

# SEVERE ASTHMA

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# OBJECTIVES

- Is it asthma?
- What is severe asthma?
- Differential diagnosis
- Workup
- Treatment

# CASE 1

- 9 year old girl
- Attends Allergy clinic since age 1 year
- Early onset wheeze – 1<sup>st</sup> presentation at age 7 weeks
- Other medical history
  - ENT grommets bilateral glue ear
  - GIT chronic constipation

# CASE 1 cont

- Allergy
  - Sensitised hdm / cat / grass mix/ dog
  - Persistent allergic rhinitis
  - Asthma – persistent severe uncontrolled
    - Seretide 25/250 initiated age 5 (trial of LTRA made no difference)
    - PEF consistently 80 – 90%expected

# CASE 1 cont

- Admission acute exacerbation March 2011
  - Amoxil commenced at primary care
  - Augmentin in acute care
  - No change and given Azithromycin
  - Prednisone 2 weeks!
  - Assumed severe viral associated excaerbation but took 3 weeks to settle completely and expected PEF not ever achieved

**FURTHER WORK UP COMMENCED**

# CASE 2

- 11 years old boy
- Asthma since age 4 years
- Adherent
- Coke bottle spacer
- Uncontrolled – SABA use daily, exertional symptoms, cough 2 / week
- Medication
  - Seretide 25/250
  - Singulair 10mg
  - Omeprazole 20mg

# CASE 2 cont

- Milk scan 2009 – mild reflux, started on PPI
- Asthma still uncontrolled
- Milk scan repeated 2011 – “no reflux”

# CASE 3

- 6 year old boy
- Referred from MOPD uncontrolled asthma on ICS 400mcg BD



# CASE 3 cont

- Initial assessment
  - No spacer use
  - Poor technique
  - Sensitised mite and grass
  - PAR and AC
- Plan
  - Adherence counselling with technique
  - Start INS and eye drops

# CASE 3 cont

- Follow up with dad
  - “Much better”
  - No exertional symptoms, no nocturnal cough, no SABA use

# CASE 3 cont

- Follow up with mom
  - “Still bad”
  - Nebs at CHC twice a week, multiple prednisone courses
  - SABA use bi-daily, coughs every night
  - Exertional symptoms

## **MEDICINE REVISION AND FURTHER WORK UP**

# CASE 4

- 7 year old girl
- Allergy clinic since age 2 years
- Environmental tobacco smoke exposure
- Uncontrolled and treatment escalated
- Combination LABA / ICS started age 5 years
- Good adherence / technique
- Sensitised hdm/ cat/ dog/ grass

**WORKUP DONE AND TOBACCO SMOKE  
COUNSELLING (TO NO AVAIL)**

# CASE 5

- 10 year old girl
- Background severe laryngomalacia requiring trimming age 2 weeks
- Early wheeze – recurrent LRTIs
- Allergy Clinic attendance age 2 – 5 years then failed to attend follow up. Was controlled on budesonide 200mcg BD

# CASE 5 cont

- Referred back to Allergy Clinic at age 7 years uncontrolled asthma
- Nebs at CHC weekly
- Multiple courses of prednisone
- SABA use 3/ day; no effort tolerance, persistent cough
- Medication escalated to
  - Budeflam 400mcg BD
  - Serevent 25mcg BD
  - Singulair 5mg nocte

# CASE 5 cont

- Patient handed over to the “Difficult Asthma” clinic

**WORKUP DONE**

# Is it asthma?

- Acute?
- Reversible cough, wheeze or SOB?
- Atopy?
- Sensitisation
- Intermittent
- Responds to SABA
- Exacerbators



# MASQUERADERS

- Aspiration syndromes
- FB
- Tracheomalacia / bronchomalacia
- Vocal cord dysfunction
- Bronchiectasis
- Bronchiolitis
- CF
- Tracheal / bronchial compression syndromes
- Tuberculosis
- ABPA

Paediatric Allergy, Leung et al, 2010

If it is asthma – then...

- **ADHERANCE?**
- **TECHNIQUE?**
- **EXACERBATORS?**
- OR IS THEIR ASTHMA THAT SEVERE?????

# ADHERANCE

- Check repeats – were the meds collected
- If the MDI has a dose counter, check it
- Ask the patient directly
- Non judgemental questions
  - “how many times do you forget your meds”
  - “how often does your dog sleep on your bed with you”
  - “do you enjoying playing on the grass”

# TECHNIQUE

- Spacer use?
- Look at the spacer
  - Is it intact
  - Is it clean
  - Is it the appropriate volume for age

# Exacerbators

## - Comorbidities and cofactors

- Rhinosinusitis
- GORD
- OSA
- Ongoing allergen exposure
- History of psychiatric disease
- Psychosocial factors
- Medications – aspirin, NSAIDs, B blockers, ACE-I and oestrogens

\*The last 3 mainly apply to adult patients\*

# Medical history

- History of asthma
  - Age of onset
  - Family history of asthma
  - Management of disease and response to treatment
- Exacerbations
  - Frequency of severe asthma exacerbations
  - Number of hospitalizations and intensive care unit admissions
- Environmental exposures
  - Exposure to allergens, occupational agents, and
  - Chemicals/pollutants
  - Smoking history

