Great Ormond Street Hospital for Children
NHS Foundation Trust

Asthma
Clinical update

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Clinical guideline updates

New updates since 2023

- Global Initiative for Asthma (GINA) annual report (May 2024)
- Incorporating guidance on difficult-to-treat and severe asthma

Updates in last 3 years

- GINA difficult-to-treat and severe asthma short guide (2023)
- ERS clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years (2021)

Anticipated updates

- BTS/SIGN/NICE joint guideline for the diagnosis, monitoring and management of chronic asthma (expected publication date: Nov 2024)

NICE National Institute for Health and Care Excellence

Asthma: diagnosis, monitoring and chronic asthma management

In development [GID-NG10186] Expected publication date: 27 November 2024 Register as a stakeholder

This guideline is being developed jointly by NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the British Thoracic Society (BTS).

Guideline scope

- Joint update to NICE (2017) and BTS/SIGN (2019) guidelines
- Children, young people, adults
- Updated evidence review and combined recommendations:
  - Diagnosis
  - Pharmacological treatment
  - Monitoring

National Bundle of Care for Children and Young People with Asthma: Phase one

Version 1, September 2021

- Environmental impacts
- Accurate and early diagnosis
- Effective preventative medicine
- Managing exacerbations
- Severe asthma

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Accurate and early diagnosis

- Why is this challenging?
  - A diagnosis of asthma is made on:
    - clinical history of characteristic symptoms that vary over time and in severity
    - supported by objective tests demonstrating variable expiratory airflow limitation and/or airway inflammation
    - No single gold-standard test for asthma
  - Many other respiratory conditions can mimic asthma
  - Chronic disease with variable symptoms/test results (spirometry, BDR) FeNO)
    - over time
    - in response to exposures
    - with (ICS-containing) treatment

Accurate and early diagnosis

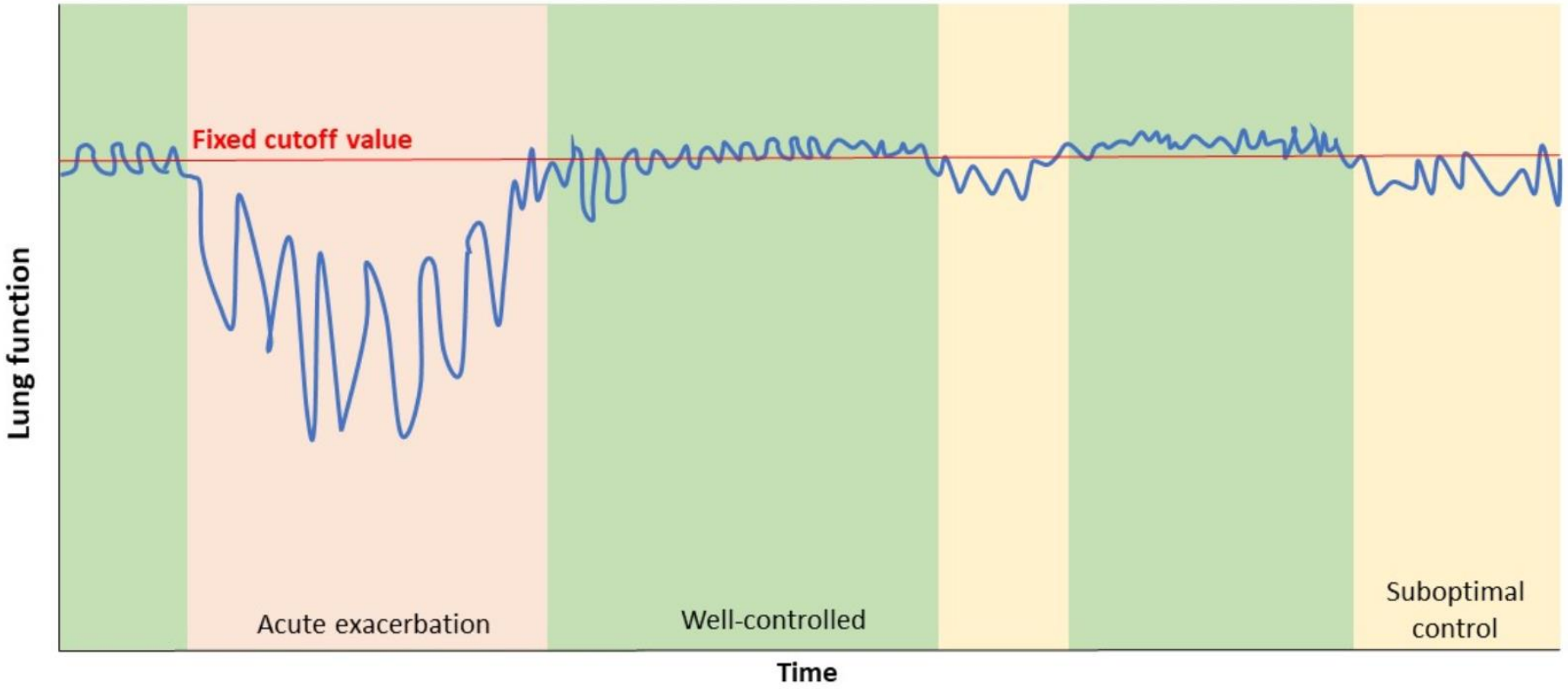
- Why is this so important?
  - Under- and over-diagnosis of asthma is common

Under-diagnosis	Over-diagnosis
Delayed treatment initiation	Exposure to unnecessary medications
Delayed patient/carer education	Risk of medication side-effects
Excess morbidity and poor quality of life	Risk of alternative diagnoses being missed
High risk of asthma attacks	Inappropriate healthcare costs
Persistent airway inflammation/airway remodeling/impaired lung function growth	

Diagnostic pathways

- Different recommendations in NICE (2017) and BTS/SIGN (2019)
  - Greater emphasis on objective testing in NICE guidance: spirometry/FeNO
- ERS (2021) diagnostic pathway
  - Emphasis on objective testing (spirometry/FeNO)
- GINA 2024
  - Emphasis on objective testing where available (spirometry/Peak Expiratory Flow variability second line)
  - Recommendations on steps to establish diagnosis when no objective testing done initially or test results (on treatment) are normal

Asthma: variability in lung function with time



Well-controlled period: characterised by better lung function and less diurnal variability. However, diurnal variation may straddle diagnostic cut offs in some patients.

Period of suboptimal control: may be predictable in individual patients based on the triggers, such as cold weather or during pollen seasons.

