Drugs used in Asthma and COPD

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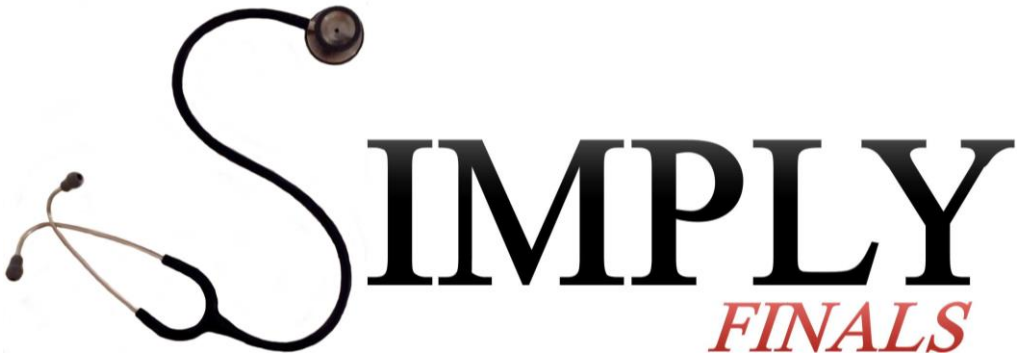


Outline

- Modes of Delivery

- Overview of the drugs used in Asthma and COPD
  - ß-Agonists
  - Anti-Muscarinics
  - Xanthines
  - Corticosteroids
  - Leukotriene Receptor Antagonists
  - Monoclonal Antibodies
  - Others inc. LTOT
  - Pregnancy and Breastfeeding

- Summary

- *Treatment Regimens:*
  - *Long-term management of Asthma*
  - *Acute Exacerbation of Asthma*
  - *Long-term Management of COPD*
  - *Acute Exacerbation of COPD*

SIMPLY FINALS

Modes of Delivery

- **Oral**
- **Inhalers:**
  - **Metered dose** – the standard inhaler. Fixed amount of aerosol drug is administered.
  - **Breath-activated** (may still be pressurised, or dry powder). Easier to use. Examples are the Accuhaler or Turbohaler.
  - **Spacers** can be used to help increase drug delivery.
  - *Inhaler Technique: www.asthma.org.uk/Sites/healthcare-professionals/pages/inhaler-demos*
- **Nebulisers** – air or oxygen is driven through liquid drug via face mask.
- **Intravenous**

SIMPLY FINALS

ß2-Agonists

- Act directly on smooth muscle causing bronchodilation.
  - *"Beta-adrenergic receptors are coupled to stimulatory G proteins which activate adenylyl cyclase, which catalyzes the production of cAMP. In the lung, cAMP causes a decrease in the intracellular calcium concentration and, via activation of protein kinase A, both inactivates myosin light chain kinase and activates myosin light chain phosphatase. In addition, beta-2 agonists open large conductance calcium-activated potassium channels. The combination of decreased intracellular calcium, increased membrane potassium conductance, and decreased myosin light chain kinase activity leads to smooth muscle relaxation and bronchodilation."*
  - ***In short:*** *β2-agonist → Raised cAMP → Decreased* Ca^{2+} *→ Bronchodilatation*
- Have a rapid onset of action so can be used symptomatically or before exercise.
- Long acting versions are used when preventative therapy is required.
- Used in both asthma and COPD. Also as a tocolytic in obstetrics
- Limited benefit in infants due to minimal β-receptors in the lungs.

ß2-Agonists

Short acting (3-5 hours) – ***INH, NEB, PO, SC, IM and/or IV***

- Salbutamol – Inh 100-200µg qds, Neb 2.5-5mg, IV from 5µg/min
- Terbutaline – Inh 500µg qds, Neb 5-10mg, IV from 90µg/min

Long Acting (12 hours) – *Inhaled only*

- Salmeterol – 50-100µg bd
- Formoterol – 12µg bd

Side-effects

Fine tremor, muscle cramps, nervous tension, palpitations, tachycardia, sleep disturbance, hypokalaemia *(a therapeutic aim in some situations)*
Paroxysmal bronchospasm can occur.

