

Severe Asthma

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Outline

- terminology
- Definition
- Epidemiology
- Approach
- Recognition
- Treatment
- ICU/MV
- Extreme measures

Other terminology

- **Difficult asthma**
- **Persistent asthma**
- **Refractory asthma**
- **Therapy resistant asthma**
- **Problematic asthma**
- **Brittle asthma**

what is the most appropriate definition of severe asthma?



ERS taskforce definition of “difficult asthma” 1999

“ failure to achieve asthma control when maximally recommended doses of **inhaled therapy** are prescribed for at least **6 - 12** months”

ATS Criteria Severe / Refractory Asthma 2000

Major characteristics

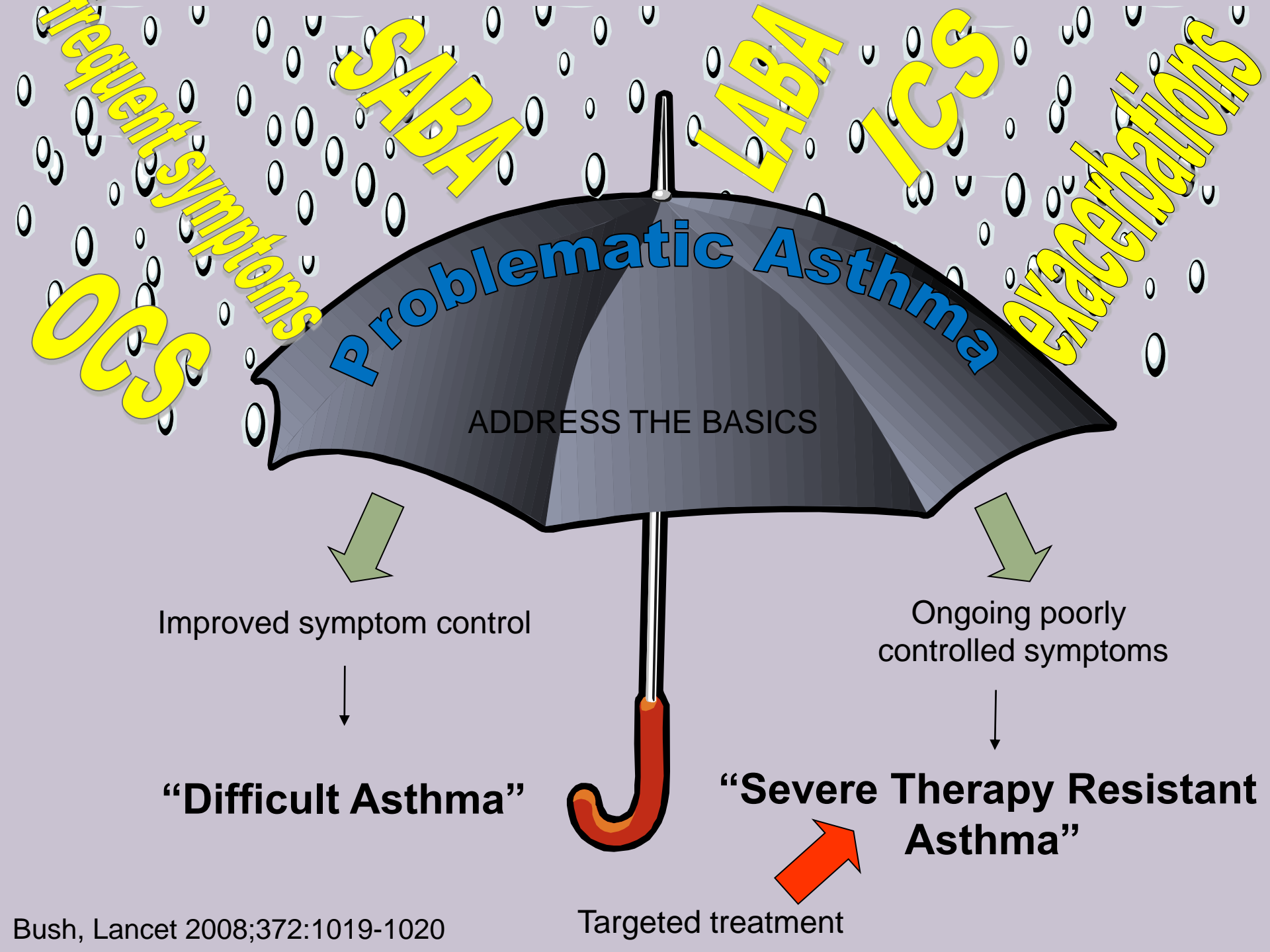
- Treatment with continuous or near continuous ($\geq 50\%$ of year) **OCS**
-
- Need for treatment with **high-dose inhaled corticosteroids**

Minor characteristics

- Need for additional daily treatment with a **controller** medication
- Asthma symptoms needing **SABA use on a daily** or near-daily basis
- Persistent airway obstruction (**FEV1 <80%** predicted)
- One or more **urgent care visits** for asthma per year
- **Three or more oral steroid bursts** per year
- **Prompt deterioration** with $\leq 25\%$ reduction in oral or intravenous corticosteroid dose
- **Near-fatal** asthma event in the past

Definition Requires

- at least **one major** criterion and two minor criteria are met,
- **other disorders** have been excluded,
- **exacerbating factors** have been treated,
- and patient is generally **compliant**.



Frequent symptoms

OCS

SABA

LABA

ICS

Exacerbations

Problematic Asthma

ADDRESS THE BASICS



Improved symptom control



“Difficult Asthma”



Ongoing poorly controlled symptoms



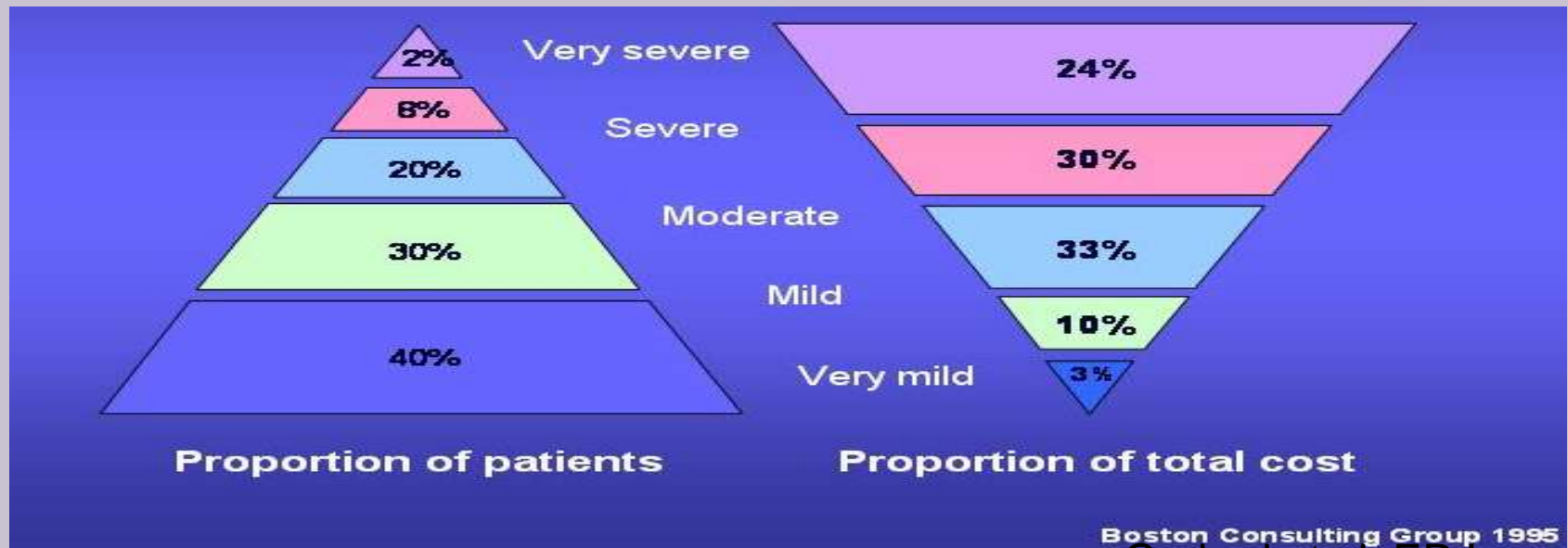
“Severe Therapy Resistant Asthma”



Targeted treatment

Severe and difficult to treat asthma

- 2-12% of asthmatic patients
- 50% of asthma costs
- Severe impact on health and QoL



Boston Consulting Group 1995

Godard et al, ERJ

Epidemiology-Genetics

Genes and genetic-environmental interactions are associated with severity

- ADAM33 BHR, decline in lung function
- TGF- β 1 lower FEV1
- IL-4 lower FEV1, severe exacerbations
- IL-4R α lower FEV1, severe exacerbations

Jongepier et al, Clin Exp Allergy 2004

Pulleyn et al, Hum Genet 2001

Sandford et al, JACI 2000

Lee et al Am J Respir Crit Care Med 2006

Epidemiology - Allergens

- **Atopy is less frequent** in severe asthma as compared to mild to moderate asthma.
- **Certain allergen exposures** are associated with severe asthma (**cockroach, Alternaria**).