Acute exacerbation: characterised by marked deterioration in lung function and exaggerated diurnal variability

Wang R, et al. *Thorax* 2021

Algorithm B Objective tests for asthma in children and young people aged 5 to 16

Order of tests

- Perform spirometry in children and young people with symptoms of asthma
- Consider BDR test if spirometry shows an obstruction

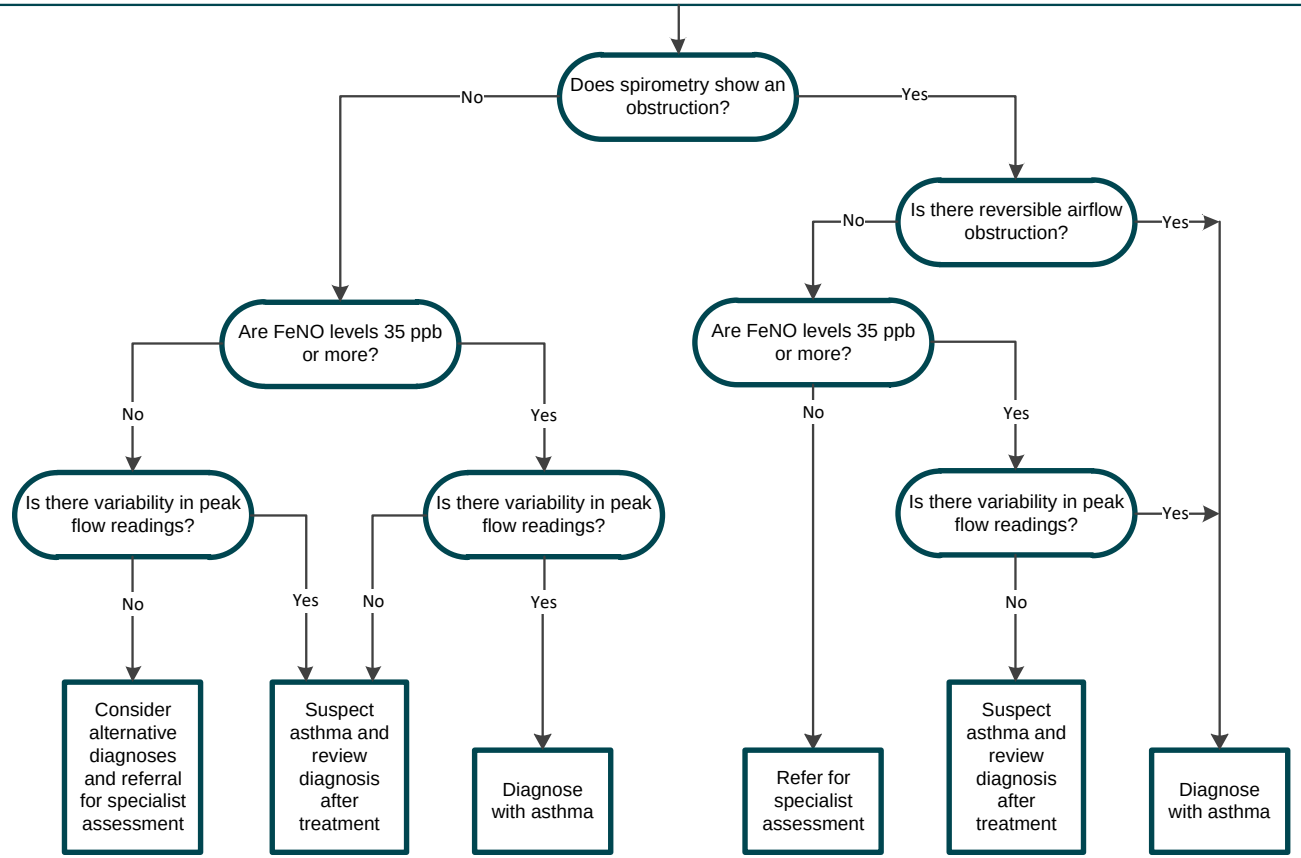
If a child is unable to perform objective tests:
- treat based on observation and clinical judgement **and**
- try doing the tests again every 6 to 12 months

If diagnostic uncertainty remains after spirometry and BDR, consider FeNO

If diagnostic uncertainty remains after FeNO, monitor peak flow variability for 2 to 4 weeks

Abbreviations:
FeNO, fractional exhaled nitric oxide
BDR, bronchodilator reversibility

Interpretation of test results for children and young people aged 5 to 16 with symptoms suggestive of asthma

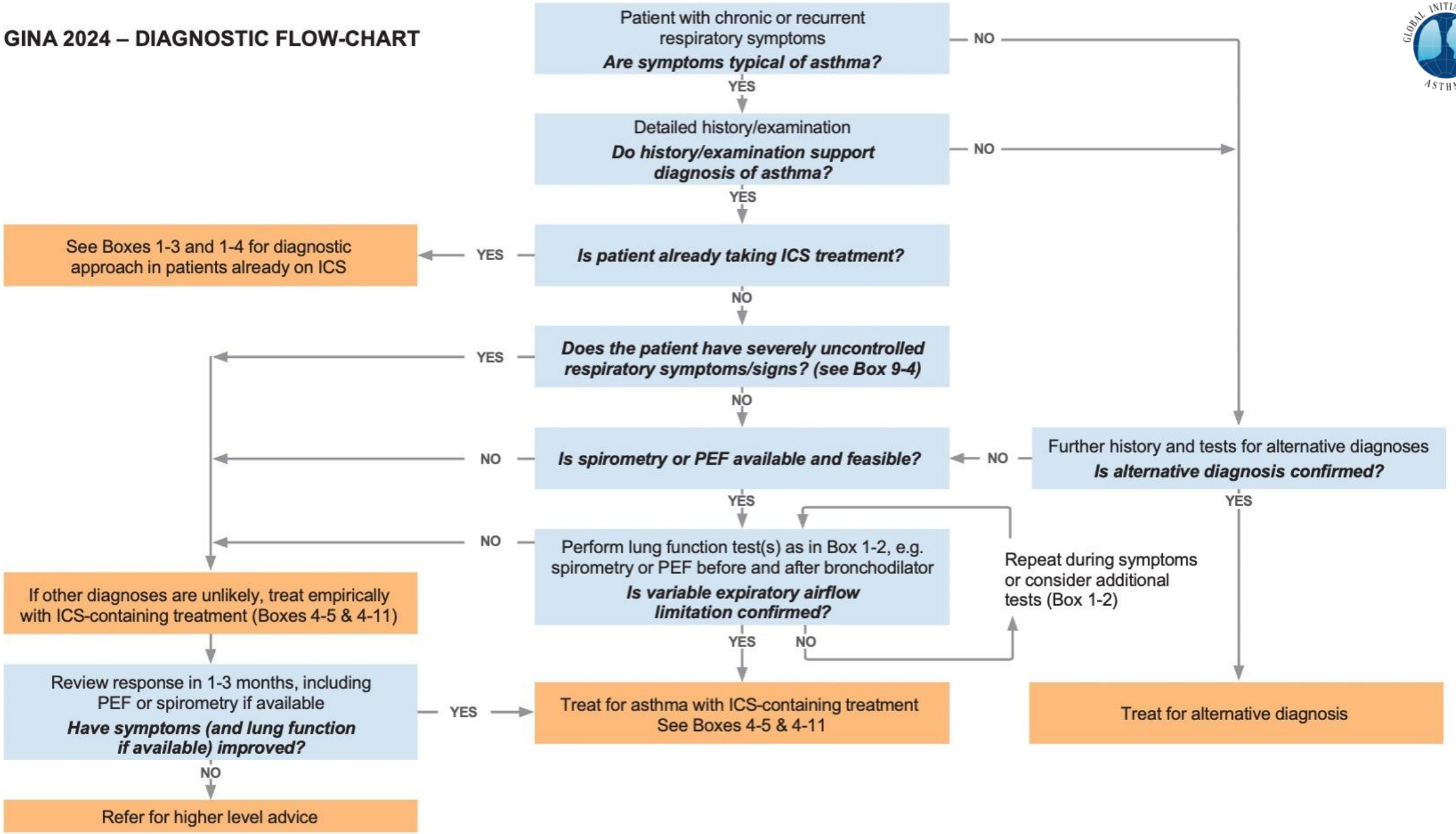


Positive test thresholds
Obstructive spirometry: FEV1/FVC ratio less than 70% (or below the lower limit of normal if available)
FeNO: 35 ppb or more
BDR: improvement in FEV1 of 12% or more
Peak flow variability: variability over 20%