SIMPLY FINALS

Anti-Muscarinics

- Cause bronchodilation and reduce mucus secretion by blocking muscarinic acetylcholine receptors in the lung which promotes the degradation of cGMP.
- They have longer action and greater bronchodilator effect than the ß2 agonists.
- Used in both asthma and COPD.

Short Acting – *Inhalation and nebulised*

- Ipratropium Bromide – Neb 250-500mcg, INH 20-40mcg

Long Acting - *Inhaled only*

- Tiotropium – 18mcg

Side Effects

- Dry mouth, nausea, constipation. Caution in those with bladder outlet obstruction and glaucoma.

Methylxanthines

Types:

- Theophylline – given PO
- Aminophylline (more soluble) – given PO or IV

- A loading dose is required for the xanthine-naive

- They act as a:
  - **Phosphodiesterase inhibitor** – raising cAMP and therefore bronchodilation
  - **Adenosine receptor blocker** – causing bronchodilation
  - **Histone deacetylase activator** – suppressing genes involved in inflammation.

- Primarily used in acute/chronic asthma. There is still debate for its use in COPD.

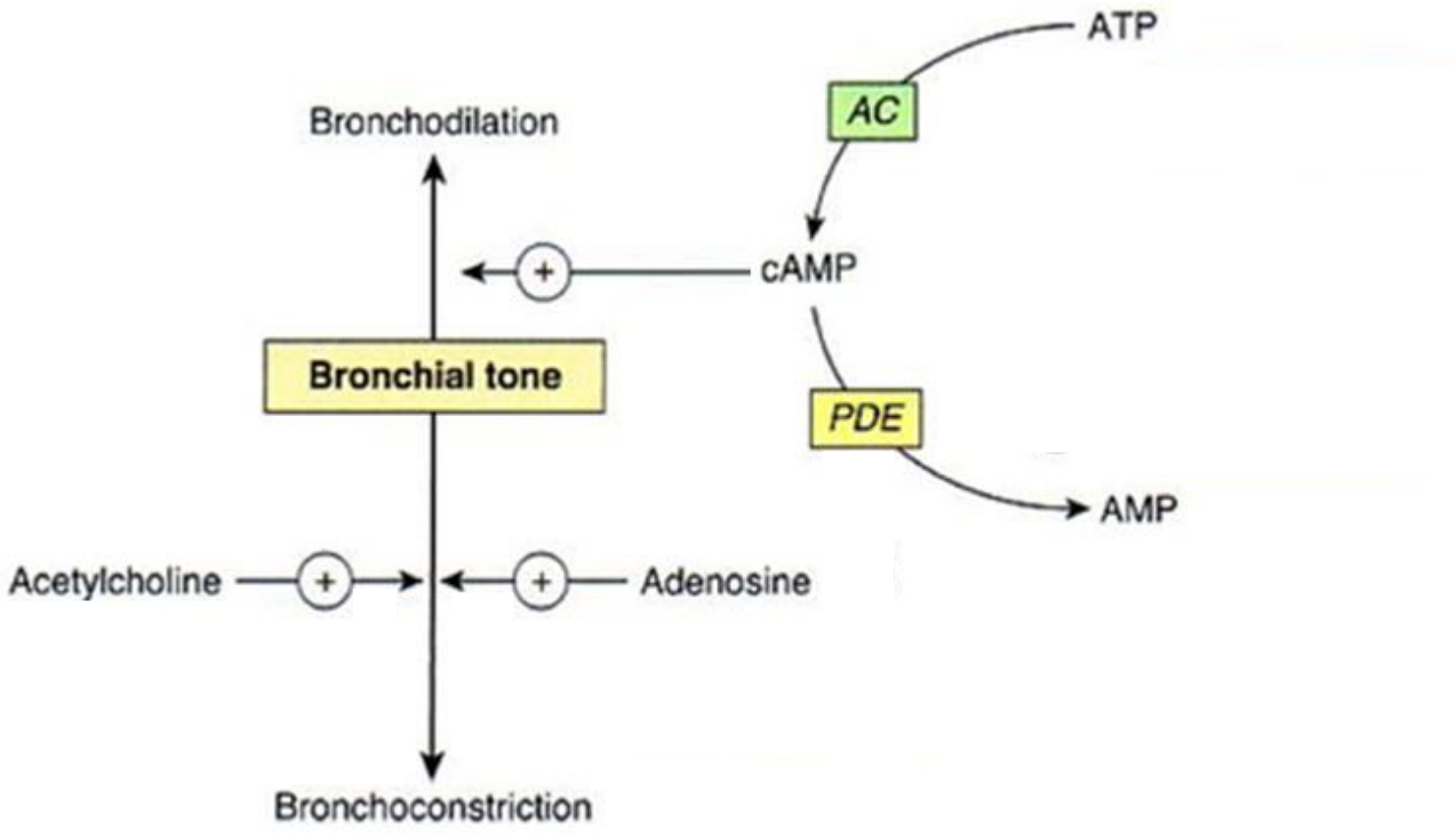
Methylxanthines

- The therapeutic range is narrow (10-20mg/L). Plasma level monitoring is therefore required.
- It is metabolised in the liver by cytochrome P450 so its concentration is affected by liver disease and enzyme inhibitors/inducers.

Side effects

- Gastro – Nausea, vomiting, gastric irritation, diarrhoea
- Cardiac – palpitations, tachycardia, arrhythmias (mainly due to its effect on adenosine)
- CNS – headache, insomnia, convulsions

Summary of ß-agonists, Anti-Muscarinics and Theophylline



AC: Adenylate Cyclase
PDE: Phosphodiesterase
(c)AMP: (cyclic) Adenosine Monophospate

SIMPLY FINALS

Corticosteroids

- Used in the prevention and acute management of both asthma and COPD. In COPD, their preventative use should be assessed by a steroid trial.

- *"The anti-inflammatory effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors, altering gene transcription.*
- *Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. They also up-regulate anti-inflammatory molecules"*

- **All in all, they reduce inflammation, oedema and secretions.**

Corticosteroids

Can be given by numerous routes:

Inhaled

- Beclometasone – 200-400 µg bd, up to 800µg bd
- Budenoside – 100-800 µg bd

Oral

- Prednisolone – 30-60mg od

IV

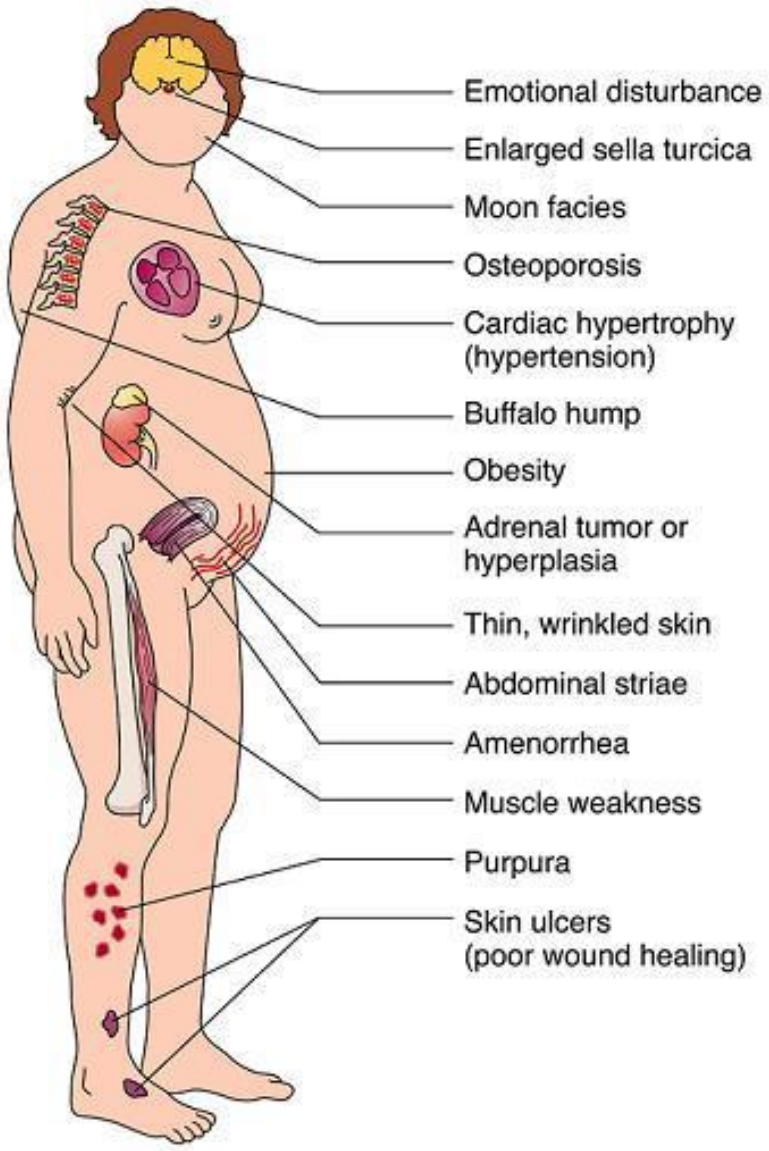
- Hydrocortisone – 100-200mg

Note, oral and IV steroids have the same benefit in the acute setting (presuming the patient can swallow and isn't vomiting)

Inhaled Side-effects

- Inhaled steroids have lowered systemic absorption but systemic effects can occur; especially with long use and high doses.
- Furthermore, inhaled steroids can increase oral thrush and lower respiratory tract infections (advise the patient to wash mouth out after use)

Corticosteroids –Systemic Side Effects!



Endocrine: HPA suppression, hyperglycemia

Musculoskeletal: growth retardation, skeletal-muscle myopathy, osteoporosis/fractures, aseptic necrosis of bone, subcutaneous tissue atrophy

