

Drugs used in Asthma and COPD

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Outline

- Modes of Delivery
- Overview of the drugs used in Asthma and COPD
 - β -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*



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**



β₂-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 Ca²⁺ → 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.



β 2-Agonists

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

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

Long Acting (12 hours) – *Inhaled only*

- Salmeterol – 50-100 μ g bd
- Formoterol – 12 μ g bd



Side-effects

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



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 β_2 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.



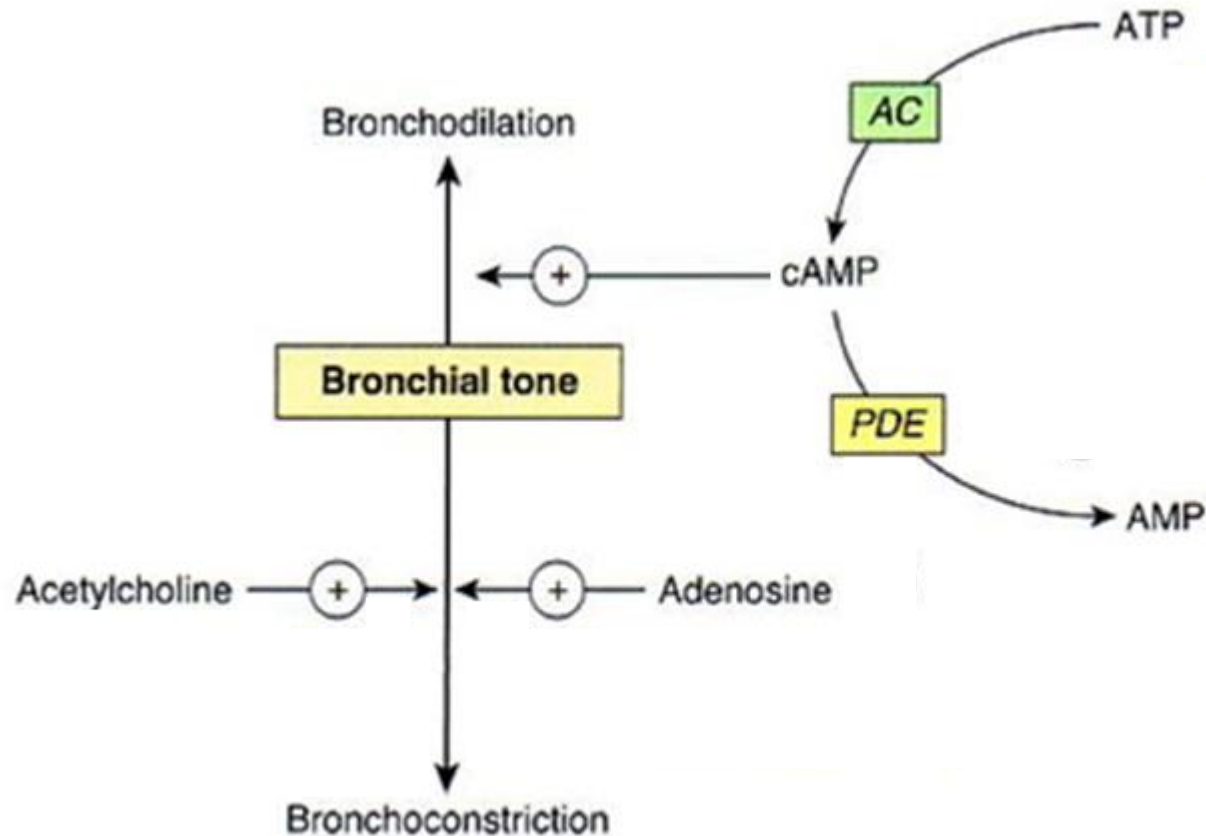
Methylxanthines

- 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 β -agonists, Anti-Muscarinics and Theophylline



AC: Adenylate Cyclase

PDE: Phosphodiesterase

(c)AMP: (cyclic) Adenosine Monophosphate

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
- Budesonide – 100-800 µg bd