This algorithm is based on recommendations from NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management (2017)

NICE National Institute for Health and Care Excellence

GINA 2024 – DIAGNOSTIC FLOW-CHART



Steps to confirm a suspected diagnosis

- Patient already taking ICS-containing treatment and variable airflow limitation has not been confirmed
  - Review the history – do the symptoms remain typical of asthma?
  - If yes:
    - Consider repeat spirometry (withholding SABA 4 hrs, LABA 24-48 hrs)
    - Assess between-visit FEV_1 variability and bronchodilator responsiveness
    - Consider stepping down ICS-containing treatment and review with repeat spirometry + bronchial responsiveness testing after 2-4 wks
    - Consider referral +/- bronchial provocation tests
  - Are the symptoms suggestive of an alternative diagnosis?
    - Investigate/refer as needed

Accurate and early diagnosis

Key messages

- Ask: is the diagnosis supported by objective assessments?
  - If not, revisit
  - consider effect of treatment on test results
- Asthma is characterized by disease variability
  - repeat testing if clinical suspicion persists (spirometry, BDR, FeNO)
- Interpret test results in clinical context
  - be cautious of binary cut-off values for continuous variables (e.g. FeNO)

Requirements

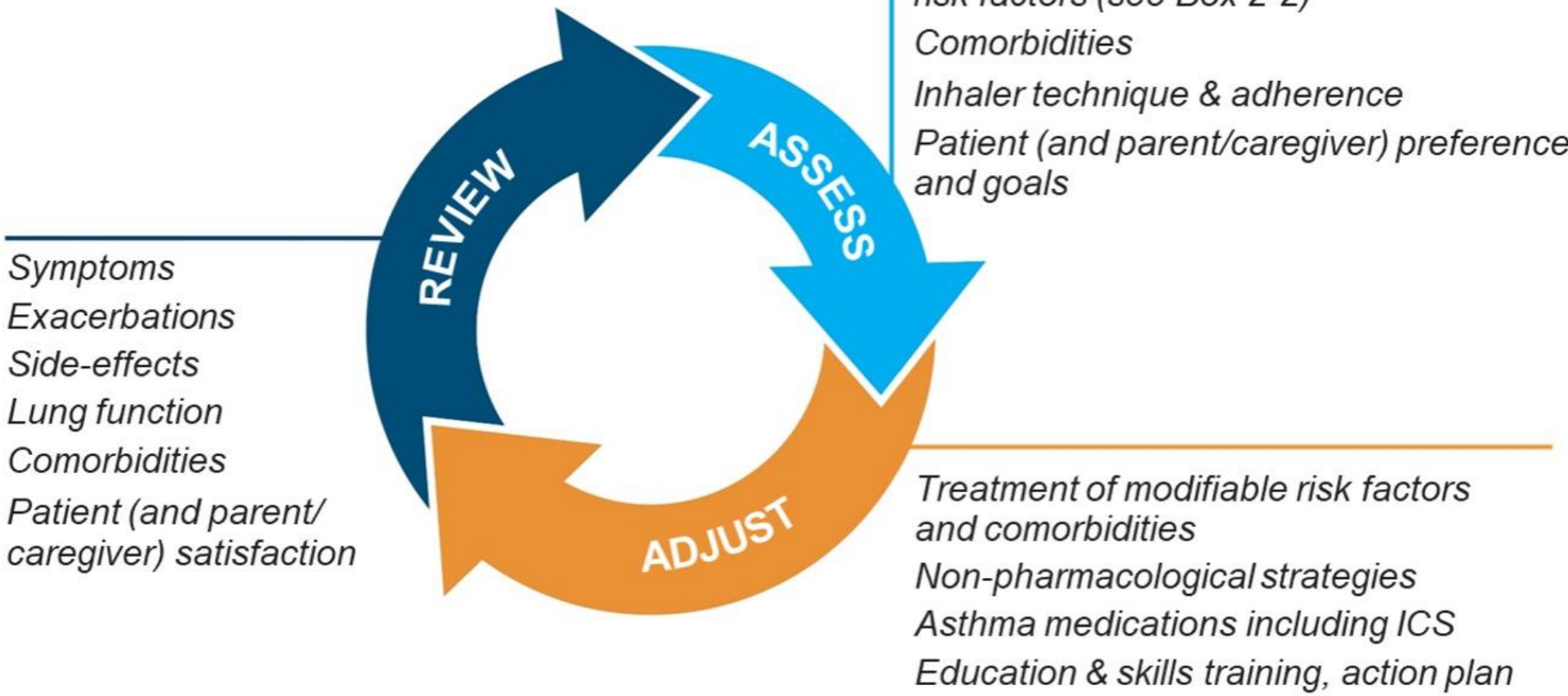
- Clear evidence-based diagnostic pathways
- Access to objective tests
  - Diagnostic hubs
  - Equipment and resources appropriate for CYP
  - Training
  - Clear referral criteria access to secondary + tertiary asthma services

Effective preventative medicine

- Aims of asthma treatment
  - Achieve symptom control
    - No daytime or night-time symptoms
    - No limitation to activity/exercise
    - No requirement for rescue medication
    - Normal lung function
  - Reduce risk of:
    - Asthma attacks
    - Low lung function trajectories
    - Adverse effects from medication

Assessing symptom control alone does not address risk.
People with minimal symptoms can have severe asthma attacks

