## Asthma Update Somerset

• Steve Holmes

## Asthma is a variable condition

- Beware of single assessments that are normal (or abnormal)
- Clinically shift from active to inactive disease and vice versa
- Use of time is important



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

# The same systematic review for use in guidelines



National Institute for Clinical Excellence. Asthma: diagnosis and monitoring of asthma in adults, children and young people (National Guideline NG80). 2017 (Nov).

British Thoracic Society, Scottish Intercollegiate Guideline Network. British Guidelines for the Management of Asthma, Guideline, 2016 (Sept)

## Tests of reversibility for asthma

Tests	Sensitivity	Specificity
Bronchodilator reversibility (>12% and 200mls) (2ry care studies only)	17-69%	55-81%
Bronchodilator revers (child) >12% (one trial)	50%	86%
Challenge metacholine	51-100%	39-100%
Challenge – exercise	26-80%	100%
Peak flow rate >20%	46%	80%
Peak flow >15%	3-5%	98-99%

British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

# Tests for eosinophilic inflammation / atopy for asthma

	Sensitivity	Specificity			
FeNO (adults)	43-88%	60-92%			
FeNO (schoolchildren) (one trial)	57%	87%			
Blood eosinophils raised (adults)15-36%39-100%					
Blood eosinophils raised (children)	55-62%	67-84%			
British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016					

## Fractional exhaled nitric oxide (FENO)

• "During inflammation, higherthan-normal levels of nitric oxide (NO) are released from epithelial cells of the bronchial wall.<sup>1</sup> The concentration of NO in exhaled breath, or fractional exhaled nitric oxide (FeNO), can help identify airway inflammation, and thereby support a diagnosis of asthma when other objective evidence is lacking.<sup>2</sup>



1- van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med. 2001;164(11):2107-13

2- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15.

## FeNO levels

#### **Higher levels**

#### Lower levels

- Allergic rhinitis when exposed to allergen (with or without symptoms)
- Rhinovirus infection in healthy adults (inconsistent if they have asthma)
- Men, tall people, high dietary nitrates (vegetables)

• Children

- Cigarette smokers
- Inhaled or oral steroid use

British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

# The final word on NICE – about the diagnostic pathway

"We acknowledge that establishing it as routine practice will take time. NICE's advice is to use the current diagnostic approaches from the British Thoracic Society's guidance until the capacity is in place."

Dr Andrew Menzies-Gow, cochair of the NICE guideline committee on asthma



#### Menzies-Gow AN and Alexander J. BMJ 2018; 360: k899.

## Making a diagnosis

Presentation with respiratory symptoms		Wheeze, cough, breathlessness, chest tightness				
	Structured clinical assessment					
•	Recurrent episodes of symptoms Symptom variability Absence of symptoms suggesting alternative diagnosis	•	Recorded observation of wheeze Personal history of atopy Historical record of PEFR / FEV1			

Daines L, Keeley D, Gruffydd-Jones K, Holmes S, Gerrard V, Stonham C. Asthma Guidelines in Practice – A PCRS-UK Consensus 2018.



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016



# Making a diagnosis - in suspected asthma

- 1. Record patient as having "suspected asthma"
- 2. Proceed to careful therapeutic trial based on severity (usually ICS for 6w, sometimes oral steroid)
- 3. Record baseline questionnaire (eg ACT) and lung function (spirometry or PEFR)
- 4. Follow up in 6-8w to assess response using validated questionnaire and measure of lung function (FEV1 or PEFR)

British Thoracic Society, Scottish Intercollegiate Guideline Network. British Guidelines for the Management of Asthma. Guideline. 2016



## It might not be asthma?



## Characterising patients

• Severe asthma treatment: need for characterising patients



Percentage of patients with alternative or co-existent diagnoses

Alternative/co-existent diagnoses

Other:

- Chronic bronchitis
- IgA deficiency
- Cystic fibrosis
- Obliterative
  bronchiolitis
- Cardiomyopathy
- Pulmonary hypertension

Hypereosinophilia

•

- Extrinsic allergic alveolitis
- Respiratory muscle incoordination
- Obstructive sleep apnoea

#### Heaney L and Robinson DS. Lancet 2005; 365(9463): 974–976.



## Treatment of asthma

# Short acting beta agonist use in asthma deaths (NRAD)

Fig 5.1 Frequencies of SABA prescriptions issued for patients in the 12 months before death from asthma (data available for 165 patients)



- Median inhaler use: 10
- 56% more than 6 inhalers
- 39% more than 12 inhalers
- 4% more than 50 inhalers
- 50 inhalers per year is roughly 27 doses per day (every day of the year)

Royal College of Physicians of London, British Thoracic Society and British Lung Foundation. Why asthma still kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry Report. London: Healthcare Quality Improvement Partnership; 2014.