Oral

- Prednisolone – 30-60mg od

IV

- Hydrocortisone – 100-200mg

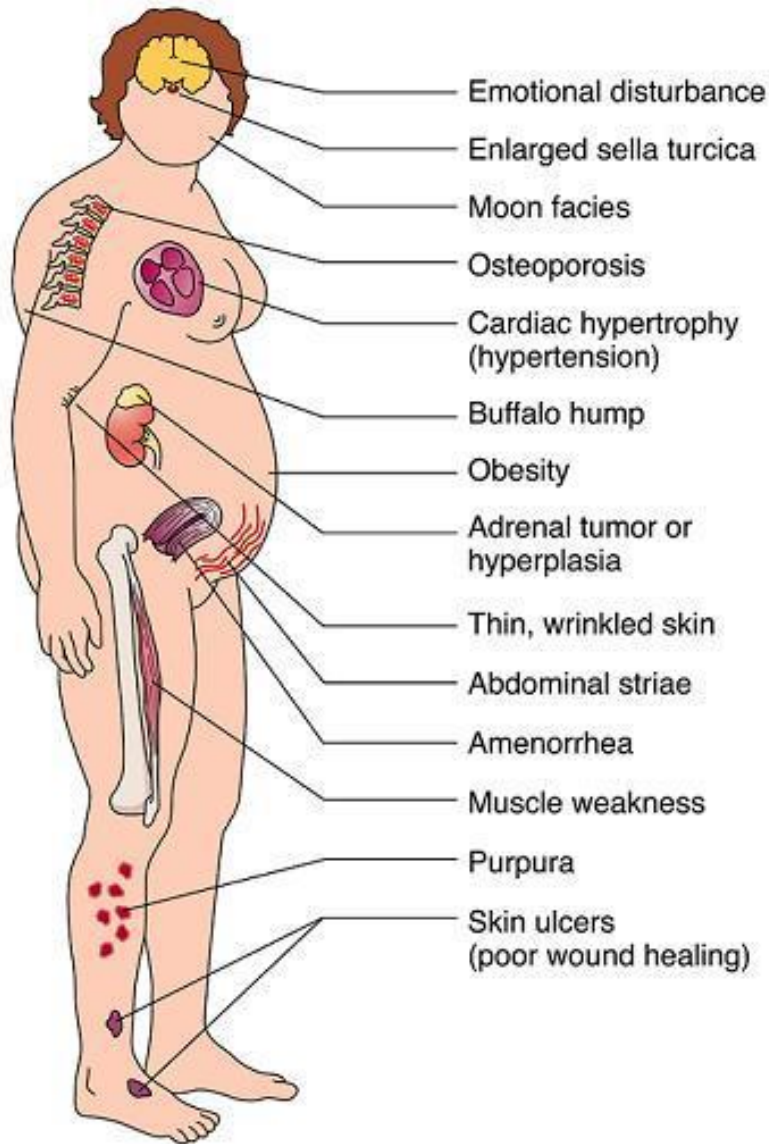
Note, oral and IV steroids have the same benefit in the acute setting (presuming the patient can swallow and isn't vomiting)

