ASTHMA

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Asthma

- Common disorder of the airway
- Characterized by the complex interaction of
  - Airway obstruction
  - Bronchial Hyper-responsiveness (BHR)
  - Airway inflammation
- Leads to recurrent episodes of wheezing, breathlessness, tightness of the chest and coughing
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
Asthma

- The commonest respiratory disease presented to A&E
- Affects more than 40% of the population, especially in children. Mortality mainly in the teenager or young adult.
- British commonwealth countries (UK, Canada, Australia and New Zealand) leads the world in prevalence (ISAAC studies)
- Prevalence going up from the 1960s, peak near 2000, then starting to reduce, while developing counties are still climbing (together with other allergic diseases)
Prevalence of asthma in children aged 13-14 years
Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals.
- Prevalence is increasing in many countries, especially in children.
- Asthma is a major cause of school and work absence.
- Health care expenditure on asthma is very high:
  - Developed economies might expect to spend 1-2 percent of total health care expenditures on asthma.
  - Developing economies likely to face increased demand due to increasing prevalence of asthma.
  - Poorly controlled asthma is expensive.
  - However, investment in prevention medication is likely to yield cost savings in emergency care.
What is known about asthma?

- Asthma can be effectively treated
- When asthma is well-controlled, patients can
  - Avoid troublesome symptoms during the day and night
  - Need little or no reliever medication
  - Have productive, physically active lives
  - Have normal or near-normal lung function
  - Avoid serious asthma flare-ups (also called exacerbations, or severe attacks)
What is known about asthma?

- Asthma is a common and potentially serious chronic disease that can be controlled but not cured.
- Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in their occurrence, frequency and intensity.
- Symptoms are associated with variable expiratory airflow, i.e. difficulty breathing air out of the lungs due to:
  - Bronchoconstriction (airway narrowing)
  - Airway wall thickening
  - Increased mucus
- Symptoms may be triggered or worsened by factors such as viral infections, allergens, tobacco smoke, exercise and stress.
Asthma - My Experiences

- Worked in New Zealand since 1970
- Started the Paediatric Asthma Clinic 1976 at then the Princess Mary Hospital (Apparently the first such clinic in the southern Hemisphere), the forerunner of the Auckland Children’s Hospital.
- President of the Auckland/New Zealand Asthma Society for a total of 29 years
- Particularly active in the field of education on asthma for the patient, parents, nurses and other medical professionals
Asthma in New Zealand

- When I started work in New Zealand as a Paediatric Registrar, I was astounded by the large number of asthma patients I have to see. The mortality rate at the time was 6 per hundred thousand population, the highest in developed countries. After 15 years of hard slog as Asthma Society president, I am delighted to see it being maintained down to 0.8, somewhat better than the average US figure of 1.2.
My “contributions” to Asthma

- Intellectual Property ownership of Diploma of Asthma Nurse with Auckland Institute of Technology. (Ownership donated to the New Zealand Asthma Society at my retirement from the Asthma Society in 2007)
- Intellectual property ownership (for a few years) of the computer analysis of the mid-segment of the spirometric analysis of the flow-volume curve
- A+3 Asthma strategy
Figure 1 The prevalence of wheeze occurs at different ages according to the type of asthma.
The Asthma Society’s initiative in New Zealand

- Started off in Auckland New Zealand’s largest city in 1969 by Dr. Alice Bush (Paediatrician).
- Initially a mutual help society for asthmatics
- Progressively involved with initiatives with Medical and Management directions in coordination with the Medical profession and Government.
A+3 Asthma Management Strategy

- A = Hospital Admission- targeting the patient who needs hospitalization
  - Causes of asthma
  - Reduction of triggers
  - Ensure correct technique of medication and establishment (if possible) objective lung function testing

- 3 = 3 home visits from asthma nurse from the Family Doctor or Asthma Society
Initially funded from the Auckland Asthma Society. Later from the Government once proven to save medical costs by significant reduction of mortality and morbidity
The Asthma Nurse

- World’s first
- Pivotal in helping the doctor in treatment and education of the asthmatic and their carers.
My first group of Nurses with diploma in Asthma Education
Receiving the Key from Mrs. Alice Li of Bohemia Society for the use of the Auckland Asthma Society