## Lets do the mathematics



- 12 x 200 = 6000 doses
- 6000 divided by 365 = 16.4 doses per day

The NRAD Danger Zone!

#### 1,4,6 or 12 per year

- "Who is right I've heard you respiratory lot say that 1 SABA inhaler is too many, some say 4, others 6 and others 12 per year?
- What should we be doing?



for the Management of Asthma. Guideline. 2016

## % of patients receiving 6 or more SABA (CCG variation versus national)







ePACT2 data NHS England (Provided September 2018)

## % of patients receiving 6 or more SABA (practice versus CCG)

#### Practices within CCG



ePACT2 data NHS England (Provided September 2018)

#### A review of asthma care in 50 general practices in Bedfordshire, United Kingdom



as % of total asthma population (range 1–14%, median 5.2%, (hashed line))

Fig 1.

Levy ML, Garnett F, Kuku A, Pertsovskaya I, McKnight E, Haughney J. A review of asthma care in 50 general practices in Bedfordshire, United Kingdom. NPJ Primary Care Respiratory Medicine. 2018;28:29.

#### Persisting inflammation in asymptomatic atopic asthma patients

• Patients in "remission" had been asymptomatic and not used medications in previous 12 months



- · Ongoing airway inflammation and airway remodeling in adolescents in clinical remission of atopic asthma
- Subclinical airway inflammation may well determine the risk of asthma relapse in later life<sup>1</sup>

van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med. 2001;164(11):2107-13.

#### Use of SABA by elite athletes?



#### 'Chris Froome's drug reading makes his Vuelta a Espana win more remarkable'



1 – Brian Lipworth (Daily Telegraph 13/12/2017) access 11/9/2018

## Salbutamol nebules

 potentially serious hypokalaemia may result from β2-agonist therapy (esp if hypoxic or if acute asthma) – hence monitor serum potassium



Ventolin nebules SPC (Accessed 8/May/2016)

## Salbutamol nebules

- High dose tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia and lactic acidosis
- rare occurrences of myocardial ischaemia associated with salbutamol

- Cardiac disorders
- Common: Tachycardia.
- Uncommon: Palpitations
- Very rare:
- Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles

#### Short acting beta agonist for asthma: regular use leads

to

- Beta 2 receptor tolerance<sup>1</sup>
- Rebound bronchoconstriction<sup>1</sup>
- Increased inflammation<sup>1</sup>
- Increased response to allergens<sup>1</sup>
- No long term data of safety of SABA only treatment<sup>1</sup>
- "Many studies show that regular treatment with b2agonists increases the sensitivity of the airways to bronchoconstrictive stimuli including exercise and allergens"<sup>2</sup>



1 - Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783-800.

2- Anderson SD, Caillaud C, Brannan JD. Beta2-agonists and exercise-induced asthma. Clinical reviews in allergy & immunology. 2006;31(2-3):163-80.

#### **Regular use of SABA = bronchial hyperresponsiveness to:**



• Stressful situations

- Viral infections
- Inhaled fumes / perfumes

• Exercise

Anderson SD, Caillaud C, Brannan JD. Beta2-agonists and exercise-induced asthma. Clinical reviews in allergy & immunology. 2006;31(2-3):163-80.





British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

## Dose response curve for inhaled

### <u>corticos</u>teroids

Dose - response curve for inhaled corticosteroids 9276 may **Clinical Barefit**  Adverse effect 100200400600800 100050 Daily dose of inhaled steroid (FP ug)

Clinical effect

<u>Top</u> of clinical dose response curve:

400 mcg/day FP = 400 mcg/day Qvar = 800 mcg/day Clenil = 800 mcg/day Bud

90% effect achieved at doses:

200 mcg/day FP = 200 mcg/day Qvar = 400 mcg/day Clenil = 400 mcg/day Bud

Masoli M et al. Thorax 2004; 59:16-20 Holt S et al. BMJ 2001: 323:253-256

## Nonadherence in difficult asthma



 182 patients from a regional difficult asthma clinic, across 6 months:

- 35% filled ≤50% of prescriptions
- among these, 88%
  - admitted non-adherence
- among 6 patients denying nonadherence, 3 had undetectable levels of prednisolone/theophyline

Gamble J et al. *Am J Respir Crit Care Med* 2009; 180(9): 817–822



•adjust dose •update self-management plan •move up and down as appropriate



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

## and NICE (2017)

#### Final version

#### Asthma

Asthma: diagnosis and monitoring of asthma in adults, children and young people

NICE guideline NG80 Methods, evidence and recommendations November 2017 • ICS at first regular step

• If not full response trial of montelukast for 1 month

- No response = stop
- Some response = add on

National Institute for Clinical Excellence. Asthma: diagnosis and monitoring of asthma in adults, children and young people (National Guideline NG80). 2017.