ENFUMOSA ERJ 2001

Peat et al, Clin Exp Allergy 1993

Neukirch et JACI, 1999

Gruchalla et al JACI 2005

Teach et al, Pediatrics 2006

Lemanske et al, JACI 2006

Epidemiology- Infections

- Respiratory **viruses** and some intracellular bacteria (Chlamydia) contribute to severe exacerbations of asthma
- Viruses can **persist** in the airways for long periods after the exacerbation
- their role in the development of severe persistent asthma remains **poorly understood**

Everard Curr Opin Allergy Clin Immunol 2006

Murray et al, Thorax 2006

Kraft et al, Chest, 2002

ten Brinke et al JACI 2001

Occupational exposure

- Occupational **sensitizers can induce persistent** severe asthma, and are a common cause of new onset severe asthma in adults

Lemiere et al, Am J Respir Crit Care Med 2000

Sayers et al, Thorax 2003

Le Moual et al, Am J Respir Crit Care Med

TENOR study, risk score

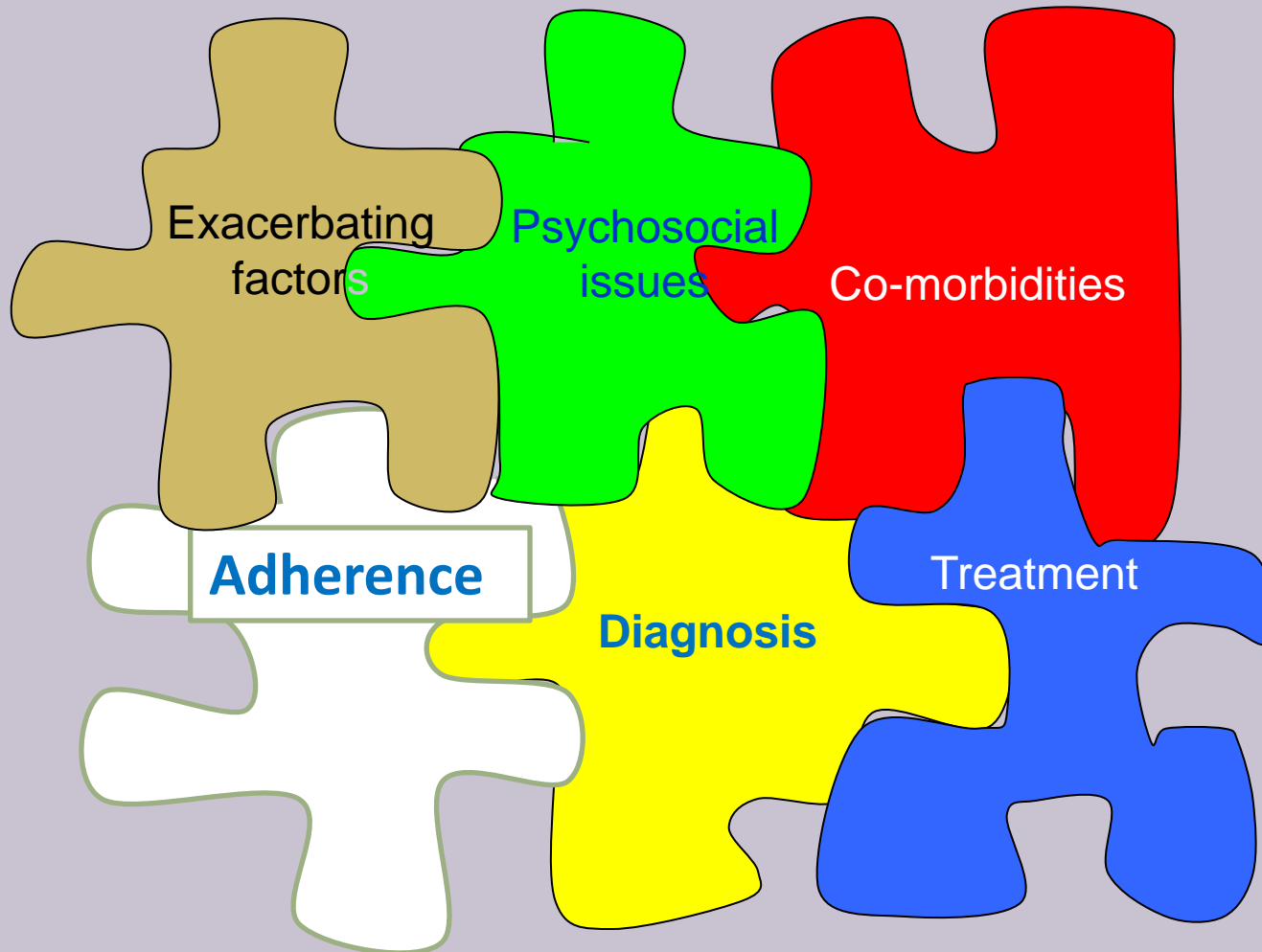
• Age	3	
• Gender	1	
• Race	2	Total score 0-18
• BMI	1	High risk score >8
• Lung Function	2	
• Previous history of pneumonia	1	
• Diabetes	1	
• Cataracts	1	
• Previous intubation	1	
• Steroid bursts	3	
• Nebuliser ipratropium bromide	1	
• Systemic corticosteroids	1	

Epidemiology - obesity

Potential mechanisms

- Genetics of asthma and obesity ?
- Respiratory functional abnormalities ?
- Hormonal abnormalities ?
- Diet abnormalities ?
- A role for inflammation ?

Approach to Diagnosis of Severe Asthma



Is it asthma?

Is it severe?

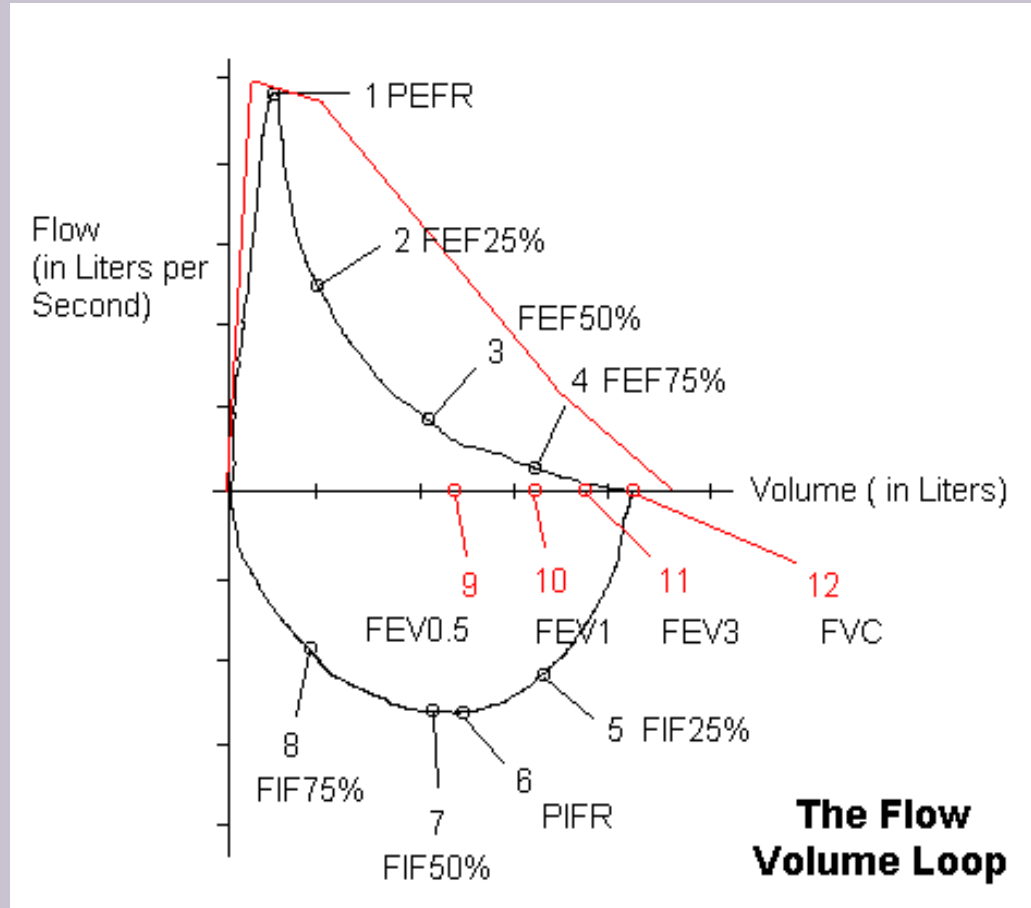
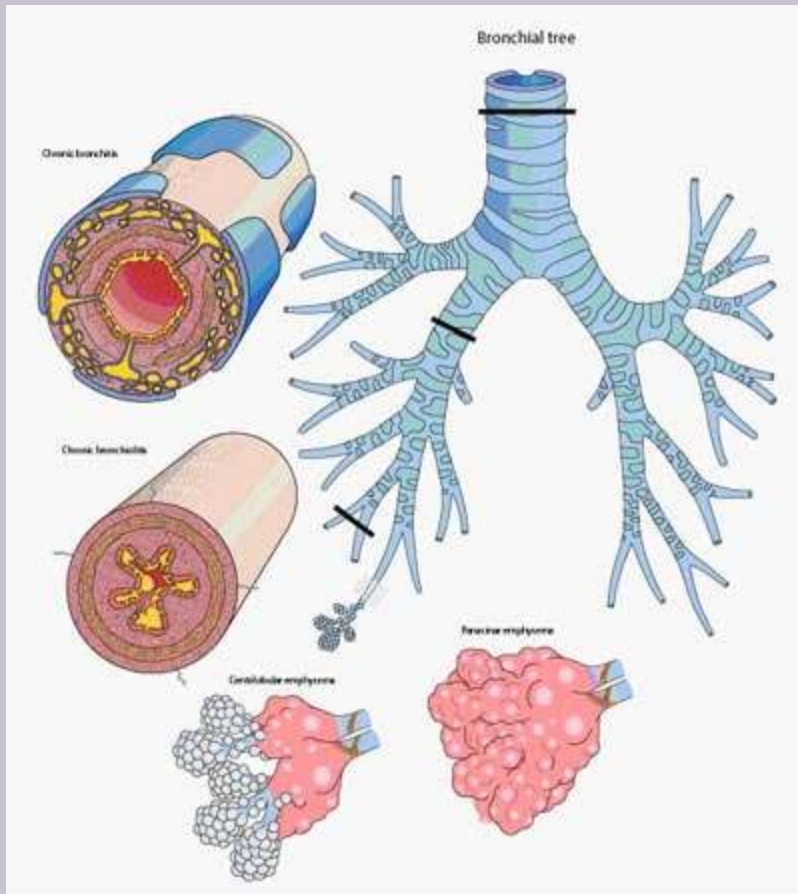
Correct Diagnosis