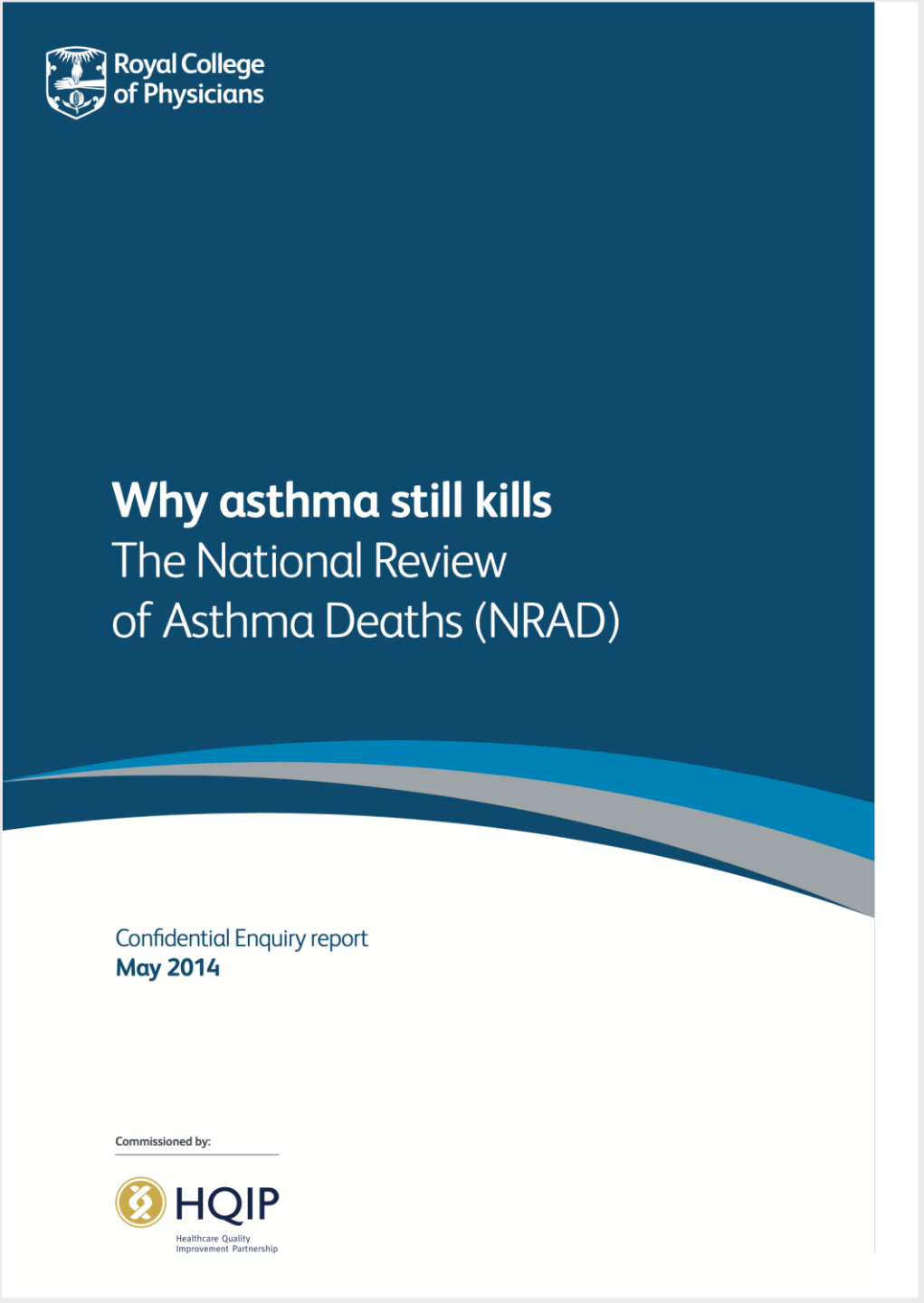
Asthma treatment is not ‘set and forget’, and not just medications



Pharmacological treatment update

- Shift in asthma treatment recommendations since 2019
  - Treatment with short-acting β_2-agonists (SABA) only not recommended
  - Inhaled corticosteroid (ICS)-containing treatment recommended from step 1
    - symptom-driven in mild asthma
    - Daily in moderate-severe asthma

- Based on
  - Safety concerns with SABA-only treatment
  - Strong evidence for ICS reducing exacerbation risk



Asthma deaths in England & Wales Feb 2012-Feb 2013

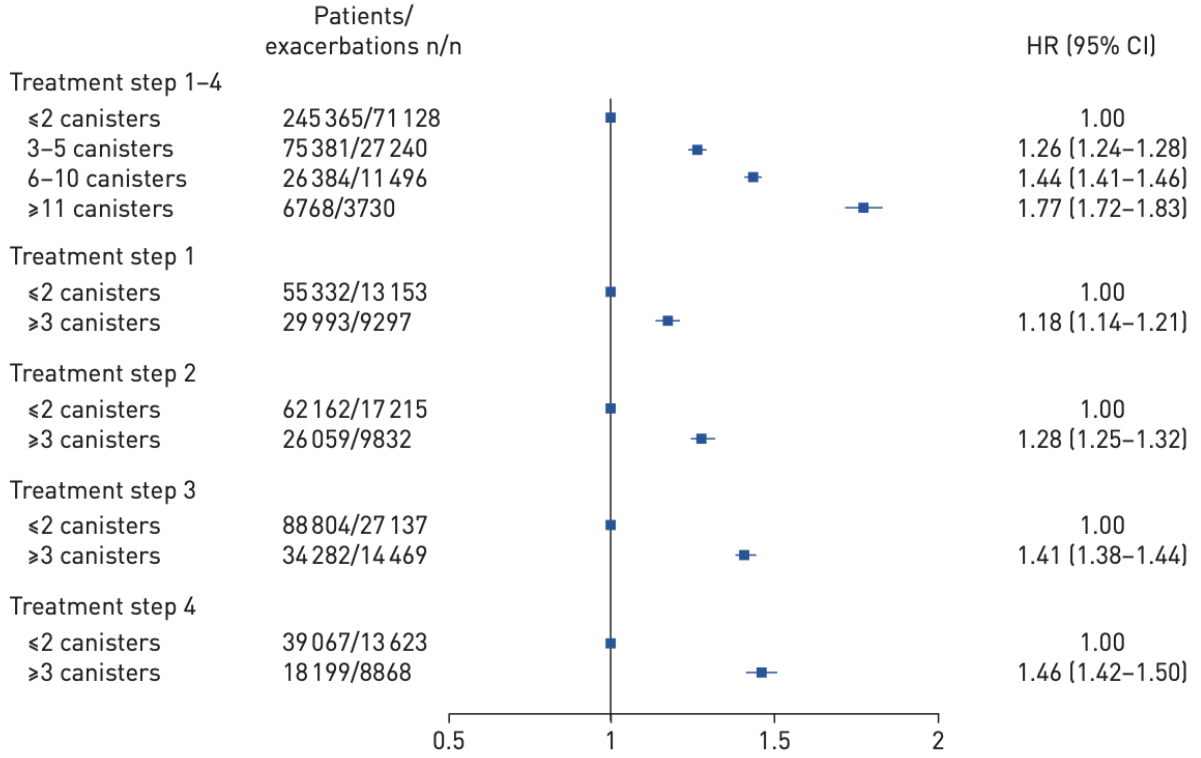
- 195 deaths reviewed
- 28 deaths in people < 19 years

Important features in those who died

- 57% treated for ‘mild’ or ‘moderate’ asthma
- 80% inadequate preventer (ICS) prescribing
- 39% >12 SABA inhalers in preceding year
- 2/3 persisting exacerbating factors/contributors
- 47%: history of previous asthma admission