# Physical Examination

- Weight and height centiles and BMI
- Evidence of comorbidities
- Evidence of alternative diagnoses such as cardiac failure
- Evidence of adverse effects of treatment

# Severe Asthma Synonyms?

- *Severe Refractory Asthma (SRA)*
- *Difficult-to-treat*
- *Therapy resistant*
- *Steroid-dependant asthma*
- *Brittle asthma*
- *Etc.....*



# Assessment of severe asthma

- Diagnosis
  - Spirometry (reversibility tests)
  - Airway challenge
- Baseline investigations
  - Serum IgE and peripheral blood eosinophil count
  - Allergy skin tests
  - Assessment of airway inflammation
  - Assessment of lung volumes
- Consider additional tests for comorbidities and alternative diagnoses
- Outcome measures
  - Health status and asthma control questionnaires
  - Assessment of airway inflammation
  - Number and severity of exacerbations and use of health care
  - Lung function

# FEATURES TO CONSIDER WHEN DEFINING SEVERE ASTHMA

- 1. Symptoms
  - Exacerbations
  - •Frequency
  - •Severity
- 2. Medication use
  - Response to treatment or intensity of treatment required to
  - control symptoms
- 3. Pulmonary functions
- 4. Bronchial responsiveness
- 5. Airway inflammation
- 6. Development of airway remodeling
- 7. Consequences of disease
  - •Respiratory failure
  - •Hospitalizations
  - •Impaired quality of life

Busse et al, Pathophysiology of severe asthma, JACI Dec 2010

# Characteristics of severe, persistent asthma

## Characteristics of severe, persistent asthma

- •Continual symptoms
- •Limited physical activity
- •Frequent exacerbations
- •Frequent nighttime symptoms
- •FEV1 or PEF < 60% of predicted
- •PEF variability > 30%

Busse et al, Pathophysiology of severe asthma, JACI Dec 2010

# FACTORS THAT MAY LEAD TO THE DEVELOPMENT OF SEVERE ASTHMA

- Genetics
- Allergens
- Respiratory infections
- Corticosteroid resistance
- Stress

# ENFUMOSA definition of severe asthma

(European Network for Understanding Mechanisms of Severe Asthma)

Patient should fulfill at least 3 of the following criteria:

- 1. Have been seen by a consultant in asthma for  $\geq 2$  years
- 2. Have persistent symptoms and decreased quality of life
- 3. Have received maximal usual asthma therapy and/or medications (high doses of inhaled corticosteroids) with documented adherence to therapy
- 4. Have previous respiratory failure/intubation/near-fatal episodes
- 5. Have repeated low FEV1  $< 70\%$  predicted

# NON INFECTIOUS PULMONARY CONDITIONS

- Reactive airways dysfunction syndrome
- World Trade Centre cough
- VCD
- Granulomatous T<sub>H</sub>1
  - Sarcoidosis
- Granulomatous T<sub>H</sub>2
  - Churg-Strauss
- T<sub>H</sub>1 related
  - COPD
  - Hypersensitivity pneumonitis
- T<sub>H</sub>2 related
  - Pulmonary Eosinophilia Syndromes

# Vocal Cord Dysfunction (VCD)

- Functional or non-anatomical obstruction
- Symptoms
  - Dyspnoea, wheeze, tightness in the neck, SOB, inability to breathe deeply, cough
- Possible comorbidity
  - Asthma, chronic rhinosinusitis, GORD or laryngopharyngeal reflux

# Recognition of VCD

- Suspect
  - Symptoms out of keeping with physical findings
  - Wheezing over the neck but a clear chest
  - Whispering voice
  - Refusal to inspire to total lung capacity or produce an appropriate forced expiratory maneuver
- Truncated inspiratory loop
- Bronchoscopy



# Treatment of VCD

- Speech therapy benefits in some cases
- Do not add on asthma therapy if no evidence of comorbid asthma

# Pulmonary Eosinophilia syndromes or conditions

- Asthma (allergic and nonallergic)
- Asthma with atelectasis from mucus plugging
- **ABPA**
- Allergic bronchopulmonary mycosis
- CSS
- Collagen vascular disease (rare)
- Drug allergy with pulmonary eosinophilia
- Eosinophilic pneumonia
- Acute (BAL fluid eosinophilia 25% to 60% with little or no peripheral blood eosinophilia)
- Chronic (high peripheral blood eosinophilia)
- Simple eosinophilia (Loffler syndrome)
- Tropical pulmonary eosinophilia
- Hypereosinophilic syndromes (interstitial infiltrates and pleural effusions, thromboembolism)
- Neoplasms
- Parasitism (helminthic)
- Sarcoidosis (very rare)

Greenburger et al, Pulmonary disorders including VCD, JACI Feb 2010

# Allergic BronchoPulmonary Aspergillosis (ABPA)

Occurs in

- Immunocompetent
- The absence of invasive aspergillosis
- Hypersensitivity disorder induced by an *Aspergillus* species
- Most patients have cystic fibrosis or asthma