Diagnosing Asthma

- History
- Clinical signs
- Variable airflow limitation
- Bronchodilator reversibility
- Challenge testing (methacholine, histamine)
- Inflammation (FeNO₅₀, induced sputum, bronchoscopy)
- HRCT

Alternative Diagnoses

- Obliterative bronchiolitis
- Vocal cord dysfunction
- Hyper-ventilation / panic disorder
- Bronchiectasis
- Cystic fibrosis
- Primary ciliary dyskinesia
- Inhaled foreign body
- Gastro-oesophageal reflux
- Extrinsic allergic alveolitis
- Allergic rhinitis
- Bronchomalacia



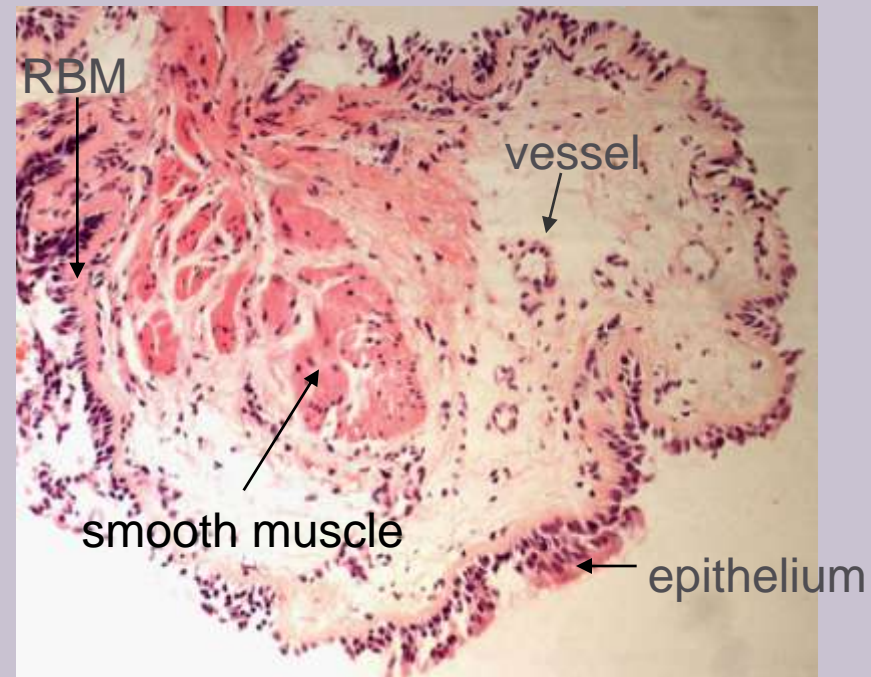
Reversibility

- reversible



Pathology: Bronchoscopy?

- Assessing inflammation²
 - Macroscopic
 - Broncho-alveolar lavage
 - Biopsy
- Airway remodelling
- Microbiology
- Therapeutic³



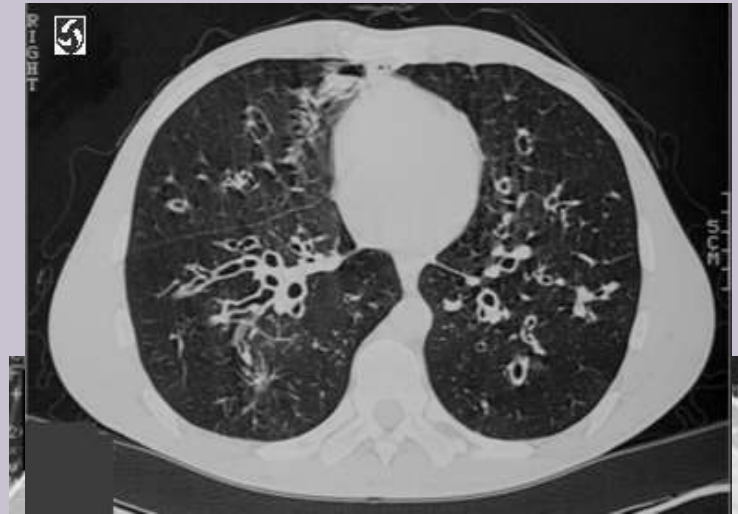
1 Payne, ADC 2001;84:423-426

2 Lex, AJRCCM 2006;174:1286-1291

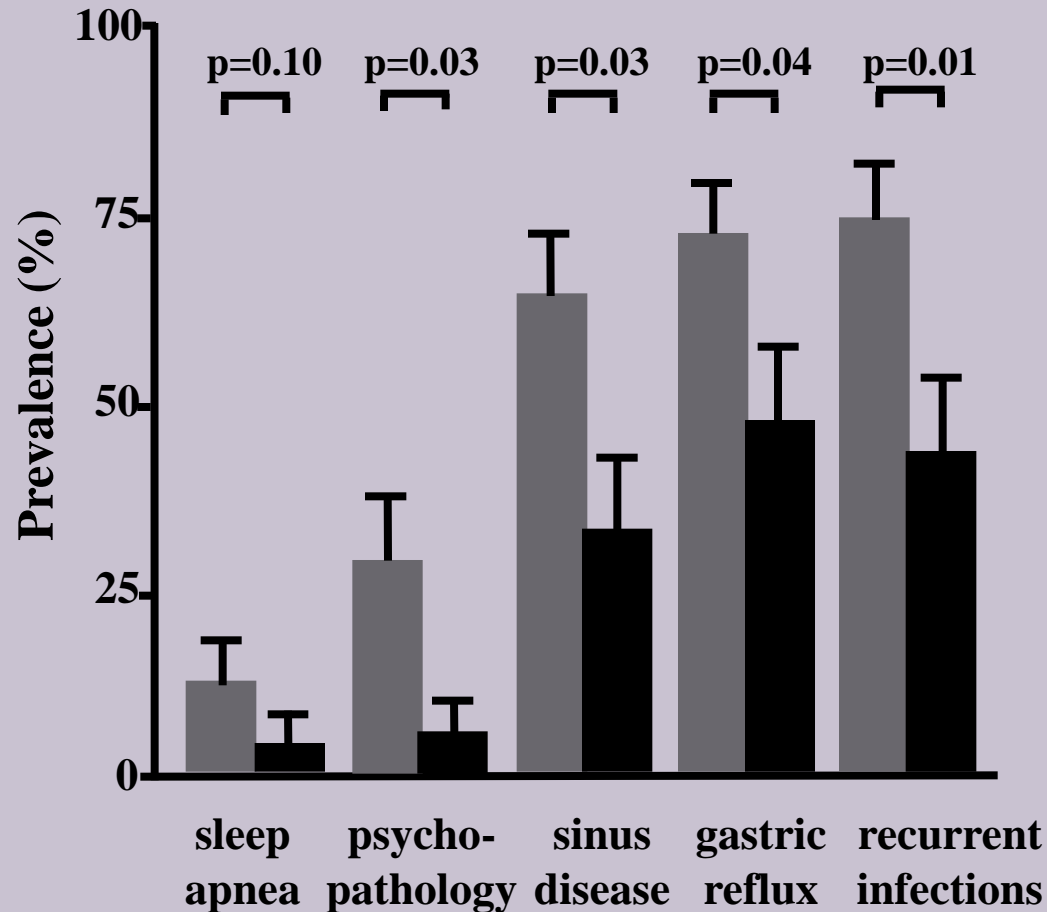
3 Cox, NEJM 2007; 356:1327-1337

Thoracic CT

- Investigation of other diagnoses
 - Chronic productive cough
 - Fixed airflow obstruction
- Findings in asthma:
 - Bronchial wall thickening, bronchial dilatation, air trapping