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

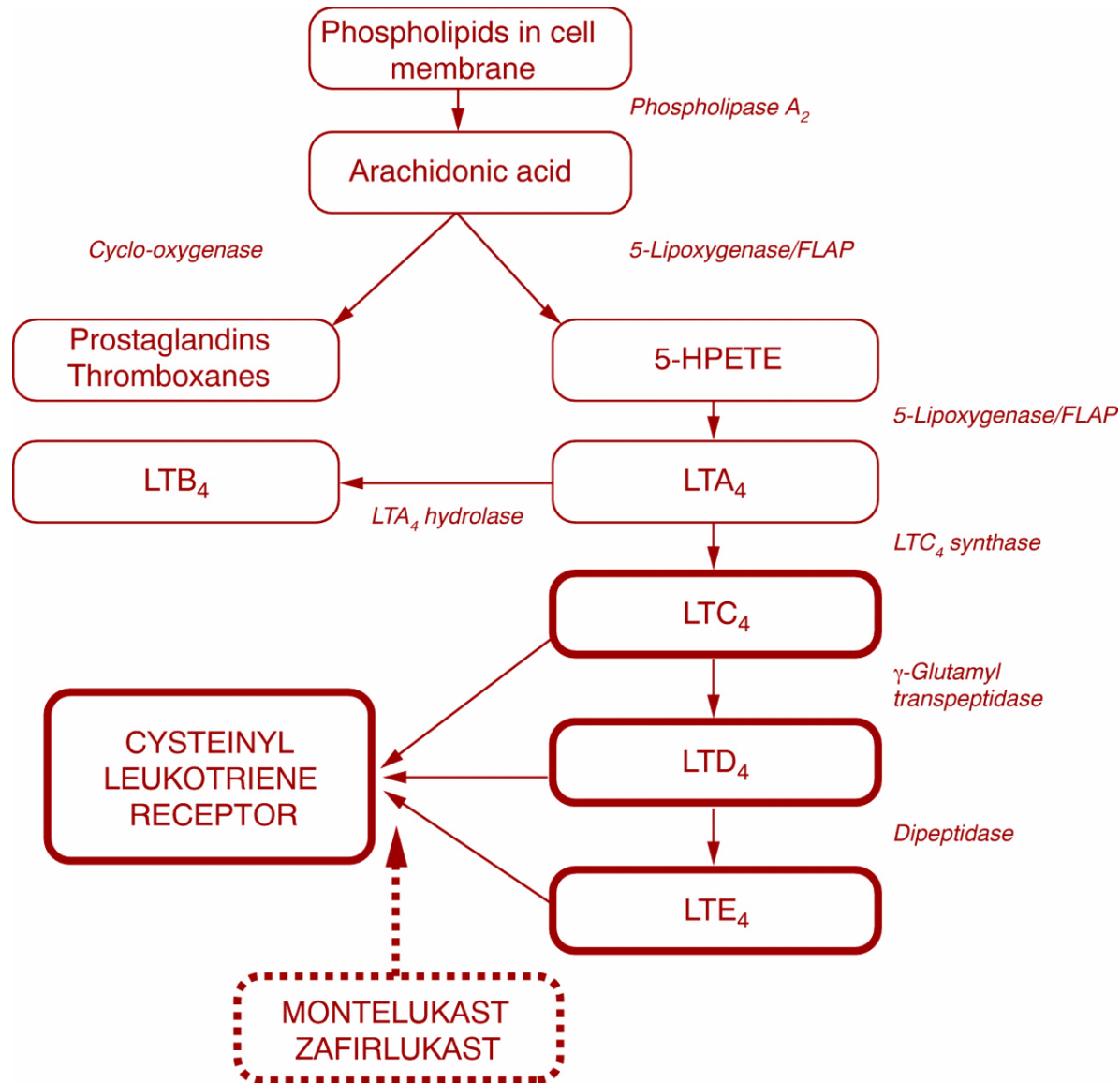
Cardiovascular: hypertension

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.

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.