Central nervous system: psychiatric disturbances, pseudotumor cerebri

Immune system: impaired wound healing, leukocyte and monocyte inhibition

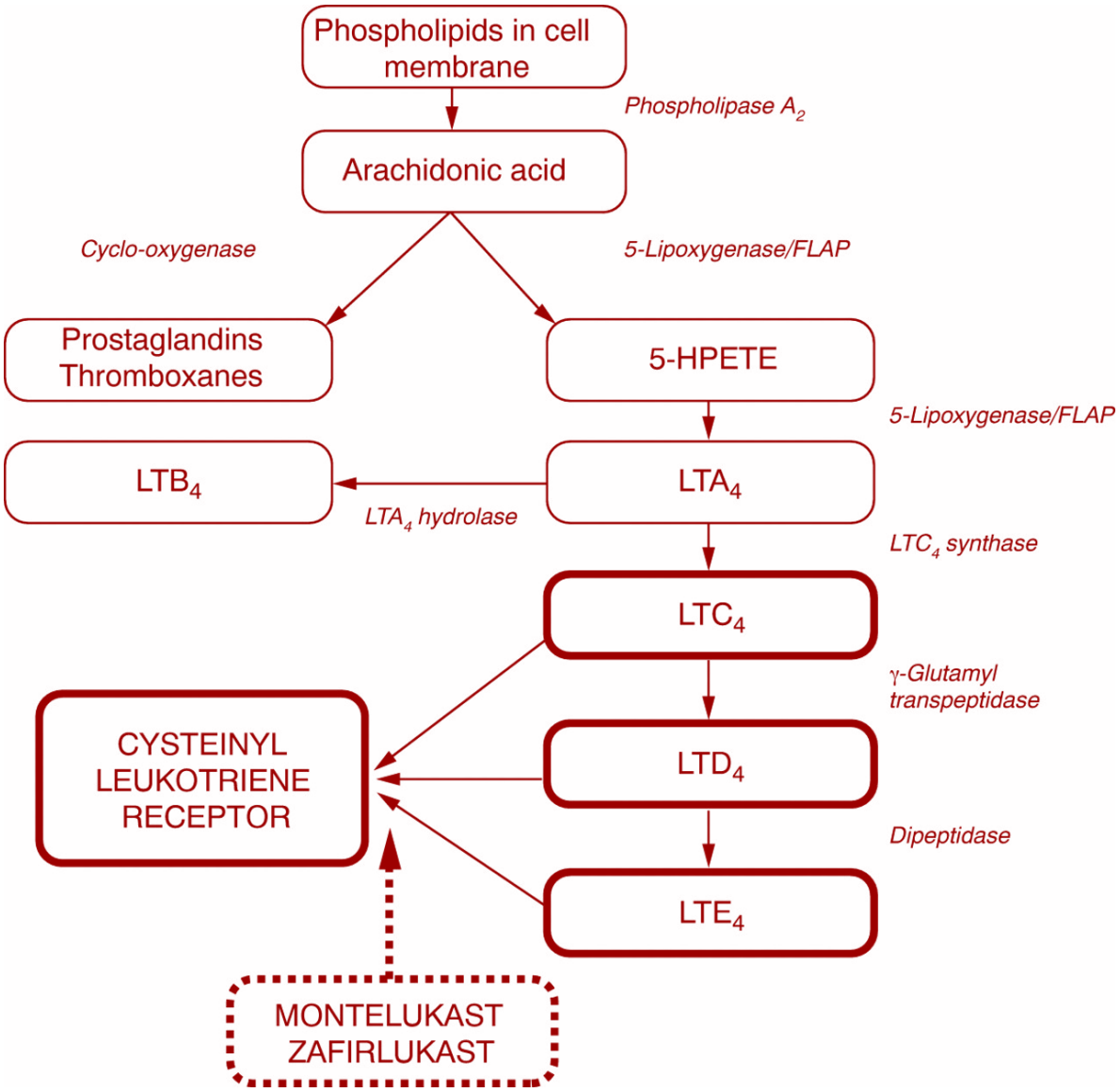
Fluid/electrolyte balance: sodium and water retention, hypokalemia

Cardiovascular: hypertension

Ophthalmologic: glaucoma, posterior subcapsular cataracts

Other: pancreatitis, skin striae, moon facies, central redistribution of fat