Safety concerns with SABA overuse

- Excess SABA use associated with higher exacerbation risk
- Toxicity from SABA overuse
  - Increased airway hyperresponsiveness
  - Reduced bronchodilator effect
- Inconsistent messaging that SABA reliance represents appropriate asthma treatment



Nwaru BI, et al. *Eur Respir J* 2020

Evidence for ICS treatment from step 1

- Large RCTs of regular low-dose ICS in adults and children (≥5 yr) with mild asthma
  - Reduction in severe asthma exacerbations by 50%
  - Improvement in daily asthma symptoms and quality of life

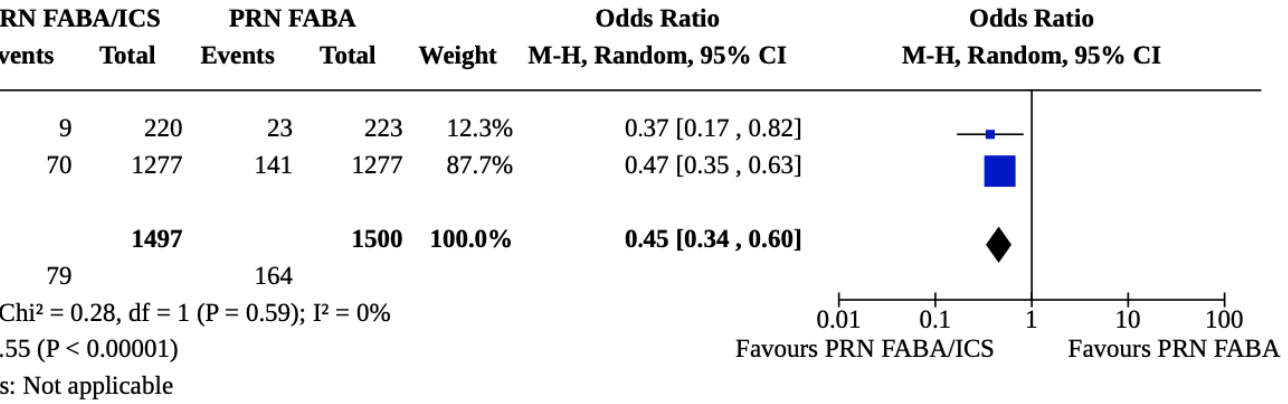
O'Byrne PM, et al. *Am J Respir Crit Care Med* 2001

Pauwels RA, et al. *Lancet* 2003

- Large studies of anti-inflammatory reliever (AIR) therapy, either as needed or as part of maintenance-and-reliever therapy (MART)
  - ICS-formoterol
  - ICS-SABA

AIR as needed (adult and adolescent data)

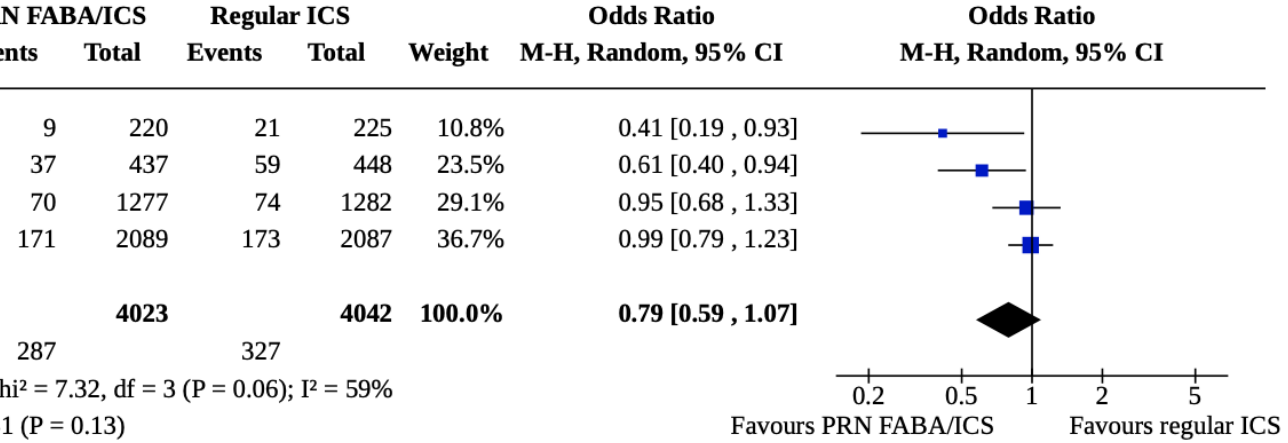
55% reduction in severe exacerbations compared with SABA alone



Study or Subgroup	PRN FABA/ICS Events	Total	PRN FABA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	9	220	23	223	12.3%	0.37 [0.17 , 0.82]
SYGMA 1 (1)	70	1277	141	1277	87.7%	0.47 [0.35 , 0.63]
Total (95% CI)		**1497**		**1500**	**100.0%**	**0.45 [0.34 , 0.60]**
Total events:	79		164			

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)
Test for subgroup differences: Not applicable

No sig difference in severe exacerbation rate compared to daily ICS + as needed SABA



Study or Subgroup	PRN FABA/ICS Events	Total	Regular ICS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	9	220	21	225	10.8%	0.41 [0.19 , 0.93]
PRACTICAL	37	437	59	448	23.5%	0.61 [0.40 , 0.94]
SYGMA 1	70	1277	74	1282	29.1%	0.95 [0.68 , 1.33]
SYGMA 2	171	2089	173	2087	36.7%	0.99 [0.79 , 1.23]
Total (95% CI)		**4023**		**4042**	**100.0%**	**0.79 [0.59 , 1.07]**
Total events:	287		327			

Heterogeneity: Tau² = 0.05; Chi² = 7.32, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

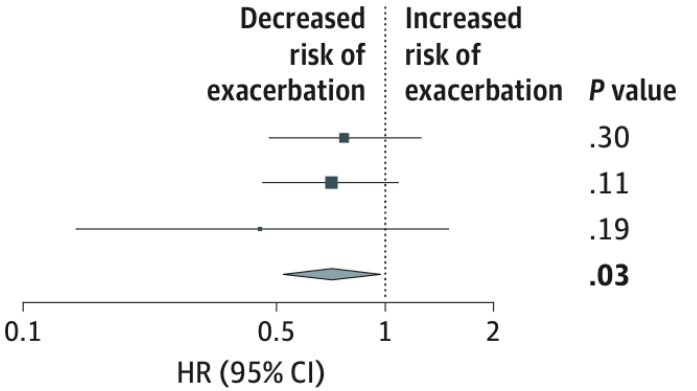
Crossingham I, et al. *Cochrane* 2021

AIR as part of MART (adult/adolescent data)

In patients with poorly controlled asthma, MART compared to GINA step 4 therapy associated with a 29% reduced risk of severe exacerbation

