Roadmap

- Few Facts n Figures – Asthma
- Diagnosis – BTS Guidelines
- Treatment – BTS Guidelines
Facts n Figures
Number of people living with asthma in the UK today

Data includes 590,000 teenagers and 700,000 people over 65.

Total 5.2 million

Men 2.3 million
Women 2.9 million

Every 8 hours someone dies from asthma

Asthma deaths occur across disease severity\(^1,2\)

- It is a myth that only severe asthma can prove fatal

- Asthma deaths occur across disease severity with deaths occurring in those patients whose asthma is considered mild-to-moderate

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10-15% population

Asthma care likely to cost average PCT £4.5million per year

Average PCT (330,000 pts) will have

- 45,000 with diagnosed asthma
- >400 emergency admissions/yr

1 in 4 have severe asthma that is under treated
Asthma and the NHS – the financial burden

Treating a patient with uncontrolled asthma costs 3 times more than treating a patient whose asthma is controlled

Patient burden

- Over 50% accept lifestyle limitations due to their asthma
- Over one third experience daily symptoms
- Over 70% experience night-time awakening

What is asthma?

- Asthma is a two-part problem comprising:
  - Airway inflammation and smooth muscle dysfunction

Smooth muscle dysfunction

- Bronchoconstriction
- Bronchial hyper-reactivity
- Hyperplasia
- Inflammatory mediator release

Airway inflammation

- Inflammatory cell infiltration/activation
- Mucosal oedema
- Cellular proliferation
- Epithelial activation
- Airway remodelling

- Daily symptoms (e.g. cough, tightness of chest, breathlessness)
- Reduced lung function
- Night-time awakenings
- Exacerbations
Asthma pathology

- Inflammation of the lungs
- Smooth muscle hyperplasia
- Basement membrane thickening
- Mucous gland hyperplasia
- Mucosal epithelial sloughing
- Tissue oedema

Airway remodelling

- Changes occurring as a consequence of inflammation in the airways have been termed remodelling
- The epithelium, basement membrane and smooth muscle are all affected
- These changes contribute to a loss of lung function
- If inflammation is untreated, this can lead to airway remodelling

Diagnosis – BTS Guidelines
Diagnosis

- The diagnosis of asthma is a clinical one.

- There is no standardised definition, therefore, it is not possible to make clear evidence based recommendations on how to make a diagnosis.

- Central to all definitions is the presence of symptoms and of variable airflow obstruction.
Features that increase the probability of asthma in adults

- >1 of the following: wheeze, breathlessness, chest tightness, cough, particularly if:
  - worse at night and early morning
  - in response to exercise, allergen exposure and cold air
  - after taking aspirin or beta blockers
  - Personal/family history of asthma/atopy

- Widespread wheeze heard on auscultation of the chest

- Unexplained low FEV$_1$ or PEF

- Unexplained peripheral blood eosinophilia
Features that lower the probability of asthma

- Prominent dizziness, light-headedness, peripheral tingling
- Chronic productive cough in the absence of wheeze or breathlessness
- Repeatedly normal physical examination of chest when symptomatic
- Voice disturbance
- Symptoms with colds only
- Significant smoking history (>20 pack-years)
- Cardiac disease
- Normal PEF or spirometry when symptomatic
Reconsider the diagnosis of asthma in those who do not respond

Preferred approach in patients with an intermediate probability of having asthma is to carry out further investigations, including an explicit trial of treatments for a specified period, before confirming a diagnosis and establishing maintenance treatment.
Following clinical assessment in adults

**HIGH PROBABILITY:**
- Diagnosis of asthma likely

**INTERMEDIATE PROBABILITY:**
- Diagnosis uncertain
  - FEV₁ / FVC < 0.7
    - Trial of treatment *
      - Response?
        - Yes: Continue treatment
        - No: Assess compliance and inhaler technique. Consider further investigation and/or referral
  - FEV₁ / FVC > 0.7

