Case-Based Interactive ARS on Difficult to Control Asthma

Focus on Confounders & Adherence

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Khon Kaen University, Khon Kaen, Thailand
Disclosure

• Lecture honorarium: Astra Zeneca, Boehringer Ingelheim

• Advisory Board Member: Astra Zeneca, Boehringer Ingelheim, GSK
Case 1

- A 15-year-old female referred from GP for uncontrolled asthma
- She was diagnosed asthma for 2 years
- She had several emergency visits despite being treated with salmeterol/fluticasone evohaler (25/125) 2 puff bid, theophylline (200) bid and salbutamol 2 puff prn
Physical Examination

- **HEENT:** swelling of turbinate, mucopurulent nasal discharge
- **Chest:** rhonchi both lung
Diagnosis

- Difficult asthma
Difficult asthma (severe/refractory asthma)

- Failure to achieve control when the maximal recommended dose are prescribed

Which is the least likely cause of difficult asthma?

A. Wrong diagnosis
B. Poor compliance
C. Unidentified aggravating factors
D. Psychosocial factors
E. Severe asthma
Which is the least likely cause of difficult asthma?

A. Wrong diagnosis
B. Poor compliance
C. Unidentified aggravating factors
D. Psychosocial factors
E. Severe asthma
Difficult asthma

- Wrong diagnosis
- Poor compliance
- Unidentified aggravating factors
- Psychosocial factors
- Severe asthma

- COPD
- CHF
- Upper airway obstruction
- Localized airway obstruction
- Vocal cord dysfunction

- Unidentified allergen
- Occupational exposure
- Upper airway disease
- Gastro-esophageal reflux
- Systemic disease
- Drugs

15F – left inferior turbinate hypertrophy with nasal septum deviation to the right
15F – Right frontal sinusitis
15F – Random distribution of centrilobular nodular infiltration at RLL
Sinobronchial syndrome

- NSS nasal irrigation
- Pseudo epredine 1x3
- AMK 1X2
- Erythomycin (250) 1x4
- Avamys 2puff OD.
- Salmeterol/fluticasone (50/250) 1x2

Case 2

- A 65 year old man was diagnosed asthma for one year.
- He was treated with salmeterol/fluticasone acuhaler (50/250) bid, salbutamol 2 puff prn and for 3 months but he still have asthma symptoms.
- He never smoke
- CXR= normal

- PE: HEENT normal, Chest Clear
## Spirometry

<table>
<thead>
<tr>
<th></th>
<th>predicted</th>
<th>PRE-RX</th>
<th>%pred</th>
<th>POST-RX</th>
<th>%pred</th>
<th>%CHG</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>4.12</td>
<td>3.25</td>
<td>79</td>
<td>3.50</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>FEV1(L)</td>
<td>3.13</td>
<td>2.15</td>
<td>60</td>
<td>2.60</td>
<td>83</td>
<td>20</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>68</td>
<td></td>
<td></td>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis

- Difficult asthma
What should we do next?

A. Change salmeterol/fluticasone 50/250 to salmeterol/fluticasone 50/500 bid
B. Add montelucast
C. Add triotropium respimat
D. Check inhaler technic
What should we do next?

A. Change salmeterol/fluticasone 50/250 to salmeterol/fluticasone 50/500 bid
B. Add montelucast
C. Add triotropium respimat
D. Check inhaler technic
### Stepwise management - pharmacotherapy

**Step 1**
- Low dose ICS
- Consider low dose ICS

**Step 2**
- Low dose ICS/LABA**
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline*

**Step 3**
- Med/high dose ICS/LABA
- Add tiotropium*
- Add med/high dose ICS + LTRA
- Add low dose OCS

**Step 4**
- Refer for add-on treatment e.g. tiotropium**, anti-IgE, anti-IL5**

**Step 5**
- High dose ICS + LTRA
- Add low dose OCS

*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

*For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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**Other controller options**

**RELIEVER**

- As-needed short-acting beta2-agonist (SABA)
- As-needed SABA or low dose ICS/formoterol#
**Provide hands-on inhaler skills training**