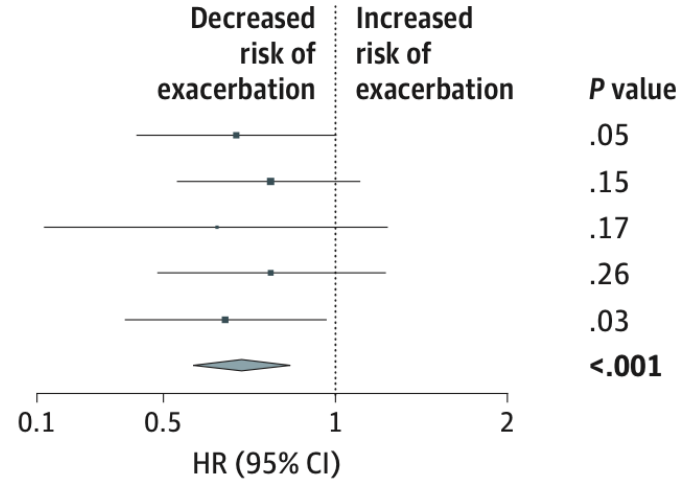
A SMART vs step up to GINA step 4

Trial	No. exacerbation, No./total No. (%) SMART	GINA step 4	HR (95% CI)	*P* value
AHEAD[10]	29/371 (7.8)	38/373 (10.2)	0.77 (0.48-1.25)	.30
COMPASS[8]	29/372 (7.8)	84/774 (10.9)	0.71 (0.46-1.08)	.11
Patel et al,[9]	5/38 (13.2)	6/22 (27.3)	0.45 (0.14-1.49)	.19
Total	**63/781 (8.1)**	**128/1169 (10.9)**	**0.71 (0.52-0.97)**	**.03**



B SMART vs same GINA step 3 or 4

Trial	No. exacerbation, No./total No. (%) SMART	GINA step 3 or 4	HR (95% CI)	*P* value
AHEAD[10]	40/327 (12.2)	61/348 (17.5)	0.67 (0.45-1.00)	.05
COMPASS[8]	41/333 (12.3)	108/681 (15.9)	0.77 (0.53-1.10)	.15
Patel et al,[9]	13/46 (28.3)	21/48 (43.8)	0.62 (0.31-1.23)	.17
SAKURA[12]	35/251 (13.9)	38/215 (17.7)	0.77 (0.49-1.22)	.26
SMILE[11]	42/339 (12.4)	58/325 (17.8)	0.64 (0.43-0.96)	.03
Total	**171/1296 (13.2)**	**286/1617 (17.7)**	**0.70 (0.58-0.85)**	**<.001**

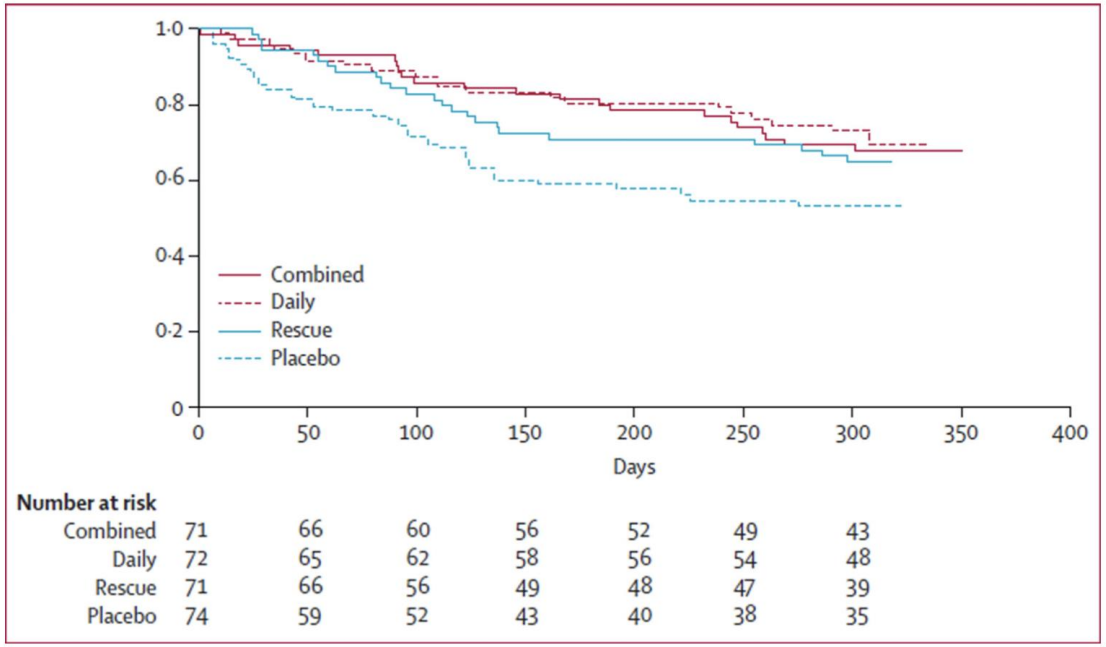


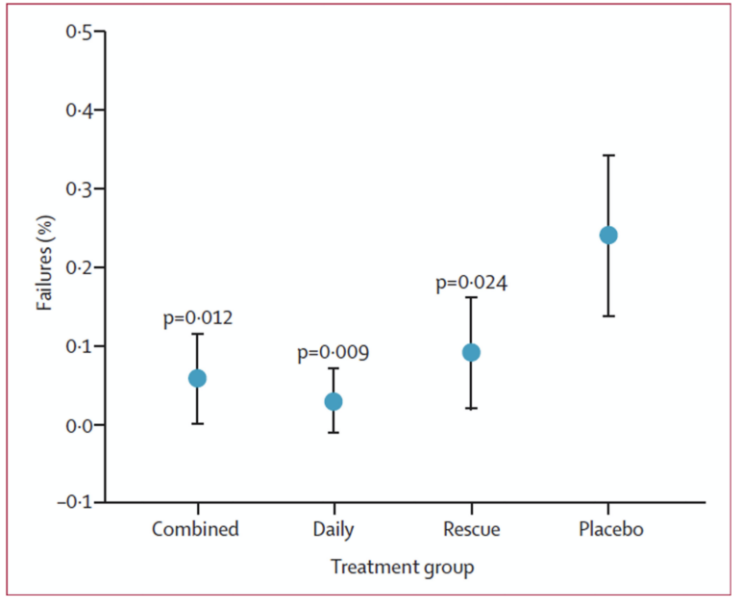
Beasley R, et al. *JAMA Network Open* 2022

AIR as needed (paediatric data)

- RCT in children (5-18 yr) with mild asthma, comparing:
  - ICS maintenance + combined (ICS+SABA) reliever
  - ICS maintenance + SABA-only reliever
  - Placebo maintenance + combined (ICS+SABA) reliever
  - Placebo maintenance + SABA-only reliever

- Exacerbation frequency lower in ICS treatment groups vs. placebo
- Treatment failure lower in all ICS treatment group vs. placebo





Martinez F, et al.
Lancet 2011

AIR as part of MART (paediatric data)

- Limited evidence in children <12 yrs
- RCT in children 4-11 yrs with asthma uncontrolled on ICS, comparing
  - Budesonide/formoterol 80/4.5mcg once daily + as reliever (MART)
  - Budesonide/formoterol 80/4.5mcg once daily + SABA reliever
  - Budesonide 320mcg once daily + SABA reliever

