Asthma (Phase 2)

Prof Ian Sabroe

Lecture outline

- The burden of asthma, economic and personal
- The pathology of asthma, asthma subtypes
- Making a correct diagnosis of asthma
- Managing asthma (chronic)
- Managing asthma, acute

The burden of asthma

Burden of asthma

- 5.4m in the UK receiving treatment. 1.1m children (1:11), and 4.3m adults (1:12)
- 1,131 asthma deaths in 2009 (12 in children ≤14 years)
- 60% of asthmatics report significant persistent symptoms or symptom burden.
- 65% of asthmatics report severe attacks (unable to talk)

The costs of asthma

- £1bn per annum costs to the NHS
  - Greatest proportion of costs are chronic therapies
- 4.1m GP consultations per annum
- 1 million lost working days per annum
- Asthma treatments are not automatically free (contrast with diabetes)

Epidemiology of asthma

Why is it so common?

Changing patterns of disease

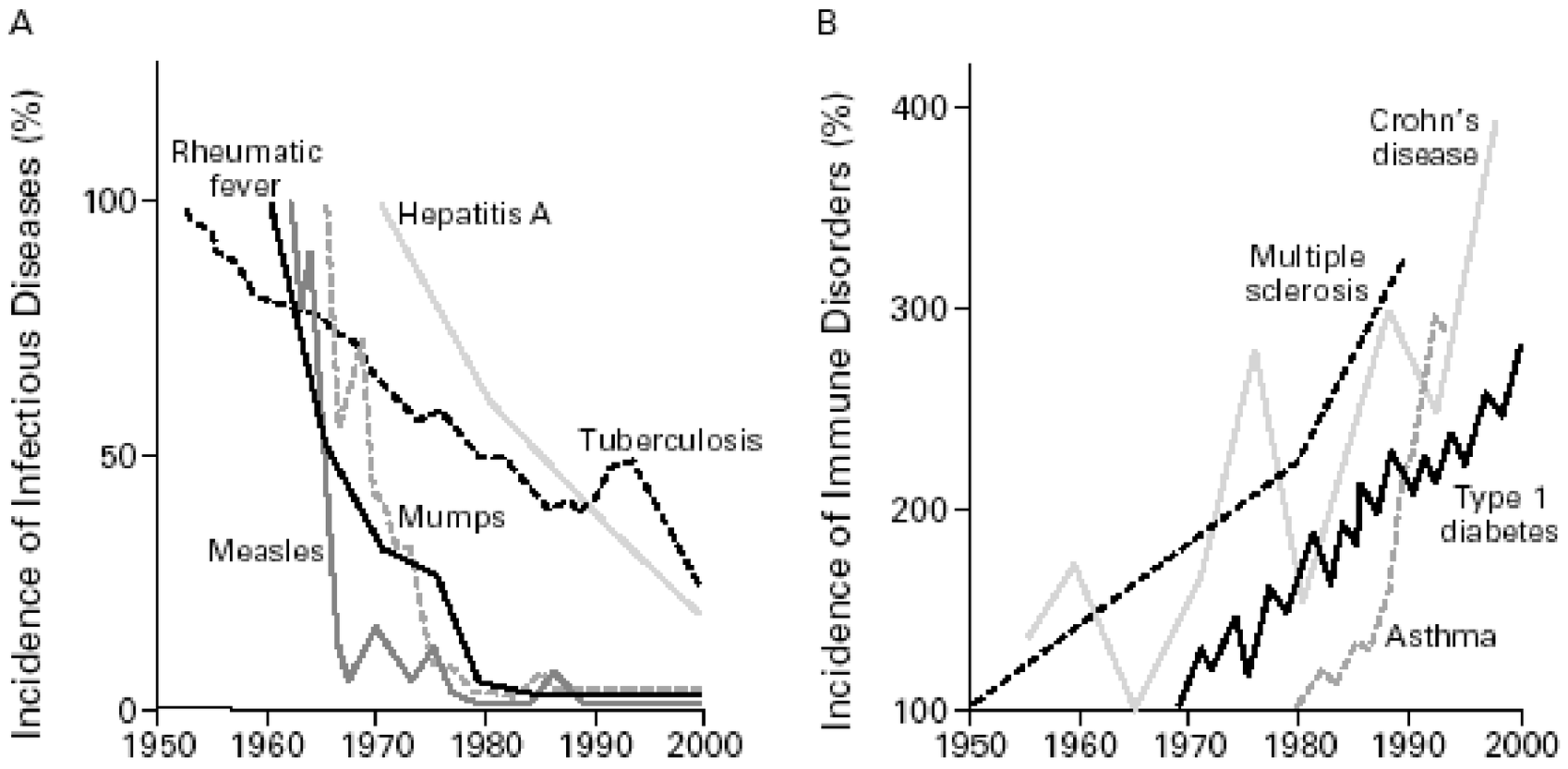


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

The roots of the problem?

Summer catarrh…only occurs in the middle or upper classes of society, some indeed of high rank. I have made inquiry at the various dispensaries in London and elsewhere, and I have not heard of a single unequivocal case occurring among the poor.

—Bostock J. On the catarrhus aestivus or summer catarrh. London: Medico-Chirurgical Transactions; 1828. p. xiv:437-446.[1]

It would seem that hay-fever has, of late years, been considerably on the increase…The persons who are most subjected to the action of the pollen belong to a class which furnishes the fewest cases of the disorder, namely, the farming class.

—Blackley CH. experimental researches on the causes and nature of Catarrhus aestivus (hay-fever or hay-asthma). London: Balliere, Tindall & Cox; 1873.

Lessons from epidemiology

Asthma incidence one-third if one year...

Twin studies
Older siblings
Roles of infections
- coughs and colds
- RSV
- Hepatitis

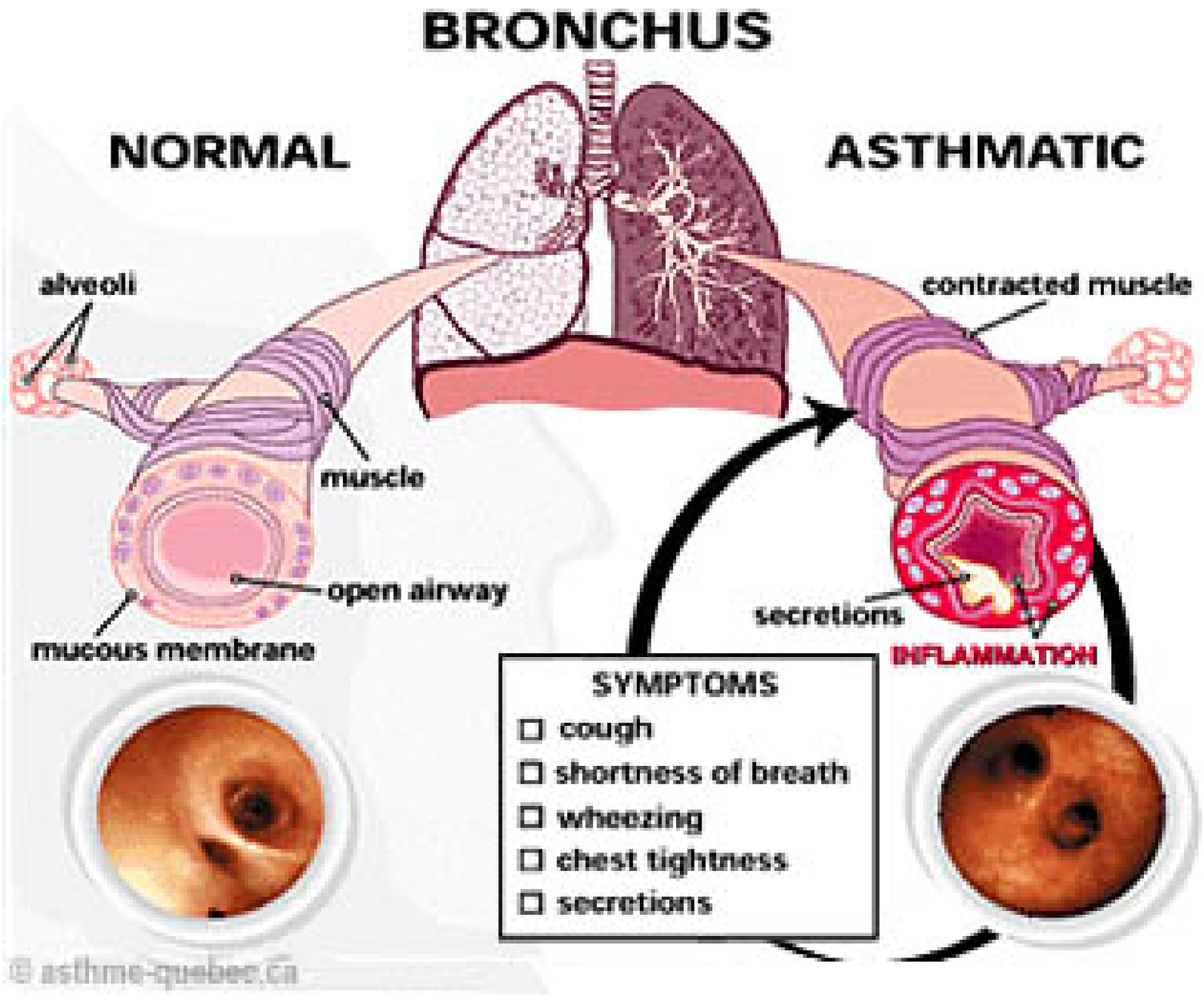
The hygiene hypothesis

- It's not pollution (East Germany, early daycare)
- Dirt is good...
  - though not in all studies
- But non-allergic inflammatory disease also increasing
- Hayfever more coincident than asthma

The pathology of asthma

Ultimately, pathology guides treatment.
Patients want to understand their disease.