<table>
<thead>
<tr>
<th>Choose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills and cost. For ICS by pMDI, prescribe a spacer</td>
</tr>
<tr>
<td>• Avoid multiple different inhaler types if possible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Check technique at every opportunity – “Can you show me how you use your inhaler at present?”</td>
</tr>
<tr>
<td>• Identify errors with a device-specific checklist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give a physical demonstration to show how to use the inhaler correctly</td>
</tr>
<tr>
<td>• Check again (up to 2-3 times)</td>
</tr>
<tr>
<td>• Re-check inhaler technique frequently, as errors often recur within 4-6 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirm</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can you demonstrate correct technique for the inhalers you prescribe?</td>
</tr>
<tr>
<td>• Brief inhaler technique training improves asthma control</td>
</tr>
</tbody>
</table>
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Case-Based Interactive ARS on Difficult to Control Asthma

Focus on Comorbidities and Triggers

Sandy Khurana, MD, FCCP
Director, Mary Parkes Asthma Center
University of Rochester, NY
Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices
Objectives

- Review systematic and multi-disciplinary approach to management of ‘difficult to treat’ asthma
- Discuss common challenges when caring for such patients with focus on role of environmental triggers and contribution from comorbidities.
Case 1

A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

Based on this information, all that can be said is that this patient has:
A. Uncontrolled Asthma
B. Difficult Asthma
C. Severe Refractory Asthma
D. Do not have enough information to answer
Case 1

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Based on this information, all that can be said is that this patient has:

A. Uncontrolled Asthma
B. Difficult Asthma
C. Severe Refractory Asthma
D. Do not have enough information to answer
Severe Asthma - Definition

Asthma that requires treatment at GINA steps 4–5 or systemic CS for >50% of the previous year to prevent it from becoming “uncontrolled” or remains “uncontrolled“ despite this therapy

Or

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)
Prevalence

50%  <10%

Uncontrolled Asthma

Difficult Asthma

Severe Refractory Asthma

Incorrect Diagnosis
Poor Adherence
Uncontrolled comorbidities
Persistent Triggers

Guidelines based stepped controller Rx

Severe Refractory Asthma

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A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Never smoker
- No atopic disease or family history of asthma
- Frequent dyspnea, cough and wheeze, limiting physical activity
- Constant fear of a severe asthma attack
A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Frequent GERD symptoms with nocturnal awakening
- Other symptoms – rapid onset of asthma symptoms, recent hoarse voice
- Asthma triggers – exercise, cold air, cigarette smoke, strong perfume, cleaning chemicals
- Medications – Budesonide/formoterol, montelukast, as needed albuterol
A 52 year old male is referred to your practice for severe asthma. He reports 2 Emergency Department (ED) visits and 1 hospitalization for asthma in the past 1 year. Asthma was diagnosed at age 48.

- Occupation – automobile mechanic
- Chest x-ray unremarkable
- Blood eosinophil count 300 cells/mm³. IgE 78 kU/L. Negative allergen specific IgE panel.
- Medication adherence and inhaler technique confirmed
Spirometry

<table>
<thead>
<tr>
<th>Spirometry at BTPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong> = Normal</td>
</tr>
<tr>
<td><strong>ATS</strong></td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; / FVC</strong></td>
</tr>
<tr>
<td><strong>FEF&lt;sub&gt;25-75&lt;/sub&gt; [ISO]</strong></td>
</tr>
<tr>
<td><strong>PEFR</strong></td>
</tr>
<tr>
<td><strong>FIF50</strong></td>
</tr>
<tr>
<td><strong>MVV</strong></td>
</tr>
</tbody>
</table>

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Connecting a Global Community in Clinical Chest Medicine
Which of the following statements is correct?

A. Patient has severe eosinophilic asthma and treatment with anti-IL5 therapy should be initiated immediately

B. The next step in management of this patient should be aggressive treatment of GERD

C. Omalizumab therapy is indicated next as patient’s IgE level is in the treatment range

D. Patient does not have asthma as spirometry is normal with no bronchodilator response
Which of the following statements is true?

