Difficult Asthma Assessment: A systematic approach

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Disclosures

- Presentations for Mundipharma
- Grant from GSK

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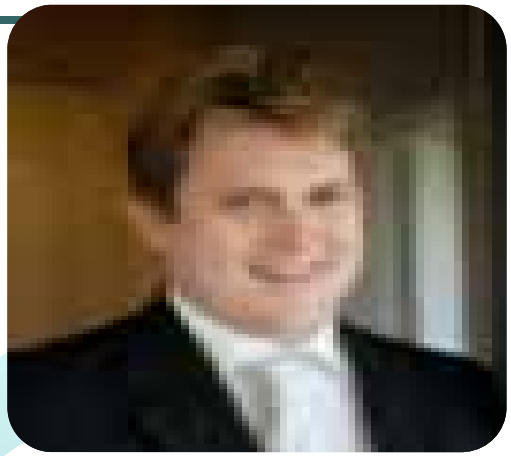

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Overview

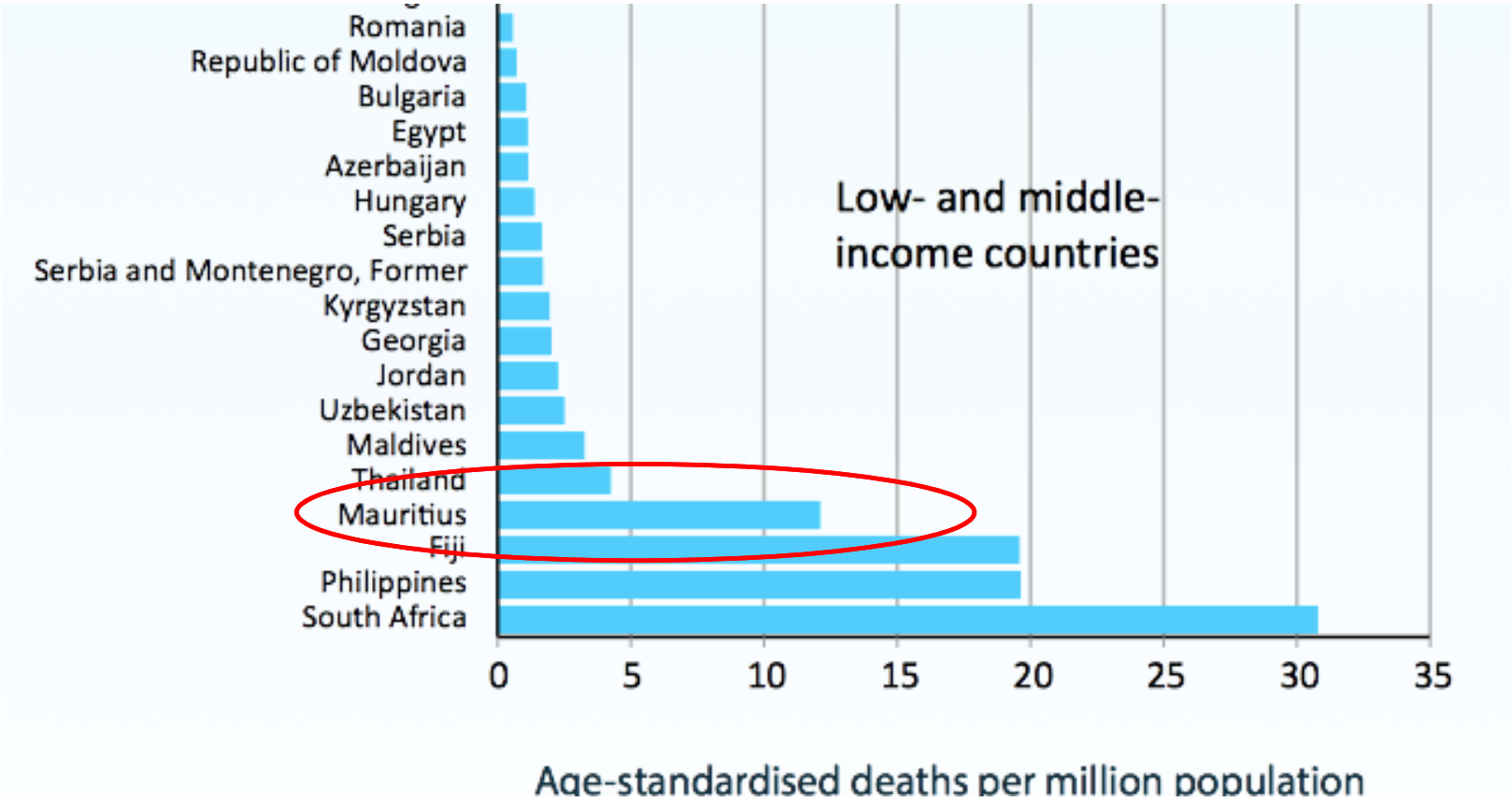
- Definitions of severe and difficult asthma
- Systematic Assessment Process
- Pharmacological options

Epidemiology

- 300 million asthmatics worldwide*
- Up to 10% are difficult to control
- High burden of illness**
  - Quality of life, mortality risk
  - Psychological
  - Economical

*WHO. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, 2007; ** GAN. Global Asthma Network: global asthma report 2014*