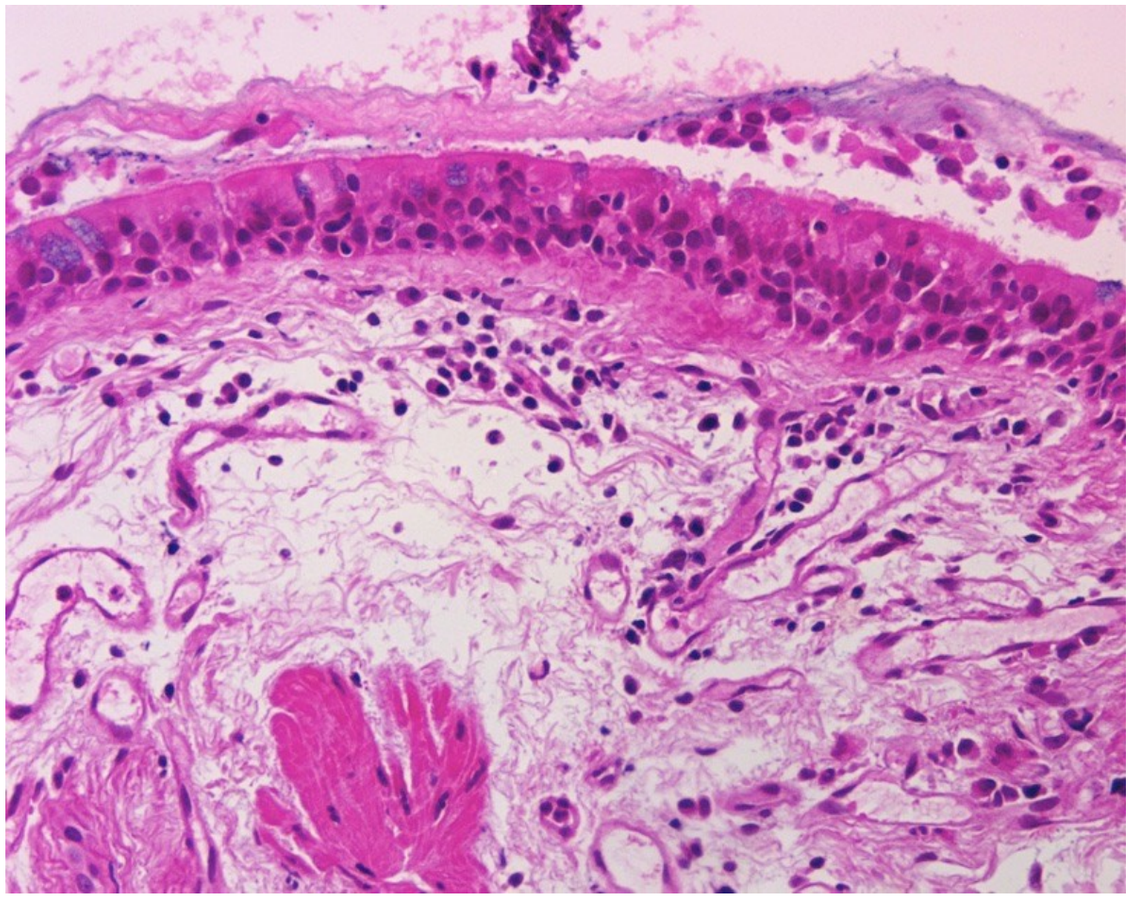
Bronchial hyperresponsiveness

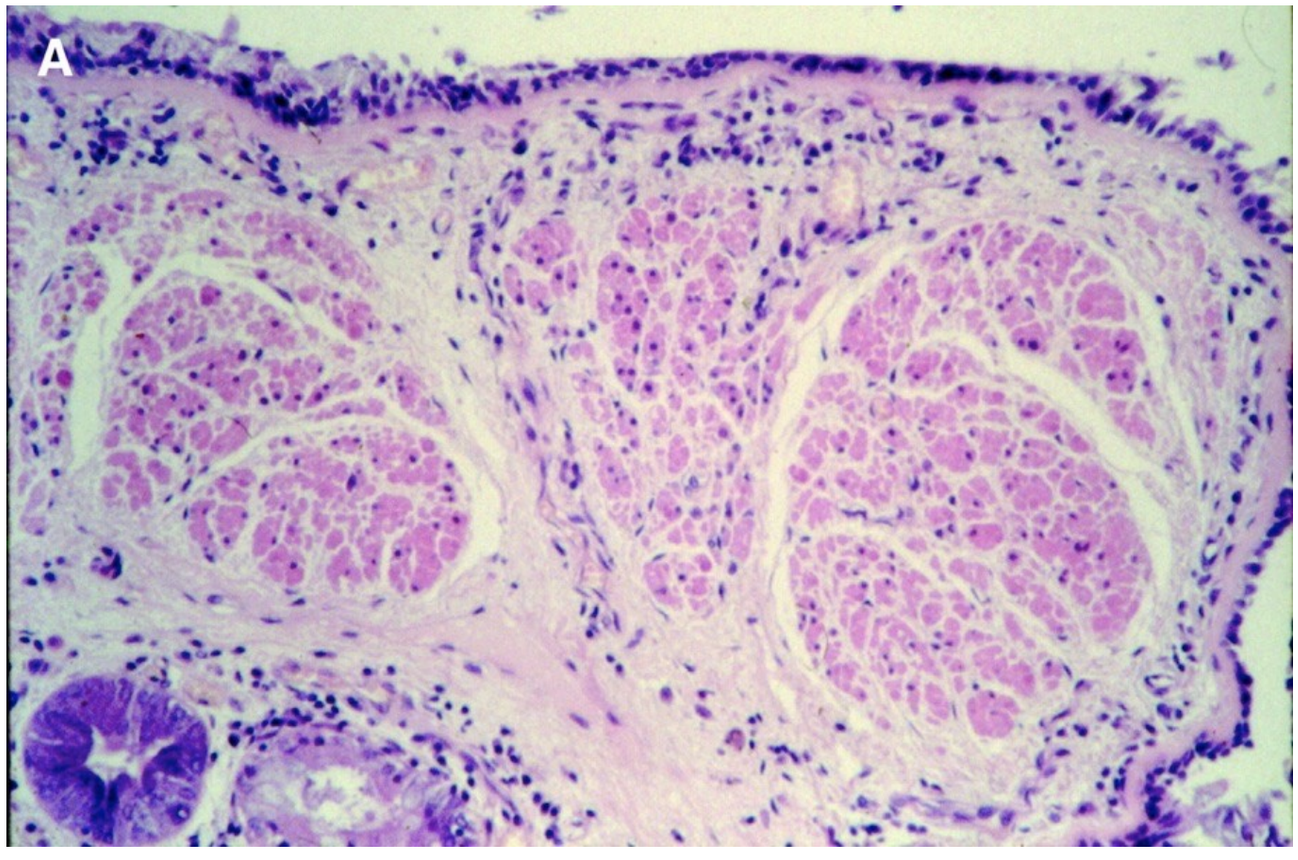


Smooth muscle

- Inappropriate and excessive contraction of smooth muscle
- Hypertrophy and proliferation of smooth muscle cells, further narrowing the airway lumen

Histopathological asthma





Two main types of asthma

- EOSINOPHILIC
  - associated with allergy
  - also non-allergic variant
- NON-EOSINOPHILIC