Mrs. Alice Li
FACTORS AFFECTING THE PREVALENCE OF ASTHMA
Patterns of Asthma last Century

- Asthma prevalence increasing worldwide
- Asthma more prevalent in Western countries
- Highest asthma prevalence in English-speaking countries
- Asthma prevalence increasing with urbanization & Westernization
- Other allergic diseases also increasing worldwide
ERS 2003 Vienna

- Antibiotics prescribed for infants within 6 months of birth contributes to increased rates of asthma
- 448 children 0 to 6-7 yrs
- Links to allergies to pets, weeds, grass and house dust mites
Factors known to stimulate or facilitate allergic “expression” 2-1

- Cigarettes
  - Primary or secondary
  - Directly or during pregnancy and breast feeding and during the early phases of growth and development
- Partially combusted hydrocarbons (Main component of city pollution & smog) by facilitating “presentation” of allergens via mucous membranes
Maternal smoking & childhood asthma

Martinez et al 1992

Bar graph showing the percentage of boys and girls with asthma associated with maternal smoking, categorized by '10 or more/day' and 'Non smoker'.
Cigarettes Smoking of either parents both in the presence of infant or not

- At least double the rate of respiratory illness of children
  - Direct effect of respiratory mucosa
  - More prolonged survival of infective agents in the smoker’s saliva and nasal fluid (via the IgA effect)
- Significantly increase the genetic allergy expression of the infant
Munich (Germany) experience

- Heavy truck traffic only allowed in certain routes thru the city
- Children living near such routes have both
  - Increase in hospitalization in upper or lower respiratory tract illnesses
  - Increase in all childhood forms of allergic illness especially hay fever
Air Pollution & Asthma

- **Indoor:-**
  - Tobacco smoke
  - Gas heating
  - Closed bedroom doors

- **Outdoor:-**
  - Ozone
  - Particulate matter
  - Other gases:- Carbon Monoxide, Sulfur Dioxide & Nitrogen Dioxide

- **Note:-** Nose block increase direct exposure of pollutants to the airways
Factors known to stimulate or facilitate allergic “expression” 2-2

- Absence of competing or life-threatening microbes or parasites (The Hygiene Hypothesis) during the first few months of life
- Medium exposure to allergens (one cat is bad, three or more is good)
- Presence of “allergen presenters”. E.g. pollutants, partially combusted hydrocarbons
- Ichthyotic skin (Filaggrin abnormality)
Gastrointestinal Bacteria & Immunity

- In early infancy, normal GI bacteria suppress TH2 responses and promotes TH1 maturation
- Antibiotics deplete GI tract bacteria
- Animal model
- Slow maturation of TH1 over the first 12-18 months predispose allergy & asthma development
  - Holt ATS 2001
Patterns of education & atopic sensitization

Matricardi et al 1998
Affluence & Asthma

Studies of genetically similar populations

- Example:-
  - Southern Chinese: asthma symptoms
    - Hong Kong 4X Guangzhou
    - Melbourne borne Chinese 2X Hong Kong
    - New Zealand borne Chinese 1.6X Hong Kong
  - Zimbabwe: EIA
    - 25-50X increase Rural vs Urban
  - South Africa: asthma prevalence
    - Xhosa children in capetown 20X rural Transkei
Early childhood antibiotic use and development of asthma

- 456 children 5-10 years
- Rudolf Steiner school in NZ
- Odds ratio for asthma
  - 4.05 if antibiotic in first year of life
  - 1.64 if used after age of 1
- Number of antibiotic courses
  - OR 2.27 for 1-2 courses
  - OR 4.02 for 3 or more courses
  - Clin Exp Allergy 1999
Healthy infant

- RSV
- PIV

Wheezing illness → Atopy

Resolution → Child or adult with asthma

Early childhood infections: Measles, TB(-): RSV(+)

Rhinovirus

Exacerbation of asthma
ASSOCIATION BETWEEN RSV INFECTION AND ASTHMA DEVELOPMENT

Review of articles in English and Spanish confirmed the relationship for the first 3 years of life, impact decreases with age

Ped Inf Dis J 2007
Prediction of Asthma in Allergic Rhinitis

273 proven allergic rhinitis patients

Skin prick test to 10 aeroallergens

Methacholine broncho-provocation test

Predictor of asthma only significant in:
- Cat \( p=0.0009 \)
- Dog \( p=0.01 \)