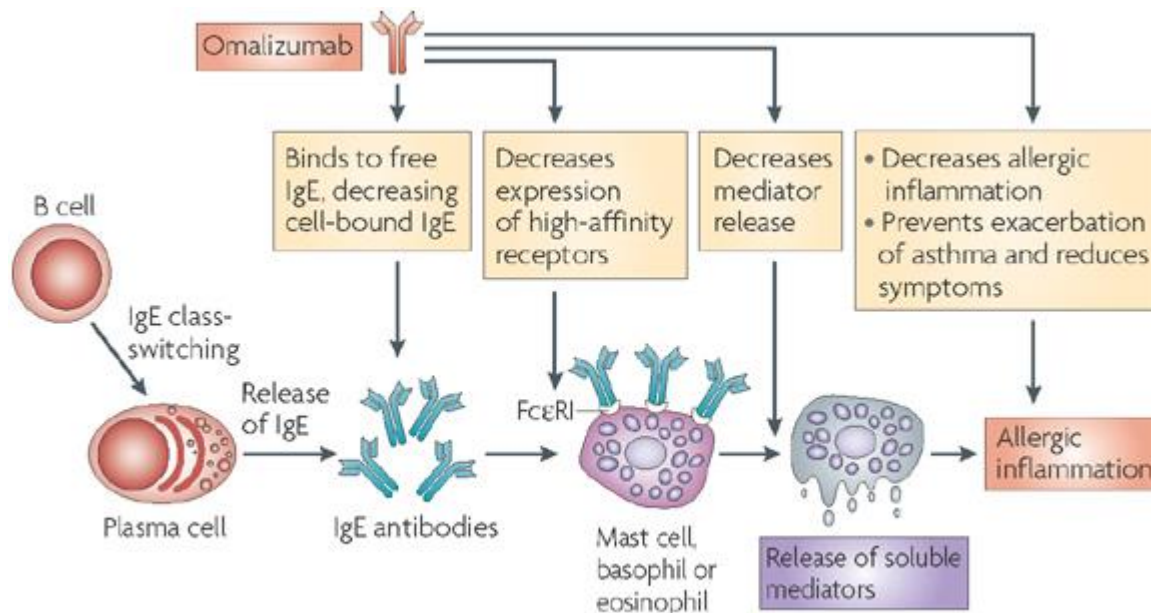


Anti-IgE Monoclonal - Omalizumab

- 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.



Other Asthma Medications

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

- β 2-agonist and steroid e.g Symbicort
- β 2-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 adjunct 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

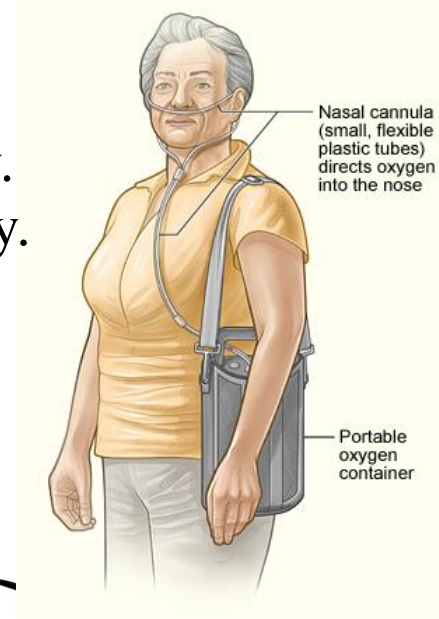
- 1.5-4mg/min
- Is a respiratory stimulant and only recommended when non-invasive ventilation is considered inappropriate
- Stimulates chemoreceptors in the carotid bodies of the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem.
- Side-effects/Cautions – see BNF!

(Briefly:) Long Term Oxygen Therapy

Main eligibility criteria in adults:

- Patients with PaO_2 of <7.3 when stable (no infection) in air.
- Patients with a PaO_2 of $7.3\text{-}8\text{kPa}$ 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