**LOW PROBABILITY:**
- Other diagnosis likely
  - Investigate/treat other condition
  - Response?
    - No
      - Further investigation. Consider referral
    - Yes: Continue treatment
CRITERIA FOR SPECIALIST REFERRAL

- Diagnosis unclear
- Unexpected clinical findings (clubbing, crackles etc)
- Unexplained restrictive spirometry
- Suspected occupational asthma
- Persistent non-variable breathlessness
- Monophonic wheeze or stridor
- Prominent systemic features (myalgia, weight loss, fever)
- Chronic sputum production
- CXR shadowing
- Marked blood eosinophilia
- Poor response to asthma treatment
- Severe asthma exacerbation
Monitoring asthma in primary care

- Symptomatic asthma control using RCP ‘3 questions’,
- Asthma Control Questionnaire or Asthma Control Test (ACT™)
- Lung function (spirometry/PEF)
- Exacerbations
- Inhaler technique
- Compliance (prescription refill frequency)
- Bronchodilator reliance (prescription refill frequency)
- Possession of and use of self management plan/personal action plans
RCP 3 QUESTIONS

3 questions to be asked at every consultation:

In the last week/month:

1. Have you had any difficulty sleeping because of your asthma symptoms (including cough)?

2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?

3. Has your asthma interfered with your usual activities (e.g. housework, work/school, etc)?

Royal College of Physicians 1999.
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

- 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

2. During the past 4 weeks, how often have you had shortness of breath?

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

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

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

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

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

5. How would you rate your asthma control during the past 4 weeks?

- Not controlled at all 1
- Poorly controlled 2
- Somewhat controlled 3
- Well controlled 4
- Completely controlled 5

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Asthma Control Test Is a Trademark of QualityMetric Incorporated.
Step 1: Mild intermittent asthma

- Prescribe inhaled short acting $\beta_2$ agonist (SABA) as short term reliever therapy for all patients with symptomatic asthma.

- Good asthma control is associated with little or no need for short-acting $\beta_2$ agonist.

- Using two or more canisters of $\beta_2$ agonists per month or > 10-12 puffs per day is a marker of poorly controlled asthma that puts individuals at risk of fatal or near-fatal asthma.

- Patients with high usage of inhaled short-acting $\beta_2$ agonists should have their asthma management reviewed.
Step 2: Regular preventer therapy

 Inhaled steroids are the recommended preventer drugs for adults in order to achieve overall treatment goals

 Consider inhaled steroids if any of the following:
  • Using inhaled $\beta_2$ agonist three times a week or more
  • Symptomatic three times a week or more
  • Waking one night a week
Step 2: Regular preventer therapy

- Adults:
  - 200-800mcg/day BDP* (reasonable starting dose 400mcg per day for many adults)

*All doses in the guideline refer to beclometasone given via CFC-MDI (metered dose inhaler).
Beclometasone 400mcg = budesonide 400mcg = fluticasone propionate 200mcg
Step 3: Initial add-on therapy

- A proportion of patients may not be adequately controlled at step 2

- Adults and Children 5-12:
  - First choice as add-on therapy is an inhaled long-acting $\beta_2$ agonist (LABA), which should be considered before going above a dose of 400mcg BDP* and certainly before going above 800mcg

*All doses in the guideline refer to beclometasone given via CFC-MDI (metered dose inhaler). Beclometasone 400mcg = budesonide 400mcg = fluticasone propionate 200mcg
Step 3: Initial add-on therapy

Assess control of asthma

- Good response to LABA and good control:
  - Continue LABA

- Benefit from LABA but control still inadequate:
  - Continue LABA and
  - Increase inhaled steroid dose to 800 mcg/day (adults) and 400 mcg/day (children 5-12 years)

- No response to LABA:
  - Stop LABA
  - Increase inhaled steroid dose to 800 mcg/day (adults) and 400 mcg/day (children 5-12 years)

  If control still inadequate go to Step 4

  Control still inadequate:
  - Trial of other add-on therapy eg leukotriene receptor antagonist or theophylline

  If control still inadequate go to Step 4
LABA safety

• Within the guideline it is mentioned that the UK Regulatory agency and guideline development group reviewed the balance of risks and benefits LABAs in the management of asthma and concluded that LABAs can continue to be used in conjunction with inhaled steroids.
Combination inhalers

- There is no difference in efficacy in giving inhaled steroid and LABA in combination or in separate inhalers.

