What's new in the management of asthma?

RCP Update in Medicine
Loughborough October 2024

Prof Ruth Green, Glenfield Hospital, Leicester

I am local PI for a clinical trial of biological asthma therapy in asthma funded by Astra Zeneca.
I have no other conflicts of interest to declare.

What's New in Asthma Management

Diagnosis

Initial Management

New Treatment Approaches

Admissions

The Green Agenda

The Future

British Thoracic Society

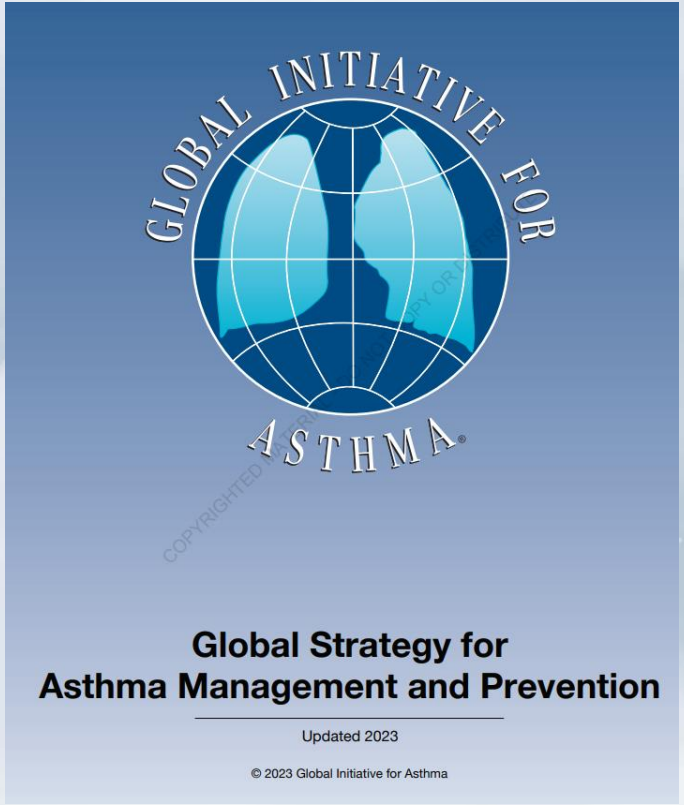
NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN Makes sense of evidence

Guideline

Asthma: diagnosis, monitoring and chronic asthma management

Draft for consultation, June 2024



Patient AL 52 yr old male

- Presents with 3 month history of intermittent cough and wheeze
- Symptoms worse on exertion
- Occasional waking at night
- Never smoker
- Family history of atopy
- Otherwise fit and well

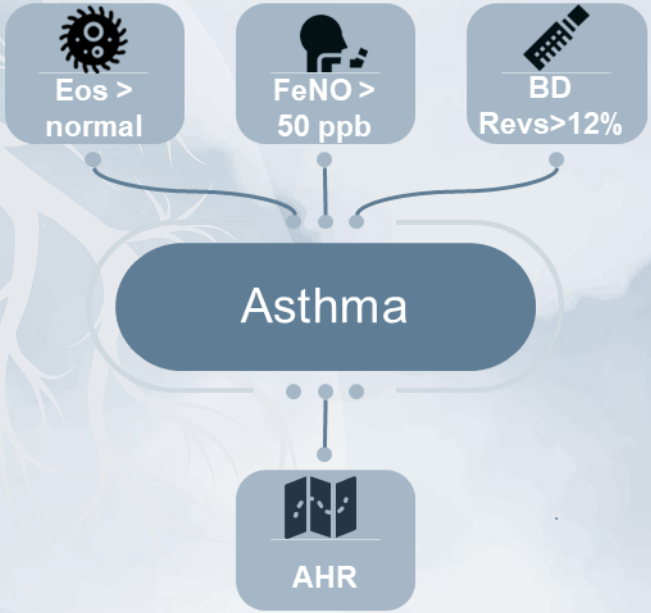
Patient AL 52 yr old male

- Examination unremarkable
- FeNO 53 ppb
- Blood eosinophil count 0.49 x10^9/L

Is this asthma?

Are other tests required?

Diagnosis

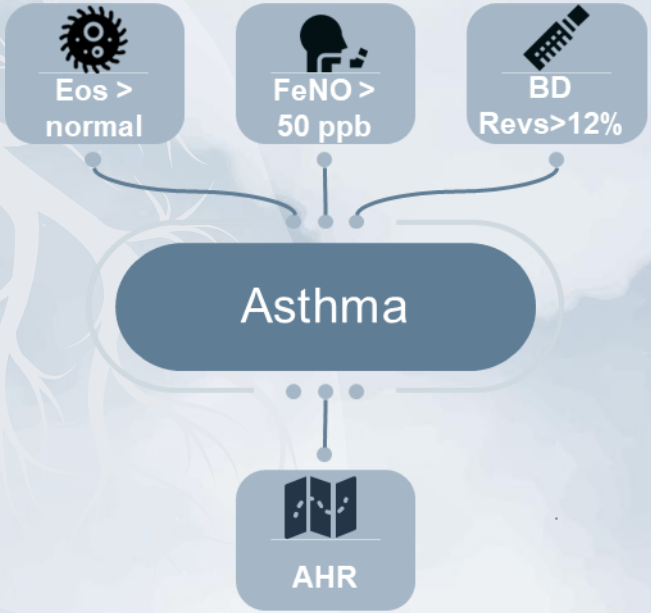


In adults with symptoms consistent with asthma:

- Measure FBC eosinophil count and FeNO
  - Diagnose asthma if Eos > ref range or FeNO >50ppb
  - If Eos and FeNO normal do spirometry and bronchodilator reversibility
  - Diagnose asthma if BDR >12% / 200ml
  - If BDR normal measure Airway Hyperresponsiveness (AHR)
  - Diagnose asthma if AHR present

British Thoracic Society | NICE National Institute for Health and Care Excellence | Healthcare Improvement Scotland | SIGN Makes sense of evidence

Diagnosis



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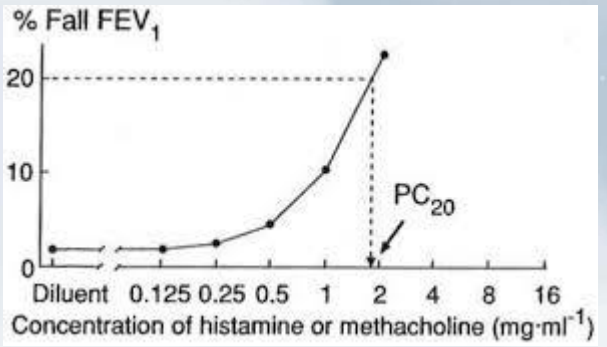
History of typical variable respiratory symptoms	
Wheeze/SOB/ Chest tightness/ cough	• Variable • >1 symptom • Worse at night/waking • Triggers • Worse with viral infection
Confirmed Variable Expiratory Airflow Limitation	
1. Documented xs variability in lung function	• +ve BD response • XS PEF variability • ↑ lung function after 4/52 Rx • +ve exercise test • +AHR test • XS variation between visits
2.Documented expiratory airflow	When FEV1 is reduced. FEV1/FVC ratio below lower limit of normal

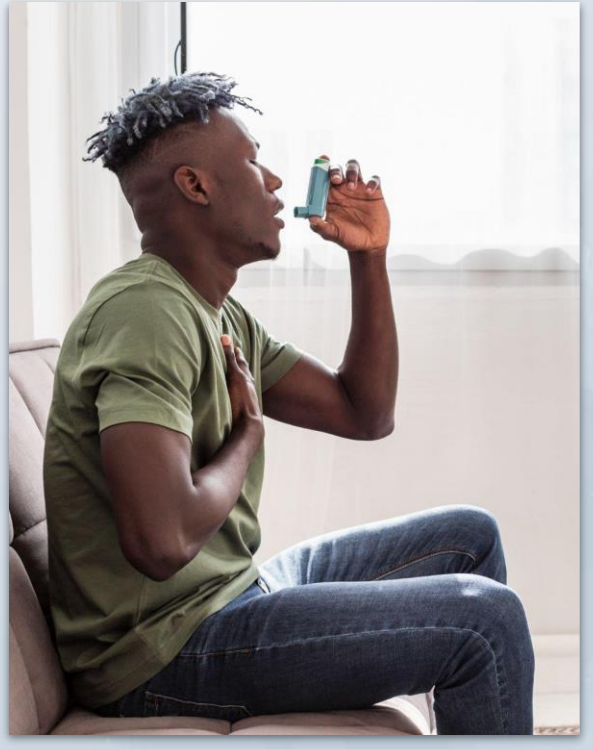
Patient AL 52 yr old male

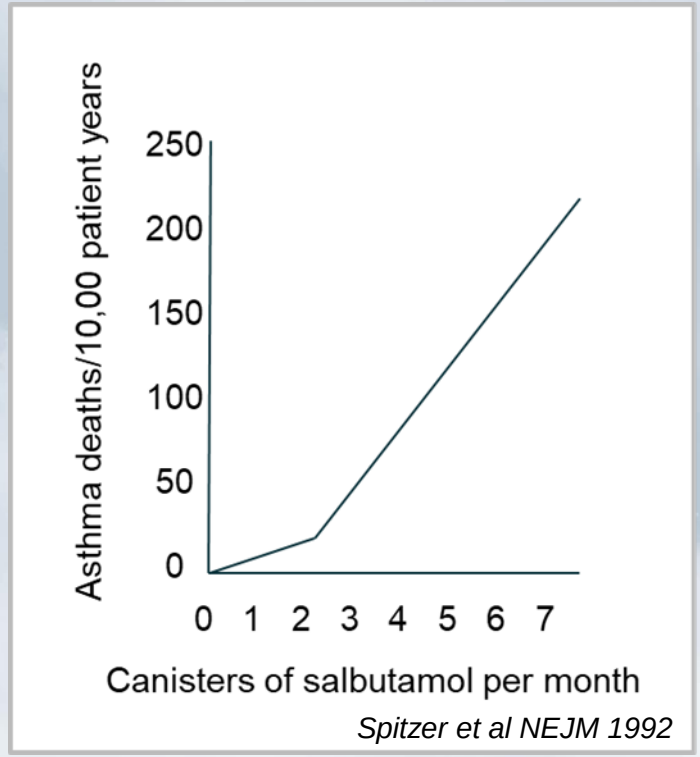
- Spirometry normal
- PEF variability < 10%
- Methacholine challenge test:



Diagnosis: Adult onset eosinophilic asthma

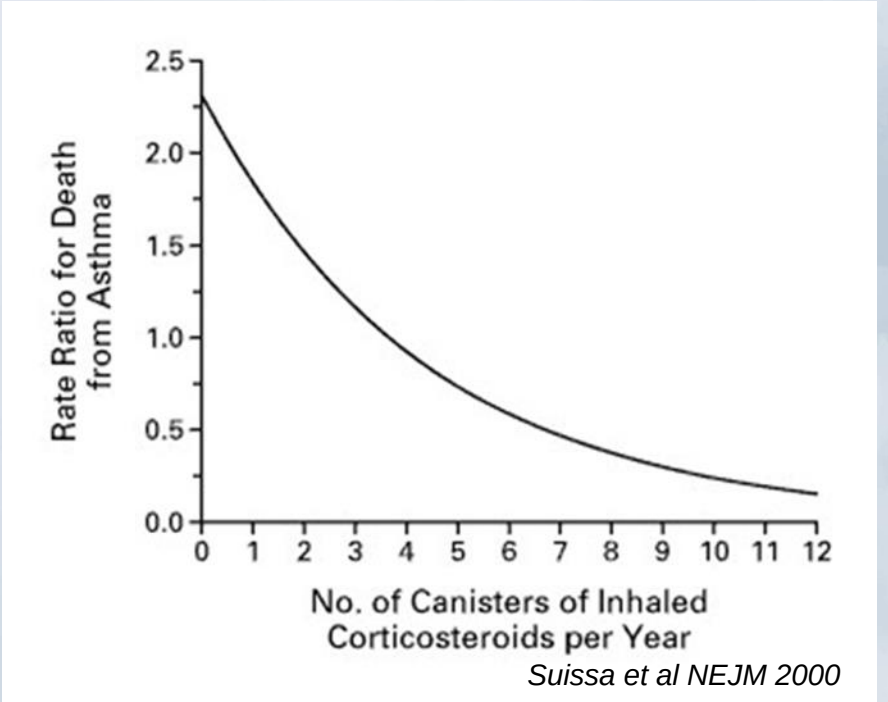
Initial management



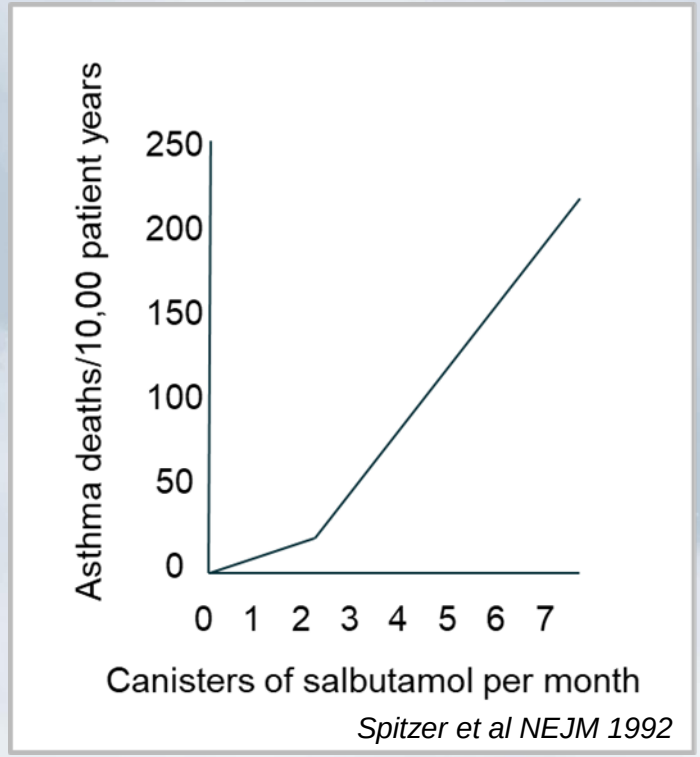


Spitzer et al NEJM 1992

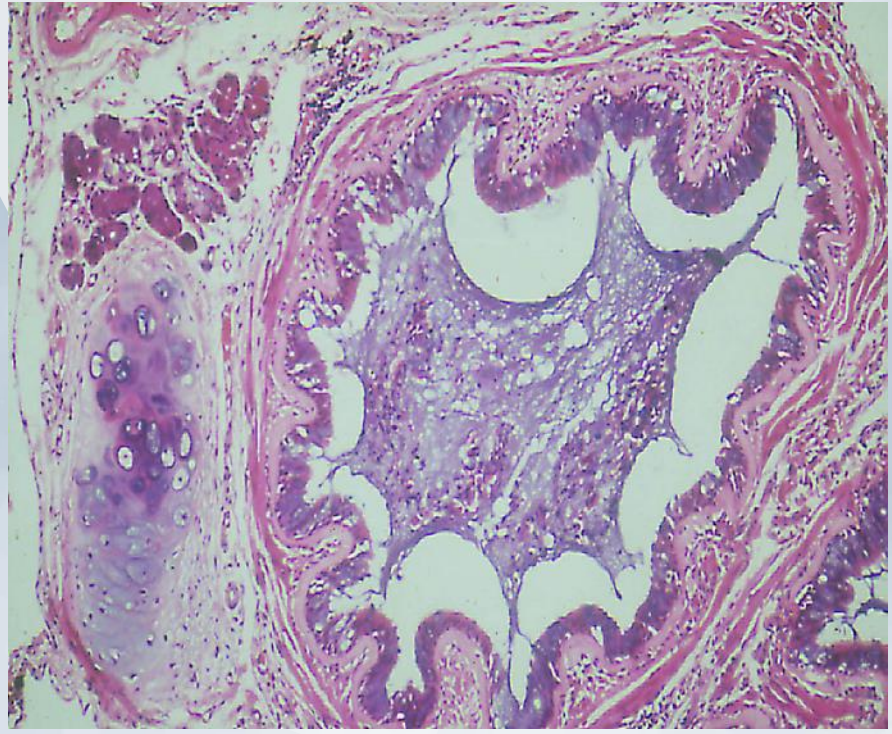
Initial management



Suissa et al NEJM 2000



Spitzer et al NEJM 1992



ASTHMA+ LUNG UK

‘Asthma care is in crisis’ - charity sounds the siren as asthma death toll rises

Over 12,000 people in the UK have died from asthma attacks since the publication of a landmark report ten years ago, which found that the majority of asthma deaths are preventable

Released on 24th April 2024

Death of boy, 10, in Essex after asthma attack was avoidable, inquest rules

Coroner finds medical professionals' neglect contributed to death of William Gray at hospital in Southend

William Gray, 10, whose death was 'tragic and avoidable', the coroner, Sonia Hayes, concluded. Photograph: Leigh Day/PA

The death of 10-year-old boy after a severe asthma attack was avoidable and was contributed to by the neglect of healthcare professionals, a coroner has concluded.

ASTHMA+ LUNG UK

'Asthma care is in crisis' - charity sounds the siren as asthma death toll rises

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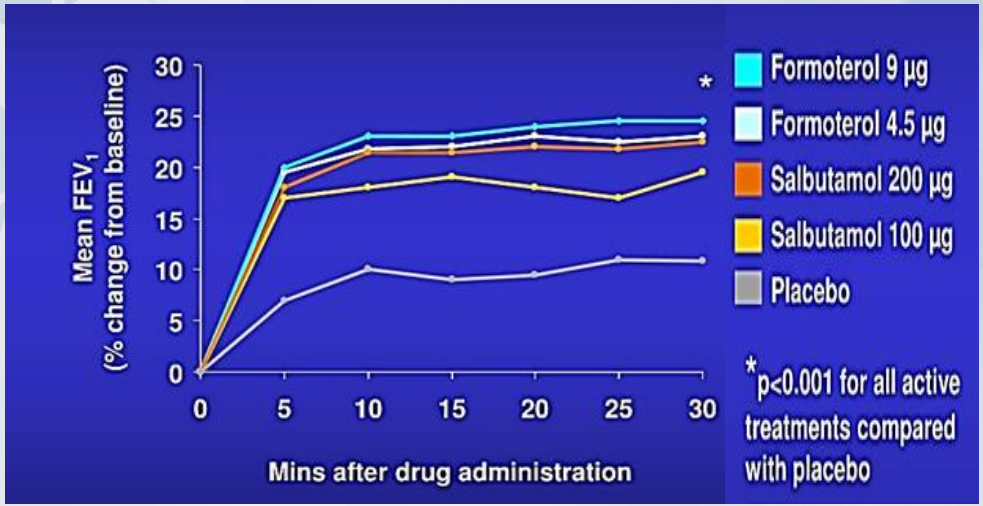
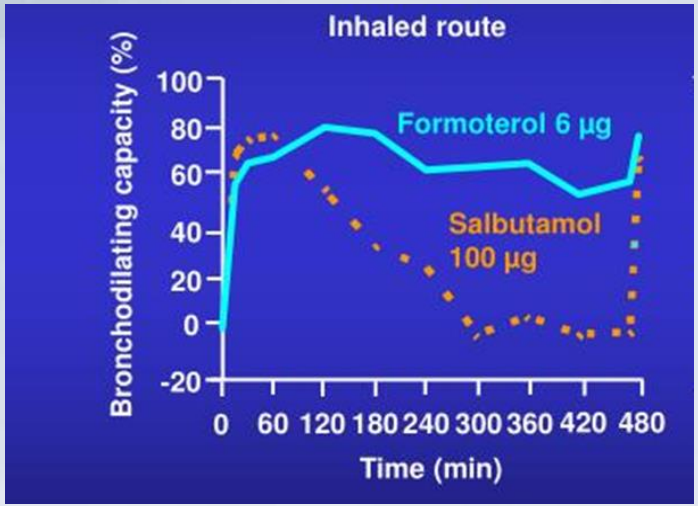
Released on 24th April 2024

