Shaping a Dynamic Future in Respiratory Practice

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Treatment Options for Severe Asthma: Past, Present and Future

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Overview

• Definition
• Prevalence
• Problems
  - Comorbidities
  - Concordance (adherence)
• Biology
• Current licensed treatment options
• Future treatments
Exacerbation, control and severity

ATS/ERS Task Force definition

Asthma exacerbation
monitor events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalisation or death from asthma

Asthma control
monitor extent to which the various manifestations of asthma have been reduced or removed by treatment

Asthma severity
monitor defined as the difficulty in controlling asthma with treatment

ERS/ATS definition of severe asthma

‘Asthma which requires treatment with guidelines suggested medications* for GINA steps 4–5 asthma for the previous year or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming “uncontrolled” ** or which remains “uncontrolled” despite this therapy’

*high-dose ICS and LABA or leukotriene modifier/theophylline

** Uncontrolled asthma if at least one of the following features is present:
   - Airflow limitation
   - Frequent severe exacerbations
   - Serious exacerbations
   - Poor symptom control

Note: among patients aged 6 years and older

ERS/ATS definition of high-dose ICS therapy

<table>
<thead>
<tr>
<th></th>
<th>6–12 years of age</th>
<th>&gt;12 years of age</th>
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<tbody>
<tr>
<td>Beclomethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dipropionate</td>
<td>≥800 μg*¹</td>
<td>≥2000 μg*¹</td>
</tr>
<tr>
<td></td>
<td>≥320 μg*²</td>
<td>≥1000 μg*²</td>
</tr>
<tr>
<td>Budesonide</td>
<td>≥800 μg</td>
<td>≥1600 μg</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>≥160 μg*³</td>
<td>≥320 μg</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>≥500 μg</td>
<td>≥1000 μg</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>≥500 μg*³</td>
<td>≥800 μg</td>
</tr>
</tbody>
</table>

Doses are total daily doses of inhaled corticosteroids (ICS)

*1 Beclomethasone dose for dry powder inhalers
*2 Beclomethasone for hydrofluoroalkane metered-dose inhalers
*3 Not approved for children under 12 years in Germany

Refractory/severe asthma
  • Poorly controlled asthma due to therapy resistance
    Steroid resistance/steroid absorption/compliance

Difficult asthma
  • Poorly controlled asthma associated due to other factors
    (Poor compliance/VCD/DSB/trigger exposure)
Severe asthma

• True prevalence unknown; estimated to affect ~3–10% of people with asthma\(^1\)

• Heterogeneous disease with multiple phenotypes\(^1\)

• Associated with high-risk from both the disease and adverse effects of therapy\(^1\)

• Distinguishing severe refractory asthma from difficult-to-control asthma is important:\(^2,3\)
  - Severe asthma is associated with high morbidity, significant mortality, and high costs
  - Identifies the patients who may benefit from novel treatment

• Biological therapies targeting specific phenotypes are increasingly showing efficacy\(^1\)

Burden of severe asthma – U-BIOPRED study

- Patients with severe asthma
  - Non-smokers, n=311; smokers/ex-smokers, n=110
- Compared to:
  - Mild/moderate asthma n=88
- More symptoms and exacerbations
  - (2.5 vs 0.4 in the prior 12 months; p<0.001)
    - Worse quality-of-life
    - Higher levels of anxiety and depression
    - Higher incidence of nasal polyps
    - Higher incidence of gastro-oesophageal reflux
    - Lower lung function
    - Higher sputum eosinophil count despite treatment with higher doses of ICS/PO corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Severe nonsmoking asthma</th>
<th>Smokers and ex-smokers with severe asthma</th>
<th>Mild/moderate nonsmoking asthma</th>
<th>Healthy nonsmoking controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>311</td>
<td>110</td>
<td>88</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>51.01±0.8 (n=311)</td>
<td>54.51±1.08 (n=110)</td>
<td>41.66±1.65 (n=88)</td>
<td>38.85±1.34 (n=101)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diagnosis years</td>
<td>20 (7–38) (n=302)</td>
<td>38 (20–48) (n=109)</td>
<td>14 (6–32) (n=83)</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td>Females</td>
<td>205/311 (66%)</td>
<td>56/110 (51%)</td>
<td>44/88 (50%)</td>
<td>39/101 (39%)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI kg·m⁻²</td>
<td>29.11±0.36 (n=311)</td>
<td>29.59±0.6 (n=110)</td>
<td>25.73±0.47 (n=88)</td>
<td>25.31±0.36 (n=101)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI &gt;30 kg·m⁻²</td>
<td>120/311 (38.6%)</td>
<td>44/110 (40%)</td>
<td>16/88 (18.18%)</td>
<td>12/101 (11.88%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum IgE IU·mL⁻¹</td>
<td>119.5 (45–342) (n=302)</td>
<td>126 (63–328) (n=104)</td>
<td>89.4 (49–244) (n=85)</td>
<td>23.45 (9–65) (n=98)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁ % pred</td>
<td>67.5±1.26 (n=308)</td>
<td>67.2±1.84 (n=110)</td>
<td>89.5±1.86 (n=87)</td>
<td>101.7±1.29 (n=101)</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>87.2±1.12 (n=308)</td>
<td>89.7±1.74 (n=110)</td>
<td>104.5±2.02 (n=87)</td>
<td>107.8±1.3 (n=101)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>0.64±0.01 (n=308)</td>
<td>0.61±0.01 (n=110)</td>
<td>0.72±0.01 (n=87)</td>
<td>0.79±0.01 (n=101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Exacerbations in previous year</td>
<td>2 (1–4) (n=47)</td>
<td>17.38 (10–26) (n=110)</td>
<td>4 (1–4) (n=13)</td>
<td>0.9 (0–3) (n=20)</td>
<td>&lt;0.001</td>
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<tr>
<td>pack-years</td>
<td></td>
<td></td>
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<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Intubation (ever)</td>
<td>35/307 (11%)</td>
<td>6/109 (6%)</td>
<td>0/87 (0%)</td>
<td>NA</td>
<td>0.083</td>
</tr>
<tr>
<td>ICU admission (ever)</td>
<td>80/307 (26%)</td>
<td>18/109 (17%)</td>
<td>1/86 (1%)</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td>Atopy test positive</td>
<td>213/272 (78.3%)</td>
<td>62/87 (71.3%)</td>
<td>72/78 (92.3%)</td>
<td>36/78 (46.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Factors to consider prior to a diagnosis of severe asthma