- Combination inhalers have the advantage of guaranteeing that LABAs are not taken without inhaled steroid.

- In adult patients at step 3 who are poorly controlled:
  - the use of budesonide/formoterol in a single inhaler as rescue medication instead of a SABA, in addition to its regular use as a controller treatment, has been shown to be an effective strategy.
  - This management technique has not been investigated with other inhalers.
  - Before instituting this management careful patient education is required.
Step 4: Persistent poor control

- Essentially unchanged
- Green = Adults

Consider trials of:
- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β₂ agonist tablet
Step 5: Continuous or frequent use of oral steroids

- Essentially unchanged
- Green = Adults

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care
Stepping down

- Stepping down therapy once asthma is controlled is recommended
- Regular review of patients as treatment is stepped down is important
- Patients should be maintained at the lowest possible dose of inhaled steroid
- Reductions should be slow, decreasing dose by ~25-30% every three months
Adolescents

- Asthma is common and underdiagnosed
- See them on their own for part of consultation
- Complementary and alternative medicine widespread and marker for non-adherence
Summary

- Asthma still a very important disease
- BTS guidelines - updates
- Questions?
Selected double-blind, randomised controlled trials
At least 6 months treatment duration
Published in peer-reviewed medical journal

ICS or ICS/LABA as regular controller treatment or
Bud/form as maintenance and rescue treatment

Exacerbation data as per ERS/ATS taskforce guidance

Patients were “uncontrolled” prior to randomisation
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Age = 35-46 years; ACQ = 1.8-2.1  * Nights with symptoms
Consider regular, dosing studies as a group and SMART studies a separate group

Both groups fairly comparable in terms of frequency of daily asthma symptoms, rescue use & age of patients

Also, for studies which measured ACQ, the baseline scores were also comparable and ranged from 1.8 to 2.1

Now consider two other baseline characteristics available to us, in general, the patients in the regular, stable dosing studies had a somewhat higher FEV1 % predicted than the Symbicort SMART studies

Based on studies that looked at exacerbation history, regular stable dosing studies had a lower percent of patients with at least one exacerbation requiring systemic steroid treatment, ER treatment and/or hospitalization
## BASELINE CHARACTERISTICS

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Age= 35-46 years; ACQ=1.8-2.1 * Nights with symptoms
However, there are two important points to consider in regard to baseline characteristics.

First, guidelines state that the targets for asthma control are achievable for all patient populations regardless of their asthma severity.

Second, for this exercise, we were comparing outcomes to guideline targets and not comparing outcomes between studies.
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<tr>
<td><strong>AHEAD</strong></td>
<td>70-71%</td>
<td>11</td>
<td>2.2-2.3</td>
<td>9-10</td>
<td>32</td>
<td>100%</td>
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<tr>
<td>Bousquet J</td>
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Age = 35-46 years; ACQ = 1.8-2.1  * Nights with symptoms
SYMPTOM-FREE DAYS ON TREATMENT

GINA Target

Mean % days

STAY  SMILE  COMPASS FBC  COMPASS SFC  AHEAD SFC  STAY  STEP  SMILE  STEAM  COMPASS  AHEAD

Fixed dosing

Bud/form rescue & maintenance

GINA objective: daily symptoms < twice a week
SYMPTOM-FREE DAYS ON TREATMENT

GINA objective: daily symptoms < twice a week

Regular controller treatment

Mean % days

GINA Target

GOAL week 1-52
GOAL Ph 2
CONCEPT
EXCEL FBC
EXCEL SFC
Jarjour NN
Busse WW

Bud/form
SFC
**GINA objective:** rescue < twice a week
Daily Rescue Use on Treatment