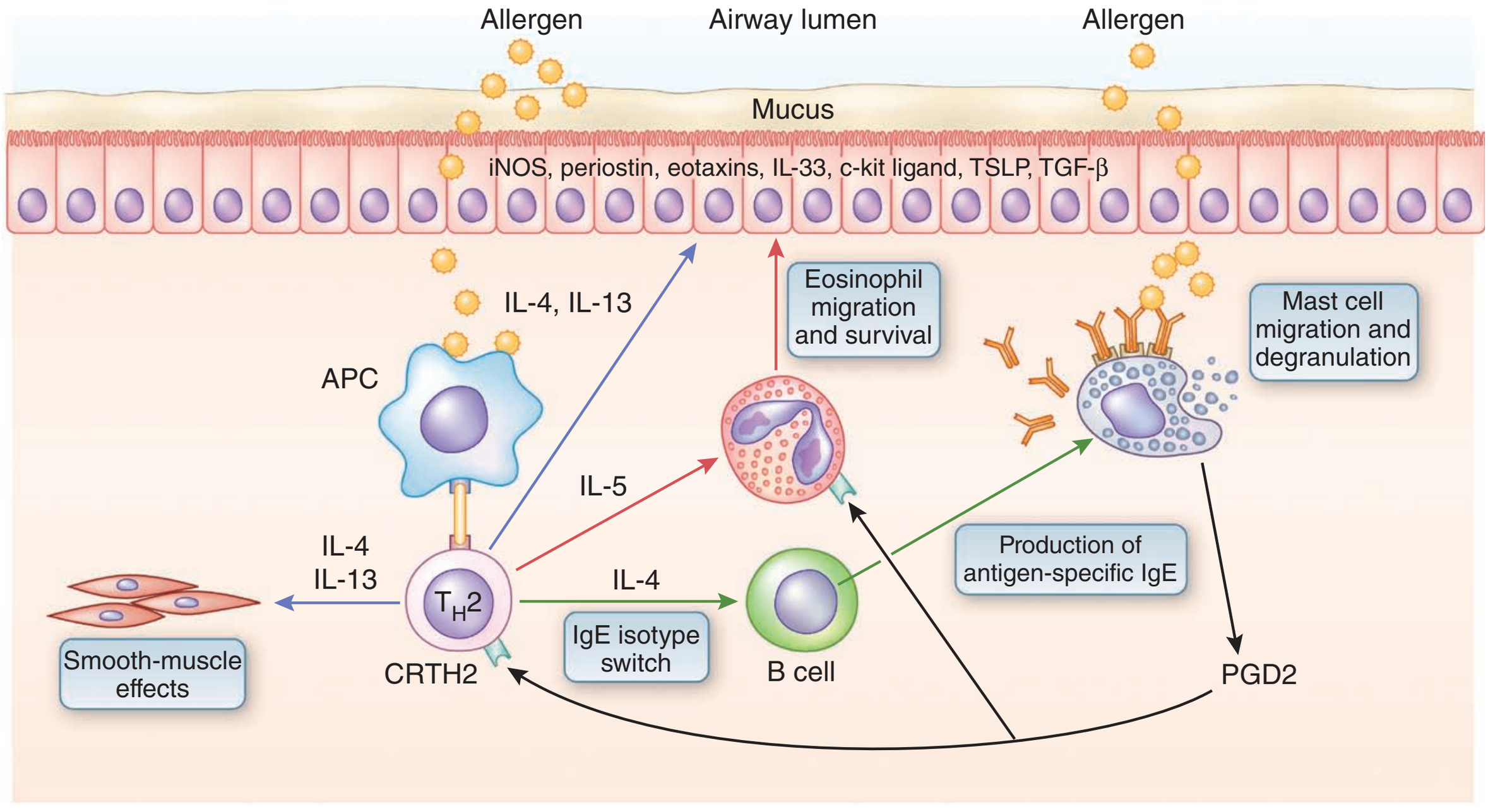
Asthma as an allergic disease…

- Allergic inflammation is characterised by the recruitment of eosinophils
- Atopic asthma
  - 25% are atopic, half get disease
  - Atopy is the tendency to develop IgE mediated reactions to common aeroallergens

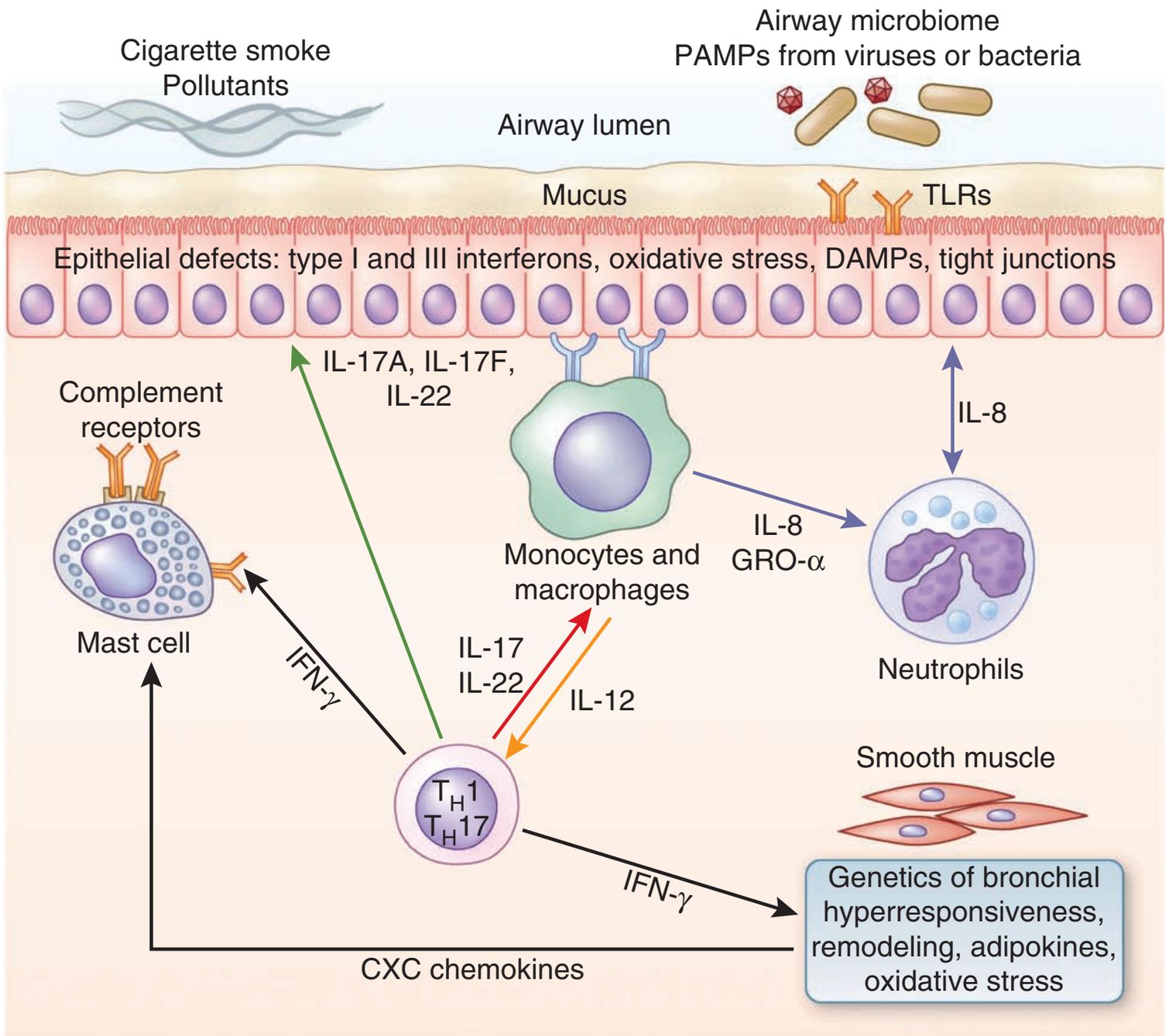
Not all asthma is eosinophilic

- About half of patients have no evidence of eosinophilic asthma
- There are overlaps with smoking, obesity