Final for publication

Health and Care Excellence

Commissioned by the National Institute for

assessment	•adjust	dose •update self-mar	lager	Additional add-on	2	
				therapies	needed	
		Move	dov	No response to LABA – stop LABA and consider increased dose of ICS	dose therapies	Continuous or frequent use of oral steroids
		Regular preventer	In	If benefit from LABA but control still inadequate – continue LABA and increase ICS to medium dose	sider trials of: asing ICS up to high dose tion of a fourth ug, eg LTRA, eophylline, beta st tablet, LAMA	Use daily steroid tablet in the lowest dose providing adequate control Maintain high-dose ICS Consider other treatments to minimize use of steroid tablets
Consider monitored initiation of treatment with low-dose ICS	l I I Infrequent, short-lived wheeze	Low-dose ICS	/ lo	If benefit from LABA but control still inadquate – continue LABA / ICS and consider trial of other	er patient for ecialist care	Refer patient for specialist care
British Thoracic Society, Scottish Intercolle therapy – LTRA, for the Management theophylline, LAMA					153 Britis	sh Guidelines



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma, Guideline, 2016



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

## Fancy stuff

- Bronchial thermoplasty
- Anti IgE monoclonal antibody (omalizumab)
- Anti-interleukin 5 monoclonal antibody (mepolizumab)
- Methotrexate / ciclosporin / oral gold
   to reduce need for oral steroids
- (Others on the horizon)
- Subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) (not recommended in routine practice)



British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016

## Tricky situations!

## A blast from the past

Doubling inhaled corticosteroid in an acute attack (no evidence – and evidence against) however in adults on very low dose – fourfold increase in dose reduced severity – further trials recently published...

#### Current guidelines

- BTS / SIGN (2016) not advised
- NICE (2017) option to try

British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016 National Institute for Clinical Excellence. Asthma: diagnosis and monitoring of asthma in adults, children and young people (National Guideline NG80). 2017.

### Quadrupling has some benefits (not doubling)

- n=1922 randomised (1871 included) on ICS +/- LABA over 1y
- 420 (45%) had a severe exacerbation in the year in quadrupling group
- 484 (52%) in the nonquadrupling group

McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. New England Journal of Medicine. 2018;378(10):902-10.

## Quintupling in children - method

- 254 children (5-11y) mild to moderate persistent asthma with at least one steroid requiring exacerbation in previous year
- 48 weeks maintenance low dose ICS (400mcg BDP CFC equivalent) (FP 44mug per inhalation 2 puffs twice daily via spacer)
- Increased in early loss of symptoms (not severe) double blind to 220mug per inhalation 2 puffs twice daily) for 7 days
- (Compliance 75% pre trial and 90-95% during the trial)

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. N Engl J Med. 2018;378(10):891-901.

## Quintupling in children - results

- Severe asthma exacerbations treated with systemic glucocorticoids did not differ significantly between groups (0.48 exacerbations per year in the high-dose group and 0.37 exacerbations per year in the lowdose group relative rate, 1.3; 95% confidence interval, 0.8 to 2.1; P=0.30)
- No difference in time to first exacerbation, treatment failure, symptom scores, and SABA.

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. N Engl J Med. 2018;378(10):891-901.

## Quintupling in children - conclusions

In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth.

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. N Engl J Med. 2018;378(10):891-901.

## What might this mean?

- Did the real world adults start high when had not been taking prior to this and had better impact than not taking at all or starting placebo?
- Do children exacerbate more rapidly (and often settle more rapidly) than adults?
- Would they be better using FENO?
- Use with care certainly ensure have PAAP and advise if symptoms not settling

SH thoughts after discussions with colleagues (primary / secondary / authors)

## **Decreasing Treatment**

- Relatively few studies (and mainly on high dose ICS)
- Reduction in ICS should be slow as patients deteriorate at different rates
- Reductions can be considered at
  - 3-6 monthly maximum time intervals
  - 30-50% ICS dose reduction

British Thoracic Society, Scottish Intercollegiate Guideline Network.SIGN 153 British Guidelines for the Management of Asthma. Guideline. 2016