Global Mortality rate 5-34 yrs*



*WHO Detailed Mortality Database, February 2014

Mauritius- Causes of death

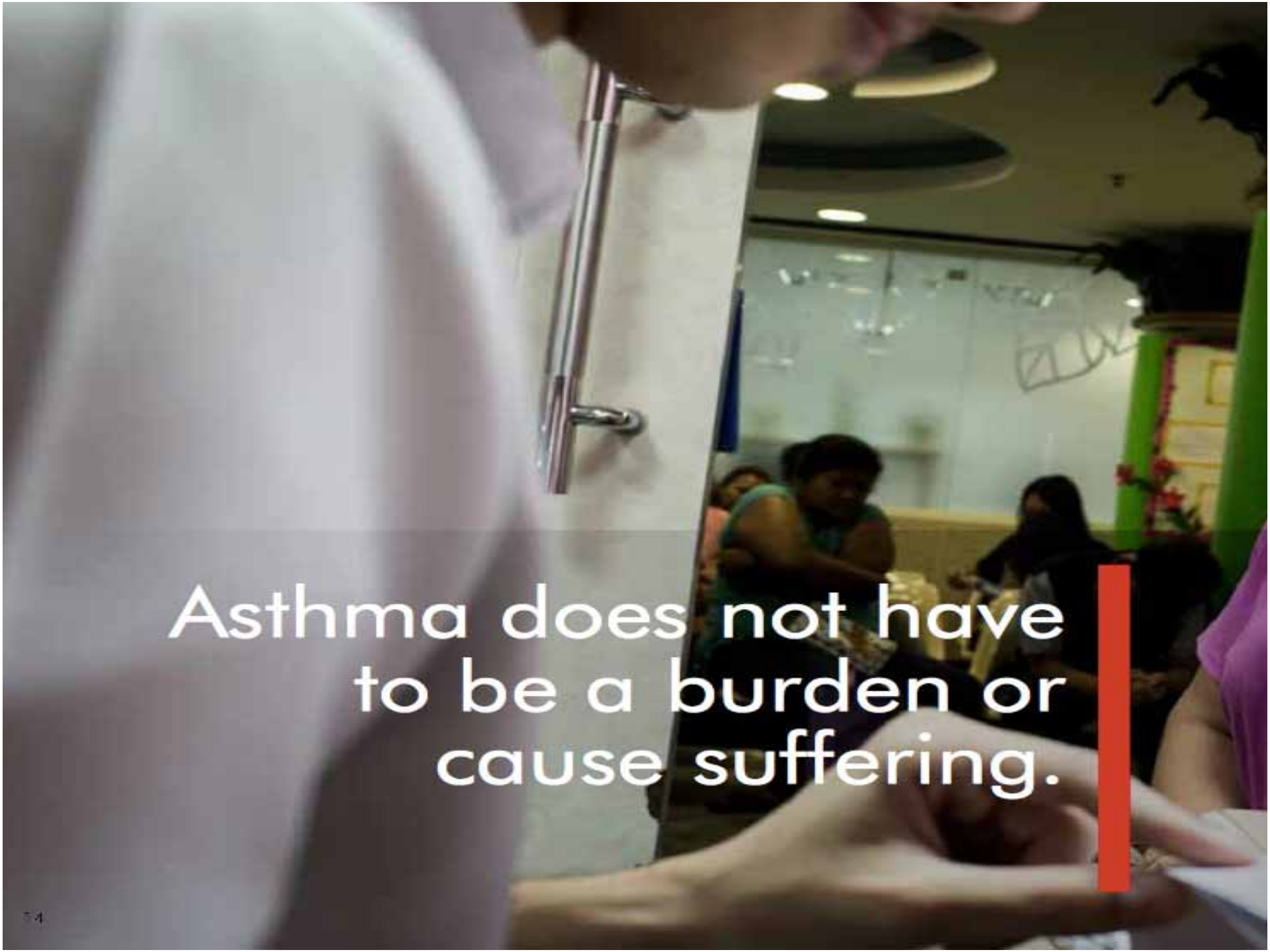
	Deaths	%
1. Diabetes Mellitus	2,094	27.06
2. Coronary Heart Disease	1,381	17.84
3. Stroke	874	11.29
4. Hypertension	511	6.60
5. Liver Disease	218	2.82
6. Road Traffic Accidents	186	2.40
7. Asthma	158	2.04
8. Lung Cancers	149	1.93
9. Influenza & Pneumonia	131	1.69
10. Kidney Disease	130	1.68

WHO. April 2011

Mauritius- Death rate

1.	Diabetes Mellitus	176.03	1
2.	Coronary Heart Disease	118.43	85
3.	Stroke	76.72	112
4.	Hypertension	44.43	41
5.	Breast Cancer	18.52	66
6.	Liver Disease	16.18	48
7.	Road Traffic Accidents	14.12	105
8.	Asthma	13.84	42
9.	Lung Cancers	12.57	96
10.	Influenza & Pneumonia	11.59	159
11.	Kidney Disease	10.78	121
12.	Other Injuries	8.58	126
13.	Colon-Rectum Cancers	7.97	86
14.	Stomach Cancer	7.70	79
15.	Suicide	6.71	103
16.	Congenital Anomalies	6.51	86
17.	Lung Disease	6.23	178
18.	Cervical Cancer	6.18	84
19.	Alcohol	5.88	10

WHO. April 2011


Asthma does not have
to be a burden or
cause suffering.

Avoidable factors in asthma deaths

- Late medical assistance
- Not being under specialist review
- No action plans
- Excessive SABA, not enough preventers
- Inappropriate prescribing of LABA

Challenges in Assessment

- Multiple co-morbidities
- Multi-disciplinary requirements
- Complex patient factors
- Diagnostic difficulty
- Time consuming

Goals

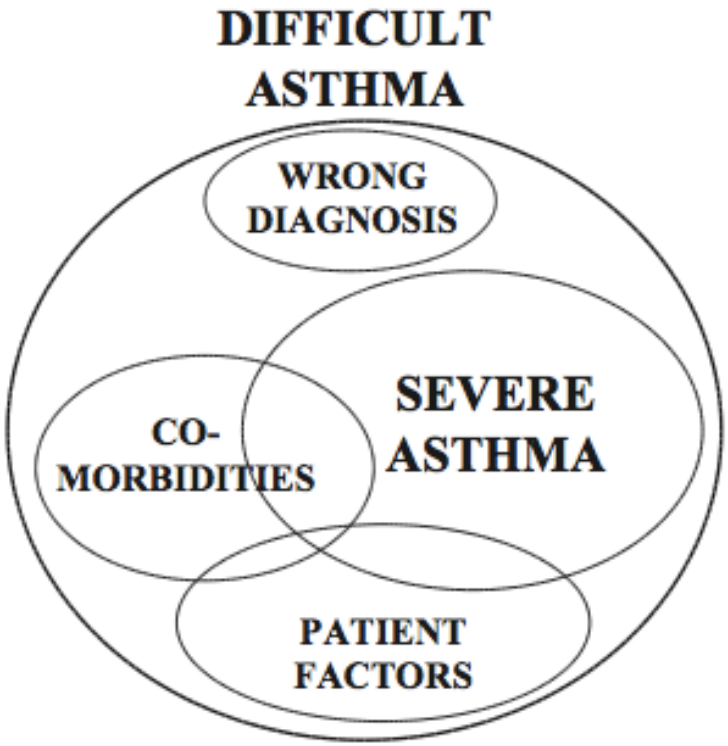
Of assessment

- Confirmed diagnosis
- Maximal inhaled therapy
- Optimize Adherence
- Assess asthma control

Of management

- **Symptom control**
  - maintain normal activity levels
- **Risk reduction**
  - future risk of exacerbations
  - fixed airflow limitation
  - medication side-effects

Definition of Difficult Asthma



Hew,Int Med Journal, 2010

Definition of Severe Asthma

ATS/ERS 2014

Diagnosis	Must be confirmed
Adherence	Must be optimized
Asthma medication	High-dose ICS + LABA/LTRA **OR**
	Systemic corticosteroids (≥ 6 months in a year)

AND

Uncontrolled asthma	• Poor symptom control (NAEPP/ GINA guidelines), ACQ >1.5 or ACT <20
	• Frequent or Severe exacerbation: ≥2 bursts of CS in past year
	• Serious exacerbation: hospitalization/ ICU/ Mech Ventilation
	• Airflow Limitation : FEV1 <80%