"Prescribed four short courses of oral steroids….insufficient to effectively manage poorly controlled asthma in a picture of vastly excessive reliever inhaler prescriptions and the absence of ongoing preventer medication"

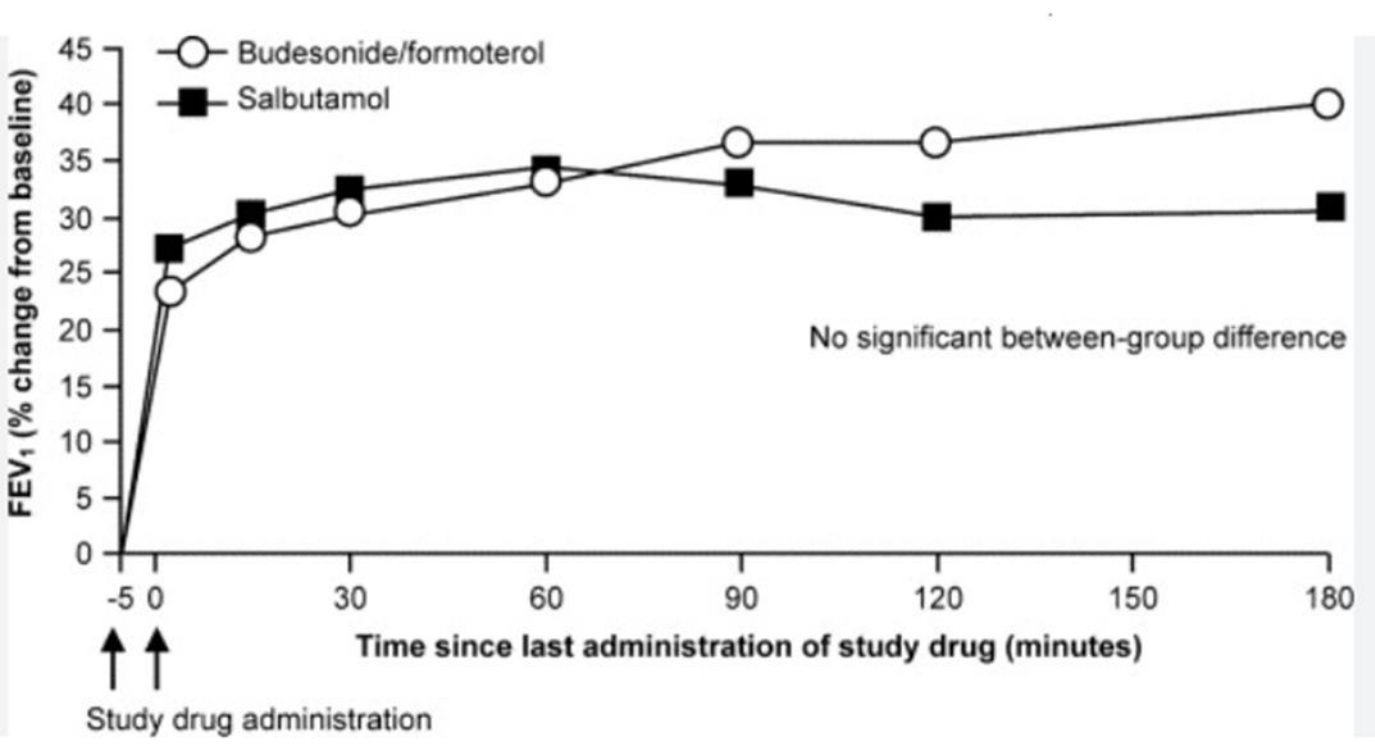
Formoterol v salbutamol

Formoterol speed of onset and duration of bronchodilator effects

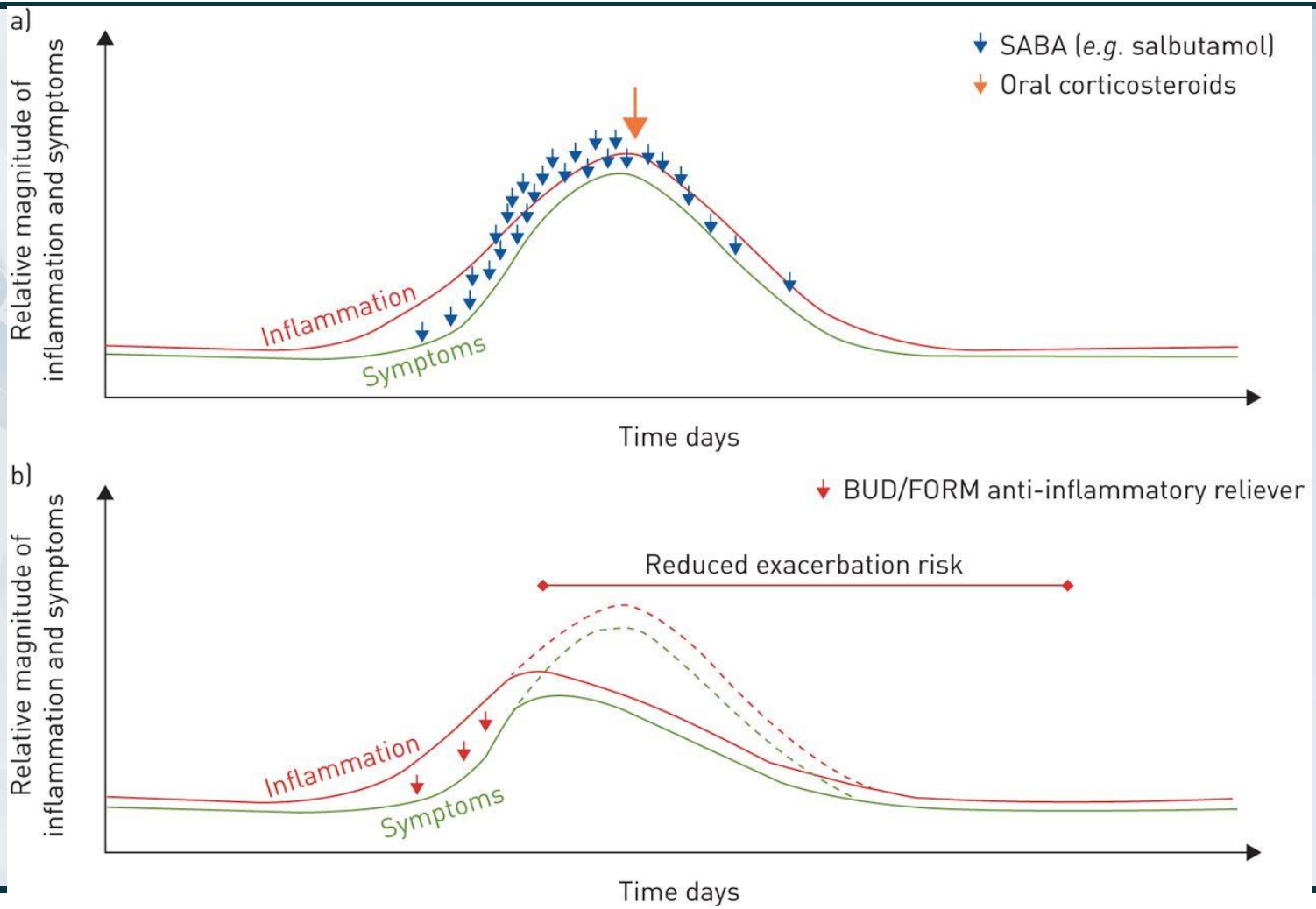




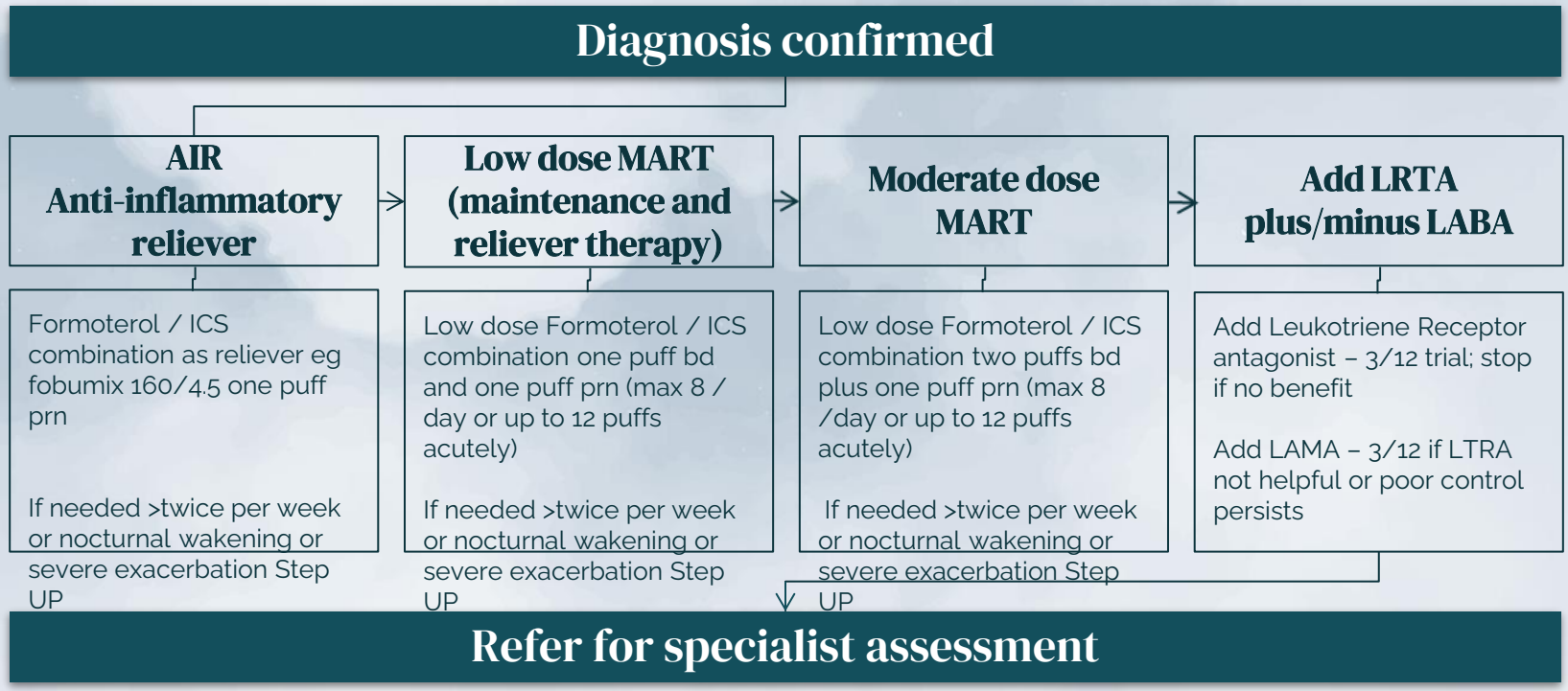
Formoterol/budesonide v salbutamol



Anti-inflammatory Reliever (AIR)

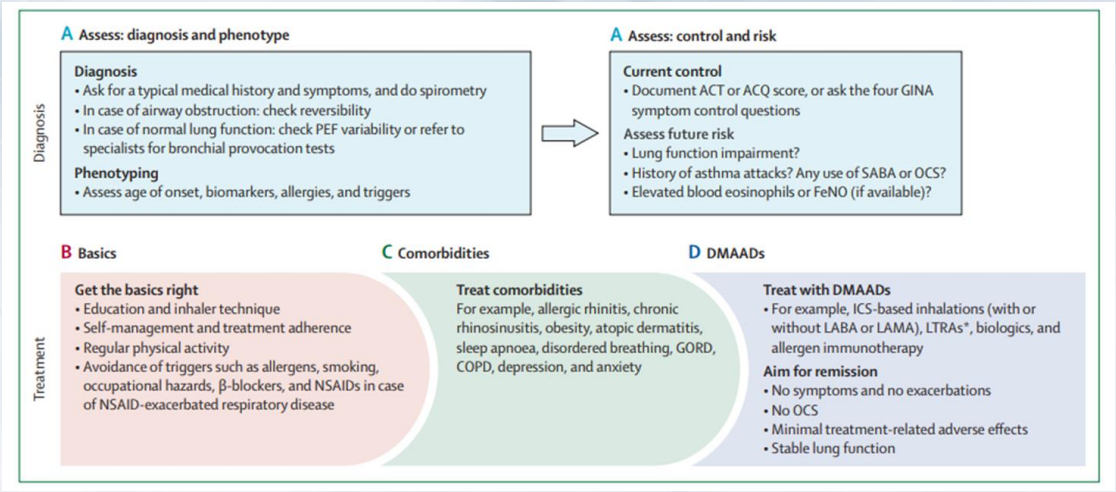

a)
Relative magnitude of inflammation and symptoms
SABA (e.g. salbutamol)
Oral corticosteroids
Inflammation
Symptoms
Time days
b)
Relative magnitude of inflammation and symptoms
BUD/FORM anti-inflammatory reliever
Reduced exacerbation risk
Inflammation
Symptoms
Time days

Asthma management flowchart



New Treatment Approaches

A²BCD : A concise guide for asthma management Lancet Resp Med 2023



A: Assess diagnosis and phenotype

DIAGNOSIS:

- **Review history: Are the symptoms consistent?**
- **Review diagnostic tests – is there objective evidence of asthma?**
- **Are more tests needed eg test for AHR?**

PHENOTYPE:

- **Age of onset**
- **Biomarkers**
- **Allergies**
- **Triggers**

A^2: Assess control and risk

CURRENT CONTROL:

- **Document symptom score (eg ACT / ACQ / GINA 4 symptoms Qs)**

FUTURE RISK:

- **Impaired lung function?**
- **History of severe attacks?**
- **Any use of SABA or OCS?**
- **Elevated blood eosinophils or FeNO?**

B: Get the BASICS right

- Education
- Inhaler Technique
- Self Management
- Treatment Adherence
- Regular Physical Activity