- Exacerbation rate reduced in MART group by 70 to 79% vs fixed-dose budesonide and fixed-dose combination

Bisgaard H, et al. *Chest* 2006

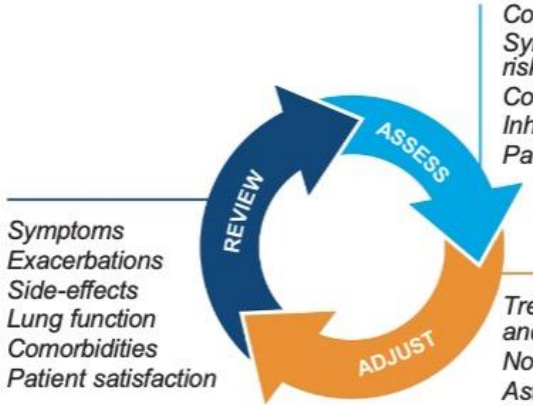
Low, medium and high doses of ICS

Inhaled corticosteroid (alone or in combination with LABA)	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 11-3, p.191			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50–100	>100–200	>200
Budesonide (DPI, or pMDI, standard particle, HFA)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

- This is a table of low, medium and high doses of various ICS
- **It does NOT imply equivalent potency**
- For example, if you switch a patient from a 'medium' dose of one ICS to a 'medium' dose of another ICS, this may represent a *decrease* in potency, so their asthma may worsen, or it might represent an *increase* in potency and the patient may experience more adverse effects
- Always monitor patients after any change in medication, dose or device, to ensure they are stable

GINA 2024 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



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

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative **CONTROLLER and RELIEVER**
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

GINA 2024 – Children 6–11 years

Personalized asthma management:
Assess, Adjust, Review

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

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Child and parent/ caregiver satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications including ICS
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever therapy (MART)	Refer for expert advice, OR medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART)	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)		*Daily leukotriene receptor antagonist (LTRA†), or low dose ICS taken whenever SABA taken**	*Low dose ICS + LTRA†*	*Add tiotropium or add LTRA†*	*As last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)				

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

Which formulations and doses of ICS-formoterol can be used as anti-inflammatory relievers in AIR-only or MART?

- **Budesonide-formoterol**
  - Adults and adolescents: 200/6 mcg metered dose [160/4.5 delivered dose] by DPI or pMDI, 1 inhalation per dose*
  - Children 6–11 years: 100/6 mcg metered dose [80/4.5 delivered dose] by DPI or pMDI, 1 inhalation per dose*
- **Beclometasone-formoterol**
  - Adults: 100/6 mcg metered dose by DPI or pMDI, 1 inhalation per dose; no data in adolescents or children to date
- Use of higher or lower dose formulations than these is **not** recommended*
- The maximum total dose of formoterol **in any one day** (reliever plus maintenance doses, if used) with any formulation is 72 mcg [54 mcg delivered dose] for adults/adolescents, and 48 mcg [36 mcg delivered dose] for children 6–11 years
- ICS-formoterol is the only ICS-LABA that can be used as an anti-inflammatory reliever

*In some countries, a budesonide-formoterol pMDI with 100/3 [80/2.25] mcg per actuation is available for adults and adolescents, and a pMDI with 50/3 mcg [40/2.25] per actuation is available for children. For these pMDIs, the recommended number of inhalations is double that for the formulations above.

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; DPI: dry powder inhaler; MART: maintenance and reliever therapy with ICS-formoterol; pMDI: pressurized metered dose inhaler

MART for children 6–11 years: medications and doses

- MART is an option for this agegroup in Steps 3 and 4
- Recommended doses: budesonide-formoterol 100/6 mcg [80/4.5 mcg delivered dose] DPI or pMDI
  - Step 3: 1 inhalation **once** daily plus 1 inhalation as needed*
  - Step 4: 1 inhalation **twice** daily plus 1 inhalation as needed*
- Evidence for MART to date in children is with budesonide-formoterol 100/6 [80/4.5] DPI
  - In children 4–11 years with a history of at least one exacerbation, MART 100/6 [80/4.5] mcg 1 inhalation once daily plus 1 inhalation as needed reduced severe exacerbations compared with the same dose of budesonide-formoterol or with 4 times the dose of ICS alone, plus SABA reliever *(O'Byrne 2005; Bisgaard 2006)*
- Maximum total dose in any one day (maintenance and reliever doses)
  - 8 inhalations* of budesonide-formoterol 100/6 mcg [80/4.5 mcg delivered dose]
- **Very few patients ever need this much!**
- Several RCTs are underway with AIR-only and MART in children
- Do not use ICS-formoterol as the reliever with other maintenance ICS-LABAs

*In some countries, a budesonide-formoterol pMDI with 50/3 [40/2.25] mcg per actuation is available. For this pMDI, the recommended number of inhalations is double that for the 100/6 [80/4.5] mcg formulation above.

Severe asthma

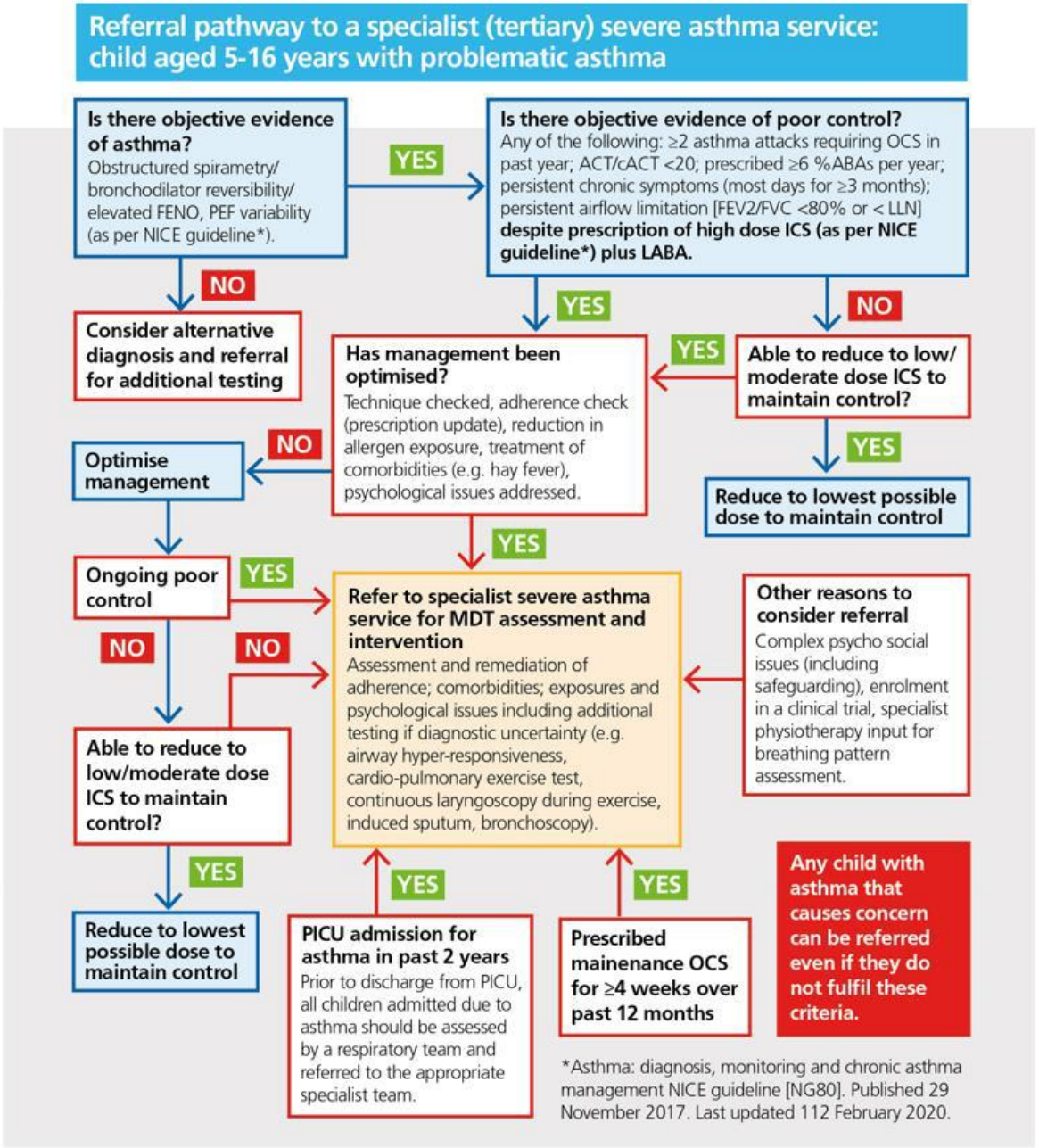
- Poorly controlled symptoms and/or frequent/severe exacerbations despite high dose treatment (GINA step 4)