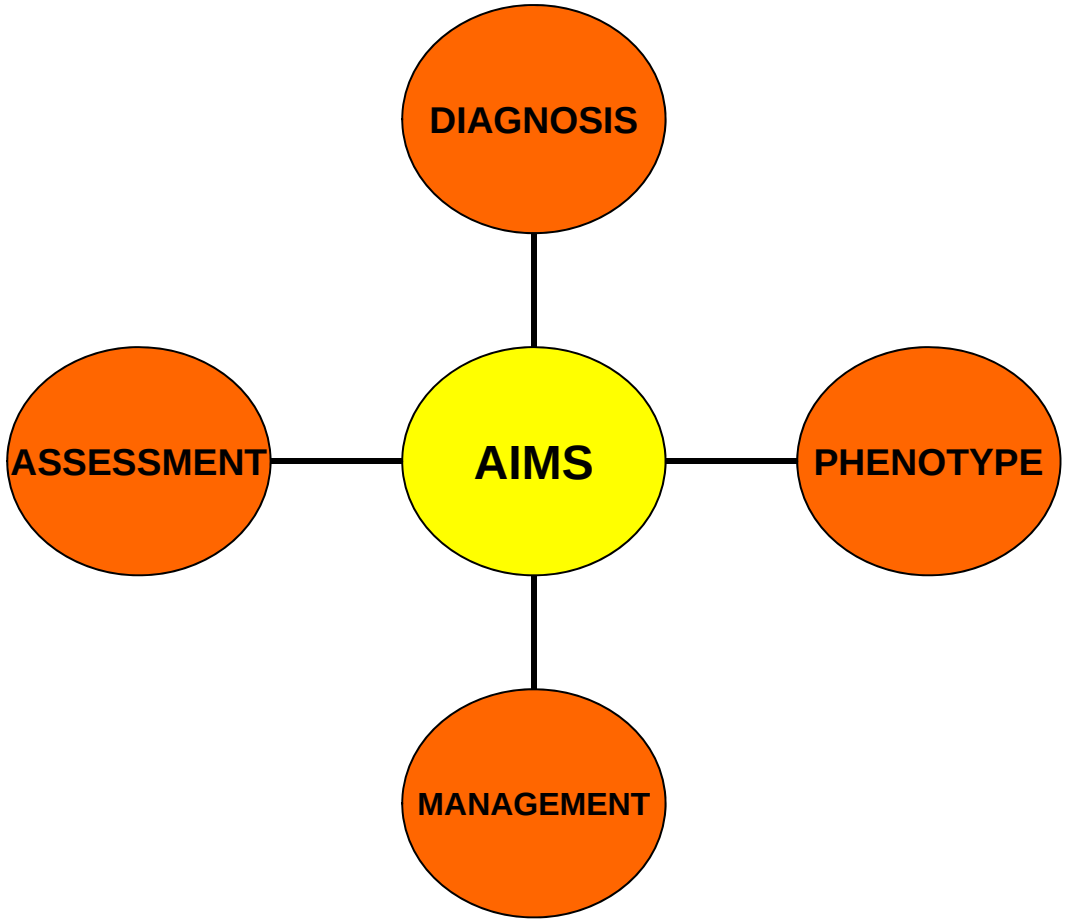
Asthma control – GINA**

Assessment of current clinical control (preferably over 4 weeks)			
Parameter	**Controlled (All of the following)**	**Partly controlled (Any present)**	**Uncontrolled**
Daytime symptoms	None (≤ 2/week)	> 2/week	Three or more features of poorly controlled asthma^
Limitation of activities	None	Any	
Nocturnal symptoms/ awaking	None	Any	
Need for reliever/ rescue inhaler	None (≤ 2/week)	> 2/week	
Lung function (PEFR or FEV_1)#	Normal	< 80% predicted or personal best (if known)	

Without administration of a bronchodilator, lung function is not a reliable test for children 5 years and under.
^ By definition, an exacerbation in any week makes that an uncontrolled asthma week
FEV_1 = forced expiratory volume in 1 second PEFR = Peak expiratory flow rate

** Adapted from FitzGerald M, *et al*. Pocket guide for asthma management and prevention (for adults and children older than 5 years). GINA 2012.

Purpose of a difficult asthma clinic



Confirm Diagnosis

- Misdiagnosis
- Objective confirmation of variable airflow obstruction with:
  - Spirometry (pre and post bronchodilator)
  - Bronchoprovocation testing
  - PEF variability

Assessment: Identify Co-morbidities

- Nasal disease
- GORD
- Vocal cord dysfunction
- COPD
- Bronchiectasis
- OSA
- Anxiety and depression
- Obesity

Co-Morbidity	Associated with asthma?	Prevalence in (difficult) asthma	Treatment improves asthma
AR	Yes	40%	Yes
CRS	Yes	70%	Yes
GORD	Yes	59%	Inconsistent
OSA	Yes	75-95%	Yes
VCD	Yes	55-75%	Inconsistent
HVD	Yes	29%	Yes
Anx/Dep	Yes	49%	Yes
COPD	Yes	20%	Yes
Bronchiectasis	Yes	25-35%	Yes

Management: Optimize adherence

- Asthma management skills
  - Inhaler technique
  - Medication adherence
  - Self-monitoring
  - Written action plan
  - Education
  - Smoking cessation

Phenotyping

- Observable characteristics resulting from interaction of genetics and the environment

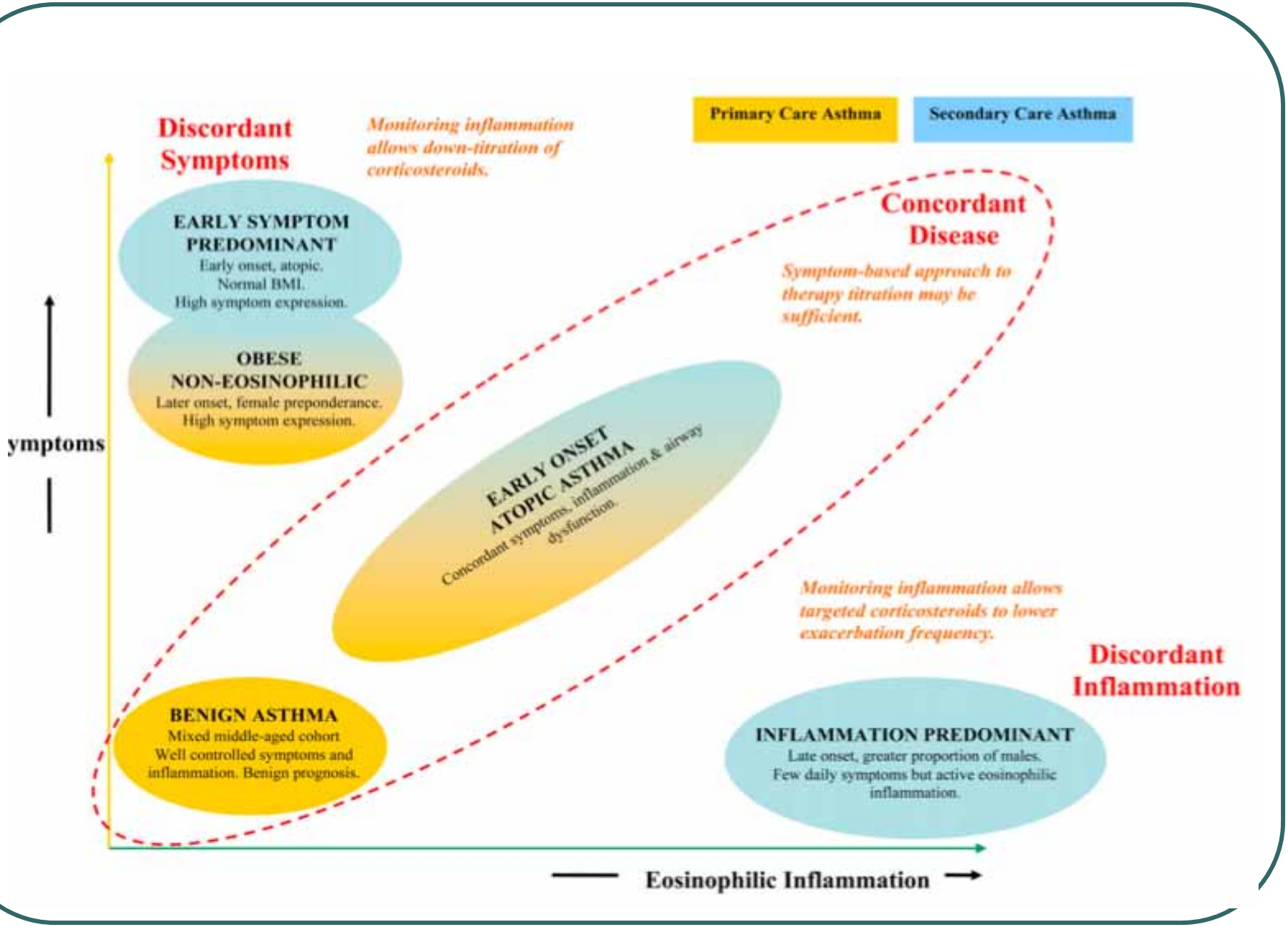
Biomarkers

- Sputum eosinophils
- Blood eosinophils
- FeNO
- e-Nose *(Montuschi, Chest 2010)*
- BAL/biopsies