- Smoking Cessation
- Avoidance of triggers eg allergens, occupational hazards, B-blockers, NSAIDS (if sensitive)

C: Comorbidities

Identify and treat eg Self Management

- Allergic rhinitis
- Chronic rhinosinusitis
- Obesity
- Atopic Dermatitis
- Sleep Apnoea
- Breathing Pattern Disorder
- Vocal Cord dysfunction
- GORD
- COPD
- Depression
- Anxiety

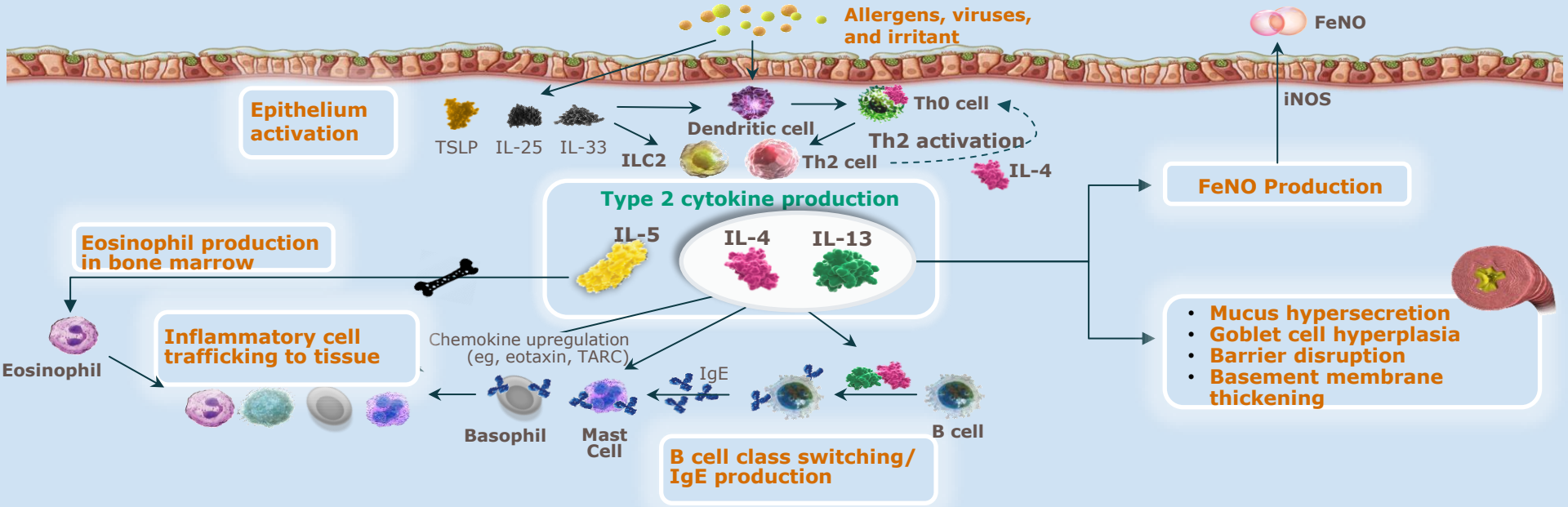
D: Disease modifying anti-inflammatory drugs

- ICS (in combination)
- LTRA
- Allergen immunotherapy
- Biologics

Aim for remission / Good asthma control:

- No symptoms
- No exacerbations
- No OCS
- Minimal treatment related adverse effects
- Stable Lung Function

Airway Pathophysiology



- IgE=immunoglobulin E; IL=interleukin; ILC2=Type 2 innate lymphoid cells; TARC=thymus and activation-regulated chemokine; Th0=naïve T-helper cell; Th2=Type 2 T-helper cells; TSLP=thymic stromal lymphopoietin.

- 1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50. 2. Fahy JV. *Nat Rev Immunol*. 2015;15(1):57-65. 3. Israel E, Reddel HK. *N Engl J Med*. 2017;377:965-976. 4. Schleimer RP, et al. *J Allergy Clin Immunol*. 2017;139:1752-1761. 5. Georas SN, et al. *J Allergy Clin Immunol*. 2014;134(3):509-520. 6. Rosenburg HR, et al. *J Allergy Clin Immunol*. 2007;119(6):1303-1310. 7. Robinson D, et al. *Clin Exp Allergy*. 2017;47(2):161-175. 8. Peters MC, et al. *Curr Allergy Asthma Rep*. 2016;16(10):71. 9. Alving K, Malinovschi A. European Respiratory Society Monograph. Lausanne: European Respiratory Society, 2010;1-31. 10. Nilsson G, et al. *Eur J Immunol*. 1995;25(3):870–873. 11. McLeod JJ, et al. *Cytokine*. 2015;75(1):57–61.

