reported outcomes (Sx/QOL)	Exacerbation	Lung function
Allergic rhinitis	Adult	Obs, RCT, Meta	x	x	—
	Pedi	Meta	x	x	—
CRSsNP	Adult	Obs, RCT	x	x	—
	Pedi	Obs	—	x	—
CRSwNP	Adult	Obs, RCT	x	x	x
	Pedi	Obs	—	—	—
Obesity	Adult	Obs, RCT	x	x	x
	Pedi	Obs, RCT	x	x	x
ILO	Adult	Obs	x	x	—
	Pedi	Obs	x	x	—
Dysfunctional breathing	Adult	Obs	x	x	—
	Pedi	Obs	x	x	—
OSA	Adult	Obs, RCT, Meta	x	x	x
	Pedi	Obs, RCT, Meta	x	x	—
GERD	Adult	Obs, RCT, Meta	x	x	x
	Pedi	Obs, RCT, Meta	x	x	—
Anxiety/depression	Adult	Obs	x	x	—
	Pedi	Obs	x	x	—
Vitamin D deficiency	Adult	Obs, RCT, Meta	—	x	—
	Pedi	Obs, RCT, Meta	x	x	x
ABPA/M	Adult	Obs, RCT	x	x	x
	Pedi	Obs	x	—	x
Smoking/SHS	Adult	Obs, RCT	x	—	x
	Pedi	Obs	x	x	x

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient (and parent/
caregiver) satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable
risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient (and parent/caregiver) preferences
and goals

Treatment of modifiable risk factors
and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/
between tracks)
Education & skills training



Thank you