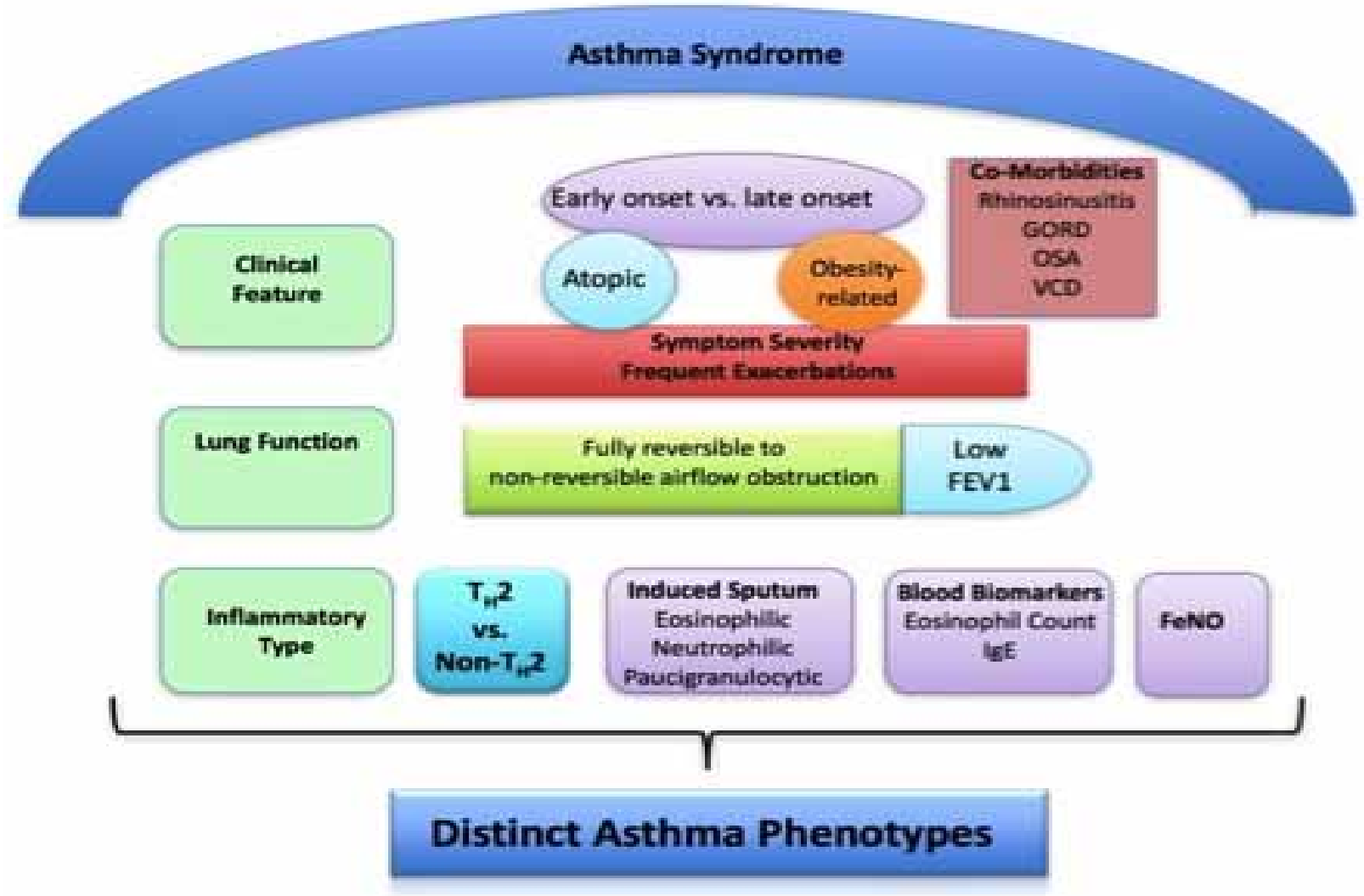
Phenotype using Cluster Analysis

Cluster	Atopy	Age of Onset	Lung Function	Medication Need
1	Yes	Early	Normal	Low
2	Yes	Early	Normal	Medium
3	No	Later	Moderate reduction	High
4	Yes	Early	Severe reduction	High
5	No	Later	Severe reduction	High