Leukotriene Receptor Antagonists – e.g. Montelukast



- Block the effects of cysteinyl leukotrienes which are related to mast cell and eosinophil bronchoconstriction and inflammation.
- Of benefit in aspirin and exercise induced asthma.

SIMPLY FINALS

Leukotriene Receptor Antagonists

Types

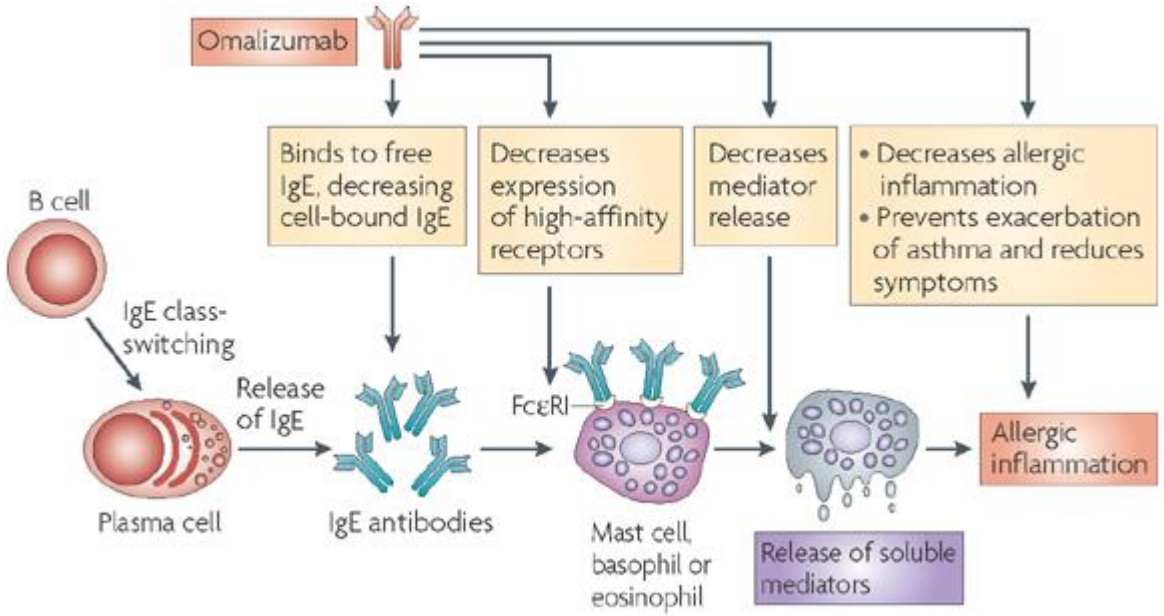
- Montelukast – 10mg in the evening PO
- Zafirlukast – 20mg bd PO