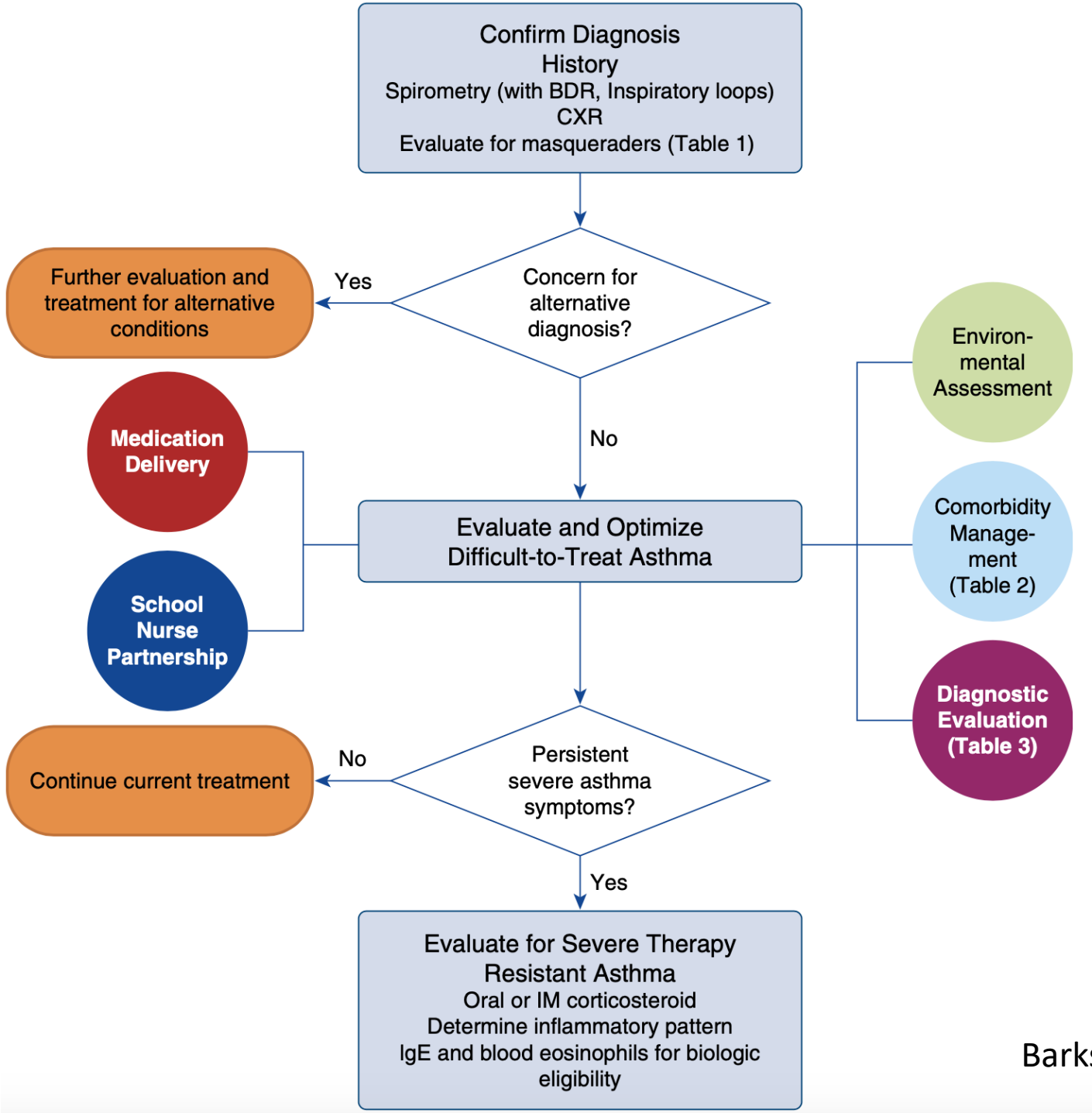
- Prevalence: 2-3% of children with asthma[1,2]
  - High vulnerability
  - High treatment burden and risk of adverse effects
  - High health care utilisation

- Requires comprehensive MDT evaluation

1. Belgrave D. C. M. et al. JACI 2013
2. Nordlund B. et al. Respir Med 2014

Referral criteria





Barksy, E. E. et al. AJRCCM 2018

Biologic therapies for severe therapy-resistant asthma

- Anti IgE
  - Omalizumab
- Drugs targeting IL-5
  - Mepolizumab
  - Reslizumab
  - Benralizumab
- Drugs targeting IL-4 and IL-13
  - Dupilumab
- Drugs targeting thymic stromal lymphopoietin (TSLP)
  - Tezepelumab

Licensed >6 yrs

Licensed >12 yrs

Licensed >12 yrs

Summary

- Accurate and early diagnosis
  - Ensure diagnosis supported by objective tests
  - When in doubt, revisit
  - When difficult to establish, consider referral

- Effective preventative medicine
  - ICS-containing treatment from step 1
  - Strong evidence for AIR and MART in patients >12 yrs
  - Growing evidence for AIR and MART in younger children

- Severe asthma
  - Poor control/severe attacks/high SABA use/low lung function: refer!

Questions