Eosinophilic asthma



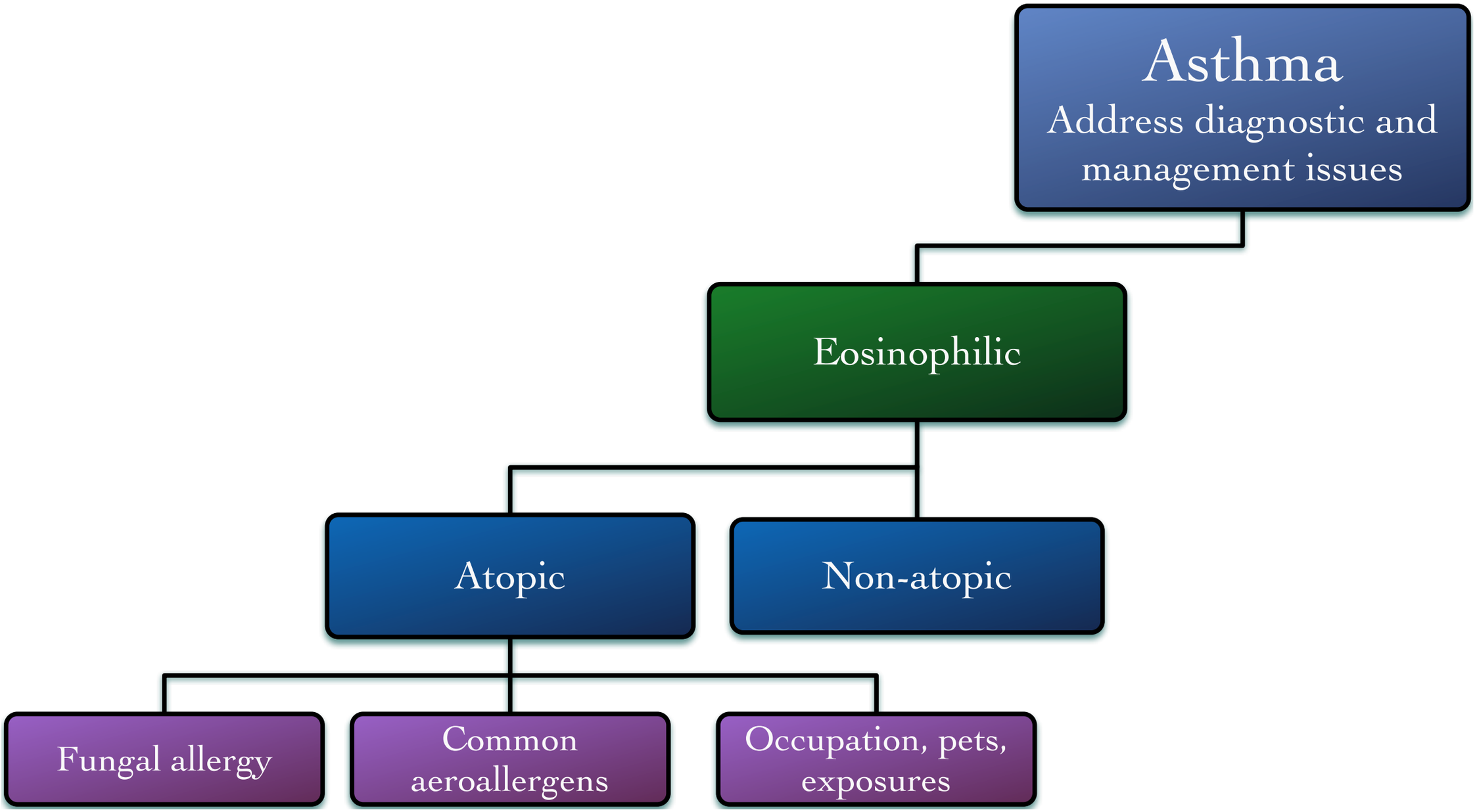
Non-eosinophilic asthma



Asthma

Address diagnostic and management issues

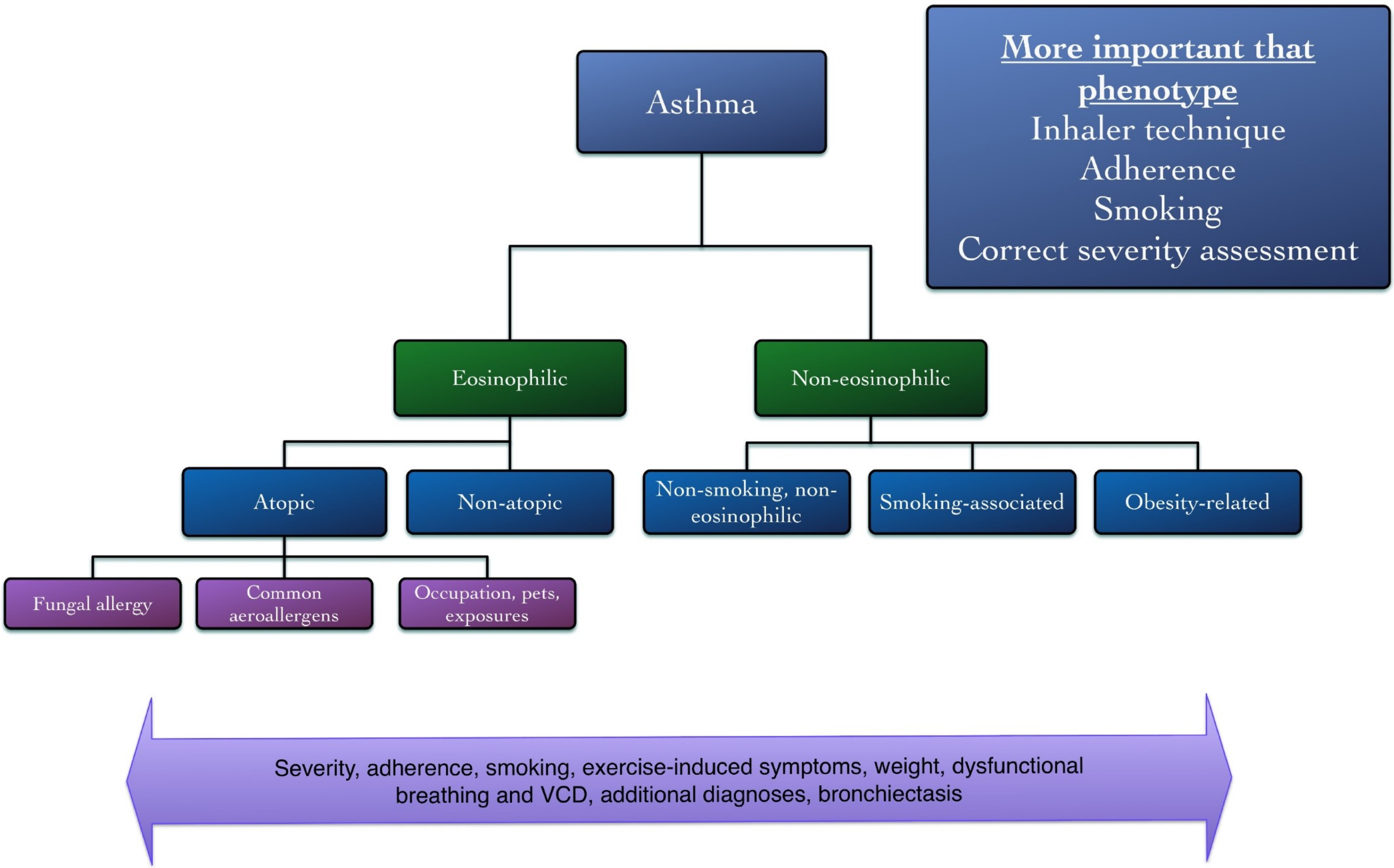
- Eosinophilic
- Non-eosinophilic


Asthma
Address diagnostic and management issues
Eosinophilic
Atopic
Non-atopic
Fungal allergy
Common aeroallergens
Occupation, pets, exposures

Asthma

Address diagnostic and management issues

- Non-eosinophilic
  - Non-smoking, non-eosinophilic
  - Smoking-associated
  - Obesity-related


Asthma
More important that phenotype
Inhaler technique
Adherence
Smoking
Correct severity assessment
Eosinophilic
Non-eosinophilic
Atopic
Non-atopic
Non-smoking, non-eosinophilic
Smoking-associated
Obesity-related
Fungal allergy
Common aeroallergens
Occupation, pets, exposures
Severity, adherence, smoking, exercise-induced symptoms, weight, dysfunctional breathing and VCD, additional diagnoses, bronchiectasis