Diemer et al 2000
DIAGNOSIS OF ASTHMA
Practical Diagnosis of Asthma

- Diagnosis for pre-schoolers on demonstration of responsiveness to bronchodilators. The Bronchodilator response test

- Need to show responsiveness within a short period of time (i.e. minutes), especially for parents

- Aim is to deliver the bronchodilator to the internal lining of the airways and to show a proper response. An obvious response would do

- For school-age children, objective demonstration of responsiveness from spirometric measurements are ideal
4 - Bronchoprovocation

(Bronchial Hyperreactivity)

**Exercise** Challenge Test:
Findings consistent with asthma include:
15% or greater decrease in FEV1

**Methacholine** challenge Test:
Findings consistent with asthma include:
20% or greater decrease in FEV1

*A negative result does not exclude the Dx. of asthma.*
Use of Bronchodilator inhaler to confirm response and for treatment

- One puff into a spacer, five slow breathes
- Wait 5 minutes (to allow deposition of bronchodilator to large and intermediate airways and time to work)
- Second puff into spacer
- Five slow breathes
- Wait another 5 minutes (to allow deposition of medication to intermediate and smaller airways, and time to work)
- Observe response
Allergic inheritance

- Allergic tendencies are inherited
- Specific allergic disease is not necessarily inherited
- Development of a specific allergic disease depends on other genetic factors as well the timing of allergy development
GENETIC FACTORS IN ASTHMA AND ALLERGY. WHO IS TO BLAME

Settle the question in the presence of BOTH parents:-
Each parent contribute to one part of each paired genes. The dominant gene shows up the feature in the child, the one that do not show up is the submissive gene. Therefore both parents are EQUALLY responsible
Chronic Cough as sole presenting manifestation of Bronchial Asthma

- Normal baseline spirometry
- Positive methacholine challenge
- Good response to bronchodilator therapy
Typical spirometric tracings

Volume

Time (seconds)

Flow

Volume

Note: Each FEV₁ represents the highest of three reproducible measurements.
Diagnostic pointers for asthma diagnosis in young children

- Bronchodilator responsiveness
  - Inhalation rather than oral
  - Good fitting spacers or nebulizers
- Check for allergy
  - Family history
  - Clinical allergy
  - Laboratory
In Asthma
Does Intensity of Wheezing = Severity?

- This may be the case in the early phases of asthma.
- In severe asthma, inadequate air movement reduces audible noises.
- Always check air entry to the lungs.
- Expiratory phase to inspiratory phase ratio important. Check other signs of hypoxia.
ASTHMA TREATMENT

1) Bronchodilators
2) Preventors
3) Delivery of treatment agents to the airways
Spacer devices / masks

Spacer Devices

AeroChamber®

Babyhaler®

AeroChamber® with Face mask
The “virtual Nebuliser”

- Actuate bronchodilator inhaler into spacer
- Rebreathe 5 breathes via mask
- Repeat total of 6 actuations
Why use a Spacer with an Inhaler?

Inhaler alone
When an inhaler is used alone, medicine ends up in the mouth, throat, stomach and lungs.

Inhaler used with spacer device
When an inhaler is used with a spacer device, more medicine is delivered to the lungs.
**RESPIMAT® SOFT MIST™ INHALER – DRUG DELIVERY TO THE LUNGS**

Lung deposition scintigraphy study in asthma patients comparing Respimat®, Turbuhaler® and CFC-pMDI

**RESPIMAT® SOFT MIST INHALER**

- **51.6%**
  - Lung deposition†

**TURBUHALER® DPI (FLOW RATE 60L/MIN)**

- **28.5%**
  - (p<0.001*)
  - Lung deposition†

Adapted from Pitcairn et al. 2005 and Anderson 2006.† vs Respimat®.
†Lung deposition (% of metered dose ex-valve, mean) measured by gamma scintigraphy.
Test drug budesonide (Respimat® and Turbuhaler®) or beclomethasone (pMDI). Asthma patients (n=14). Image represents typical scan in one individual.
CFC, chlorofluorocarbon; pMDI, pressurised metered-dose inhaler; DPI, dry powder inhaler.