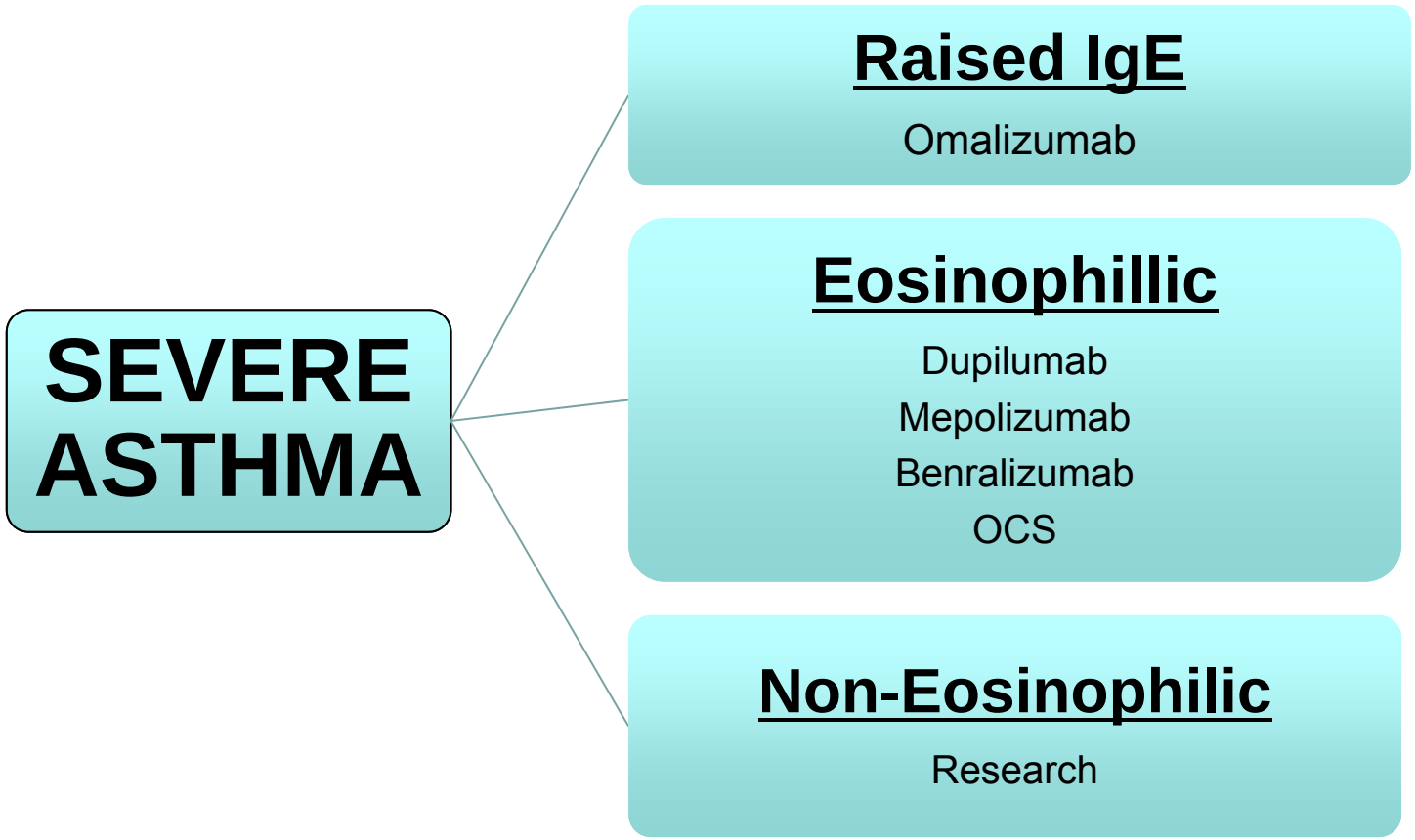
Moore, 2010


Primary Care Asthma
Secondary Care Asthma
Discordant Symptoms
Monitoring inflammation allows down-titration of corticosteroids.
Concordant Disease
Symptom-based approach to therapy titration may be sufficient.
EARLY SYMPTOM PREDOMINANT
Early onset, atopic.
Normal BMI.
High symptom expression.
OBESE NON-EOSINOPHILIC
Later onset, female preponderance.
High symptom expression.
ymptoms
EARLY ONSET ATOPIC ASTHMA
Concordant symptoms, inflammation & airway dysfunction.
Monitoring inflammation allows targeted corticosteroids to lower exacerbation frequency.
Discordant Inflammation
BENIGN ASTHMA
Mixed middle-aged cohort
Well controlled symptoms and inflammation. Benign prognosis.
INFLAMMATION PREDOMINANT
Late onset, greater proportion of males.
Few daily symptoms but active eosinophilic inflammation.
Eosinophilic Inflammation

Haldar, 2008

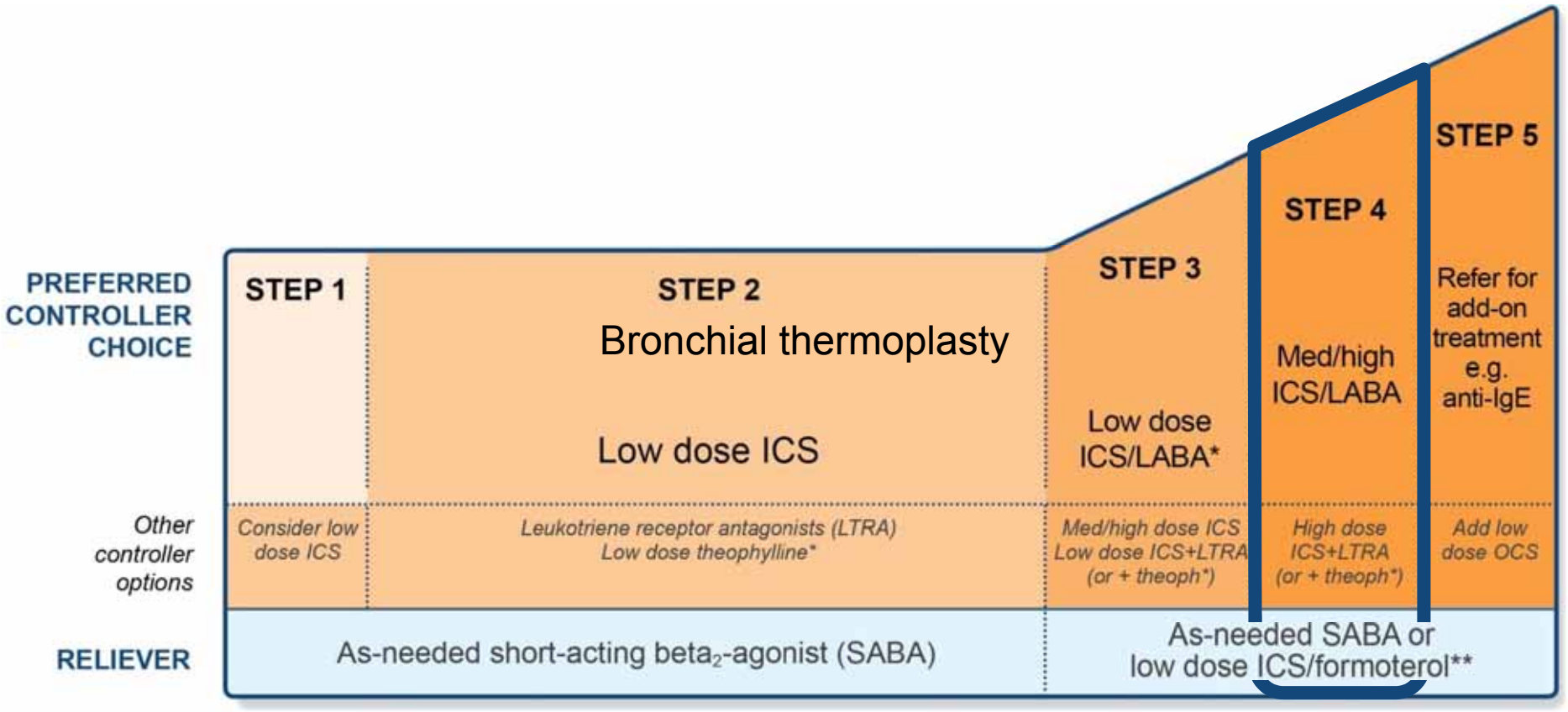

Asthma Syndrome
Clinical Feature
Early onset vs. late onset
Atopic
Obesity-related
Co-Morbidities
Rhinosinusitis
GORD
OSA
VCD
Symptom Severity
Frequent Exacerbations
Lung Function
Fully reversible to non-reversible airflow obstruction
Low FEV1
Inflammatory Type
T_H2 vs. Non-T_H2
Induced Sputum
Eosinophilic
Neutrophilic
Paucigranulocytic
Blood Biomarkers
Eosinophil Count
IgE
FeNO
Distinct Asthma Phenotypes

Management based on Phenotype



UPDATE: SEVERE ASTHMA TREATMENTS

Step 4 – two or more controllers + as-needed inhaled reliever



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Beclomethasone (QVAR)

Ciclesonide (Alvesco)