Monoclonal therapies

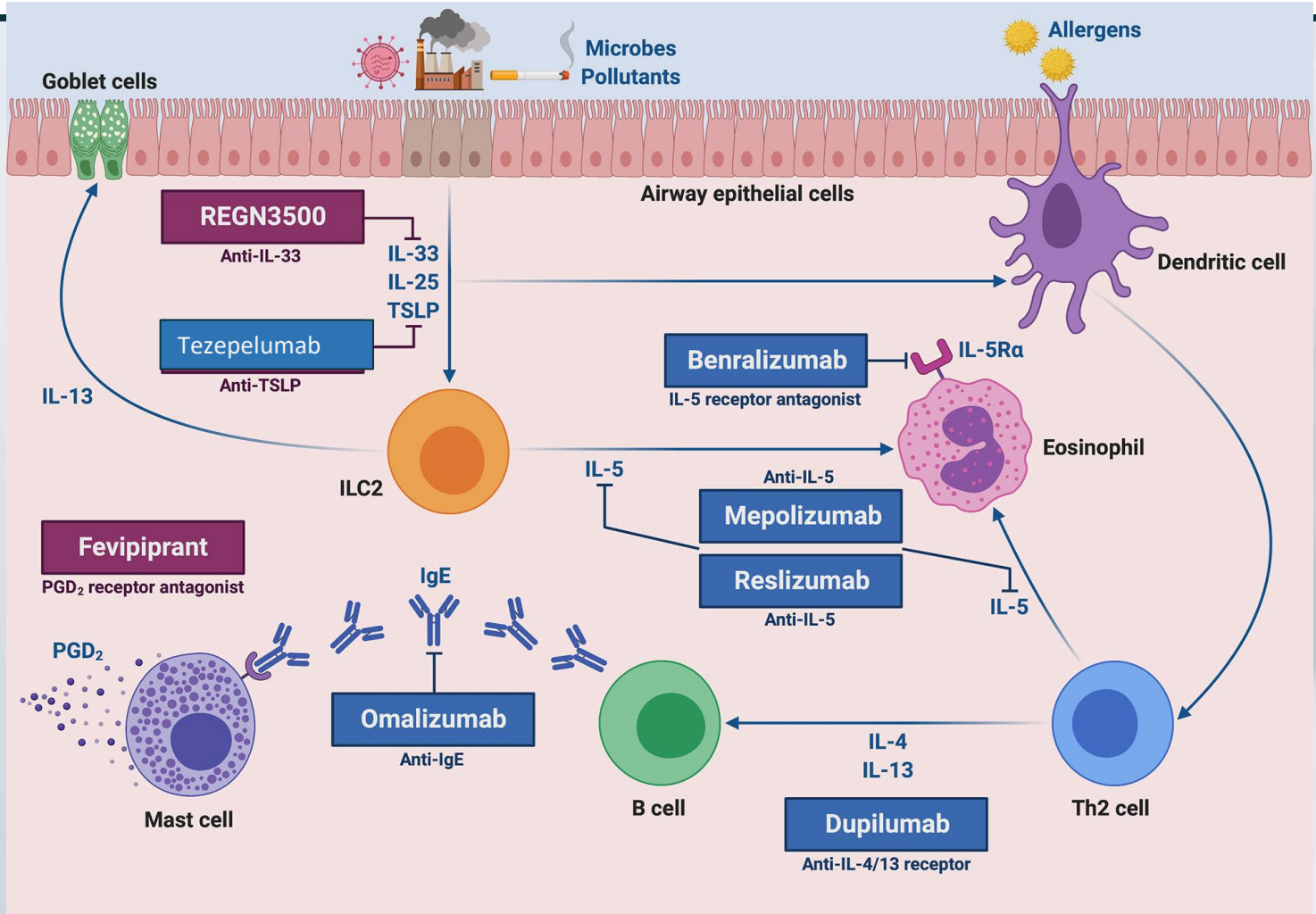
- Omalizumab anti-IgE
- Mepolizumab anti-IL5
- Reslizumab (iv) anti-IL5
- Benralizumab anti-IL5R
- Dupilumab anti-IL4/IL13
- Tezepelumab anti-TSLP

All systemic

Various dosing schedules

Expensive

Only delivered in commissioned centres


Goblet cells
Microbes
Pollutants
Allergens
Airway epithelial cells
REGN3500
Anti-IL-33
IL-33
IL-25
TSLP
Dendritic cell
Tezepelumab
Anti-TSLP
Benralizumab
IL-5Rα
IL-5 receptor antagonist
IL-13
ILC2
Eosinophil
IL-5
Anti-IL-5
Mepolizumab
Fevipiprant
PGD2 receptor antagonist
IgE
Reslizumab
Anti-IL-5
IL-5
PGD2
Omalizumab
Anti-IgE
IL-4
IL-13
B cell
Th2 cell
Dupilumab
Anti-IL-4/13 receptor
Mast cell

Indications for monoclonal therapy

NICE- To be eligible to receive monoclonal, adults must

Have asthma (!)

(not EGPA,ABPA etc)

- Agree to and followed the optimised standard treatment plan
- Assessment of adherence **80%**
- **Daily dose of ICS>1600- 2000 bdp equivalence**

Indications Mepo/Benra/Resli

- blood eos >0.3
- at least 4 exacerbations needing systemic corticosteroids in the last 12 months
- *or* has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months

or

- Eos >0.4
- at least 3 exacerbations needing systemic corticosteroids in 12 months

Indications Dupilumab/Xolair

Dupilumab

Eos > 150
Feno >25ppb
4 or more exacerbations in the previous 12 months

Patient is not eligible for mepolizumab, reslizumab or benralizumab,
or has asthma that has not responded adequately to these biological therapies

Not licensed for maintenance oral steroid reduction

Omalizumab
4 or more exacerbations in the previous 12 months
Weight and IgE based dosing, note IgE normal range

Indications Tezepelumab

- Three or more exacerbations in the previous year
- Or having maintenance oral corticosteroids

Anti-TLSP: acts on Th2 (eosinophilic) and non-Th2 (non-eosinophil) inflammation therefore patients eligible regardless of blood eosinophil count

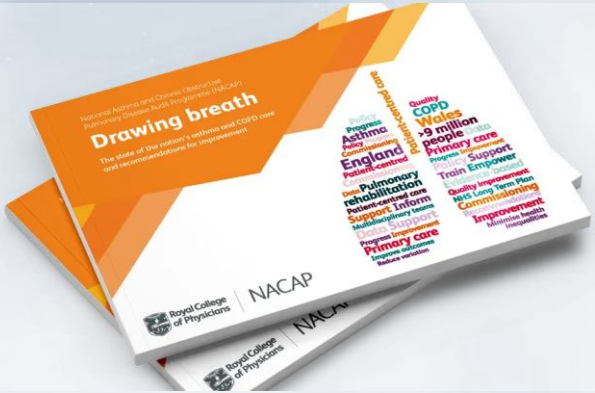
Treatment Comparison

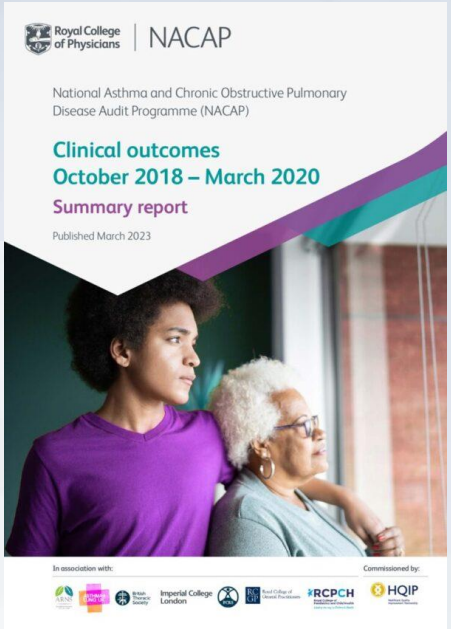
Biological medication	Target	Indication	Evidence	Reference
Omalizumab	IgE	Poor control on ICS/LABA Total serum IgE level >30iu/ml	25% reduction in all exacerbation 50% reduction in severe exacerbation	Humbert et al 2005
Mepolizumab	IL-5	Poor control on ICS/LABA >2 exacerbation per year Eos counts >150	>50% reduction all exacerbations >60% reduction hospital admission & emergency visits	Bel et al 2014
Dupilumab	IL-4	Eos count >300 FeNO >25	47% improvement in severe exacerbation 320ml improvement in FEV_1	Castro et al 2018
Tezepelumab	TSLP	Poor control on ICS/LABA >2 exacerbation per year	>60% reduction in exacerbation >110ml improvement in FEV_1	Corren at al 2017

Asthma Admissions (NACAP)

13.7% adult asthma readmitted within 30 days

26.4% readmitted within 90 days





0.4% adult asthma died within 30 days of admission

0.8% died within 90 days

Ambitions for change

These five ambitions for change describe NACAP's key goals for improving care for people with asthma and COPD.

Improve provision of early and accurate diagnosis

For everyone living with asthma and COPD to have their diagnosis confirmed by a guideline-defined approach, and to receive prompt, evidence-based care to help manage their long-term condition.

Improve provision of timely care

For everyone living with asthma or COPD to receive rapid assessment and care, including access to interventions which help prevent hospital admissions, such as pulmonary rehabilitation.

Improve provision of care received from the right people

For everyone admitted to hospital due to a deterioration in their asthma or COPD to have access to timely specialist advice and for each service to have a named person with responsibility for leading and improving asthma, COPD and pulmonary rehabilitation services.

Empower people with asthma and COPD and their carers by providing joined-up care pathways and high-quality information

For people living with asthma and COPD to be well informed about what good care looks like and know what to ask for when care falls short. Examples include a managed transition from paediatric to adult services, the importance of receiving help and advice to stop smoking and the importance of care provided by a multidisciplinary team.

Minimise variation in care contributing to health inequalities

For everyone with asthma and COPD to have timely access to excellent care irrespective of where they live, their background and personal circumstances.