RESPIMAT® SOFT MIST™ INHALER
–
A NEW GENERATION INHALER¹

How Respimat® Soft Mist™ Inhaler works

RESPIMAT® SOFT MIST™ INHALER – DRUG DELIVERY TO THE LUNGS

Lung deposition scintigraphy study in asthma patients comparing Respimat®, Turbuhaler® and CFC-pMDI

RESPIIMAT® SOFT MIST INHALER

CFC pMDI

51.6%
Lung deposition†

8.9%
(p<0.001*)
Lung deposition†

Adapted from Pitcairn et al. 2005 and Anderson 2006.1,2 *vs Respimat®.
†Lung deposition (% of metered dose ex-valve, mean) measured by gamma scintigraphy.
Test drug budesonide (Respimat® and Turbuhaler®) or beclomethasone (pMDI). Asthma patients (n=14). Image represents typical scan in one individual.
CFC, chlorofluorocarbon; pMDI, pressurised metered-dose inhaler; DPI, dry powder inhaler.

When to consider preventers

- 2 or more episodes of oral steroids
- 2 or more visits to hospital for asthma
- For patients requiring regular long-acting bronchodilators
- Need more than 3 doses of acting bronchodilators in the absence of a viral illness
Inhaled Steroid Side-effects

- Excessive inhaled steroids can have steroidal side-effects.
- Long term use can stunt growth of children, but:
  - Poor control of asthma and poor exercise stunt growth more dramatically. By controlling allergies and asthma, the child can achieve their genetic height eventually.
  - Daily dose of up to 400ug of inhaled steroids do not produce side effects of note.
  - The swallowed component are “digested” and does not contribute to steroidal side effects through the “single pass” phenomenon.
  - The inhaled steroids on the oral pharynx can be reduced by rinsing the mouth or by swallowing anything.
Treat the whole system

- The **United Airways Theory**
  - For the lower airway (lungs) to work well, one must also have good upper airways (nose & sinuses)
  - A blocked nose forces mouth breathing, dry air (perhaps laden with aero-antigens and particulate matter) have direct access to the bronchial tree.
  - Mucous & infected material dripping down
  - Mediators released from inflammation of the upper airways affecting effector cells of the lower airways.
In children with persistent asthma, the addition of LABA to ICS was not associated with significant reduction in rate of exacerbations requiring systemic steroids, but was superior for improving lung function compared to the same dose of ICS. Similarly, compared with a double dose ICS, the combination of LABA and ICS did not significantly increase the risk of exacerbations requiring oral steroids, but was associated with a significantly improving in PEF and growth.
Stepwise management - pharmacotherapy

Diagnosis
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

Asthma medications
- Non-pharmacological strategies
- Treat modifiable risk factors

Review Response
- Symptoms
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function

Adjust Treatment

Preferred controller option

Other controller options

Reliever

As-needed short-acting beta-agonist (SABA)

GINA 2016, Box 3-5 (2/8) (upper part) © Global Initiative for Asthma
Step 1 – as-needed inhaled short-acting beta\textsubscript{2}-agonist (SABA)

**STEP 1**
- As-needed short-acting beta\textsubscript{2}-agonist (SABA)
- Consider low dose ICS

**STEP 2**
- Low dose ICS
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline\(^*\)

**STEP 3**
- Low dose ICS/LABA\(^{**}\)
- Med/high dose ICS
- Low dose ICS/LABA (or + theoph\(^{**}\))

**STEP 4**
- Med/high dose ICS
- Add ICS/LABA\(^{**}\)
- Add high dose ICS
- Add medium dose ICS/LABA (or + theoph\(^{**}\))

**STEP 5**
- Refer for add-on treatment e.g. tiotropium, omalizumab, mepolizumab\(^{**}\)

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\(^*\)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

\(\dagger\)Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations
Step 1 – as-needed reliever inhaler

- Preferred option: as-needed inhaled short-acting beta$_2$-agonist (SABA)
  - SABAs are highly effective for relief of asthma symptoms
  - However …. there is insufficient evidence about the safety of treating asthma with SABA alone
  - This option should be reserved for patients with infrequent symptoms (less than twice a month) of short duration, and with no risk factors for exacerbations

- Other options
  - Consider adding regular low dose inhaled corticosteroid (ICS) for patients at risk of exacerbations
Step 2 – low-dose controller + as-needed inhaled SABA