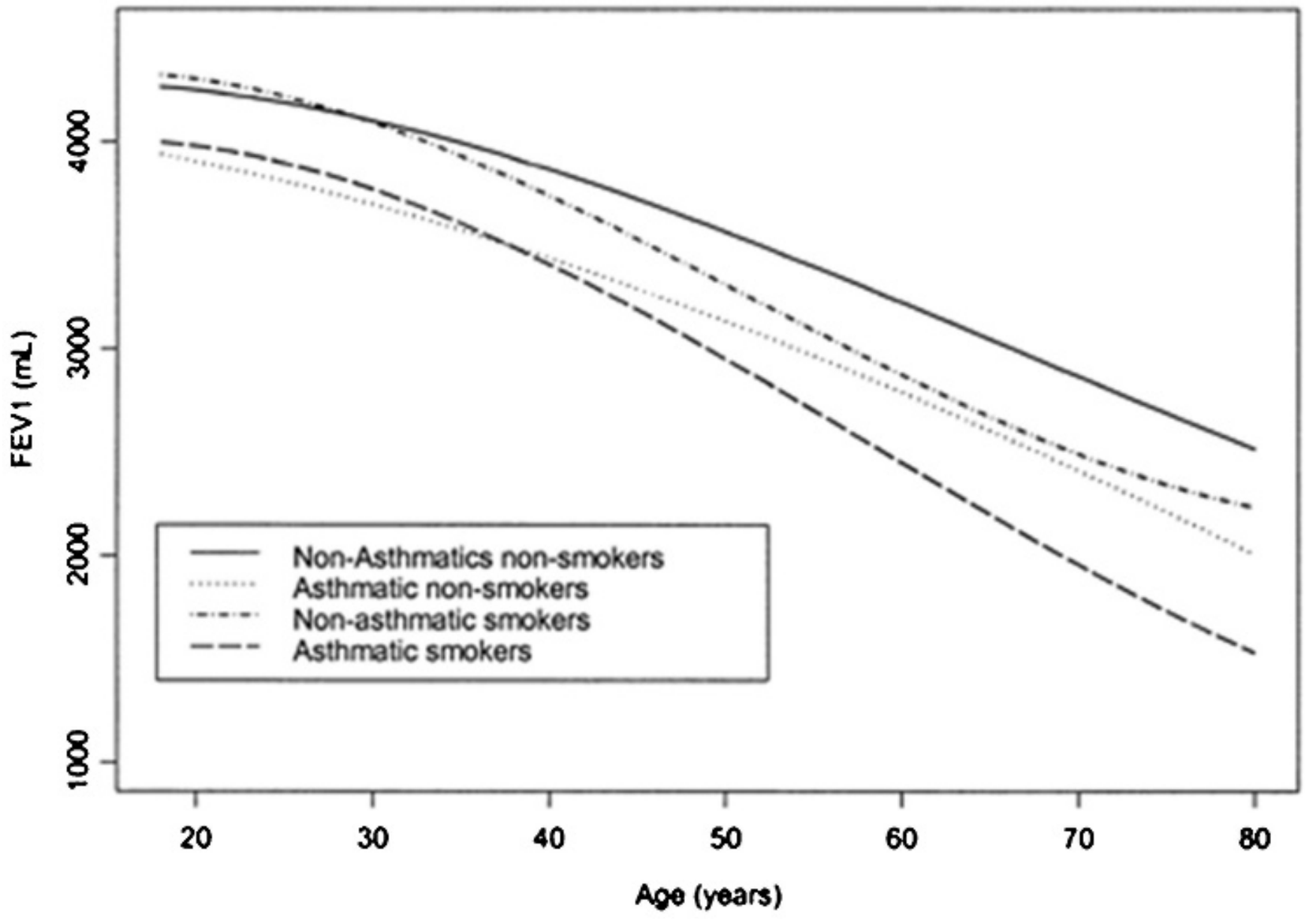
The immunopathology of acute attacks

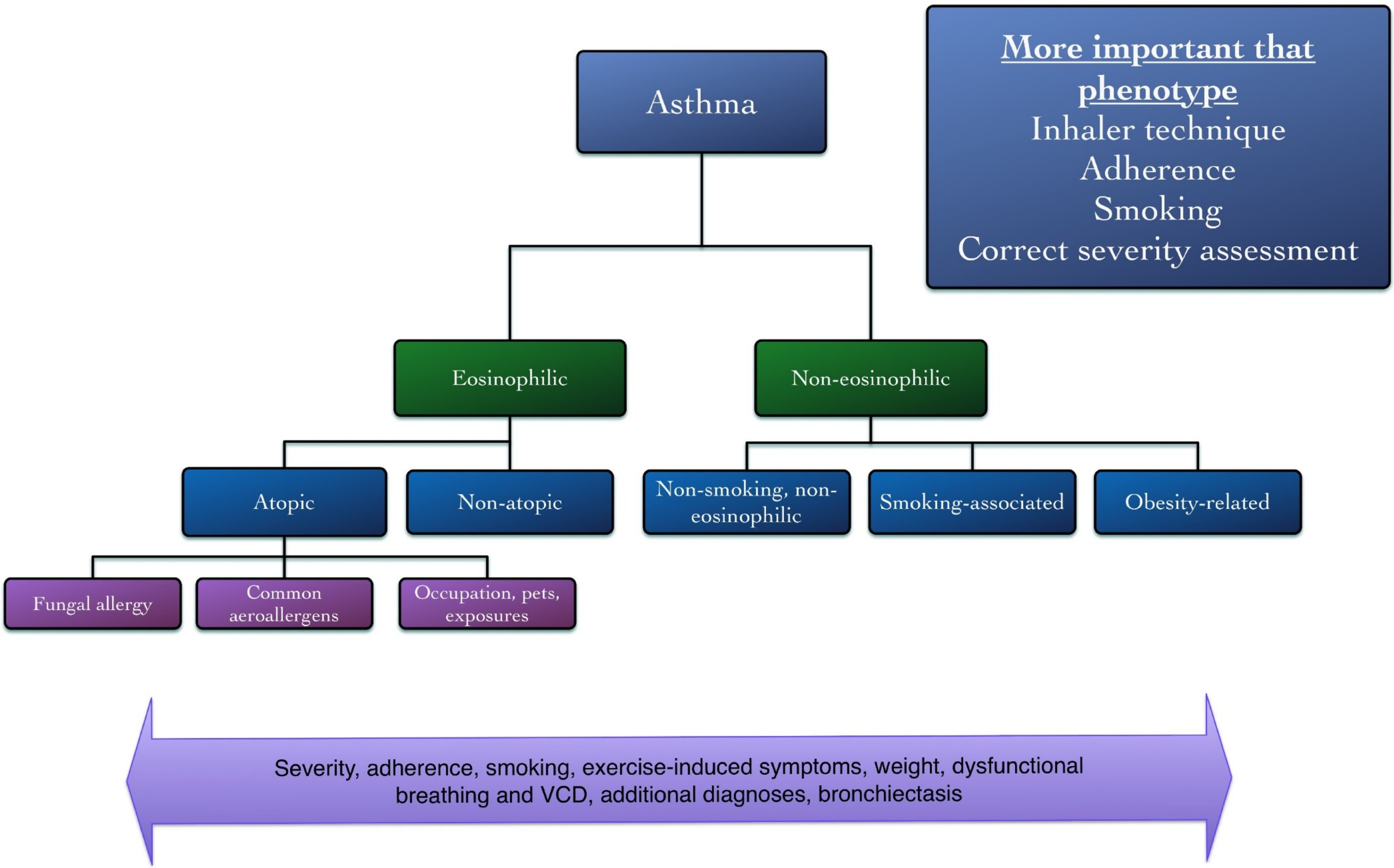
- Fatal asthma associated with variable recruitment of neutrophils and eosinophils
- Airway mucus casts, airway obstruction, airway oedema
- Many exacerbations are infective, 75% of which are viral (IFN deficiency relevant here)

Asthma COPD overlap

- Common but not much talked about
- Variable airflow obstruction, but not completely reversible
- Smoke exposure (passive, active), asthma, infections
- More symptomatic, greater healthcare burden
- Target eosinophils with steroids, use bronchodilators

Why smoking matters




Asthma
More important that phenotype
Inhaler technique
Adherence
Smoking
Correct severity assessment
Eosinophilic
Non-eosinophilic
Atopic
Non-atopic
Non-smoking, non-eosinophilic
Smoking-associated
Obesity-related
Fungal allergy
Common aeroallergens
Occupation, pets, exposures
Severity, adherence, smoking, exercise-induced symptoms, weight, dysfunctional breathing and VCD, additional diagnoses, bronchiectasis

The clinical history

The questions

- Is it asthma?
- What sort of asthma is it?
- How severe is it?
- Am I missing anything?
- Treatment…

Presenting complaint

- Episodic wheeze
- Cough, breathlessness
- Diurnal variation
- Brittle disease (type 1, chronic severe; type 2 sudden dips)
- Provoking factors: allergens, infections, menstrual cycle, exercise, cold air, laugher/ emotion

How to phenotype

- The history tells you a lot: age of onset etc
- Classic questions: age of onset, FHx, other atopic illnesses and allergies, Samter's triad, triggers, occupation
- Bonus questions: birth, menstrual relationship, sputum, how it all started (OB, PTSD)

Severity of disease

- Level of treatment required (number of inhalers)
- A&E attendances, admissions, HDU/ITU care, ventilation
- Attendance at GP for courses of antibiotics and steroids

Assessing severity

- RCP3 questions:
  - Recent nocturnal waking?
  - Usual asthma symptoms in day?
  - Interference with ADLs?
- Asthma Control Test (scores out of 25)

Q1 During the **past 4 weeks,** how often did your asthma prevent you from getting as much done at work, school or home?

Score:

All of the time 1	Most of the time 2	Some of the time 3	A little of the time 4	None of the time 5

Q2 During the **past 4 weeks,** how often have you had shortness of breath?

Score:

More than once a day 1	Once a day 2	3-6 times a week 3	1-2 times a week 4	Not at all 5

Q3 During the **past 4 weeks,** how often did your asthma symptoms (wheezing, coughing, chest tightness, shortness of breath) wake you up at night or earlier than usual in the morning?

Score:

4 or more times a week 1	2-3 nights a week 2	Once a week 3	Once or twice 4	Not at all 5

Q4 During the **past 4 weeks,** how often have you used your reliever inhaler (usually blue)?

Score:

3 or more times a day 1	1-2 times a day 2	2-3 times a week 3	Once a week or less 4	Not at all 5

Q5 How would you rate your **asthma control** during the **past 4 weeks?**

Score:

Not controlled 1	Poorly controlled 2	Somewhat controlled 3	Well controlled 4	Completely controlled 5

Total Score

What does your score mean?

Score: 25 – WELL DONE

- Your asthma appears to have been UNDER CONTROL over the last 4 weeks.
- However, if you are experiencing any problems with your asthma, you should see your doctor or nurse.

Score: 20 to 24 – ON TARGET

- Your asthma appears to have been REASONABLY WELL CONTROLLED during the past 4 weeks.
- However, if you are experiencing symptoms your doctor or nurse may be able to help you.

Score: less than 20 – OFF TARGET

- Your asthma may NOT HAVE BEEN CONTROLLED during the past 4 weeks.
- Your doctor or nurse can recommend an asthma action plan to help improve your asthma control.

History of complaint

- Age of onset (did it get better at any point?)
- Childhood ventilation/ respiratory disease
- The march of allergies
- Any particular unusual features at the start (e.g. sudden onset, weight loss)
- Obvious causes: chlorine exposure

Associated symptoms

- Eczema, hayfever
- Nasal disease (Samter's triad, relevant re rare differentials such as EGPA)
- Other food allergies, drug allergies
- Reflux disease

Past medical history

- Always vital part of history
- Previous pneumonias (bronchiectasis?)
- Neurological/renal problems (vasculitis?)

Drugs

- What are they supposed to be taking?
- What do they actually take?
- Are they taking beta blockers orally or topically?
- Are they sensitive to NSAIDs or aspirin?
- Drugs with potential interactions: theophyllines

Family and social history

- DO THEY SMOKE?
- Atopy is an inherited tendency
- Family history of asthma, eczema and hayfever
- Are there pets in the home?
- Psychological and psychiatric history

Occupational history

- Exposure to dusts, fumes, allergens
- Lab workers, veterinary staff, animal breeders
- Paint sprayers
- Bakers, etc
- Is your asthma worse at work/ better away from work? Holidays?

Distinguishing from COPD

- COPD a later disease dominantly of smokers
- More of a relentless progressive SOB with wheeze as part of the symptom complex
- Less diurnal variation, less day-to-day variation
- Winter symptoms, sputum production
- Overlap occurs

The physical examination

- May be normal
- Wheeze, polyphonic, expiratory, widespread
- Absence of crackles, sputum, other signs

Tests

- Blood count: eosinophils
- Tests for atopy and allergy: SPTs and RAST
- Chest XR often useful
- (Oxygen saturations)

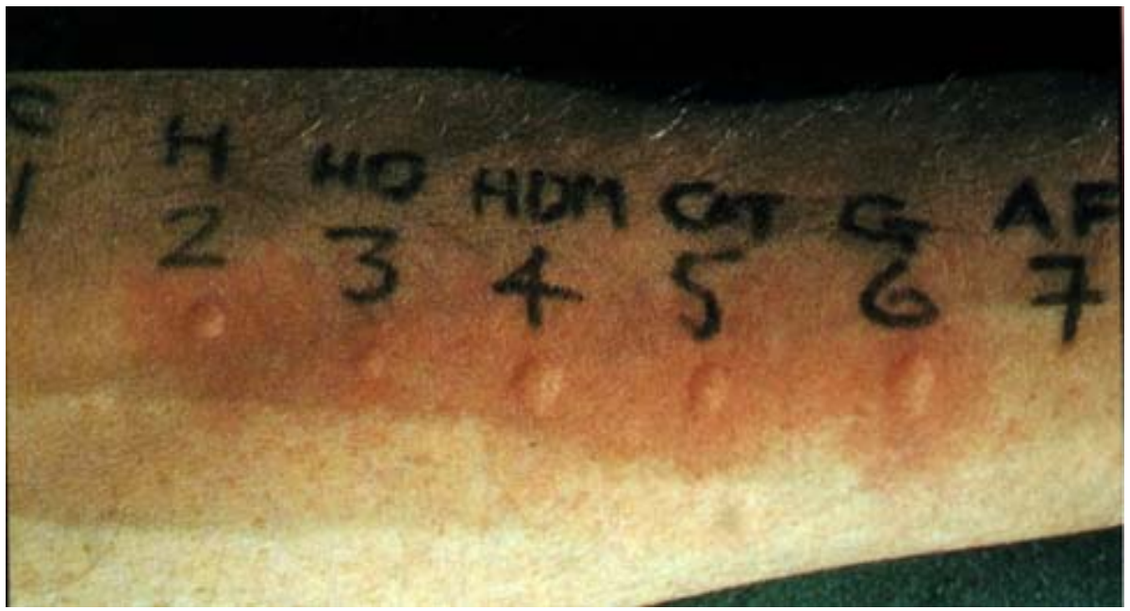
Good biomarkers

Table 2 Sensitivity, specificity, PPV and NPV of different surrogate markers using alternative cut-points to diagnose eosinophilic airway inflammation (less than, more than or equal to 3% sputum eosinophils)