A. Patient has **severe** eosinophilic asthma and treatment with anti-IL5 therapy should be initiated immediately

B. The next step in management of this patient should be aggressive treatment of GERD

C. Omalizumab therapy is indicated next as patient’s IgE level is in the treatment range

D. Patient does not have asthma as spirometry is normal with no bronchodilator response
Difficult vs. Severe asthma

Irwin et al. Chest 1993; 103:1662-69
Comorbid Factors Associated with Severe Asthma Exacerbations

- Sleep apnoea
- Psychopathology
- Sinus disease
- Gastric reflux
- Recurrent infections

Prevalence %

1 exacerbation/year
N=24

>3 exacerbations/year
N=39

Validated questionnaires can improve detection of comorbidities in difficult asthma. N=86

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Comorbidity</th>
<th>Items</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNQ [32,33]</td>
<td>Sino-nasal disease</td>
<td>5</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>SFAR [34]</td>
<td>AR</td>
<td>8</td>
<td>74</td>
<td>83</td>
</tr>
<tr>
<td>NIJMEGEN [3,5,26]</td>
<td>DB</td>
<td>16</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>PVC [37]</td>
<td>VCD</td>
<td>4</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>BERLIN [38,39]</td>
<td>OSA</td>
<td>10</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>HADS [40]</td>
<td>Anx/Dep</td>
<td>14</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>GERD-Q [41,42]</td>
<td>GORD</td>
<td>6</td>
<td>65</td>
<td>71</td>
</tr>
</tbody>
</table>

The average time for questionnaire administration was approximately 40 minutes.
### Association, prevalence and treatment outcomes of comorbidities in difficult asthma

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Associated with asthma?</th>
<th>Prevalence in asthma</th>
<th>Does treatment improve asthma?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sino-nasal disease AR</td>
<td>Yes</td>
<td>80% #</td>
<td>Yes</td>
</tr>
<tr>
<td>Sino-nasal disease CRS</td>
<td>Yes</td>
<td>70-74% *</td>
<td>Yes</td>
</tr>
<tr>
<td>GERD</td>
<td>Yes</td>
<td>59% #</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>OSA</td>
<td>Yes</td>
<td>75-95% *</td>
<td>Yes</td>
</tr>
<tr>
<td>VCD</td>
<td>Yes</td>
<td>75% *</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>DB</td>
<td>Yes</td>
<td>29% #</td>
<td>Yes</td>
</tr>
<tr>
<td>Anx/Dep</td>
<td>Yes</td>
<td>49% *</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Difficult asthma
# All asthma

Adapted from Radhakrishna N. Journal of Asthma. 2016
GERD & Asthma

• Prevalence 32-84% by esophageal pH-monitoring studies; about half are asymptomatic
  – Carefully review symptoms: Heartburn, Regurgitation, Water brash, Dysphagia, Sore throat, Choking, Hoarseness, Dental erosions, Chest pain, Cervical pain, Worsened asthma symptoms with Eating, Alcohol, Supine position, Theophylline

• Proposed mechanisms – ‘Reflux’ vs ‘Reflex’
  – Likely a bi-directional relationship

• Studies demonstrate some benefit in symptomatic GERD and uncontrolled asthma
  – Improvement in peak flow, quality of life, exacerbations
CRS & Asthma

• Symptomatic inflammation of the paranasal sinuses and the nasal cavity
  – Chronic Rhino-Sinusitis = lasting > 12 weeks
  – With or without nasal polyps (CRSwNP or CRSsNP)

• The unified airway model
  – Links the upper and lower airway as a single functional group
  – Shared systemic inflammatory pathways

• Prevalence of CRS
  – 10-12% general population
  – 23.4-74% in all asthma
  – 84% in severe asthma

• Associated with decreased lung function, QOL, severe exacerbations


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CRS: Treatment options

- **Nasal steroids:** first line
  - Technique

- **Oral steroids:**
  - CRSsNP: No evidence for benefit
  - CRSwNP: Benefit

- **Antibiotics:**
  - CRSsNP: No placebo controlled study for short courses of antibiotics
  - CRSwNP: 1 study showing doxycycline has limited benefit

- **Nasal saline irrigation:** Improves symptoms

- **Surgery:** For medical management failures

- **Biologics:** In clinical trials
Obesity & Asthma

- Obesity is associated with:
  - Worse asthma control
  - Higher health care utilization
  - Poor response to standard controller therapy

- Weight loss – dietary or surgical – is effective

- Recent studies support a role for exercise

- Diet quality – high protein/low glycemic index, plant-based, Mediterranean

Comorbidities:
- Anxiety/Depression
- GERD
- OSA

Mechanical factors:
- Increased peripheral airway closure
- Increased impedance
- Mass loading
- Decreased ERV

Inflammation:
- High fat/low fiber diet
- Adipose tissue & adipokines

Innate & adaptive immune function:
- Gut microbiome

Mechanical factors:
- Increased peripheral airway closure
- Increased impedance
- Mass loading
- Decreased ERV