• Is asthma the true diagnosis?
  - Exclude differential diagnoses including COPD, vocal cord dysfunction, bronchiolitis (in children)

• Identification and avoidance/management of exacerbating factors and comorbidities
  - Full assessment for exacerbating factors including allergens, passive/active smoking, polyps

• Assessment of adherence and inhaler technique
  - Poor adherence and suboptimal inhaler technique are common in practice
Risks of under treatment

No. of canisters of inhaled corticosteroids per year

Rate ratio for death from asthma

Suissa S et al. NEJM 2000;343:332-6

Asthma deaths/10,000 patient-years

Canisters of SABA per month

Suissa S et al. AJRCCM 1994:149:604-10
Exacerbating (trigger) factors

- Smoking
- Medication – beta blockers, aspirin, NSAIDS
- Allergy, atopy (pets)
- Gastro-oesophageal reflux
- Rhinitis
- Dysfunctional breathing/vocal cord dysfunction
- Occupation
- Lower respiratory tract infection (LRTI)
- Bronchiectasis
- Poor treatment concordance
- Weather
- Exercise
- Menstrual cycle
- Pregnancy
Oral steroid compliance

• Difficult to distinguish malabsorption from non-compliance
  - Steroid absorption assay
    ▪ Cortisol
    ▪ Prednisolone level

• Avoid enteric coated oral steroids

• Can consider IM triamcinolone if still unsure
BTS 2016 Treatment

**Asthma - suspected**
- Diagnosis and Assessment

**Evaluation:**
- Assess symptoms, measure lung function, check inhaler technique and adherence
- Adjust dose, update self-management plan, move up and down as appropriate

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**Adult asthma - diagnosed**

<table>
<thead>
<tr>
<th>Continuous or frequent use of oral steroids</th>
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<tbody>
<tr>
<td>Use daily steroid tablet in the lowest dose providing adequate control</td>
</tr>
<tr>
<td>Maintain high dose ICS</td>
</tr>
<tr>
<td>Consider other treatments to minimize use of steroid tablets</td>
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<tr>
<th>High dose therapies</th>
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</thead>
<tbody>
<tr>
<td>Consider trials of:</td>
</tr>
<tr>
<td>Increasing ICS up to high dose</td>
</tr>
<tr>
<td>Addition of a fourth drug, e.g. LTRA, SR theophylline, beta agonist tablet, LAMA</td>
</tr>
<tr>
<td>Refer patient for specialist care</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Additional add-on therapies</th>
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<tbody>
<tr>
<td>No response to LABA – stop LABA and consider increased dose of ICS</td>
</tr>
<tr>
<td>If benefit from LABA but control still inadequate – continue LABA and increase ICS to medium dose</td>
</tr>
<tr>
<td>If benefit from LABA but control still inadequate – continue LABA and ICS and consider trial of other therapy – LTRA, SR theophylline, LAMA</td>
</tr>
<tr>
<td>Refer patient for specialist care</td>
</tr>
</tbody>
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<th>Initial add-on therapy</th>
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<tr>
<td>Add inhaled LABA to low-dose ICS (normally as a combination inhaler)</td>
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<th>Regular preventer</th>
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<tr>
<td>Low dose ICS</td>
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**Infrequent, short-lived wheeze**
- Consider monitored initiation of treatment with low dose ICS.