	Threshold	Sensitivity	Specificity	PPV	NPV
Blood eosinophils	>0.22×10^9/L	86	79	60	93
Blood eosinophils	≥0.25×10^9/L	79	84	64	91
Blood eosinophils	≥0.27×10^9/L	78	91	79	91
FE_{NO} level	>20 ppb	74	57	40	87
FE_{NO} level	≥24 ppb	74	63	42	87
FE_{NO} level	≥42 ppb	63	92	74	89
FE_{NO} level	>50 ppb	56	92	67	84
Serum periostin (in-house)	>26 ng/mL	54	57	29	77

NPV, negative predictive value; PPV, positive predictive value.

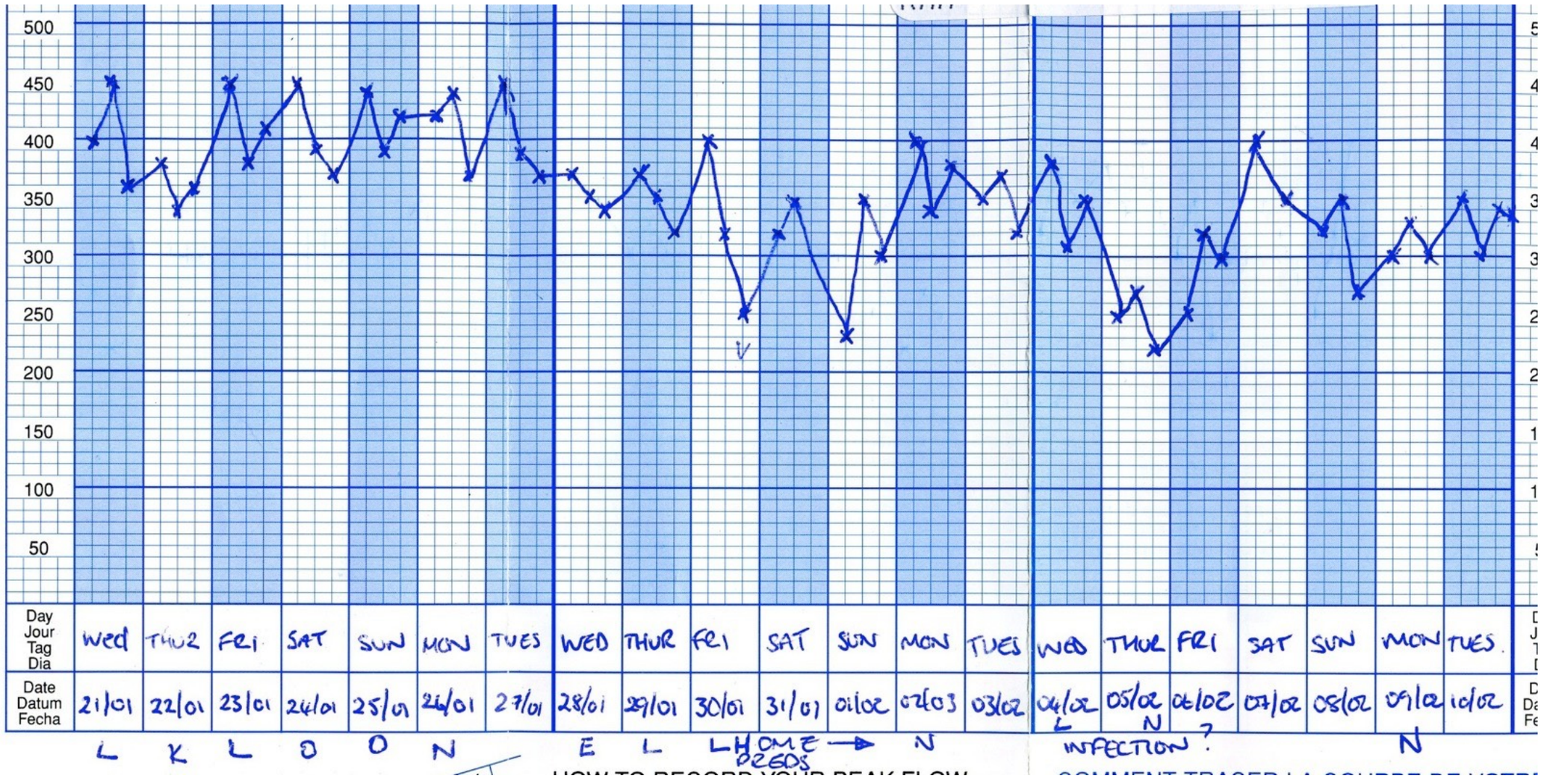
Skin prick tests

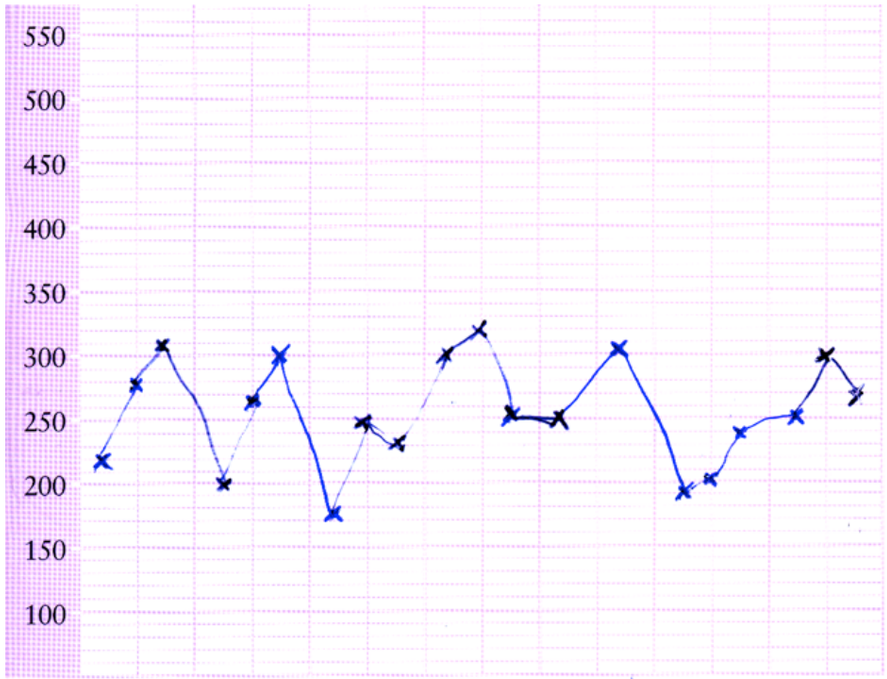


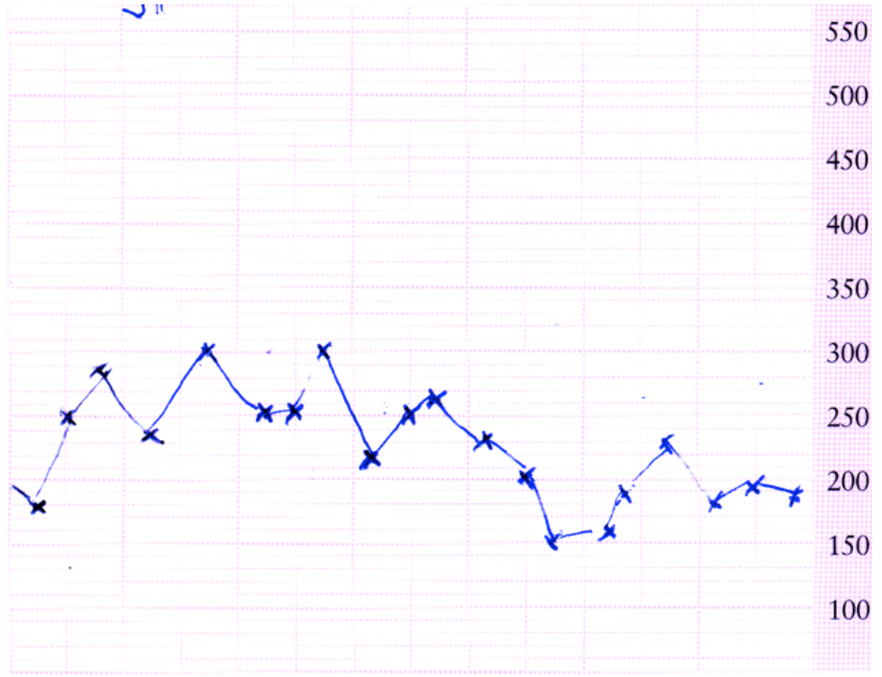
Lung function testing

- Airways obstruction may be present (reduced FEV1, reduced FEV1/FVC ratio)
- PEFR reductions from percent predicted, variability (>20% predicated 3/7 days)
- Increased responsiveness to challenge agents (mannitol, methacholine)