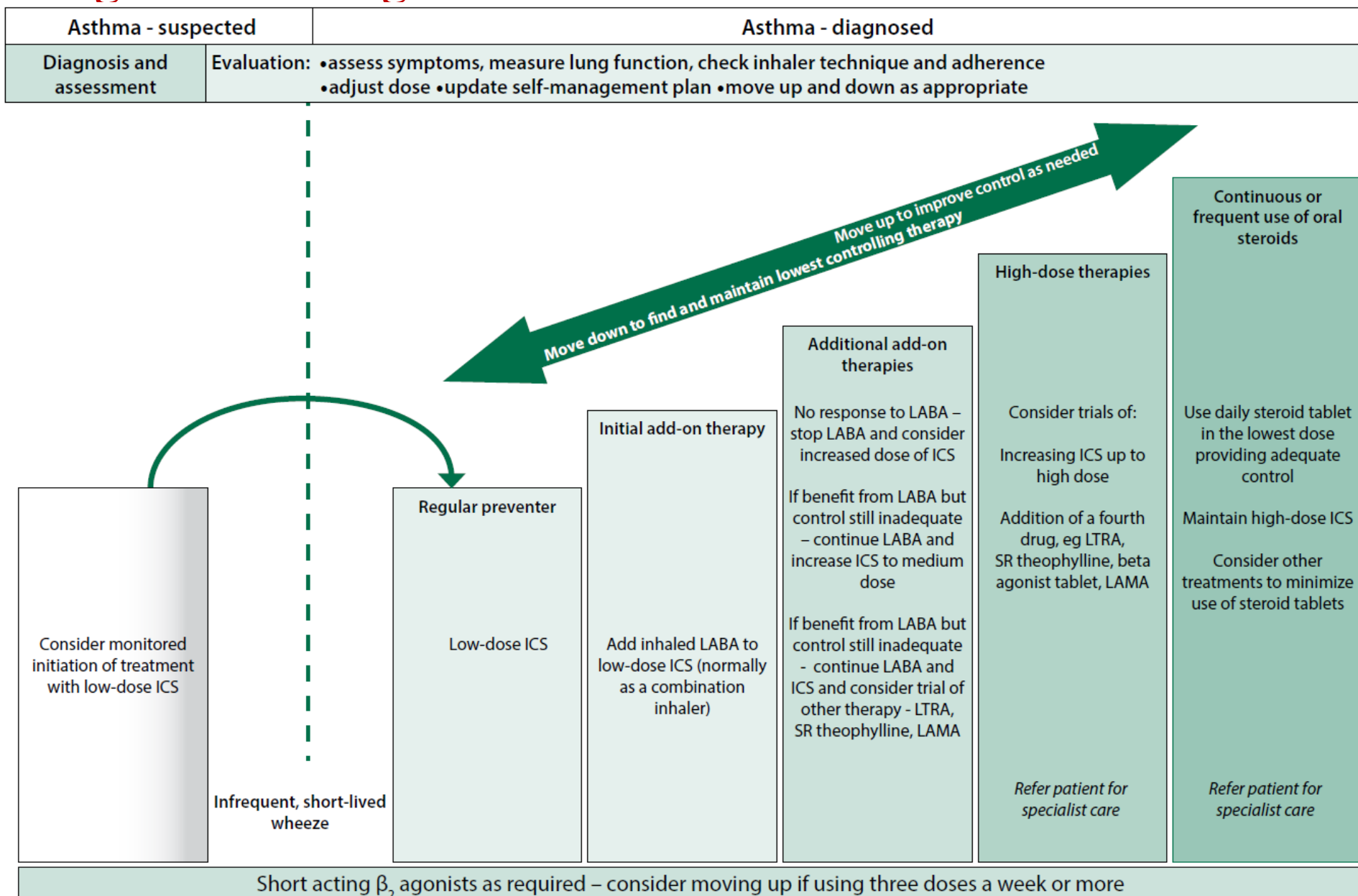


Summary

- 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.*



Long Term Management of Asthma in Adults



*Acute Asthma Exacerbation Management

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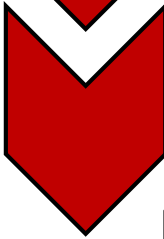
- O₂ via Non-Rebreathe mask



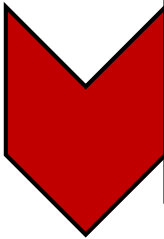
- Nebulised Salbutamol (2.5-5mg)



- Nebulised Ipratropium (500µg)



- Corticosteroids (100-200mg IV, 40mg PO)



- IV MgSO₄ (1.2-2g) (*Consider in acute severe asthma*)
- IV Salbutamol (5µg/min)
- IV Aminophylline (5mg/kg loading then 500mcg/kg/hr)