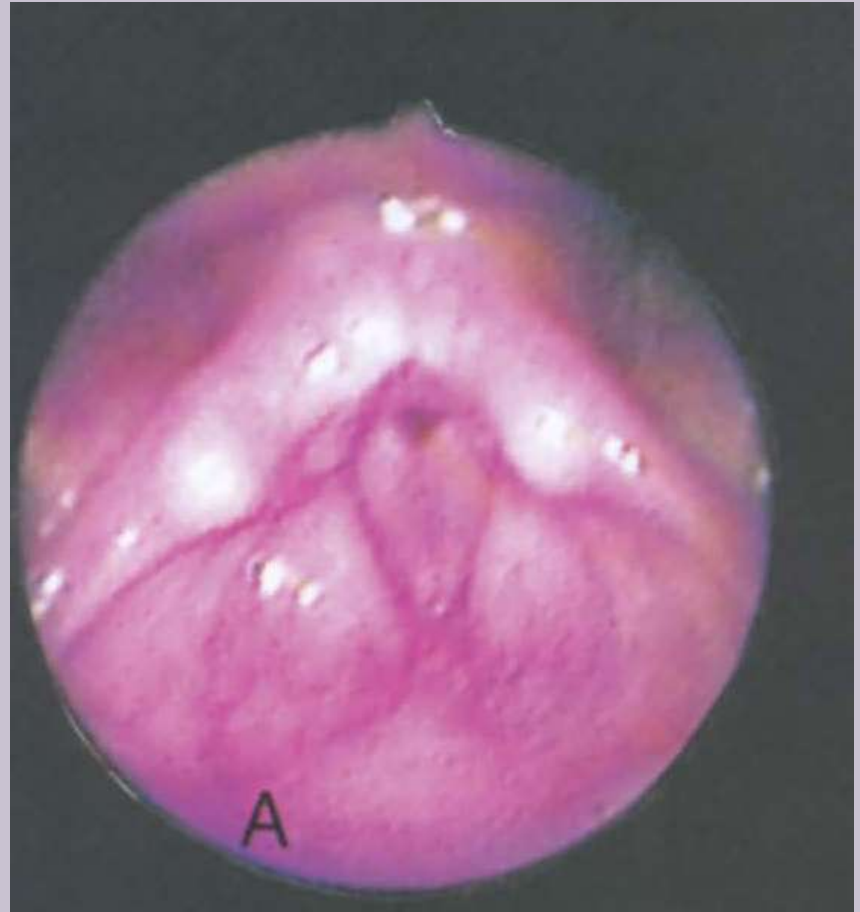


patients with frequent severe exacerbations have more co-morbidities



Co-Morbidity: Vocal Cord Dysfunction

- Abnormal adduction of vocal cords in **inspiration**
- **Absence of nocturnal symptoms**
- Normal flow volume **loop** in miniature
- Physiotherapy / breathing exercises
- Psychology referral

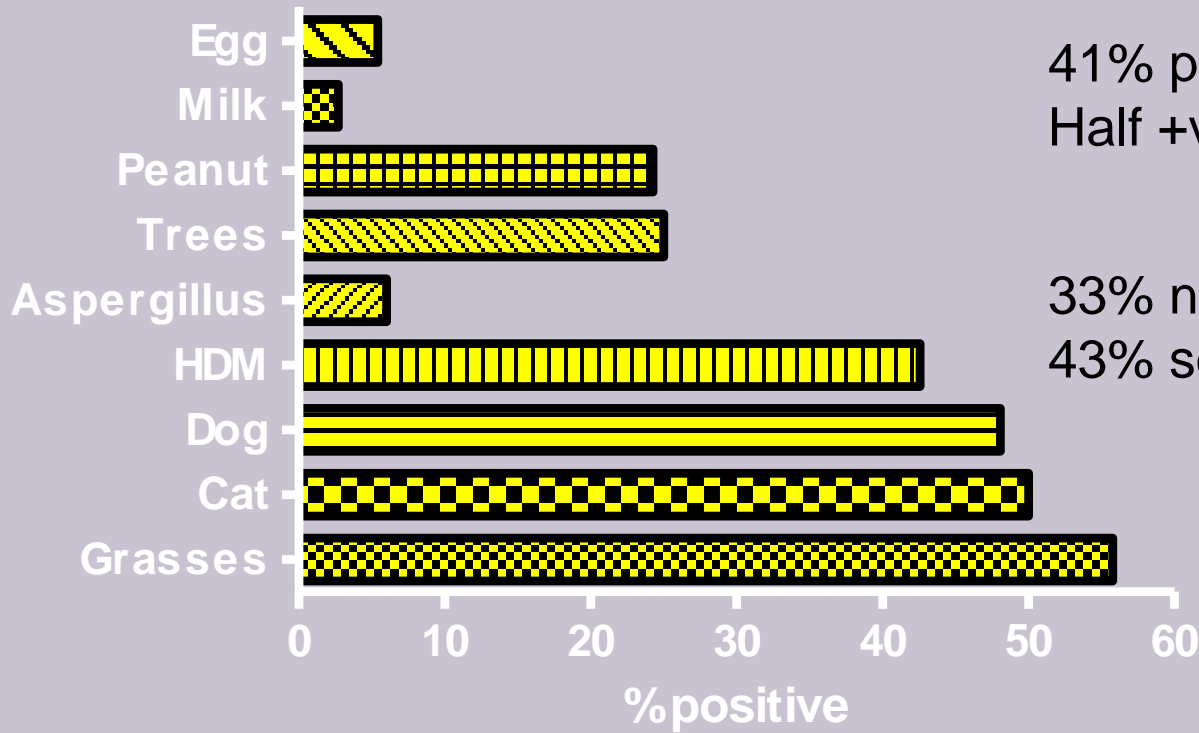


Exacerbating Factors – Allergen Exposure

- Exposure to allergen exacerbates asthma in sensitised individuals
- Increase bronchial hyper-responsiveness¹
- Multiple exposures and triggers
- **Identify** allergens (skin prick tests, specific IgE)
- Take steps to minimise exposure



Skin Prick Tests – RBH Cohort



41% pet owners
Half +ve SPT to own pet

33% no HDM avoidance measures
43% some avoidance measures

All negative 13 (22%)

Minimising Allergen Exposure

- Cochrane review:¹ **HDM** control measures
 - “**unable** to demonstrate clinical benefit”
- Patient selection
- Reduction of multiple **indoor** allergens shown to be of benefit²

1 Gøtzsche, Cochrane Database of Systematic reviews 2008;(2):CD001187

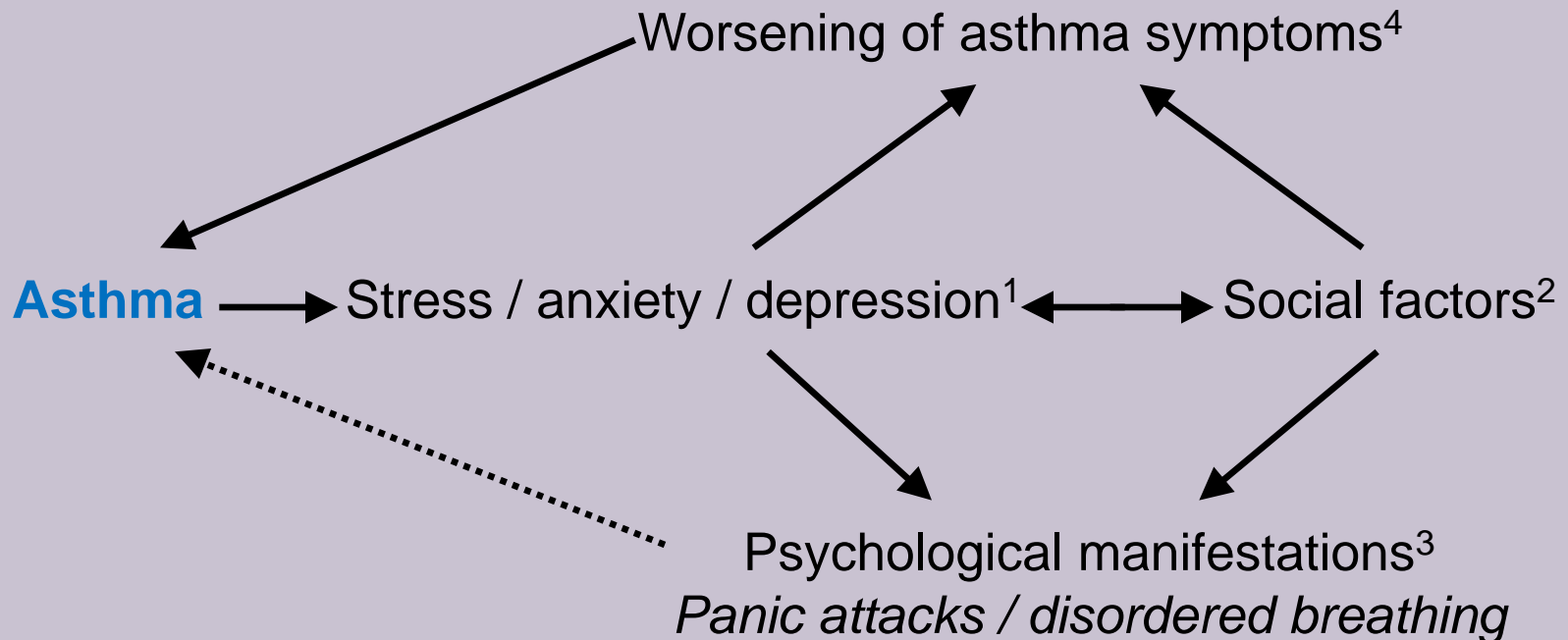
2 Morgan, NEJM 2004;351:1068-80

Exacerbating Factors - Smoking

- **Environmental tobacco smoke** is linked with impaired lung function and worsening of asthma: ¹
- Increased bronchial hyper-reactivity, heightened sensitisation to allergens, irritant effect, increased steroid **resistance**
- RBH cohort: **30%** at least one **parent smoked** (half inside the family home)
- Smoking cessation advice given