**Short acting β₂ agonists as required – consider moving up if using three doses a week or more**
Consider trials of:

• Increasing ICS up to 2000 mcg/day

• Addition of a fourth drug
  - leukotriene modifier
  - theophylline
  - β agonist tablet
  - tiotropium bromide monohydrate

Evidence for combining treatments limited

Omalizumab if indicated
Severe asthma pathophysiology

- Normal airway
- Asthmatic airway
- Asthmatic airway during attack

- Relaxed smooth muscles
- Wall inflamed and thickened
- Tightened smooth muscles
- Air trapped in alveoli
Target driven treatment
Anti-IgE; omalizumab

• Recombinant DNA-derived humanised IgG monoclonal antibody –
  - binds to free IgE in the blood

• Observed benefits and response rates approximately 70%¹
  - Reduced numbers of exacerbations
  - Improved lung function
  - Reduced days of hospitalisation
  - Increased quality-of-life measurements

Omalizumab licensed indications

- Severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:
  - who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)
  - a positive skin test or in vitro reactivity to a *perennial* aeroallergen
  - reduced lung function (FEV1 less than 80% in adults and adolescents)
  - frequent day-time symptoms or night-time awakenings
  - multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled β₂ agonist
Mepolizumab

Trialled in severe refractory eosinophilic asthma

- Significantly reduced exacerbation rates
- Improved quality-of-life in patients
- Associated with a reduction in sputum and blood eosinophils

Less effect on improving symptoms FEV1 or airway hyperresponsiveness
Anti-IL5

Mepolizumab

• Severe refractory eosinophilic asthma in adults
• The blood eosinophil count is 300 cells/microlitre or more in the previous 12 months
• The person has agreed to and followed the optimised standard treatment plan
  - with four or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
  - continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months
Reslizumab

• Anti-IL5 monoclonal antibody
• Similar effect on exacerbations (halving)
  - Positive effect on FEV1 and AQLQ
• IV infusion
• Currently approved in the USA for patients aged >18 years as add-on maintenance treatment for severe asthma with an eosinophilic phenotype
• NICE decision due June/July
Antifungals; Itraconazole

• Allergic bronchopulmonary aspergillosis (ABPA)
  - Elevated total IgE>1000
  - SPT positive (IgE)
  - Aspergillus precipitin (IgG)

• Two placebo-controlled trials have supported the use of itraconazole in patients with (mild) ABPA
  - Steroid sparing effect

Azithromycin

- Macrolide antibiotic
  - Anti-inflammatory
  - Modulates tight junctions – may protect bronchial epithelium

- Widely used in CF (with pseudomonas)
- Evidence for use in COPD and non-CF bronchiectasis

- Normal dose 250 mg three times/week

- Problems – prolonged QT, deafness, resistance
Azithromycin – not licensed

- Evidence in Asthma
  - 12 studies included
  - Effect on FEV1 (eight trials, 381 subjects) not significant
  - Significant increase in PEF (four trials, 419 subjects)
  - Macrolides may therefore be beneficial as adjunct asthma therapy

Bronchial thermoplasty
Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma
A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial Am J Respir Crit Care Med Vol 181. pp 116–124, 2010
Compliance with inhalers can save your life

SAVED BY MY INHALER AS THE BULLETS FLEW

Man’s lucky escape in shooting outside pub

By Rebecca Sherdley

AN asthma inhaler saved a man from injury during a “gang warfare” shooting in a pub car park, a jury heard.

Daniel McKenzie told Nottingham Crown Court that he was in the vehicle when a gunman opened fire.

His cousin Malakai McKenzie was sitting on the back seat next to him and was killed in the crossfire, as a bullet fractured his skull.

But Mr McKenzie told the court he was uninjured because a shot bounced off the inhaler that was in his jacket pocket.

He was giving evidence yesterday during the trial of Shakir Robinson, 27, of Shortwood Close, Nottingham, who denies murdering 19-year-old Malakai and trying to kill Mr McKenzie and two other car occupants. The prosecution claims that Robinson was part of a “hit squad” that had gone to the Hub pub, in Hucknall Road, Sherwood, on April 21 2012, on a mission to shoot Malakai dead.

The gunman, Cameron Cashin, has already been convicted of Malakai’s murder following a trial last year.

Timothy Spencer QC, prosecuting, told the jury at a continuing trial that Robinson was part of a “squad” and was guilty by “joint enterprise”.

He asked them to question whether Robinson knew that Cashin had a gun.

He said: “He (Robinson) was one of a team of four. They were on a mission; they had a purpose.”

Full report: Pages 4 and 5