- **Mean usage per day**
  - **GINA Target**
  - **GINA objective: rescue < twice a week**

- **GOAL week 1-52**
  - **CONCEPT**
  - **EXCEL FBC**
  - **EXCEL SFC**
  - **Jarjour NN**
  - **Busse WW**

Bar chart showing mean usage per day comparing Bud/form (red) and SFC (purple) for different groups with GINA target highlighted.
EXACERBATIONS REQUIRING ER TREATMENT OR HOSPITALISATION

% pts with one or more exacerbation(s)

- Bud/form
- SFC

STAY
- COMPASS - FBC
- SMILE
- AHEAD - SFC

AHEAD – SFC
- Bud/form rescue & maintenance

Fixed dosing
EXACERBATIONS REQUIRING ER TREATMENT OR HOSPITALISATION

Regular controller treatment

% pts with one or more exacerbation(s)

- Bud/form
- SFC

GOAL Wks 1-52
GOAL Phase 2
CONCEPT
EXCEL - SFC
EXCEL - FBC
Jarjour NN
Busse WW

0%
1%
2%
3%
4%
5%
6%
7%
8%
9%
10%
One could suppose...

Under-treatment of underlying inflammation means that when an exacerbation occurs it is more likely to be severe and require hospitalisation.

Primary end point: Time to first severe exacerbation.
TREATMENT STRATEGIES FOR ASTHMA: CONCLUSION

Bud/form as rescue and maintenance treatment is a possible option but there is a lack of data that it meets the GINA criteria of asthma control.

Regular controller treatment can achieve and maintain GINA guideline-defined control including prevention of exacerbations.
The use of a combination inhaler containing budesonide and formoterol as both maintenance and quick relief therapy (SMART) has been recommended as an improved method of using inhaled corticosteroid/long-acting β agonist (ICS/LABA) therapy.

Published double-blind trials show that budesonide/formoterol therapy delivered in SMART fashion achieves better asthma outcomes than budesonide monotherapy or lower doses of budesonide/formoterol therapy delivered in constant dosage.
Attempts to compare budesonide/formoterol SMART therapy with regular combination ICS/LABA dosing using other compounds have been confounded by a lack of blinding and unspecified dose adjustment strategies.

The asthma control outcomes in SMART-treated patients are poor;

it has been reported that only 17.1% of SMART-treated patients are controlled.
In seven trials of 6–12 months duration, patients using SMART have

1. Used quick reliever daily (weighted average 0.92 inhalations/day)
2. Awakened with asthma symptoms once every 7–10 days (weighted average 11.5% of nights),
3. Suffered asthma symptoms more than half of days (weighted average 54.0% of days)
4. Had a severe exacerbation rate of one in five patients per year (weighted average 0.22 severe exacerbations/patient/year)

These poor outcomes may reflect the recruitment of a skewed patient population
Although improvement from baseline has been attributed to these patients receiving additional ICS therapy at pivotal times, electronic monitoring has not been used to test this hypothesis nor the equally plausible hypothesis that patients who are non-compliant with maintenance medication have used budesonide/formoterol as needed for self-treatment of exacerbations.

Although the long-term consequences of SMART therapy have not been studied, its use over 1 year has been associated with significant increases in sputum and biopsy eosinophilia.
At present, there is no evidence that better asthma treatment outcomes can be obtained by moment-to-moment symptom-driven use of ICS/LABA therapy than conventional physician-monitored and adjusted ICS/LABA therapy.
Summary

- Asthma still very important disease
- BTS guidelines Work in real life (GOAL Study)!
- Step 3: a few observations
- High quality care is cost-effective care
- 21 Century - guidelines/meritocracy we should about achieving the gold standard :
  - Clinical & Cost Effectiveness
  - Questions?