Psychosocial Factors

Complex relationship:



1 Sandberg Lancet 2000;368:982-987

2 Chen JACI 2006;117:1014-1020

3 Roy-Byrne Lancet 2006;368:1023-1032

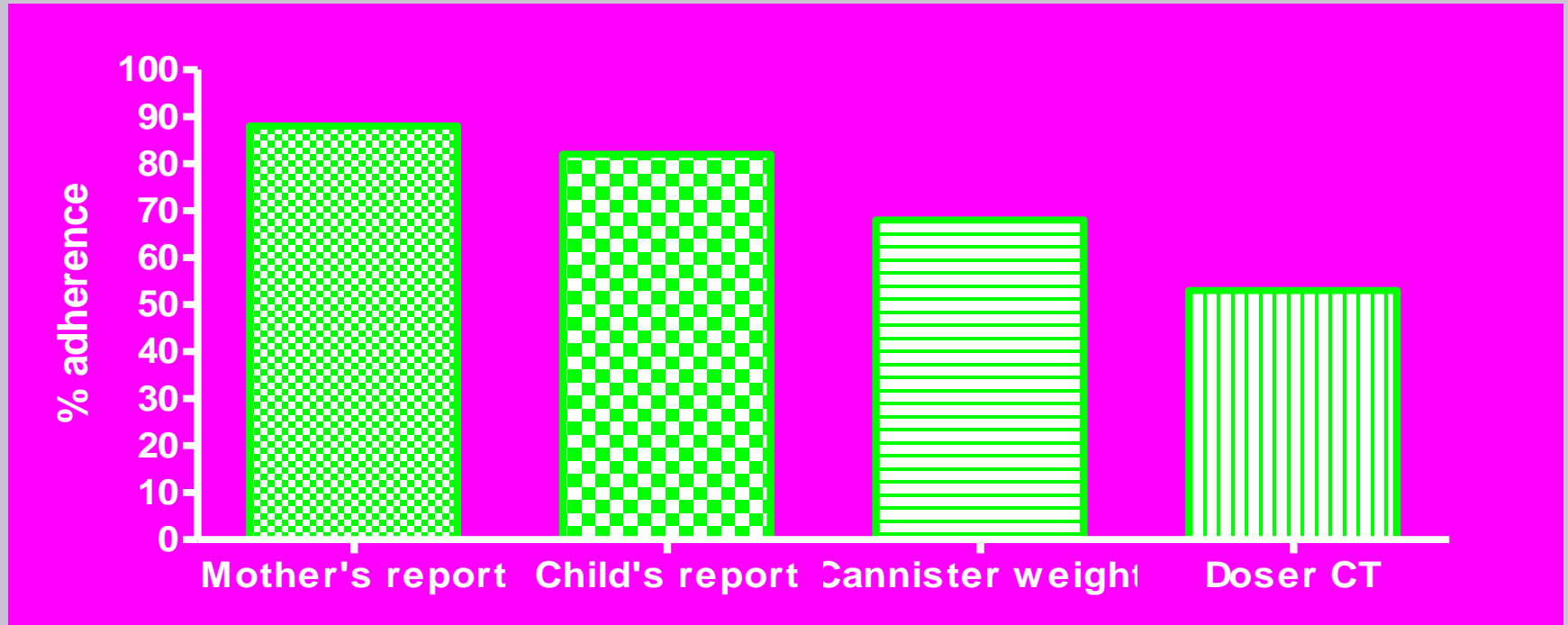
4 Richardson Pediatrics 2006;118:1042-1051

Adherence

- **Major obstacle** to effective management
- **Reasons** for non-adherence / barriers to adherence
 - Patient beliefs
 - Concerns regarding side effects
 - Lack of understanding of correct usage
 - Depression
 - Risk taking
- Provide a rationale for persistence

Assessment of Adherence

- Ask the patient / parent
- Weighing canisters
- Prescription checking
- Monitoring device



Other Treatment Issues

- Age appropriate device
- Correct technique



Approach to Treatment

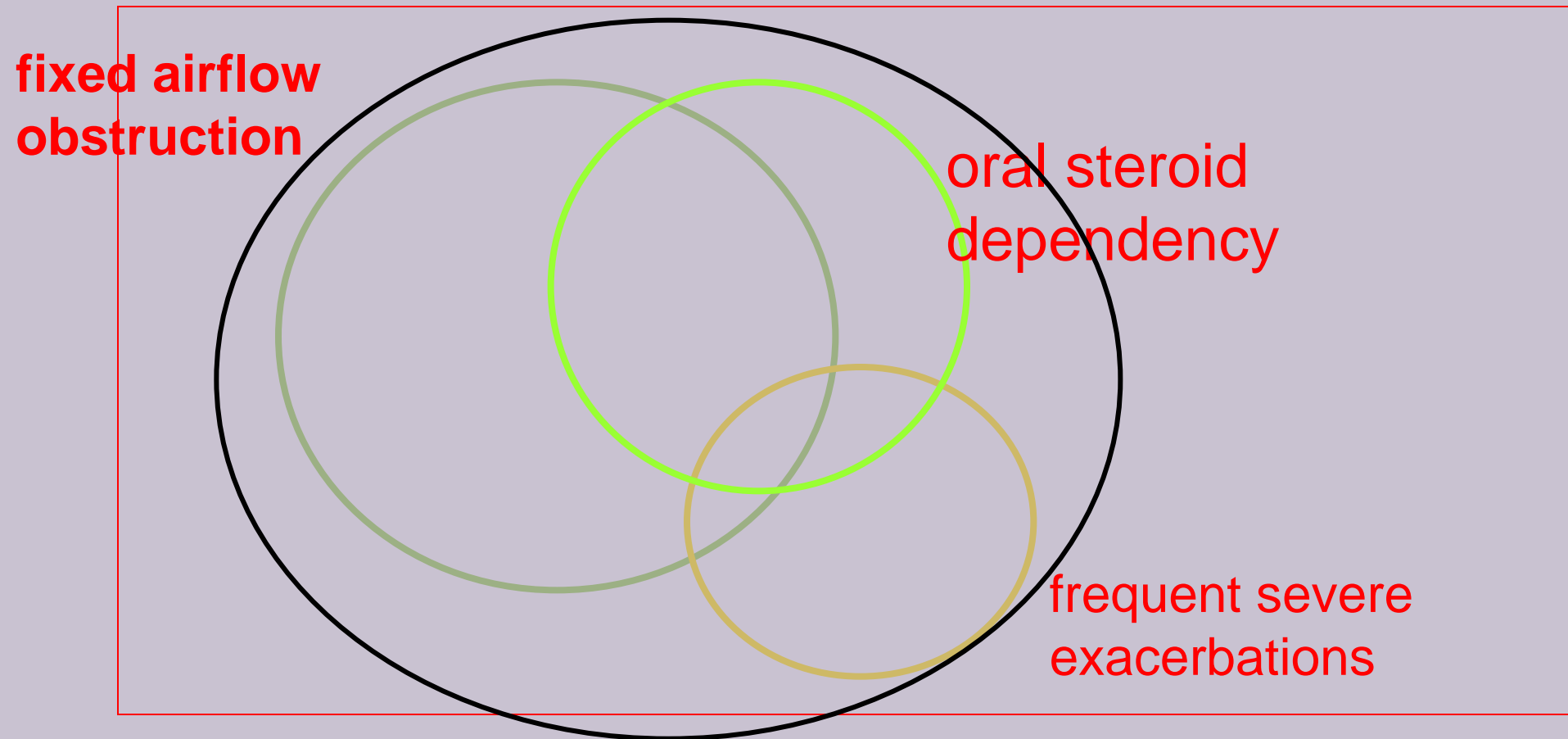
Define phenotype

- Clinical
- Inflammatory
- Lung function
- Response to treatment
- Trigger related
- (Genotype)



TARGETED
TREATMENT

3 clinical subtypes of severe asthma



adapted from ten Brinke, thesis 2002

Clinical / Physiological Phenotypes

History (Pattern):

- Frequent symptoms
- Exacerbation prone

Lung Function

- Chronic airflow limitation
- Bronchodilator reversibility

Response to Treatment

- Steroid responsive / resistant

Approach to Treatment – Current Guidelines (GINA)