NACAP Asthma organisation of care: Key Performance Indicators (KPIs)

- Make 7 day respiratory specialist advice available to all people with an asthma exacerbation
- Designated clinical lead for asthma
- Transition service in place for children and young people moving to adult asthma services
- Provide access to a severe asthma service

NACAP Asthma admissions delivery of care: (KPIs)

- Respiratory specialist review within 24 hours of arrival
- Peak Expiratory Flow within one hour of arrival
- Give systemic steroids within one hour of arrival
- Key elements of BTS discharge bundle provided
- Current smokers have tobacco dependency addressed
- Patients in receipt of inhaled corticosteroids on discharge

British Thoracic Society

BTS Asthma 4: an asthma attack bundle: 2024

This care bundle describes 4 high impact actions to ensure the best clinical outcome for patients with an acute asthma attack (often referred to as an exacerbation). The aim is to reduce the risk of further asthma attacks, reduce the number of patients who are readmitted to hospital following discharge, and encourage follow-up and appropriate onward referral (if necessary).

The asthma care bundle is designed to be used in any healthcare setting where a patient could present with an asthma attack.
It applies to adults, or adolescents (16+) transitioning to adult services. For children who have an asthma attack, we refer you to the advice outlined in the National Bundle of Care for CYP with Asthma.

Patient sticker

COMPLETE FOR PATIENTS WITH AN ASTHMA ATTACK

ACTION 1: MEDICATION REVIEW

MEDICATION REVIEW

a) The patient should be observed using their inhalers and coached to improve their technique as necessary (links to videos available below).
b) Preventer (inhaled corticosteroid [ICS] containing) inhaler should be prescribed if the patient does not have a preventer inhaler.
c) Adherence to the preventer (ICS-containing) inhaler should be assessed objectively (e.g., medication pick up rate). If it is suboptimal (<75% pick up rate in the previous 6-12 [illegible] support provided to improve this.

n.b. If the attack occu[illegible]k up rate), treatment should be stepped up

Preventer (ICS-containing) inhaler prescribed	**Yes** ☐	**Already prescribed** ☐		**Patient inhaler technique observed and optimised**	**Yes** ☐	**No** ☐	
Adherence assessed objectively	**Yes** ☐	**No** ☐	**Unable to assess** ☐	**Importance of adherence to ICS inhaler discussed**	**Yes** ☐	**No** ☐	

Signature

Date

ACTION 2: PERSONALISED ASTHMA ACTION PLAN

ASTHMA ACTION PLAN

A Personalised As[illegible]ding identifying factors in their ho[illegible]ciated with improved patient/ca[illegible]

Personalised Asthm[illegible] ☐ ☐ ☐ ☐ ☐ ☐ **No** ☐ **N/A** ☐

Signature

Date

ACTION 3: TOBACCO [illegible]

SMOKING CESSATION

Patients who are current[illegible] Advice (VBA) on tobacco dependence should be g[illegible]

Current smoker provide[illegible]

Signature

Date

ACTION 4: CLINICAL REVIEW WITHIN 4 WEEKS

REVIEW WITHIN FOUR WEEKS

A clinical review should take place within 4 weeks for all patients, although some patients may require one sooner. Clinical review can be by any healthcare profe[illegible]rral if nee[illegible]

*If th[illegible]ose ICS th[illegible]

*If the patient is on maintenance oral corticosteroids for their asthma, please refer directly to a severe asthma centre

Clinical review within 4 weeks arranged **Yes** ☐ **No** ☐

Signature

Date

ISSN 2040-2023 British Thoracic Society Reports, Vol 15, Issue 2, 2024 BTS Report: The Asthma 4: an asthma attack bundle

Patient DP: 54 year old female

- Admitted with acute SOB & wheeze
- 3-4/12 history of cough
- Limited English
- RR25
- Widespread wheeze
- PEF 140
- FBC : eosinophils 0.72

Patient DP: 54 year old female

- Diagnosis: New onset eosinophilic asthma
- Rx: Oral Prednisolone, nebs, ICS/LABA started
- Discharged after 72 hours (RR<20, PEF 300, wheeze resolved, off nebs)
- Plan: to refer to asthma nurses, see GP in 48 hours, consultant review 1/12

6/52 later:

- Re-admission: Acute severe asthma with life threatening features:
  - RR 27 with paradoxical movement
  - PaO2 11.4, PaCO2 6.1
  - PEF unrecordable

- Admitted to ICU: received iv magnesium, back to back nebs, observed. Did not require ventilation. Back to respiratory ward after 48 hours

Patient DP: Missed opportunities

- 48 hr GP review did not happen
- Asthma nurse referral had not been made
- Consultant FU delayed

Asthma nurse review before discharge

- Poor understanding of need for ICS
- Poor inhaler technique
- Asthma action plan had not been translated
- Effectively not taking preventer Rx: high risk
- "Near miss": How can we do better?

Asthma Virtual Ward

Asthma admission

Asthma Guideline Senior Respiratory Review

Suitable for Virtual ward?

Complete asthma bundle
Refer to on boarder

Onboarder registers patient with Clinitouch platform. Discharge to VW documented

Patient home with tablet, peak flow meter, oximeter

Patient followed for 7-14 days. Discussed at weekly integrated MDT

1/12 F2F nurse led review.

Possible outcomes:

- **Discharge to GP**
- **Refer asthma MDT**
- **Consultant FU**

Asthma Virtual Ward

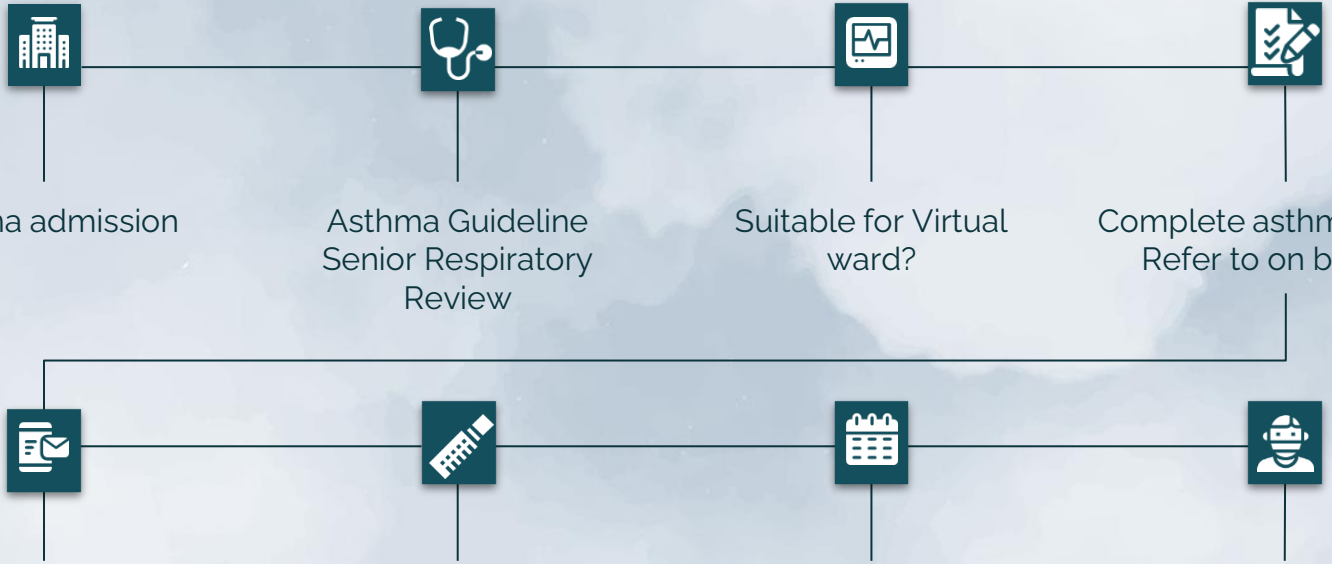
Virtual Ward Inclusion Criteria:

-Treated for asthma exacerbation this admission
-On oral steroids
-Receiving inhaled corticosteroids

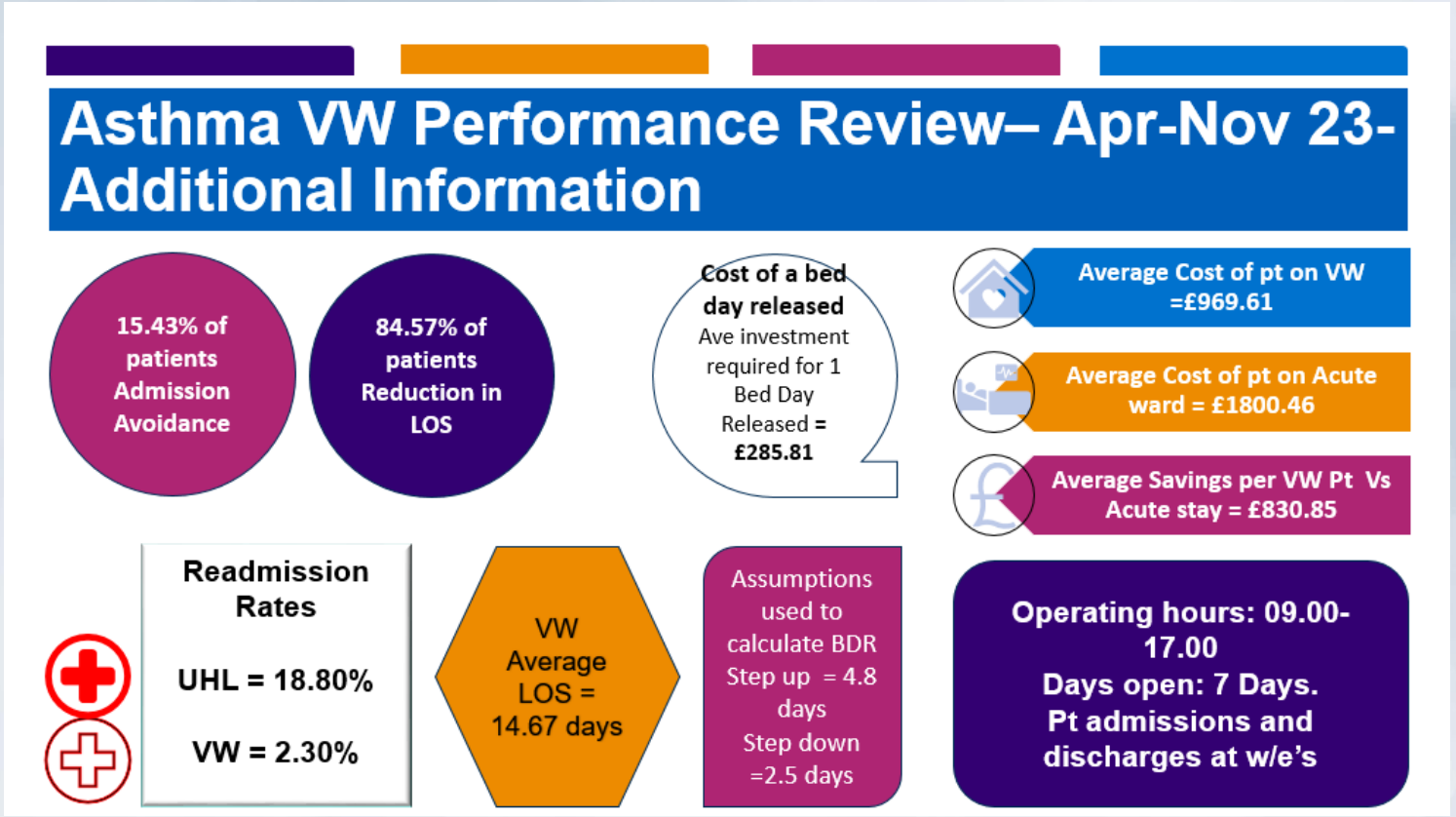
Virtual Ward Exclusion Criteria:

-Any feature of ongoing acute severe asthma:
    Peak Flow <50% best or predicted
    HR>110
    RR >25
-Saturation <94% on air
-Under the severe asthma service

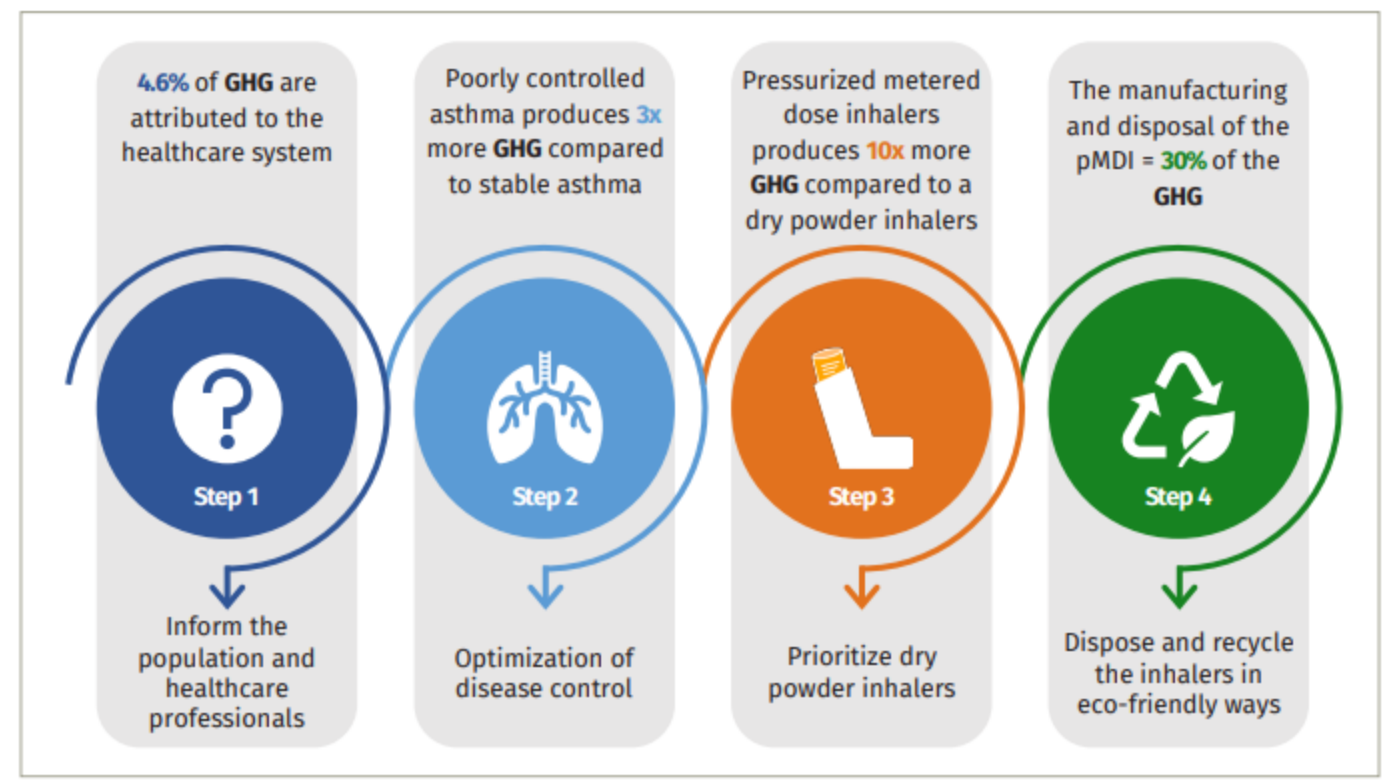
Asthma Virtual Ward

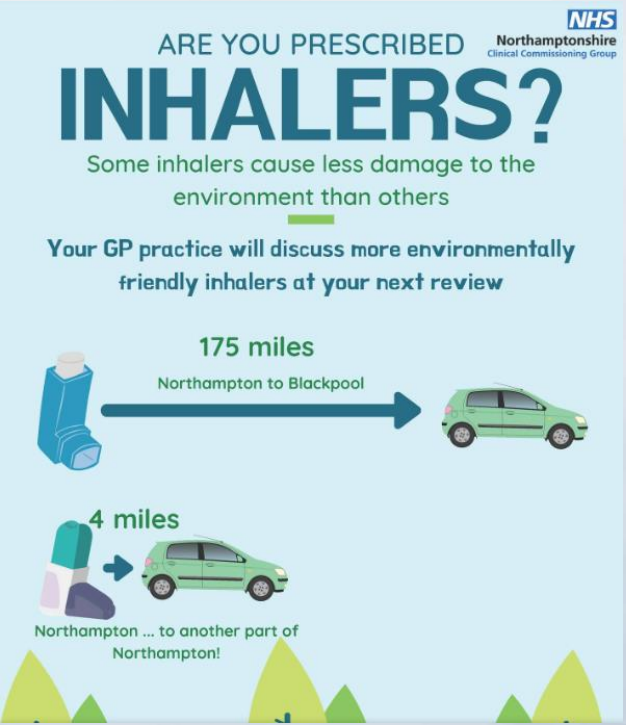


Virtual Ward Outcomes



Green Agenda


4.6% of GHG are attributed to the healthcare system
Step 1
Inform the population and healthcare professionals
Poorly controlled asthma produces 3x more GHG compared to stable asthma
Step 2
Optimization of disease control
Pressurized metered dose inhalers produces 10x more GHG compared to a dry powder inhalers
Step 3
Prioritize dry powder inhalers
The manufacturing and disposal of the pMDI = 30% of the GHG
Step 4
Dispose and recycle the inhalers in eco-friendly ways


ARE YOU PRESCRIBED
INHALERS?
NHS
Northamptonshire
Clinical Commissioning Group
Some inhalers cause less damage to the environment than others
Your GP practice will discuss more environmentally friendly inhalers at your next review
175 miles
Northampton to Blackpool
4 miles
Northampton ... to another part of Northampton!

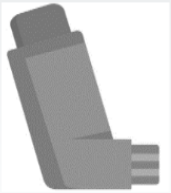

Choose a green inhaler to help fight climate change.
Ask about green inhalers at your next routine respiratory review.
Improving lives together
Norfolk and Waveney Integrated Care System