Seretide**:**
FP/Salm

Symbicort Rapihaler -
Bud/ Efom

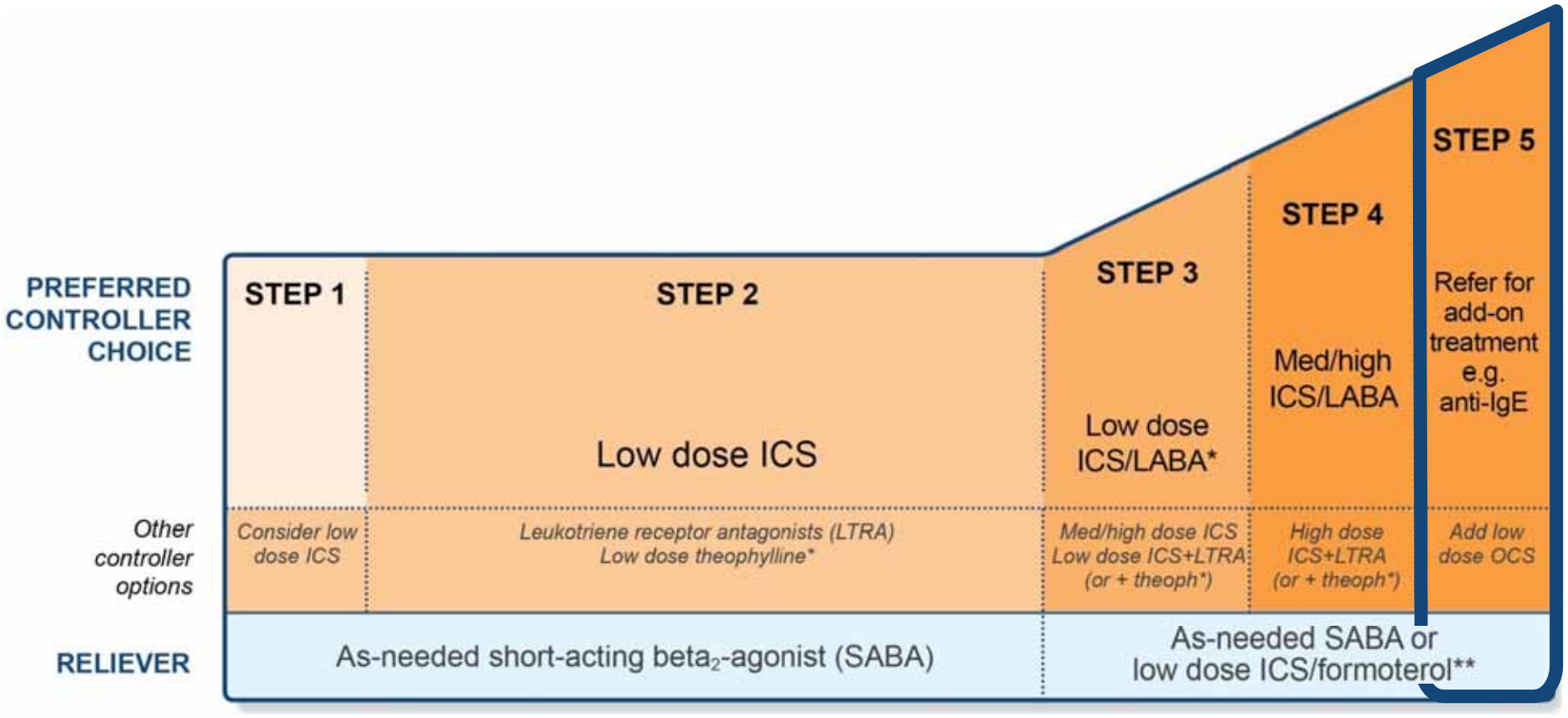
Flutiform:
FP/Efom

Breo Ellipta :
FF/Vilanterol

Management: ICS/LABA

- High dose combination therapy needed
- 30% severe asthmatics require OCS
- Little data for use of high dose ICS/LABA + ultra fine particle therapy (alvesco)
- Medications side effects

Step 5 – higher level care and/or add-on treatment



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

? Add on therapy

FOR EVERYONE

- **ICS/LABA**
- Fine particle ICS
  - **Ciclesonide**
- **LAMA**
- **LTRA**

FOR SELECT GROUPS

- Macrolides
- Targeted therapy
  - Anti-IgE: Omalizumab
  - Anti-IL5: Mepolizumab, Reslizumab

LAMA: tiotropium

- Improvements in
  - FEV1
  - reduced SABA use
  - modestly reduced risk of severe exacerbation
- No studies in children

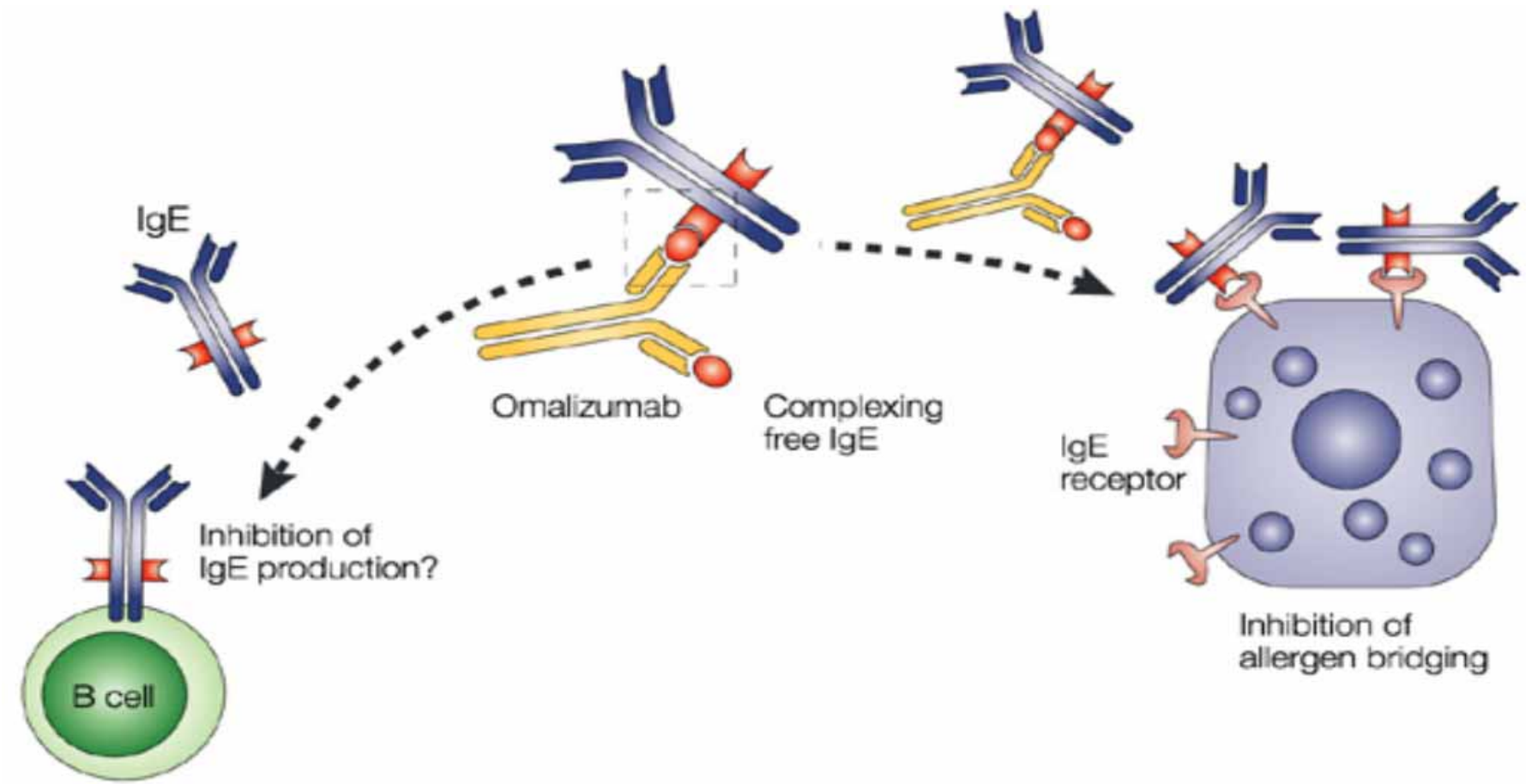
LTRA: Montelukast

- Not as effective as LABAs when added to ICS to prevent exacerbation/improve symptoms
- Improves lung function
- ?better in phenotyped patients : aspirin sensitive asthma / exercise induced asthma