Variable PEFR



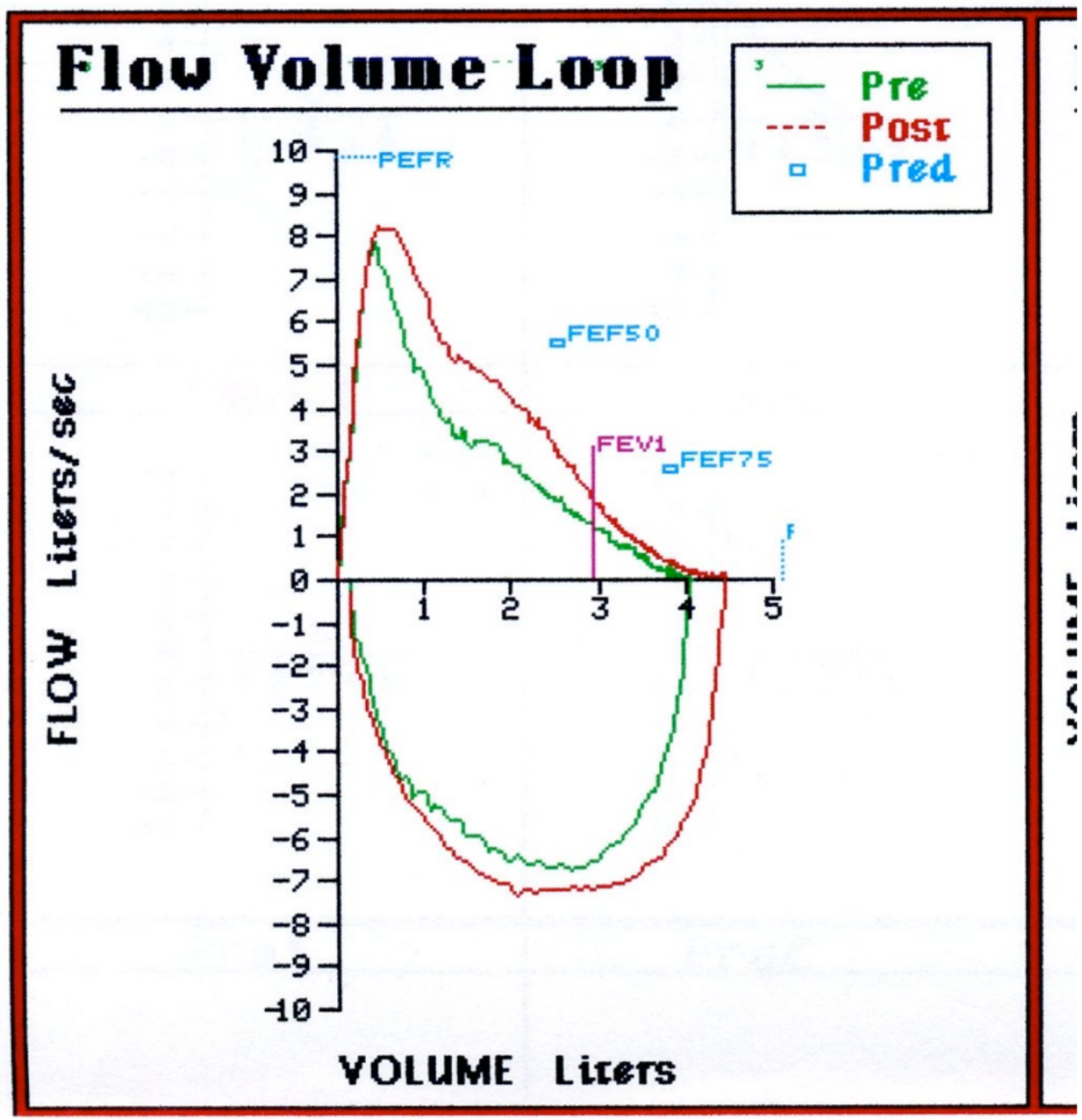




1.	3	4	5	5	4	6	5
2.	2	2	2	2	2	2	2

1.	5	3	3	6	6	8	8
2.	2	2	2	2	2	2	2

Formal lung function more accurate



Reversibility testing

- Increase in lung capacity with bronchodilators or anti-inflammatory treatment
- Increase of 400 ml in FEV1 with beta agonist, 4-8 weeks inhaled steroid, or 2 weeks oral steroid = asthma highly likely
- 20% improvement in PEFR or 15% in FEV1 also useful figures

Specific tests of airway inflammation

- Becoming more common
- Exhaled nitric oxide (FeNO), a marker of eosinophilic inflammation
    - But not specific, suppressed in smokers, elevated with viral infections and rhinitis
- Direct measurement of cells in the airways can reliably guide treatment

Presentation with respiratory symptoms: wheeze, cough, breathlessness, chest tightness[1]

Structured clinical assessment (from history and examination of previous medical records) Look for:

- recurrent episodes of symptoms
- symptom variability
- absence of symptoms of alternative diagnosis
- recorded observation of wheeze
- personal history of atopy
- historical record of variable PEF or FEV_1

High probability of asthma

Code as: suspected asthma

Initiation of treatment

Poor response

Assess response objectively (lung function/ validated symptom score)

Good response

Asthma

Adjust maintenance dose. Provide self-management Arrange on-going review

Intermediate probability of asthma

Test for airway obstruction spirometry + bronchodilator reversibility

Options for investigations are:	
Test for variability: • reversibility • PEF charting • challenge tests	**Test for eosinophilic inflammation or atopy:** • FeNO • blood eosinophils, • skin-prick test, IgE

Good response

Suspected asthma: Watchful waiting (if asymptomatic) or Commence treatment assess response objectively

Poor response

Low probability of asthma

Other diagnosis unlikely

Investigate/treat for other more likely diagnosis

Other diagnosis confirmed

[1] In children under 5 years and others unable to undertake spirometry in whom there is a high or intermediate probability of asthma, the options are monitored initiation of treatment or watchful waiting according to the assessed probabilityof asthma.

What is severe asthma?

- ATS consensus definition (one major + two minor)

- Major characteristics
  - Treatment with continuous or near continuous oral steroids
  - Requirement for high dose inhaled steroids
- Minor characteristics
  - Additional daily reliever medication (beta agonists, theophylline, LTRA)
  - Symptoms needing reliever medication on daily or near daily basis
  - Persistent airway obstruction (FEV1<80%, diurnal variation PEFR >20%)
  - ≥1 emergency visits p.a.
  - ≥3 steroid courses p.a.
  - Prompt deterioration with ≤25% reduction in oral or inhaled steroid dose
  - Near-fatal event in past

WHO IS AT RISK OF ASTHMA DEATH?

- ≥3 classes of treatment
- recent admission/ frequent attender
- previous near-fatal disease
- brittle disease
- psychosocial factors

Differential diagnosis

- Not everything that wheezes is asthma
- Not all breathless is asthma

Differential diagnoses

- Bronchiolitis
- Bronchiectasis*
- CF
- PE
- CEA
- CFA
- Hyperventilation*
- Bronchial obstruction - foreign body, tumour, etc
- Vocal cord dysfunction*
- Aspiration
- CCF
- COPD

- *often complicate co-existing asthma

Treatment of asthma

Separate airways pharmacology lecture

Goals of treatment

- Most patients have poor control
- Aim to improve control
- Address important issues for patient (exercise, for example)
- Maximum symptoms for minimum side effects

Not just drugs

- Avoidance of triggers
  - Allergen avoidance, occupational issues

Classes of drug available

- Bronchodilators: beta agonists, leukotriene receptor antagonists, theophyllines, long acting beta agonists, anticholinergics
- Anti-inflammatory drugs: steroids

Why do we need steroids?

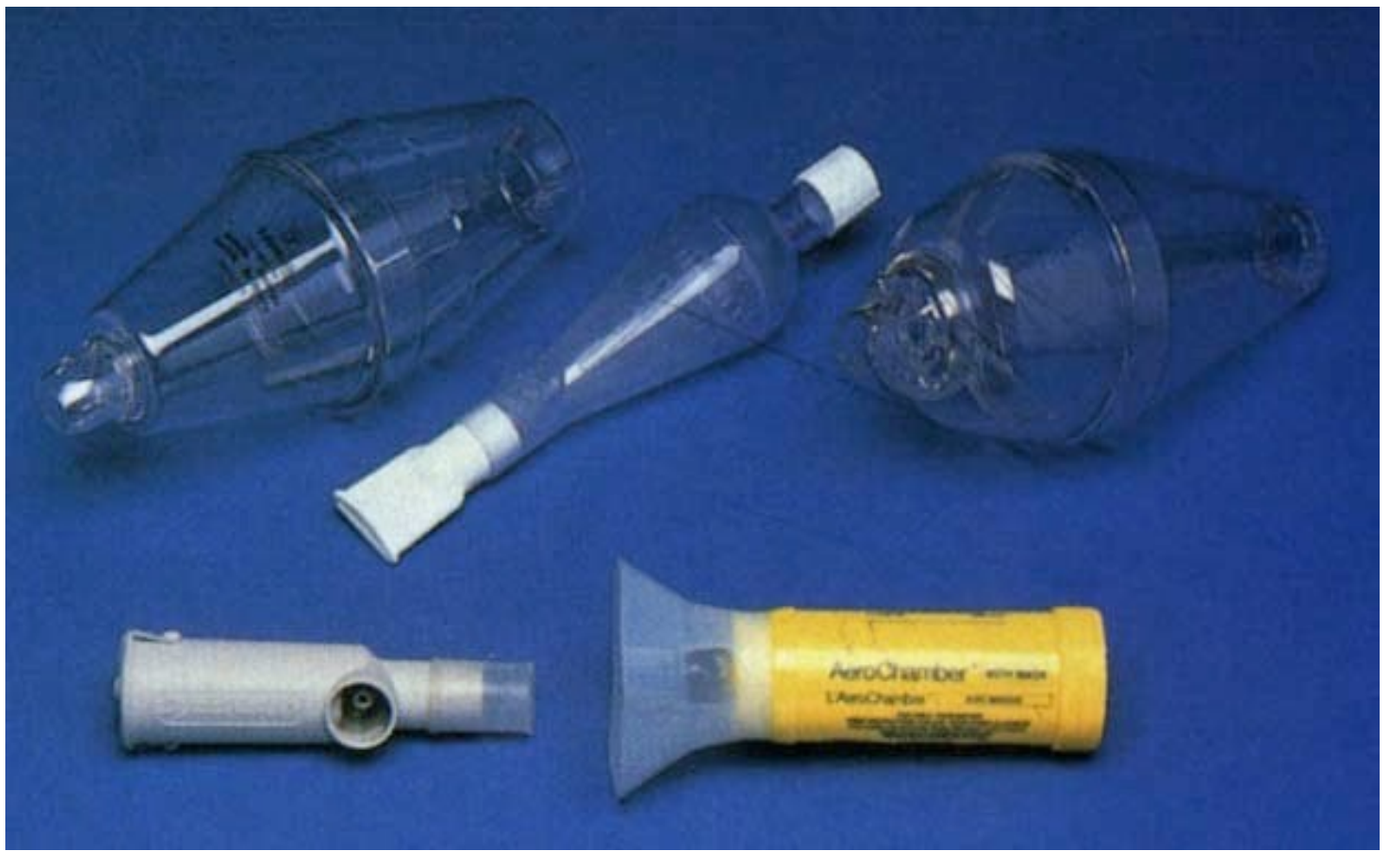
- Bronchodilators treat symptoms, not the disease
- We need steroids to reduce airway inflammation and decrease mortality risks.