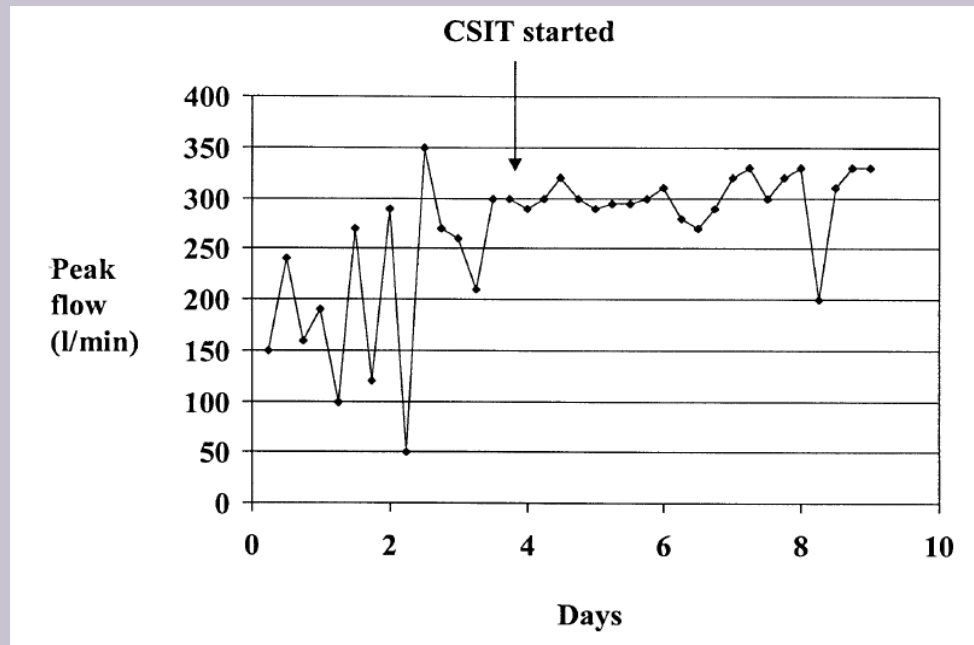
REDUCE		TREATMENT STEPS					INCREASE	
		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5		
		asthma education						
		environmental control						
		as needed rapid-acting β_2 -agonist	as needed rapid-acting β_2 -agonist					
CONTROLLER OPTIONS		SELECT ONE	SELECT ONE	ADD ONE OR MORE	ADD ONE OR MORE	ADD ONE OR BOTH		
		low-dose ICS*	low-dose ICS <i>plus</i> long-acting β_2 -agonist	medium- or high-dose ICS <i>plus</i> long-acting β_2 -agonist	leukotriene modifier	oral glucocorticosteroid (lowest dose)		
		leukotriene modifier**	medium- or high-dose ICS	leukotriene modifier	sustained-release theophylline	anti-IgE treatment		
			low-dose ICS <i>plus</i> leukotriene modifier	sustained-release theophylline				
			low-dose ICS <i>plus</i> sustained-release theophylline					

*inhaled glucocorticosteroids

** receptor antagonist or synthesis inhibitors

Bronchodilator Reversibility

- Optimise long acting beta agonist (combination inhalers)
- Sub-cutaneous terbutaline¹



Assessment of Steroid Responsiveness

Following **high dose parenteral** corticosteroids (i/m triamcinolone to ensure compliance)¹:

- **Clinical**
 - improvement in symptom score
- **Inflammatory**
 - “normalisation” of non-invasive markers of inflammation (sputum eosinophils and FeNO₅₀)
- **Spirometry**
 - Post BD FEV1 ≥80% predicted
 - BDR <12%

¹ Panickar Pediatr Pulmonol 2005;39:421–425.

Steroid Responsive

- **Optimise steroids**
 - Dose response plateau
 - Monitor for side effects
 - Ciclesonide¹
- **Consider immunomodulators**
 - Cyclosporin²
 - Methotrexate
 - Azathioprine

1 Gelfand, J Pediatrics 2006;148:377-383

2 Coren ADC 1997;77:522-523

Mechanisms of relative steroid resistance

- low avidity between GC and GR
- Low avidity between GC-GCR complex and GRE
- High GR- β expression
- Abnormal HDAC activity secondary to oxidative and nitrative stress
 - severe inflammation
 - smoking asthmatic patients
 - latent adenovirus infections

Steroid Resistant

- Reduce steroids
- Consider immunomodulators
 - Cyclosporin
 - Methotrexate
 - Azathioprine
- Other treatment strategies
 - Anti-IgE
 - Azithromycin
 - Theophylline

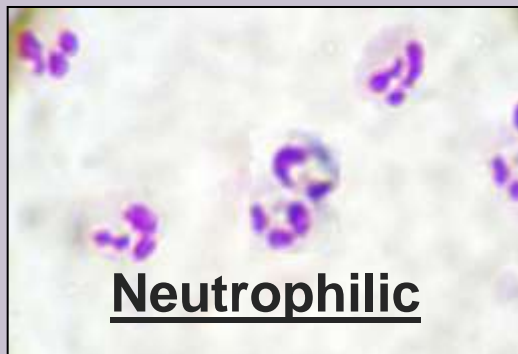
Trigger Related - Atopy

- **Omalizumab¹**
 - **Recombinant IgG₁** monoclonal anti-IgE antibody
 - Licensed for children >12 years with severe persistent IgE-mediated asthma
 - IgE level 30 – 700IU/ml
- Allergen Specific **Immunotherapy**
 - Recommended for mild asthma only

Inflammatory Phenotypes



- **Corticosteroid sensitive disease**
- Symptom frequency associated with higher sputum **eosinophils**¹, however not necessarily a marker of disease severity
- **20-40% of children** with severe asthma have sputum eosinophilia



- Cause of **neutrophilic** inflammation is unknown
- Possibly related to innate immune system²
- Associated with **viral infections**, corticosteroid use

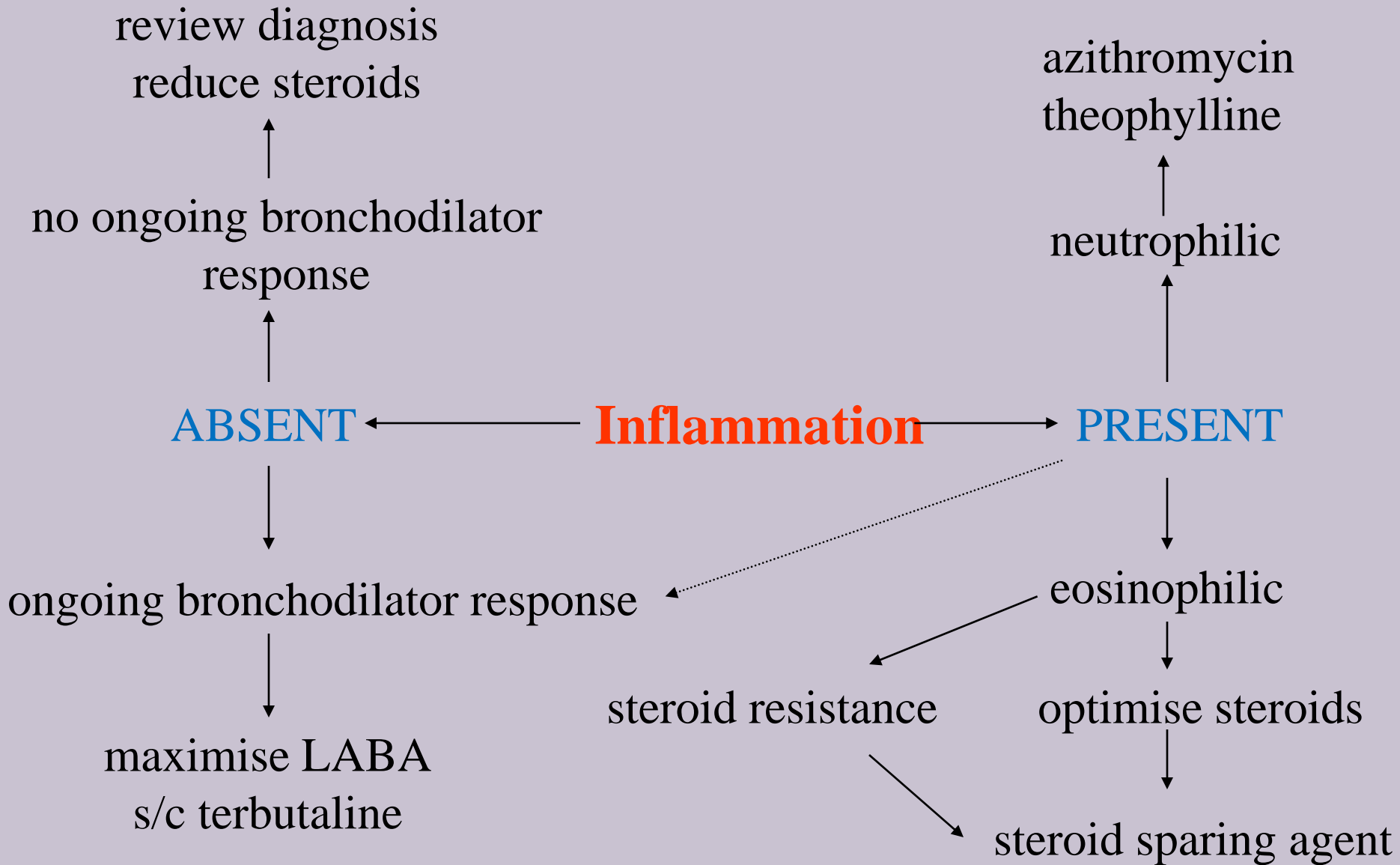


- Inflammation **controlled by high doses of CS** or distinct non-eosinophilic phenotype
- On going symptoms caused by other pathological processes

1 Gibson, Thorax 2003;58:116–121

2 Simpson, Thorax 2007;62:211-218

Targeted Treatment



Exacerbation

- IV steroids
- B2 agonists
- Ach
- Antibiotics? Macrolides
- MV
- Other measures

Assessment of severity

- **Respiratory**

- Respiratory rate, SpO₂, degree of breathlessness, ↓speech, refusal to lie down, accessory muscle use, wheezing (expiratory, biphasic or silent)

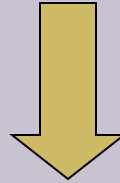
- **CNS**

- Agitation, confusion, coma

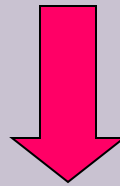
- **Cardiovascular**

- Tachycardia, pulsus paradoxus, sweating, bradycardia

Supportive care, O₂, fluids, specific treatment

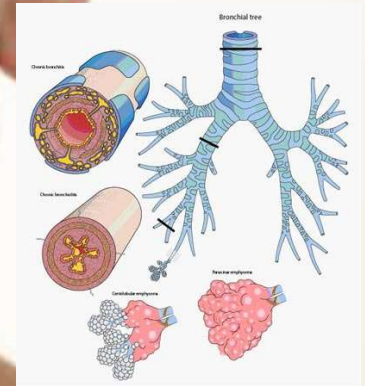


Reassess response to treatment



- Respiratory
- Cardiovascular
- CNS

Inhaled bronchodilators



Inhaled bronchodilators (1)

- Nebulised **salbutamol** 0.15mg/kg
- Nebulised **ipratropium** bromide 3 times in first 60 minutes
- Prolonged bronchodilatation
- ↓ hospitalization rate, ↑ lung function

Inhaled bronchodilators (2)

- **MDI spacer for mild** to moderate asthma
- **Levalbuterol** = salbutamol/ipratropium
- **Continuous** nebulisation > intermittent
- **Nebulised MgSO₄** may ↑ bronchodilation?