Macrolides

- Azithromycin in Severe Asthma trial
  - Reduction in exacerbation rate
  - Non eosinophilic asthma phenotype
- Not recommended
- Development of resistance
- Uncertain clinical benefits

Anti IgE: Omalizumab (Xolair)

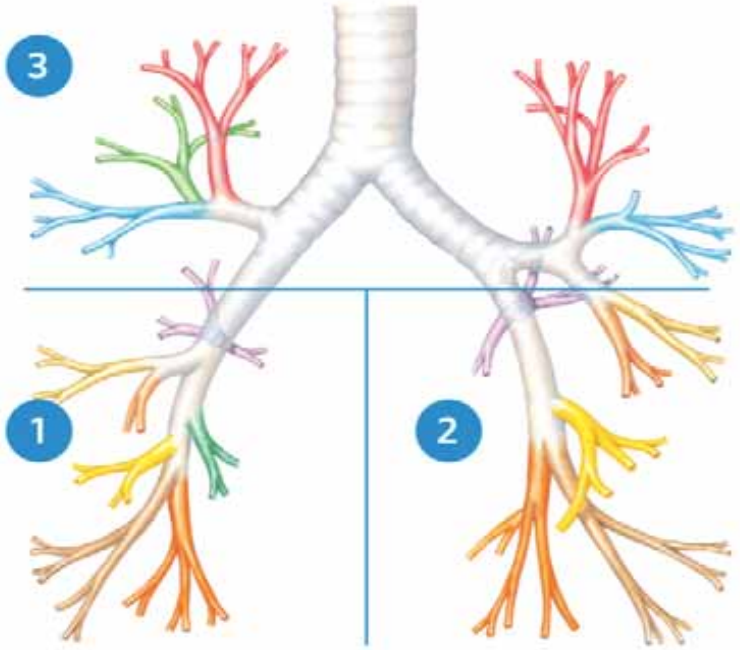


Anti IgE: Omalizumab (Xolair)

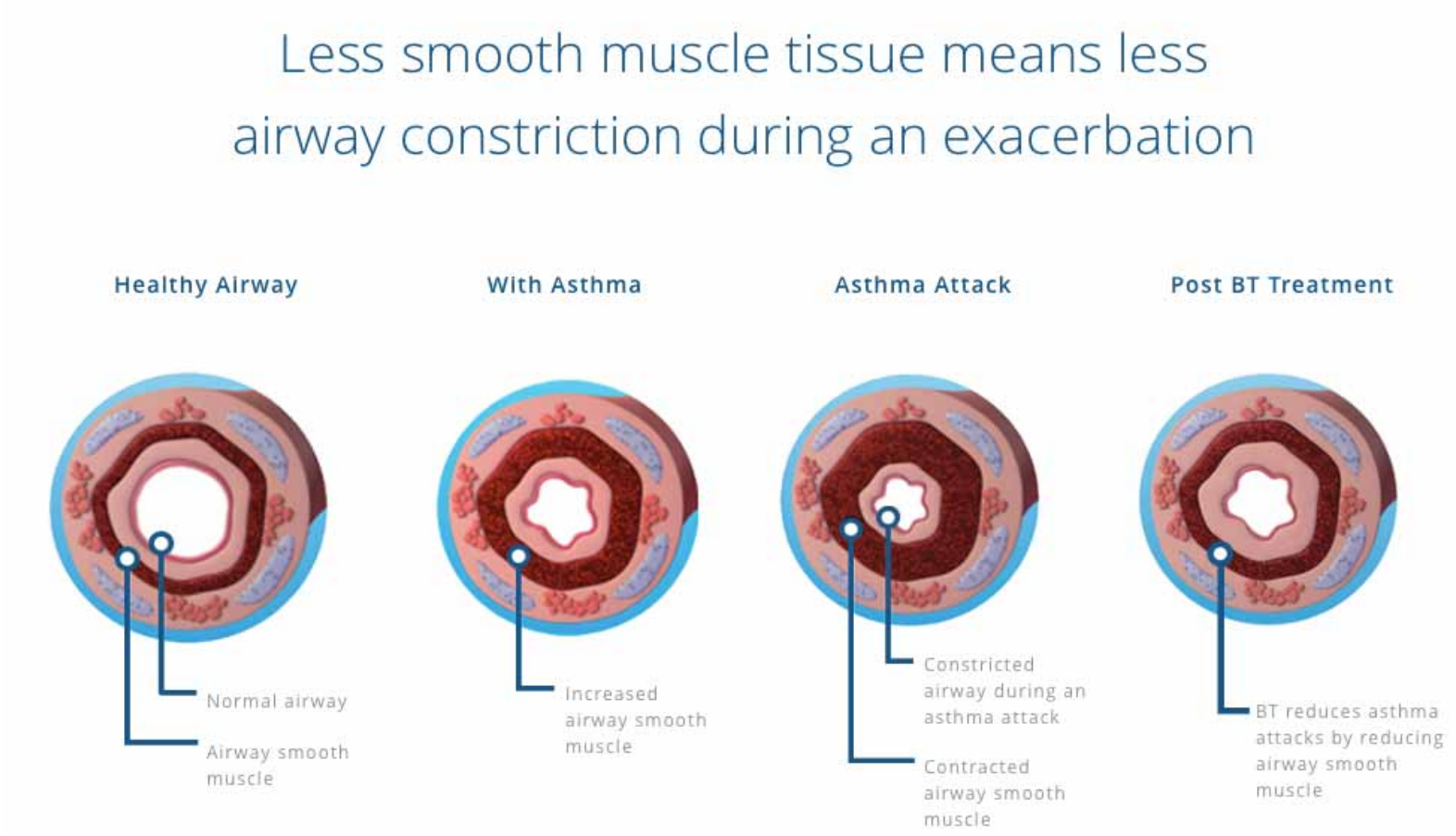
- Severe allergic asthma
- IgE 30-700
- Expensive
- 4 months trial
- Prefilled syringes now