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<td>Add low dose ICS</td>
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<td>Preferred controller choice</td>
<td>Low dose theophylline*</td>
<td>Med/high dose ICS</td>
<td>High dose ICS + LTRA (or a theophyl)</td>
<td>As-needed SABA or low dose ICS/formoterol*</td>
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*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
Step 2 – Low dose controller + as-needed SABA

- Preferred option: regular low dose ICS with as-needed inhaled SABA
  - Low dose ICS reduces symptoms and reduces risk of exacerbations and asthma-related hospitalization and death

- Other options
  - Leukotriene receptor antagonists (LTRA) with as-needed SABA
    - Less effective than low dose ICS
    - May be used for some patients with both asthma and allergic rhinitis, or if patient will not use ICS
  - Combination low dose ICS/long-acting beta$_2$-agonist (LABA) with as-needed SABA
    - Reduces symptoms and increases lung function compared with ICS
    - More expensive, and does not further reduce exacerbations
  - Intermittent ICS with as-needed SABA for purely seasonal allergic asthma with no interval symptoms
    - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

GINA 2016 © Global Initiative for Asthma
Step 3 – one or two controllers + as-needed inhaled reliever

- **PREFERRED CONTROLLER CHOICE**
  - **STEP 1**
    - Consider low dose ICS
  - **STEP 2**
    - Low dose ICS
      - Leukotriene receptor antagonists (LTRA)
      - Low dose theophylline
  - **STEP 3**
    - Low dose ICS/LABA
      - Med/high dose ICS
      - High dose ICS + LTRA
  - **STEP 4**
    - Med/high dose ICS + LABA
      - Add tiotropium
  - **STEP 5**
    - Refer for add-on treatment
      - e.g. tiotropium, omalizumab, mepolizumab

- **RELEIVER**
  - As-needed short-acting beta₂-agonist (SABA)
  - As-needed SABA or low dose ICS/formoterol

*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
Step 3 – one or two controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence, confirm diagnosis
- Adults/adolescents: preferred options are either combination low dose ICS/LABA maintenance with as-needed SABA, OR combination low dose ICS/formoterol maintenance and reliever regimen*
  - Adding LABA reduces symptoms and exacerbations and increases FEV₁, while allowing lower dose of ICS
  - In at-risk patients, maintenance and reliever regimen significantly reduces exacerbations with similar level of symptom control and lower ICS doses compared with other regimens
- Children 6-11 years: preferred option is medium dose ICS with as-needed SABA

- Other options
  - Adults/adolescents: Increase ICS dose or add LTRA or theophylline (less effective than ICS/LABA)
  - Children 6-11 years – add LABA (similar effect as increasing ICS)

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol
Step 4 – two or more controllers + as-needed inhaled reliever

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Other controller options:
- Consider low dose ICS
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline

As-needed short-acting beta₂-agonist (SABA)

As-needed SABA or low dose ICS/formoterol

*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
†Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

GINA 2010, Box 3-5, Step 4 (7/8) © Global Initiative for Asthma
Step 4 – two or more controllers + as-needed inhaled reliever

Before considering step-up
- Check inhaler technique and adherence

Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA

Children 6–11 years: preferred option is to refer for expert advice

Other options (adults or adolescents)
- Tiotropium by mist inhaler may be used as add-on therapy for patients aged ≥12 years with a history of exacerbations
- Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
- Increase dosing frequency (for budesonide-containing inhalers)
- Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol
Step 5 – higher level care and/or add-on treatment

**PREFERRED CONTROLLER CHOICE**

**RELIEVER**

**STEP 1**
- Consider low dose ICS

**STEP 2**
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline

**STEP 3**
- Low dose ICS/LABA
- Med/high dose ICS + LTRA
- Add LTRA oropharyngeal (or 4 theoph)

**STEP 4**
- Med/high dose ICS
- Add LTRA
- Add low dose DCS
- Refer for add-on treatment e.g. mepolizumab, omalizumab

**STEP 5**
- As-needed SABA or low dose ICS/formoterol

*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
†Tioprolom by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations
Step 5 – higher level care and/or add-on treatment

- Preferred option is referral for specialist investigation and consideration of add-on treatment
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on tiotropium for patients ≥12 years with history of exacerbations
  - Add-on omalizumab (anti-IgE) for patients with severe allergic asthma
  - Add-on mepolizumab (anti-IL5) for severe eosinophilic asthma (≥12 yrs)