Eco-friendly inhalers are a breath of fresh air for inhaler users and our planet

“Take AIR” scheme : UHL/Chiesi

A successful pilot: Feb 2021 to Feb 2022

5686
envelopes posted by patients



20,049
inhalers returned by patients

3.5
Average number of inhalers per envelope

386
Average weekly return rate (2% of all inhalers prescribed in LLR)

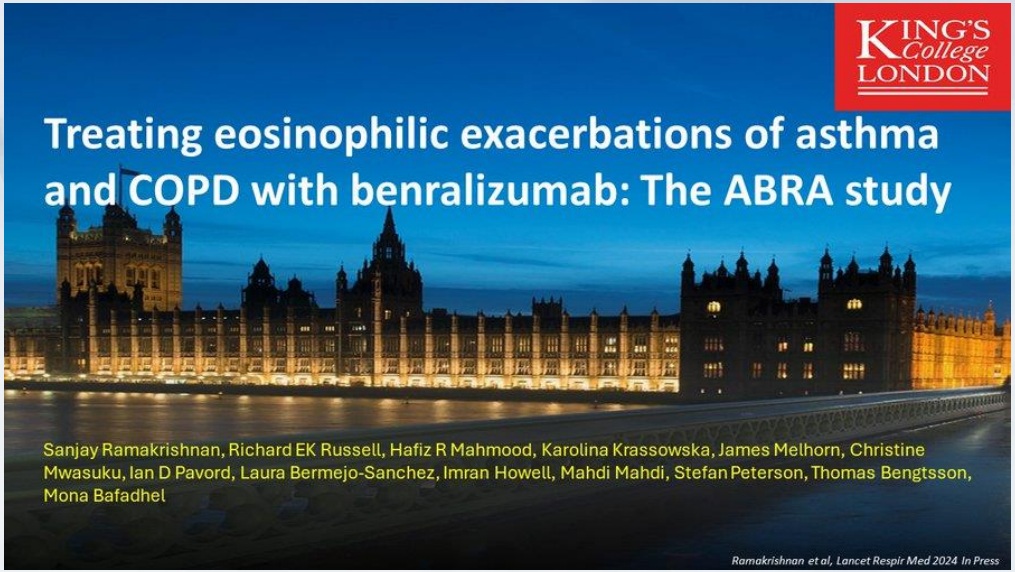
119.3
tonnes of CO_2e saved

=

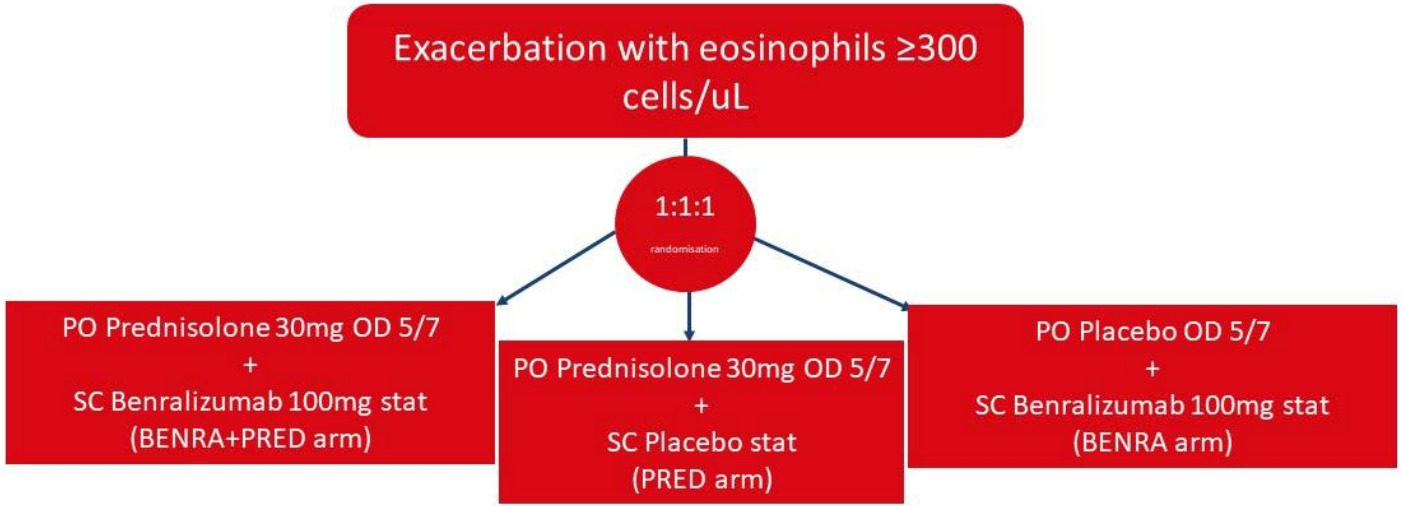
1973
tree seedlings growing for 10 years or
141 acres of US forestry in 12 months[1]

The Future?

Targeted biological therapy to treat exacerbations



Multicentre, double-blind, double-dummy, active-comparator, placebo controlled randomised clinical trial



Co-primary outcome	Day 28 VAS symptoms & Day 90 treatment failure rates (death, hospitalisation, retreatment)
Secondary outcomes	Time to treatment failure; day 30 treatment failure rates, lung function, day 28 ACQ-7, ACT, MRC, AQLQ, CAT and EuroQoL

Ramakrishnan et al, Lancet Respir Med 2024 In Press

Co-primary outcome (VAS symptoms)

Endpoint	PRED (n=53)	Pooled BENRA (n=105)	P value
Treatment failure at 90 days, n (%)	39 (73.6)	47 (45.2)	<0.001
Odds ratio vs. PRED (95%CI)	-	0.264 (0.125, 0.556)	
Mean total VAS change (95%CI) d28	103 (75 - 132)	152 (131 - 173)	
Least Square Mean difference (95%CI)		49 (14 - 84)	0.006

Conclusion

- The ABRA study shows the first new treatment for exacerbations of asthma and COPD
- Benralizumab as a single injection at the time of an acute eosinophilic exacerbation was superior to standard of care with prednisolone
  - NNT of 4 to reduce treatment failure

Sub-group analysis

Endpoint	PRED (n=53)	BENRA (n=53)	BENRA+PRED (n=52)
Treatment failure at 90 days, n (%)	39 (73.6)	25 (47.2)	22 (42.3)
Odds ratio vs. PRED (95%CI)	-	0.298 (0.129-0.688) p=0.005	0.232 (0.099-0.544) p<0.001
Mean total VAS change (95%CI) d28	-	46 (5 to 87) P=0.027	52 (11 to 93) P=0.013
LSM difference (95%CI)			

No difference between BENRA and BENRA+PRED for co-primary outcome and any of the secondary outcomes

Ramakrishnan et al, Lancet Respir Med 2024 In Press

The Future?

Ultra-long acting biological therapy

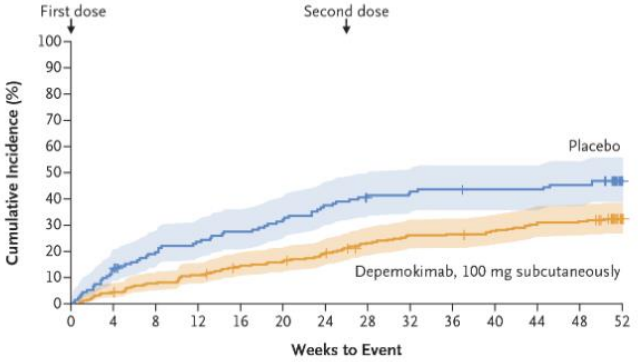
ORIGINAL ARTICLE

Twice-Yearly Depemokimab in Severe Asthma with an Eosinophilic Phenotype

Authors: David J. Jackson, Ph.D., Michael E. Wechsler, M.D., Daniel J. Jackson, M.D., David Bernstein, M.D., Stephanie Korn, M.D., Ph.D., Paul E. Pfeffer, Ph.D., Ruchong Chen, M.D., Ph.D., +9, for the SWIFT-1 and SWIFT-2 Investigators* Author Info & Affiliations

Published September 9, 2024

A Time to First Exacerbation in SWIFT-1

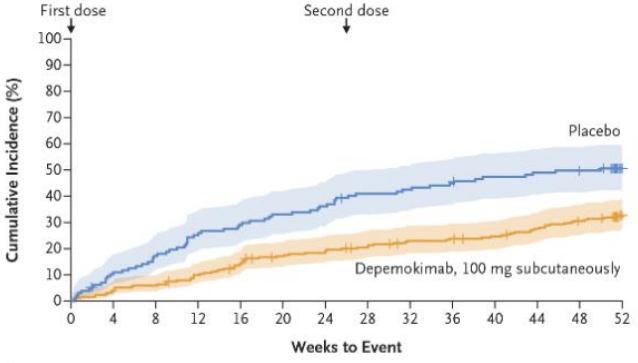


No. at Risk														
Placebo	132	115	105	99	94	89	81	76	74	72	71	71	69	55
Depemokimab	250	239	230	222	212	208	199	186	179	178	174	168	165	132

	No. of Patients	Patients with ≥1 Event	Patients with 0 Events
		no. (%)	
Placebo	132	61 (46)	71 (54)
Depemokimab	250	79 (32)	171 (68)

Hazard ratio, 0.56 (95% CI, 0.40–0.79)

B Time to First Exacerbation in SWIFT-2

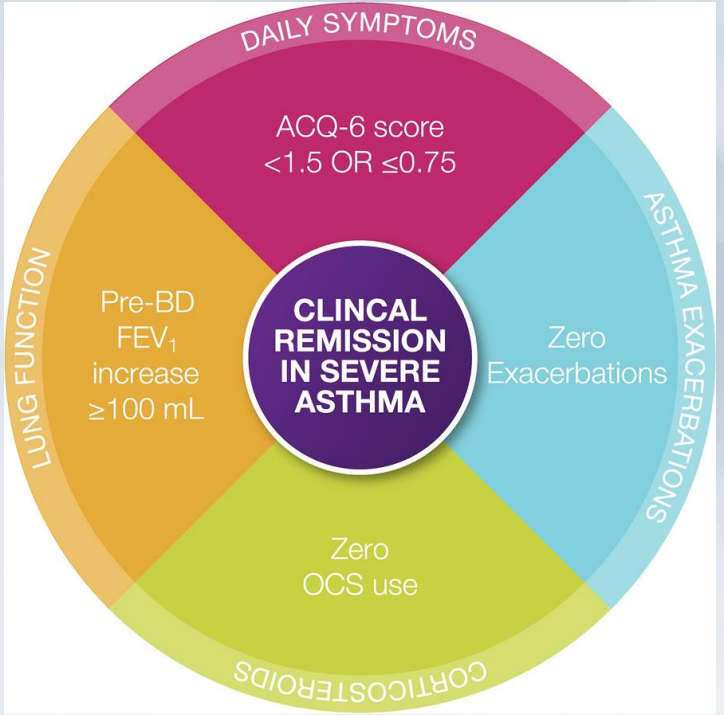


No. at Risk														
Placebo	128	114	105	95	90	85	81	74	72	69	65	63	62	41
Depemokimab	252	242	237	225	214	203	200	193	185	183	179	171	163	128

	No. of Patients	Patients with ≥1 Event	Patients with 0 Events
		no. (%)	
Placebo	128	64 (50)	64 (50)
Depemokimab	252	81 (32)	171 (68)

Hazard ratio, 0.53 (95% CI, 0.38–0.74)

The Future?



Optimal dosing and duration of biological therapy?

Can asthma remission be obtained off treatment?

Thanks

Any questions?