Bronchial thermoplasty

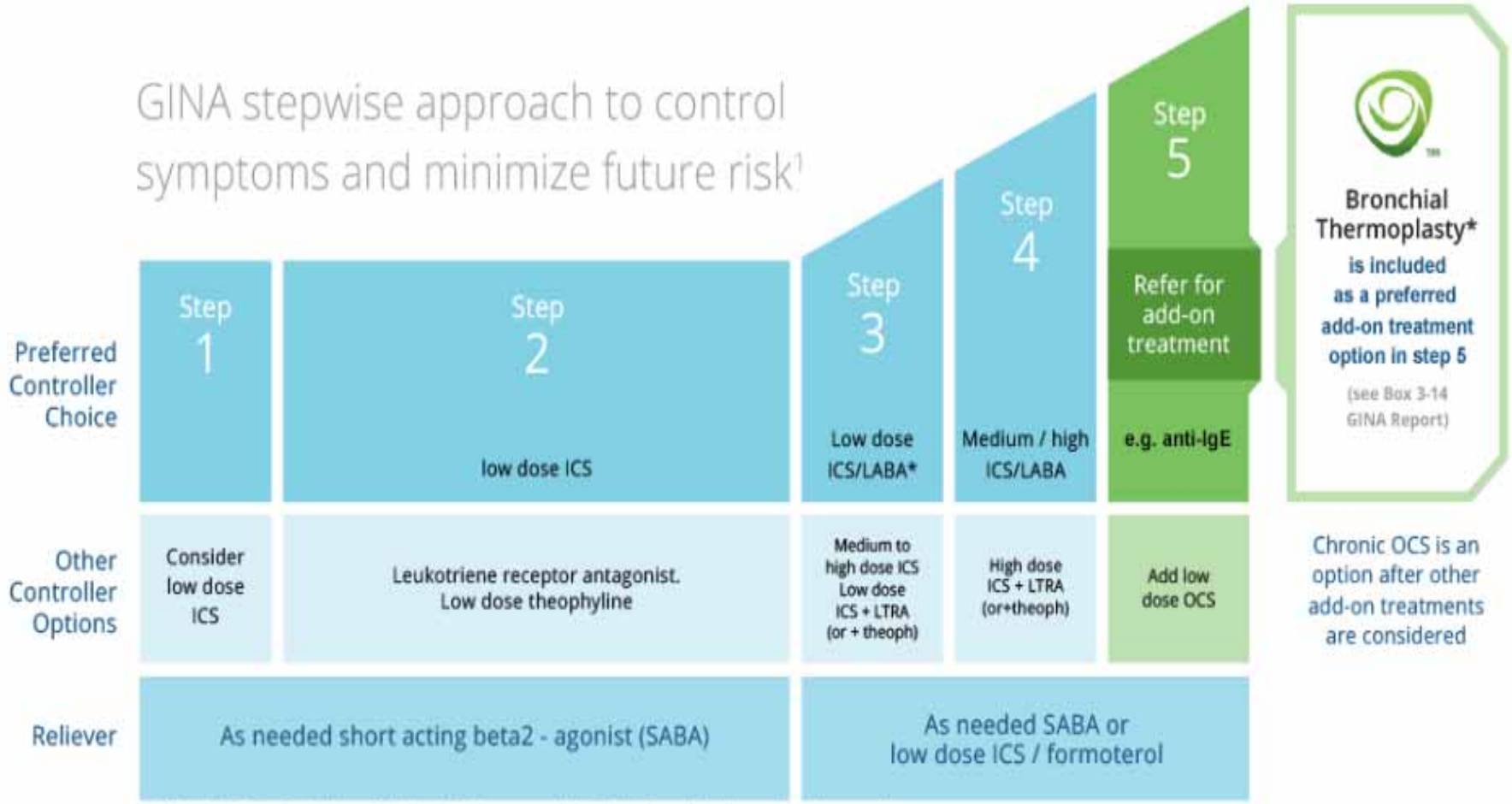
BT is done in 3 sessions



Bronchial thermoplasty



The Global Initiative for Asthma (GINA) now includes BT as an add-on therapy option for step 5 to help patients who are still symptomatic on ICS and LABA[1]



*Non pharmacological add on intervention

Biologicals

- Side effects of ICS- need for other therapy
- Benefits in persistent eosinophillic asthma
- Anti IL-5 : Mepolizumab
- Anti IL-5R : Benralizumab
- Anti IL-13: Lebrikizumab
- Anti IL-4: Pitrakinra
- Anti IL-4R: Dupilumab

First author [ref.]	Severity	Subjects n	Design	Treatment	Outcomes	Summary results
Wenzel [99]	Severe	309	R, db, pc, p	Golimumab, anti TNF-α, 24 weeks	FEV_1, exacerbations AQLQ, PEFR	FEV_1 unchanged, no reduction in exacerbations, AQLQ, PEFR Adverse profile side-effects
Pavord [56]	Severe, with ⩾2 exacerbations in past year	621	R, db, pc, p	Mepolizumab [75, 250 or 750 mg infusions at 4 weeks], anti-IL-5, 52 weeks	Rate of exacerbations	All doses reduced exacerbations by 39–52% No effect on ACQ, AQLQ or FEV_1
Haldar [157]	Severe	61	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, symptoms, FEV_1, AQLQ, AHR, sputum and blood eosinophils	Reduced exacerbations Improved AQLQ Reduced eosinophils
Nair [58]	Severe	20	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, oral steroid reduction	Reduced exacerbations, eosinophils and OCS dose
Kips [159]	Severe	26	R, db, pc, p	SCH55700, anti-IL-5, 12 weeks	Sputum and blood eosinophils, symptoms, FEV_1	Reduced blood sputum eosinophils No other significant outcomes
Castro [57]	Poorly controlled on high-dose inhaled CS	53	R, db, pc, p	Reslimuzab, anti-IL-5, 12 weeks	ACQ, FEV_1, Sputum eosinophils	Improved ACQ score Reduction in sputum eosinophils Improved FEV_1
Corren [160]	Moderate-severe	294	R, db, pc, p	AMG317, anti-IL-4Rα antibody, blocks IL-4 and IL-13, 12 weeks	ACQ scores, exacerbations	No effect on ACQ or exacerbations
Corren [59]	Moderate-severe	219	R, db, pc, p	Lebrikizumab, anti-IL13 antibody, 24 weeks	Change in pre-bronchodilator FEV_1	Improved FEV_1, compared with placebo, with greatest changes in high levels of periostin or Fe_{NO} group [*post hoc* analyses] No effect on ACQ-5 or diary measures Exacerbations were 60% lower in treated group with high Th2
Piper [60]	Moderate-to-severe	194	R, db, pc, p	Tralokinumab [150, 300, or 600 mg], IL-13 neutralising monoclonal antibody, 3 months	Change from baseline in ACQ-6 at week 13	No change in ACQ-6 at 13 weeks FEV_1 increase of 0.21 L *versus* 0.06 L with placebo [p=0.072] β_2-agonist use decrease of -0.68 *versus* -0.10 with placebo (p=0.020) Better response in those with higher IL-13 levels in sputum
Humbert [161]	Severe, CS-dependent	44	R, db, pc, p	Masitinib [3, 4.5 and 6 $mg \cdot kg^{-1} \cdot day^{-1}$], c-kit and PDGFR tyrosine kinase inhibitor, 16 weeks	OCS dose ACQ, FEV_1	No difference in OCS dose ACQ improved, no difference in FEV_1
Busse [162]	Moderate-to-severe		R, db, pc, p	Daclizumab, IL-2Rα chain antibody, 20 weeks	Change in FEV_1 (%) Asthma exacerbations	Improved FEV_1 Reduction in day-time asthma scores, use of SABA Prolonged time to severe exacerbations Reduction in blood eosinophils
Nair [163]	Severe asthma	34	R, db, pc, p	SCH527123, CXCR2 receptor antagonist, 4 weeks	Changes in sputum and neutrophil activation markers	Reduction in blood and sputum neutrophil Reduction in mild exacerbations No reduction in ACQ score (p=0.053)

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High *F*ENO	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High *F*ENO	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

Review of asthmatic patient

- **When to review?**
  - 1-3 monthly reviews after treatment inititiation
  - Pregnancy and post exacerbation
- **Step down:**
  - Symptoms controlled /lung function stable for ≥3m
- **Aim:**
  - Minimum dose required
  - Stopping ICS is not recommended in adults with asthma

Summary

- Difficult asthma is challenging
- Systematic assessment is key!!
- Management should aim to control symptoms and risk reduction
- Consider alternative add on treatments if available

Thank you

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