Steroids



Steroids

- **Oral** prednisolone 0.5 -2 mg/kg
- **Early** treatment is better
- **IV = oral = Intramuscular** therapy
- **Nebulised** steroids **less effective** than oral
- **Nebulised budesonide** early response?



**Intravenous
bronchodilators**

Intravenous aminophylline

- In those **unresponsive** to standard treatment
- Better lung function **at 6 hours**
- More vomiting
- Equivalent to terbutaline IV
- Early administration no better
- Better than IV salbutamol?

Intravenous salbutamol

- Use in **those unresponsive** to initial treatment
- Needs loading dose
- Effective if continuous/repeated boluses
- **Hypokalaemia**
- High dependency monitoring

Intravenous magnesium

- Effective in children
- Improved respiratory function from baseline
- ↓admission by 30%
- 25-100mg/kg bolus

Other therapies

- Adrenaline/Epinephrine = salbutamol

Is it anaphylaxis?

- Leukotriene antagonists

Montelukast may help in mild -moderate asthma

Failure to improve

- Chest X-ray, blood gas
- Supportive care
- Intubation



**Make repeated
assessments**

To take home...

- Repeated assessments
- Oxygen to keep $SpO_2 > 92\%$
- Nebulised salbutamol/ ipratropium X 3
- Early steroids
- Consider IV therapy if no improvement
 - Salbutamol/Aminophylline \longrightarrow Magnesium

MV

- 4 percent of all hospitalized for acute asthma
- Life-saving
- Can cause M/M.

– Anzueto A et al. Intensive Care Med 2004 (4):612-9.

Indication of MV

- should be considered **early**
 - respiratory failure (oxygenation +/- ventilation).
 - physiologic derangements
 - clinical judgement

GENERAL APPROACH

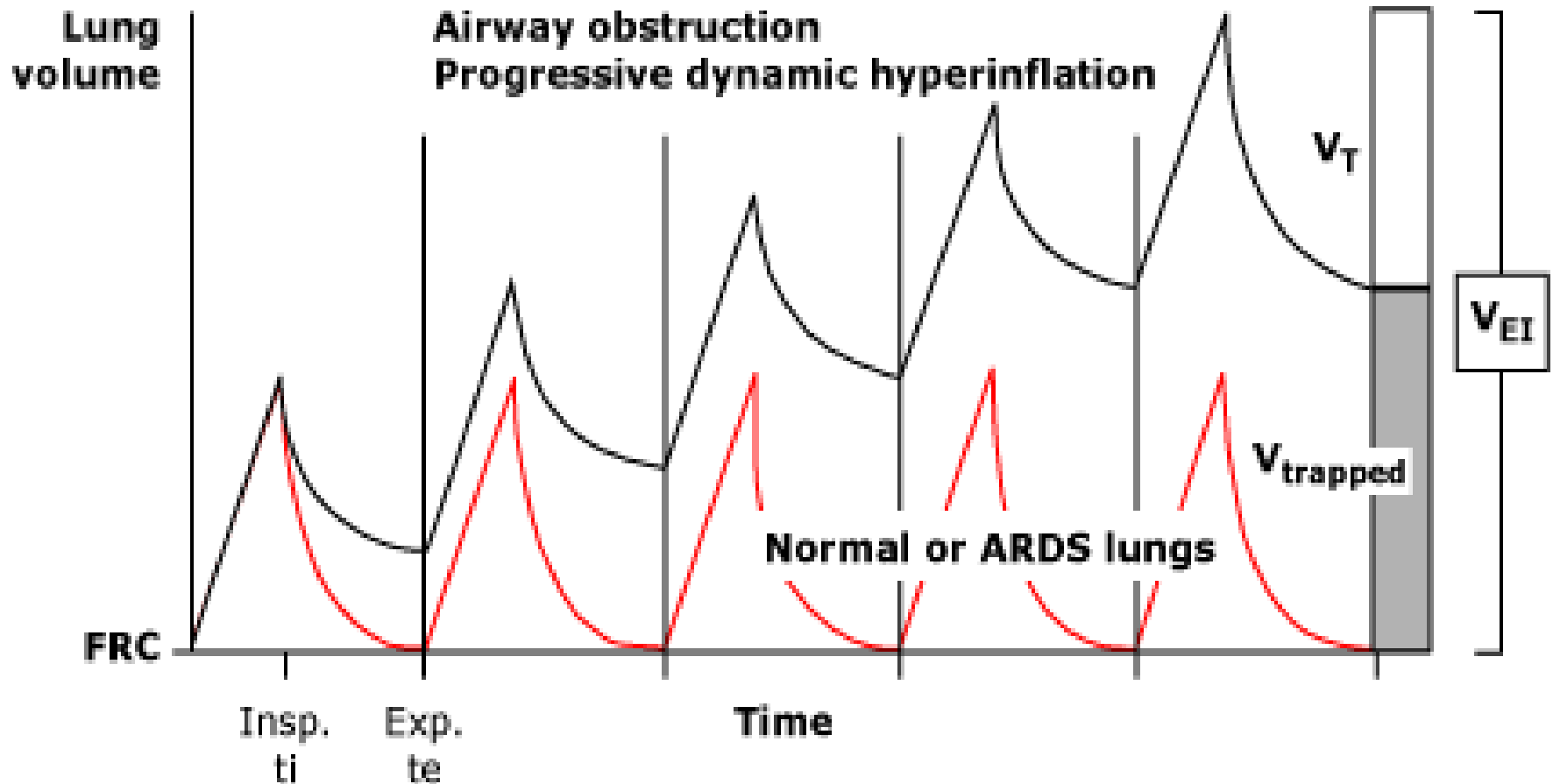
- **Intubation**

- **Caution:** can cause increased airflow obstruction
- Adequate **venous** access
- Noninvasive **monitoring**
- **sedation** should be optimized prior to intubation.
- most experienced **clinician**
- preferably with a large-bore (≥ 8.0 mm) **ET**.

Ventilator settings

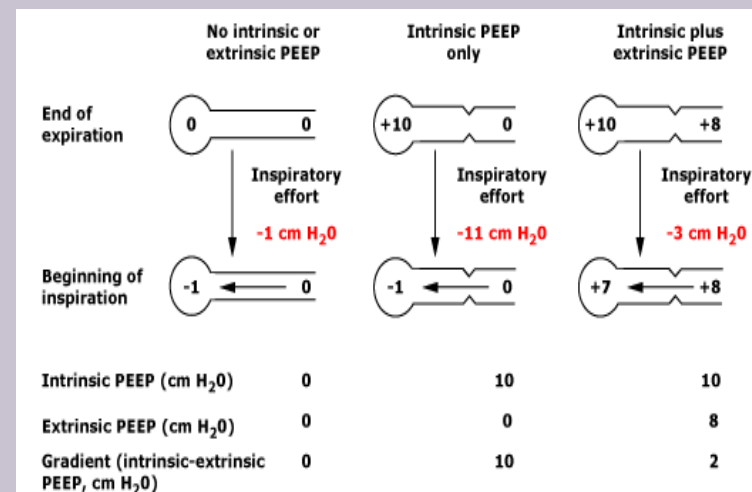
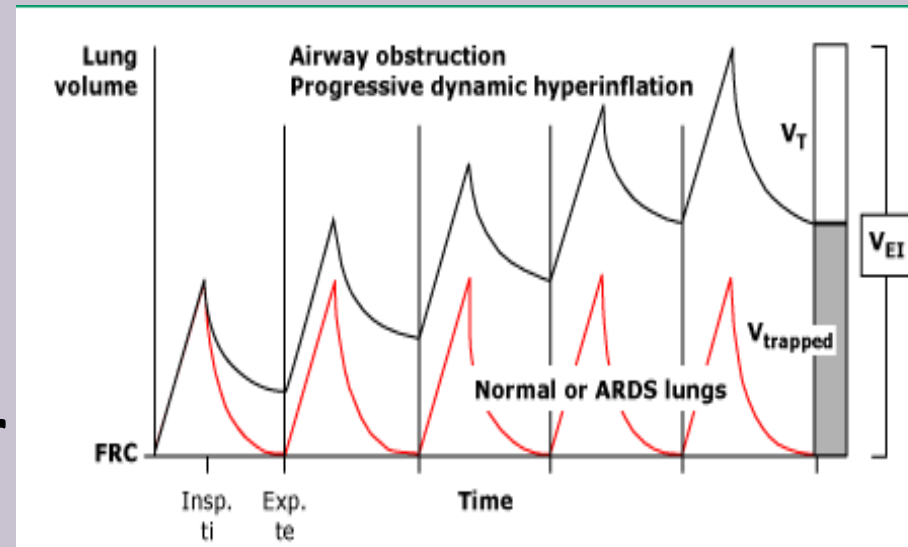
- initial ventilator settings
 - **RR** 10 to 14 breaths/min
 - **Tidal volume** less than 8 mL/kg
 - **Minute ventilation** less than 115 mL/kg
 - Inspiratory **flow** of 80 to 100 L/min
 - **Extrinsic PEEP** less than 80 percent of the intrinsic PEEP