# Aspergillus

- Aspergillus Fumigatus causes the majority of ABPA
- Ubiquitous in the environment – water, decaying organic matter, mown vegetation, basements, walls ceilings
- Occupational disease in farming industry

# DIAGNOSIS

## Patients with Asthma

- Asthma
- Immediate cutaneous reaction to *A. fumigatus*
- Total serum IgE concentration (>1000 ng/ml)
- Elevated *A. fumigatus*-specific serum IgE levels
- Precipitating antibodies to *A. fumigatus* in the serum
- Peripheral blood eosinophilia (not essential for diagnosis)
- Chest Roentgenographic infiltrates (not essential for diagnosis)
- Central bronchiectasis

## Patients with CF

- clinical deterioration (coughing, wheezing, increased sputum production, exercise intolerance and decrease in pulmonary function);
- immediate hypersensitivity to *A. fumigatus* (positive skin test or IgE response);
- total serum IgE concentration >1000 kUI/l;
- precipitating antibodies to *A. fumigatus*;
- abnormal chest roentgenogram (infiltrate, mucus plugs or unexplained changes compared to previous chest X-ray).

# STAGES OF ABPA

STAGES	CLINICAL CHARACTERISTICS	BIOLOGY	RADIOLOGY
I Acute	Fever, cough, chest pain, haemoptysis, sputum	Elevated IgE	Pulmonary infiltrates
II Remission	Asymptomatic / stable asthma	Normal or elevated IgE	No infiltrates
III Exacerbation	Symptoms mimicking acute or asymptomatic	Elevated IgE +- blood eosinophilia	Pulmonary infiltrates
IV Corticosteroid dependent asthma	Persistent severe asthma	Normal or elevated IgE	With or without pulmonary infiltrates
V Fibrosis	Cyanosis, severe dyspnoea	Normal or elevated IgE	Cavitary lesions, extensive bronchiectasis, fibrosis
			Patterson et al

# TREATMENT ABPA

- Oral corticosteroids
  - 0.5mg/kg/day 2 weeks then taper over 6-8 weeks
  - Assess treatment based on symptom control (fever, chest pain, haemoptysis, wheeze and sputum production)
  - CXR +/- HRCT
  - IgE levels every 6 to 8 weeks in the first year after diagnosis (increase in the level >100% above baseline equals high risk of an exacerbation)
  - PFTs

# TREATMENT ABPA

- Antifungals
  - Itraconazole as adjunctive therapy
  - 16 week randomised double blind placebo controlled trial BD treatment Itraconazole vs placebo
  - Itraconazole prevented disease progression in corticosteroid dependent ABPA patients
  - 46% patients responded to Itraconazole vs 19% in the placebo group (p=0.04)

Stevens et al, A randomised trial of itraconazole in ABPA, N Engl J Med, 2000



# TREATMENT ABPA

- Itraconazole decreased eosinophilic airway inflammation, systemic immune activation and the number of exacerbations

Warks et al, Antiinflammatory effect of Itraconazole in stable ABPA, JACI 2003

# TREATMENT ABPA

- Meta-analysis (3 studies)
  - Itraconazole improves clinical outcome (at least over a 16 week period)
  - Modifies immunologic activation associated with ABPA
  - Dose 200mg / day 16 weeks

Wark et al, Azoles for ABPA associated with asthma, Cochrane database 2003

# MANAGEMENT

## Severe Asthma

- High dose ICS
- LABA
- LTRA
- Theophylline
- Oral glucocorticoids

# EXPERIMENTAL IMMUNOMODULATORS

- Methotrexate
- Cyclosporin
- Tacrolimus
- Gold
- IVIG

# EXPERIMENTAL BIOLOGICS

- Anti IgE
  - Omalizumab
- TNF alpha blockers
  - Etanercept
  - Infliximab
  - Golimumab
- Anti IL5
  - Mepolizumab

# CASE 1 conclusion

- Sweat chloride 73 then 86
- DNA test positive
- No pancreatic insufficiency

# CASE 2 conclusion

- FBC normal
- Differential 5% eosinophils
- ESR 51
- Sweat test negative
- Total IgE
- IgE Aspergillus
- IgG Aspergillus

# CASE 3 conclusion

- FBC normal
- Differential 4% eosinophils (absolute  $0.33 \times 10^9$ )
- HIV negative
- Immunoglobulins within normal range
- Total IgE 1540kU / l
- IgE Aspergillus 0.82kU / l
- IgG Aspergillus 35.8kU / l



# CASE 4 conclusion

- All workup negative
- FeNO 49ppm
- Controlled on LA Theophylline
  - No exertional symptoms
  - No nocturnal cough
  - SABA 2/month
- PFTs no longer show reversibility
- Due for repeat FeNO today!

# CASE 5 conclusion

- Immunoglobulins normal
- FBC normal
- Differential 6% eosinophils
- Milk scan – severe reflux
- Total IgE
- IgE Aspergillus
- IgG aspergillus