Side-effects

- Gastrointestinal disturbances, headache, insomnia, arthralgia, myalgia, bleeding disorders.
- Rare reports of Churg-Strauss syndrome, especially when corticosteroids are reduced. Be aware of eosinophilia, vasculitic rash and worsening pulmonary symptoms.

Anti-IgE Monoclonal - Omalizumab

- Used in allergic asthma for those who have failed all conventional treatment.
- Initiated only by specialists (£256 per 1ml).
- Given by subcutaneous injection every 2-4 weeks – dose varies for bodyweight and IgE concentration



• Little evidence so manufacturer advises caution in hepatic and renal disease.

• Side effects are legion. Can cause hypersensitivity reactions.

SIMPLY FINALS

Other Asthma Medications

Note, you can get compound medications which are mixtures of two drugs, e.g.:

- ß2-agonist and steroid e.g Symbicort
- ß2-agonist and anti-muscarinic e.g. Combivent

Magnesium Sulphate

- 1.2-2g given by IV infusion over 20 minutes
- Used in acute severe asthma.
- Believed to antagonise calcium; raised intracellular calcium causes histamine release and bronchospasm.
- Caution in kidney disease due to renal excretion. Side effects: As per hypermagnesaemia – nausea, vomiting, thirst, hypotension, arrhythmias, weakness, respiratory depression, coma.

Cromoglicate

- Inhaled 10mg qds up to 6-8 times daily.
- Mode of action is not completely understood although believed to stabilise mast cells, reducing cytokine release.
- Side effects are usually local – throat irritation, cough. Paradoxical bronchospasm can occur.

Pregnancy and Breastfeeding with Asthma

- It is important to maintain adequate control of asthma during pregnancy.
- ~1/3 will get better, ~1/3 will get worse, ~1/3 will stay the same
- All medications are considered safe for breastfeeding

- β-agonists – deemed safe in all forms
- Inhaled steroids – safe
- PO steroids – may increase congenital defects if used in first trimester, but shouldn't be withheld if asthma is severe Xanthines - reports of neonatal apnoeas and irritable infants, but still indicated as safe.
- Leukotriene inhibitors - continue if demonstrable benefit
- No human studies for Omalizumab yet.

Other COPD Medications

Carbocisteine

- Given orally – 375mg tablets
- Mucolytic which reduces mucus viscosity. Shown to reduce exacerbations in those with productive coughs.
- Caution in those with previous gastric ulcer disease due to effects on gastric mucosal barrier

Roflumilast

- Given orally – 500µg od.
- Is a Phosphodiesterase Type-4 Inhibitors
- Licensed as an adjunt to bronchodilators in severe COPD associated with bronchitis.
- Caution in hepatic disease, latent infection and past psychiatric disease. Side-effects: gastrointestinal disturbance, myalgia and mood change.