Dynamic Hyperinflation



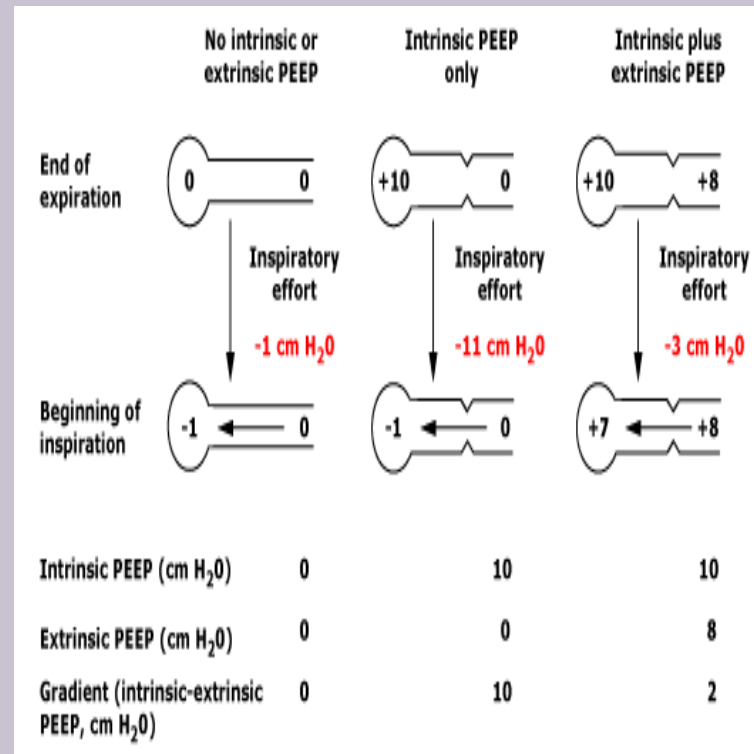
Consequences of Hyperinflation

- creates **intrinsic PEEP**
- Elevates **P_{plat}**
- can lead to **cardiovascular collapse**
- **barotrauma**
- increases the **work of breathing**.
- **Asynchrony**



Increased work of breathing

- **Intrinsic PEEP** increases the magnitude of the drop in airway pressure that the patient must generate to trigger a breath thereby increasing the patient's workload.
- **Extrinsic PEEP** at levels less than the intrinsic PEEP will reduce this **gradient** and the work of breathing
- Extrinsic PEEP should not exceed **80 percent** of the measured intrinsic PEEP in order to avoid worsening the dynamic hyperinflation



– Mechanical ventilation of the patient with severe chronic obstructive pulmonary disease. Gladwin MT; Pierson DJ. Intensive Care Med. 1998 Sep;24(9):898-910.

Other consequences

Cardiovascular collapse

- **Hyperinflation** increases intrathoracic pressure
- Intravascular **volume depletion**
- **sedatives** can accelerate the deterioration.
- Tx: volume resuscitation and alleviation of the hyperinflation, usually by temporarily disconnecting the ventilator circuit from the endotracheal tube.

Barotrauma

- **overdistension**
- loss of the airway's structural integrity
- Interstitial emphysema, pneumothorax, pneumomediastinum, subcutaneous emphysema, and/or pneumoperitoneum
- Causes **cardiac arrest**

Asynchrony

- Even after sedation
- **Paralytic** agents may be necessary in this setting.
- **Adequate sedation** must be maintained if paralysis is used
- increases the risk of **post-paralytic myopathy**

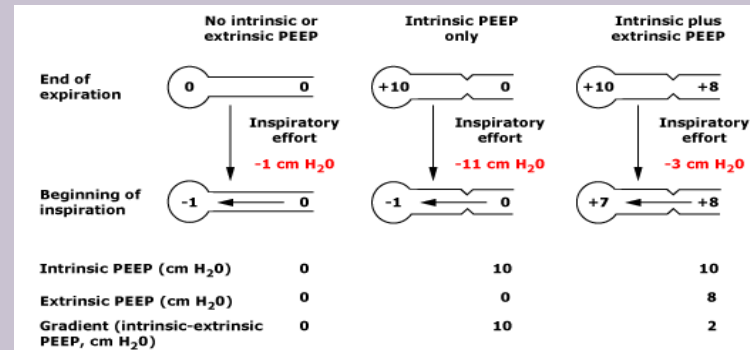
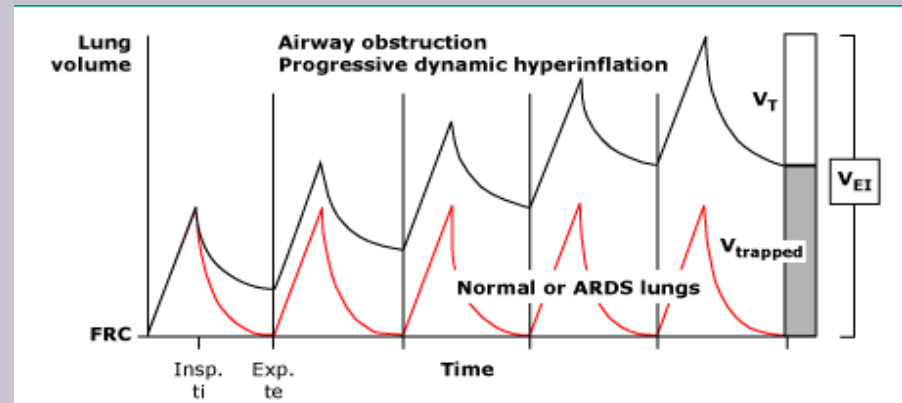
Managing Hyperinflation

Principle: decrease air trapping by

- Maintaining P_{plat} less than 30 cm H₂O
- intrinsic PEEP less than 10 cm H₂O.

The following adjustments may help

- increase the **expiratory time**
- Decreasing the **tidal volume** : less lung inflation smaller volume to exhale before the next breath.
- Decreasing **RR**: increases the expiratory time
- Adding low levels of **extrinsic PEEP** (eg, less than 80 percent of the intrinsic PEEP): reduce the effort necessary to trigger inspiration during spontaneous breaths.
- Decreasing the respiratory rate and tidal volume may require **permissive hypercapnia**



Other Supportive Measures

General anesthesia

- reduce bronchospasm
- intravenous infusion (eg, ketamine)
- inhalation (eg, isoflurane) .

Heliox

- blend of helium and oxygen that has a **lower density** than air
- reduces **resistance** to airflow
- enhances delivery of nebulized **bronchodilators**
- improves **oxygenation** compared to standard nitrogen-oxygen mixtures.
- Problems: inaccurate measurement of tidal volume and oxygen concentration
 - Am J Respir Crit Care Med 2002 May 1;165(9):1317-21.

Extracorporeal life support

- Oxygenation and carbon dioxide removal through an artificial membrane

MV in summary

- intravenous corticosteroids
- Inhaled bronchodilators
- Deep sedation
- Protective lung strategy : decrease HI
- Paralysis
- General anesthesia
- Heliox
- Extracorporeal life support

Mortality

- **Prior to 1990:** MV for severe acute asthma caused mortality rates as high as **38 %**
- Cause was **pneumothorax** or ventilator malfunction
- **in 2000:** decreased dramatically to **7 percent** : permissive hypercapnic
 - Am J Respir Crit Care Med. 2006 Sep 15;174(6):633-8.
- **A high PIP is not a reliable indicator** of lung overdistension
 - PIP can be elevated due to increased **airway resistance** or high inspiratory **flow rates**
- **Pplat is a more accurate measure** of distending pressures
 - **measured** by occluding the proximal airway at **end inspiration (typically for 0.5 sec)** to allow equilibration of airway pressures with more distal regions of the lung.
 - A safe upper limit **below 30 cmH2O**.
 - An alternative strategy is limiting the end-inspiratory volume (VEI) to less than 1.4 L [19] .

PROGNOSIS

- status asthmaticus on MV have increased in-hospital mortality (**7 versus 0.2 percent**) .
- **Survivors** remain at high risk of death: may be worse than some malignancies.
- The one-, three-, and six-year mortality rates were **10, 14 and 23%** due to recurrent asthma.
 - Am Rev Respir Dis 1992 Jul;146(1):76-81
- Close medical **follow-up** may be a key to long-term survival.
- Survivors demonstrate a lot of **denial**
- **Anxiety** appears to be more common among close family members
- Denial is an understandable psychological mechanism for dealing with fear.
- **Depression** is strongly associated with an increased risk of asthma mortality: lethal mix

severe

- XXX
- Rather be here



Thank you

asthma

- XXX