- Other add-on treatment options at Step 5 include:
  - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - Add-on low dose oral corticosteroids (≤7.5mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
  - See ERS/ATS Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail
General principles for stepping down controller treatment

- **Aim**
  - To find the lowest dose that controls symptoms and exacerbations, and minimizes the risk of side-effects

- **When to consider stepping down**
  - When symptoms have been well controlled and lung function stable for ≥3 months
  - No respiratory infection, patient not travelling, not pregnant

- **Prepare for step-down**
  - Record the level of symptom control and consider risk factors
  - Make sure the patient has a written asthma action plan
  - Book a follow-up visit in 1-3 months

- **Step down through available formulations**
  - Stepping down ICS doses by 25–50% at 3 month intervals is feasible and safe for most patients (Hagan et al, Allergy 2014)
  - See GINA 2016 report Box 3-7 for specific step-down options

- Stopping ICS is not recommended in adults with asthma because of risk of exacerbations (Rank et al, JACI 2013)
Effective asthma self-management education requires:

- Self-monitoring of symptoms and/or lung function
- Written asthma action plan
- Regular medical review

**All patients**
- Increase reliever
- Early increase in controller as below
- Review response

**If PEF or FEV₁ < 60% best, or not improving after 48 hours**
- Continue reliever
- Continue controller
- Add prednisolone 40–50 mg/day
- Contact doctor

EARLY OR MILD  LATE OR SEVERE
Airway remodeling

- Airway remodeling: structural alterations
- Wide array of pathophysiologic features

1. Epithelial changes
2. Increased smooth muscle mass
3. Increased numbers of activated fibroblasts/myofibroblasts
4. Subepithelial fibrosis
5. Vascular changes (angiogenesis)

Narrowed airway (limited air flow)

Tightened muscles constrict airway

Inflamed/thickened airway wall

Mucus

Muscle

Airway wall

Airway x-section

Thickened airway wall

Muscle

Mucus
Airway remodelling
molecular and cellular pathways underlying development and resolution

- Epithelial Cells
- Extra cellular Matrix
- Airway Smooth Muscle
- Mucus production
- Fibrogenic growth factor production
- Matrix disorganization
- Smooth muscle cell proliferation
- Cytokine/chemokine production
Histopathological features of remodeling
Asthma Disease Progression: Clinical Evidence Summary

Research question: Are outcomes in adult asthma primarily determined in early childhood?

- Melbourne Asthma Study: N=479; 35 years of follow-up; only subjects with asthma or severe asthma before age 7 had lung function significantly worse than controls at age 35.1,2
- Sears: N >1,000; aged 9–26 years; >1 in 4 children had wheezing that persisted to adulthood or relapsed after remission.3
- Tucson Children’s Respiratory Study: N=826; newborns, follow-up at ages 3 and 6; deficits in lung function already present by age 6 in children with asthma.4
- Apostol: N=4,000; aged 18–30 years; increased rate of FEV₁ decline in subjects with asthma.5
- Covar CAMP analysis: N=253; aged 5–12 years; the higher lung function at baseline, the less steep the reduction in postbronchodilator FEV₁ % predicted.6

Asthma Disease Progression: Clinical Evidence Summary (cont)

- **Research question:** Does ICS therapy alter disease progression?
  - Haahtela Continuation Study: N=74; aged 15–64 years; first-line therapy with budesonide significantly improved PEF and PC_{15} responsiveness vs delayed therapy.
  - CAMP: N=1041; aged 5–12 years; 4–6 years of treatment; postbronchodilator FEV₁ in budesonide group did not significantly differ from placebo.

Asthma Disease Progression: Clinical Evidence Summary (cont)

- Research question: Is the clinical benefit of ICS therapy a result of suppression of inflammation rather than permanent changes in the airways?
  - CAMP: N=1041; aged 5–12 years; 4–6 years of budesonide; on discontinuation of therapy, $PC_{20}$ decreased to levels similar to placebo and nedocromil.

- More studies are needed on all research questions.

We now have excellent preventers and long (as well as short) acting bronchodilators. Future research hopefully would allow reversal of airway remodelling of asthmatics.