Why don't we give everyone oral steroids?

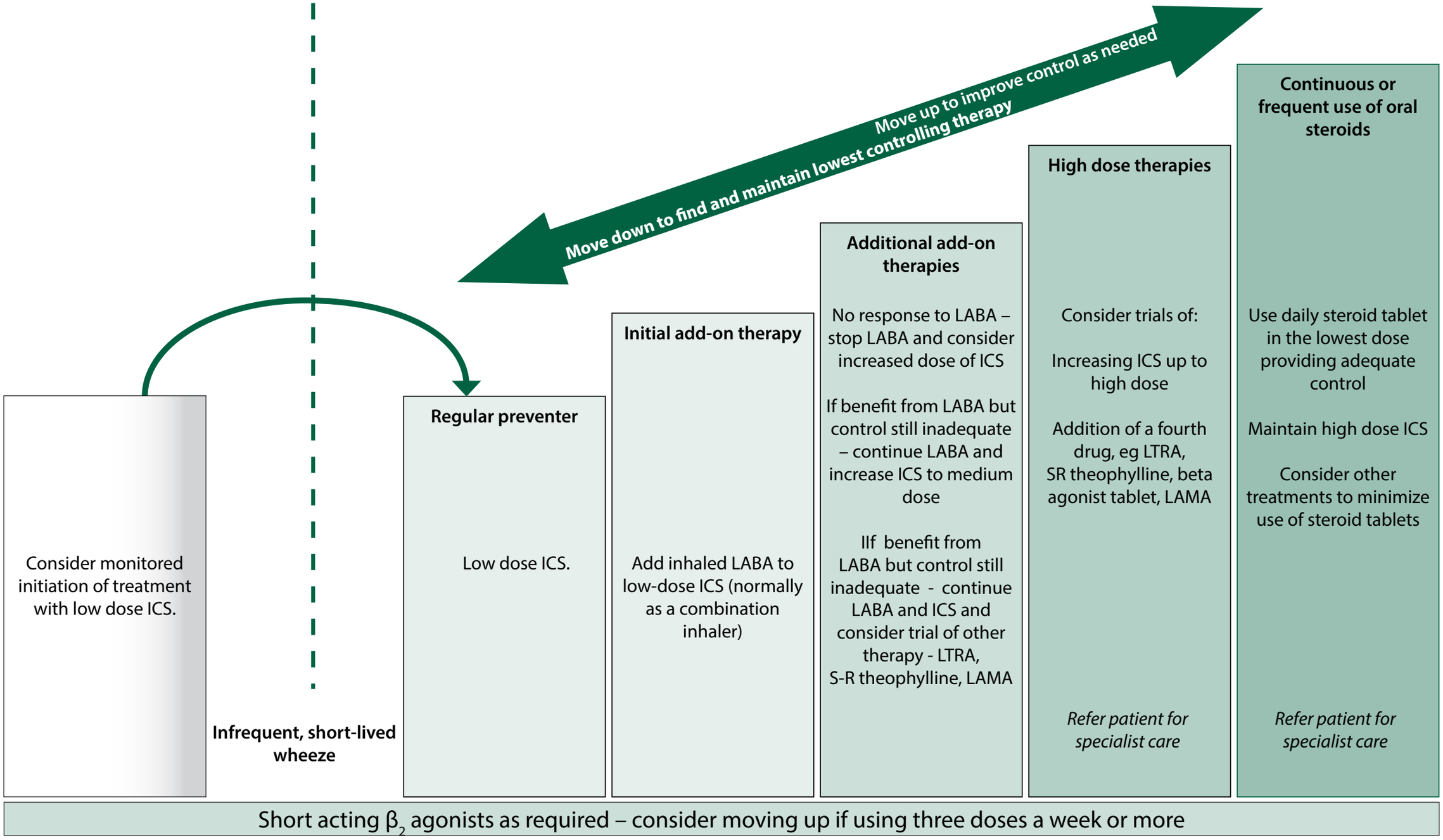
- Systemic: diabetes, cataracts, osteoporosis, hypertension, skin thinning, easy bruising, growth retardation, osteonecrosis of the femoral head
- Topical: hoarse voice, oral candida, skin thinning, easy bruising, cataracts (in high dose)
- Adrenal suppression

The right device

- Multiple different delivery devices: MDIs, dry powder.
- Use of a spacer to improve delivery and minimise side effects.



Asthma - suspected	Adult asthma - diagnosed
Diagnosis and Assessment	Evaluation: •assess symptoms, measure lung function, check inhaler technique and adherence •adjust dose •update self-management plan •move up and down as appropriate



What do we do when these don't work?

- Re-visit the basics, particularly technique and adherence
- Investigate and treat
- Second line immunosuppression
- Phenotype-specific management

Severe eosinophilic asthma

- Anti-IgE (omalizumab) for atopic allergic disease
- anti-IL-5 (mepolizumab)
- Oral steroids, additional immunosuppressants (guided by overall atopic disease burden)

Non-eosinophilic asthma

- Maintain appropriate level of steroid therapy
- Focus more on bronchodilator treatment
- Consider bronchial thermoplasty

Special situations

- Asthma in pregnancy: keep mum well, and baby is well

Acute asthma

- 80,000 admissions per year
- 1,200 deaths per year
- 80% of deaths were potentially avoidable

The acute asthmatic

- Start with high flow oxygen, emergency beta agonists, and a brief history/ examination

Recognising a severe attack

- Do PEFR, full clinical assessment
- Do oximetry
- Gases of acute severe or low saturations (<92% on air, or needing O2)
- CXR if suspect pneumothorax, consolidation, life threatening asthma, failure to respond

Classifying attacks

- Uncontrolled/ moderate
  - PEFR > 50%
  - RR < 25
  - Pulse < 110
  - Normal speech, no other severe markers

- Severe: any ONE of...
  - PEFR 33-50% predicted
  - RR ≥25
  - HR ≥110
  - inability to complete sentences

- Life-threatening: any ONE of...
  - PEFR <33%
  - SaO2 <92% or PaO2 < 8 kPa
  - Normal PaCO2 4.6 - 6 kPa
  - altered conscious level, exhaustion, arrhythmia, hypotension, silent chest, poor effort, cyanosis

- Near fatal
- Raised PaCO2 and/or requiring ventilation with raised airway pressures

Immediate management

- Oxygen 40-60% (CO_2 retention not usually a problem)
- Salbutamol neb 5 mg (+ipratropium neb 0.5mg if life threatening) - repeated/ i.v. infusion
- Prednisolone 30-60 mg (±hydrocortisone 200mg iv)
- Magnesium or aminophylline i.v. (bolus/load)
- ABGs
- CXR if suspect pneumothorax, consolidation, or fails to respond to treatment (or is very severe)

Monitoring response to treatment

- PEFR check within 15-30 mins / regularly
- Oximetry to maintain SaO2 > 92 %
- Repeat ABG within 2 hrs if severe attack or patient deteriorating
- If deteriorating despite maximal treatment with worsening hypoxia, hypercapnia or coma / exhaustion - ITU transfer

Monitoring therapy

- Watch out for hypokalaemia
- Rehydrate
- Be aware of drug interactions with iv aminophylline
  - Do not load if on oral theophyllines- give standard bolus dose
  - decrease maintenance dose by 1/2 if on ciprofloxacin or macrolide

Discharge

- Opportunity to educate and prevent readmissions
- Achieve PEFR > 75% and <25% variability
- Prednisolone for minimum 7-14 days (never decrease until improving)
- Step up treatment
- Asthma action plan
- Nurse-led follow-up
- Early clinical review (48 hours at GP surgery)

Conclusions

- Asthma
  - Needs correct diagnosis
  - Understanding pathology guides treatment
  - Good treatment means avoiding exacerbations and minimising symptoms