Doxapram

- 1.5-4mg/min
- Is a respiratory stimulant and only recommended when non-invasive ventilation is considered inappropriate
- Stimulates chemoreceptors in the carotid bodies of the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem.
- Side-effects/Cautions – see BNF!

(Briefly:) Long Term Oxygen Therapy

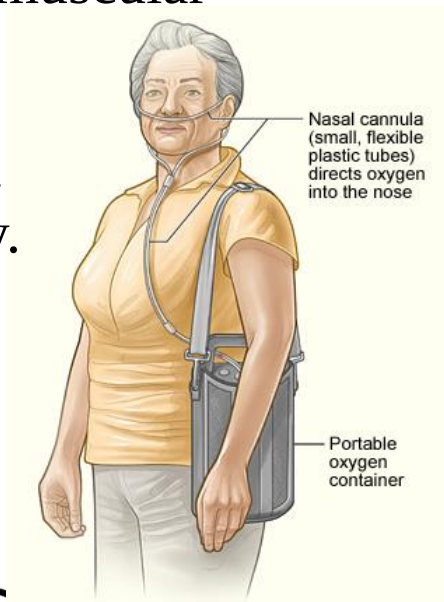
Main eligibility criteria in adults:

- Patients with PaO2 of <7.3 when stable (no infection) in air.
- Patients with a PaO2 of 7.3-8kPa with evidence of polycythaemia, nocturnal hypoxaemia, peripheral oedema or pulmonary hypertension.

- Also used in chronic severe asthma, cystic fibrosis, neuromuscular conditions, chronic lung disease of prematurity etc.

- Benefit is only seen with use of more than 15 hours a day.
- Substantial benefit only seen with over 19 hours use a day.

- Patients require lots of education and regular review.
- Smoking can cause burns and explosions!



Acute Oxygen delivery, including NIV, is covered in a separate talk

SIMPLY FINALS

Summary

- Many of the same drugs are used in both asthma and COPD, albeit with differing importance.
- Inhaled treatments are preferred where possible, so as to limit systemic absorption.
- Nebulised treatments are the mainstay in the acute setting.
- As with most conditions, MDT input, education and lifestyle advice is important.

- *The following slides provide brief summaries of the management of acute and chronic asthma/COPD.*

SIMPLY FINALS

Long Term Management of Asthma in Adults

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

MOVE UP TO IMPROVE CONTROL AS NEEDED

MOVE DOWN TO FIND AND MAINTAIN LOWEST CONTROLLING STEP

STEP 1
Mild intermittent asthma

Inhaled short-acting β_2 agonist as required

STEP 2
Regular preventer therapy

Add inhaled steroid 200-800 mcg/day*
400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 3
Initial add-on therapy

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
   - **good response to LABA** - continue LABA
   - **benefit from LABA but control still inadequate** - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
   - **no response to LABA** - stop LABA and increase inhaled steroid to 800 mcg/ day.*If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 4
Persistent poor control

Consider trials of:
- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 5
Continuous or frequent use of oral steroids