Inflammation:
- High fat/low fiber diet
- Adipose tissue & adipokines

Innate & adaptive immune function:
- Gut microbiome
OSA & Asthma

- **Mechanisms**
  - Mechanical stress, intermittent hypoxemia activate proinflammatory pathways
  - Apneas may trigger activation of muscarinic receptors
  - Negative intrathoracic pressure during Muller maneuver
    - Edema of airway wall ~ decreased airway diameter

- **Treatment of OSA**
  - Improves nocturnal asthma control and PEFR
  - Reduces bronchial reactivity
  - Improves asthma quality of life
  - Improves asthma night-time symptom scores

---

![Graph showing comparison between Control, Moderate Asthma, and Severe Asthma](image)

N=26 in each group
OSA diagnosed by HST

Psychopathologies & Asthma

- Pooled data from MENSA and SIRIUS trials of mepolizumab in severe eosinophilic asthma (N=681)
- Higher depressive symptoms scores (BDI-II) were associated with worse asthma control, QOL,
Case continued

- Treatment with omeprazole 20 mg daily initiated
- OSA diagnosed and started CPAP therapy
- Improved GERD and nocturnal asthma symptoms

- Continues to experience frequent cough, wheeze and shortness of breath
- Symptoms most notable at work and with certain chemical smells
What would you recommend next?

A. Removal from work place as this patient has occupational asthma
B. Evaluation for suspected paradoxical vocal fold motion (PVFM)
C. Consideration of allergen immunotherapy
D. Referral for bronchial thermoplasty
What would you recommend next?

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PVFM & Asthma

- VCD/ILO/PVFM
- Laryngeal hypersensitivity
- Occurs commonly as asthma mimic and comorbidity
- Prevalence
  - 19% in all asthma
  - 32% in difficult asthma
- Clinical suspicion and detailed history
  - Triggers, rapid onset/offset, phase of respiration affected, other laryngeal symptoms
- Objective confirmation often elusive - Questionnaire screening, Laryngoscopy, Challenge tests.
- Respiratory retraining
Evaluated by laryngologist and Speech Pathologist colleagues

Laryngoscopy revealed LPRD and PVFM


Follow-up visit: much improved asthma symptoms but continues to have increased rescue inhaler use at work.

Asthma better on weekends and on vacation

Next step? Focus on triggers’ evaluation
Relevant triggers in difficult asthma

- **Allergic Triggers**
  - Indoor: HDM, pets, pests, mold
  - Outdoor: Pollen, mold

- **Non-allergic triggers**
  - Irritants: Air pollution, active/passive smoking
  - Viral infections
  - Stress
  - Drugs/Food

- **Occupational triggers are especially important**
  - Can account for up to 25% of adult onset asthma
  - Immunologic or irritant
  - For immunologic triggers, prompt and complete avoidance is necessary
Triggers negatively impact asthma control and QoL

- TENOR 3-yr observational study
- Difficult asthma; N 2675
- Age >12 years
- Increasing number of triggers associated with worse QoL and higher frequency of exacerbations
## Common Environmental Triggers

<table>
<thead>
<tr>
<th>House Dust - Mite</th>
<th>Furry pets</th>
<th>Pests (roaches, rodents)</th>
<th>Indoor Mold</th>
<th>Air pollutants Tobacco smoke</th>
<th>Immunologic triggers High or Low MW</th>
<th>Irritant triggers</th>
</tr>
</thead>
</table>

Data on effectiveness of trigger mitigation show variable effectiveness

Most studies focus on occupational, indoor environmental allergens, pediatric population, inner city environment

Significant heterogeneity in methods and outcomes

Allergen reduction does not always translate to improved clinical outcomes

More studies are needed to identify interventions that are effective, cost efficient and practical
The 3P Framework

Disease Development

Predisposing Factors: Risk Factors

Perpetuating Factors: Comorbidities

Precipitating Factors: Triggers

Acute Exacerbations/Lack of Control

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Summary

- True prevalence of severe refractory asthma is low
- Many factors other than intrinsic severity of asthma make it ‘difficult’ to treat
- A successful management plan for asthma needs to include a structured multi-faceted assessment of confounders, adherence, comorbidities and triggers
- Identification and mitigation of these factors will
  - Improve asthma outcomes
  - Ensure appropriate utilization of novel and expensive therapies
  - Limit unnecessary drug exposure by allowing step-down in asthma therapy
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