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

* BDP or equivalent

SYMPTOMS vs TREATMENT

Summary of stepwise management in adults

*Acute Asthma Exacerbation Management

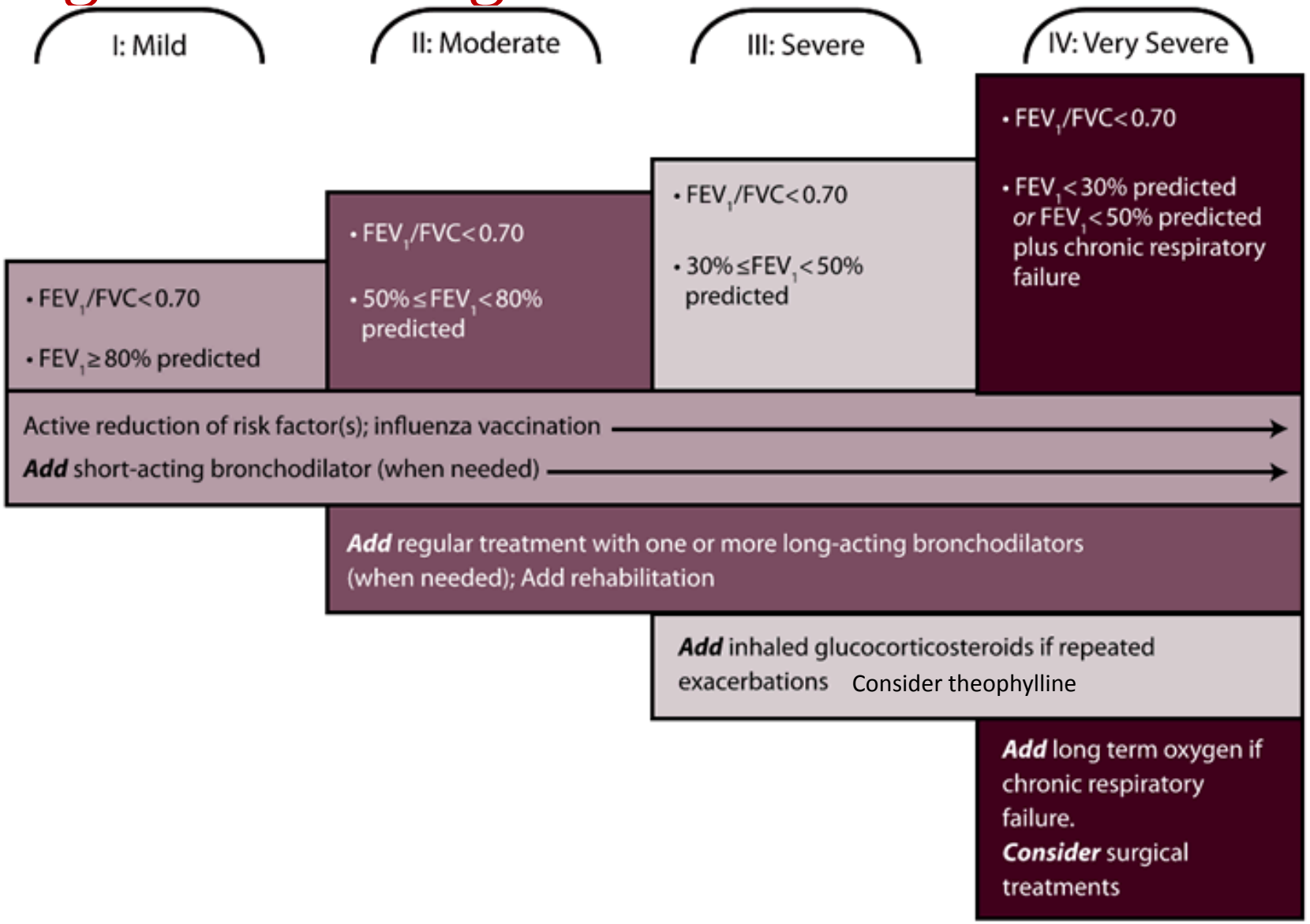
REASSESS

- O2 via Non-Rebreathe mask
- Nebulised Salbutamol (2.5-5mg)
- Nebulised Ipratopium (500µg)
- Corticosteroids (100-200mg IV, 40mg PO)
- IV $MgSO_4$ (1.2-2g)
- IV Salbutamol (5µg/min)
- IV Aminophylline (5mg/kg loading then 500mcg/kg/hr)

CALL FOR HELP

***Brief overview of...** (See www.sign.ac.uk/pdf/qrg101.pdf or Oxford Handbook for more detail)

Long Term Management of COPD



***Brief overview of...** (See www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf or OHCM)

*Acute COPD Exacerbation Management

- Controlled Oxygen Therapy
- *(remember, hypoxia kills before hypercapnia)*

REASSESS

- Nebulised Salbutamol and Ipratropium
- IV or PO corticosteroids
- Are Antibiotics Needed?
- Consider Non-invasive ventilation

CALL FOR HELP

***Brief overview of...** (See www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf or OHCM)

Thank-You

Any Questions?