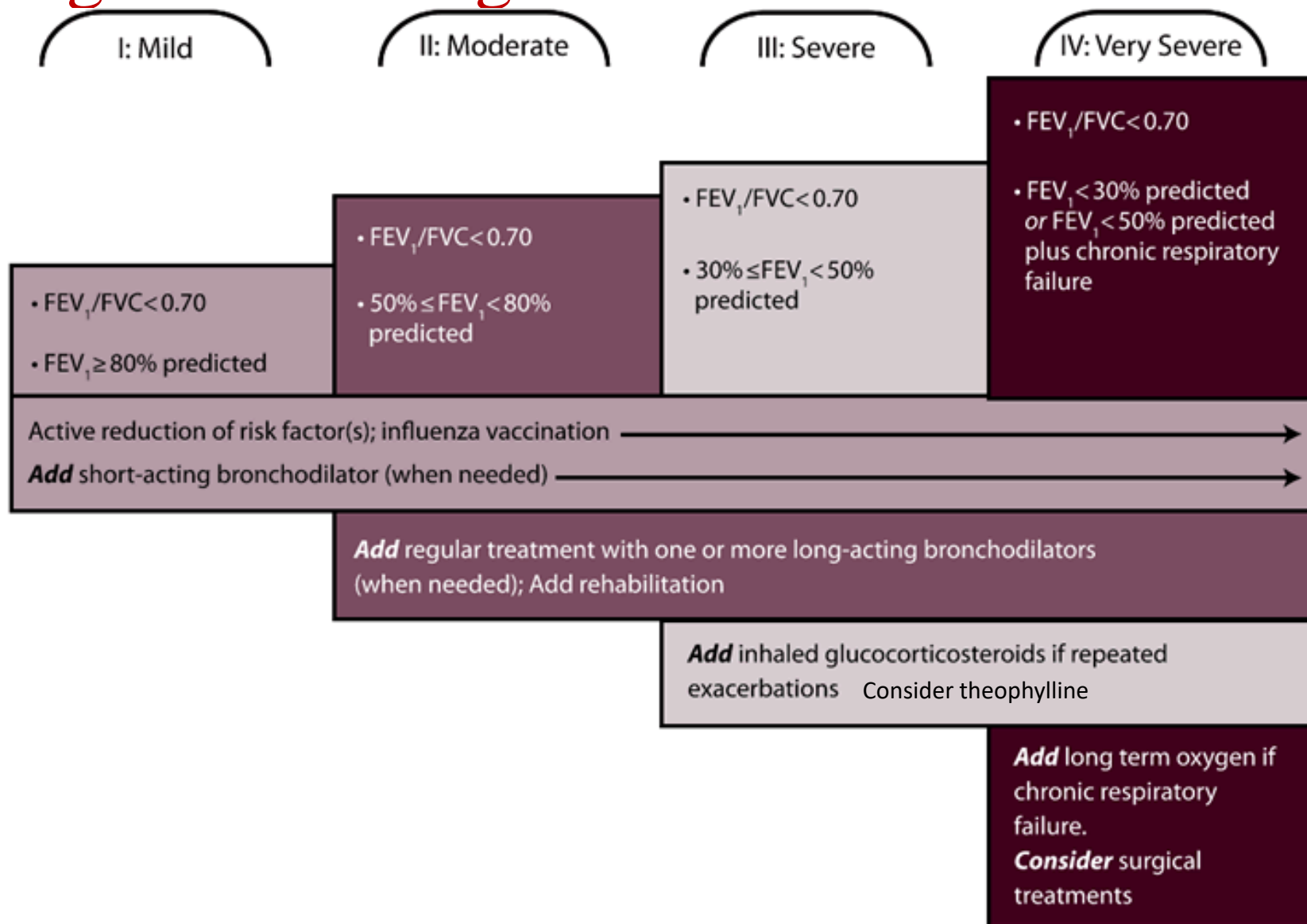
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*Brief overview of... (Check following website for more detail: <http://tinyurl.com/asthmaquickreference>)

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

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

- Nebulised Salbutamol and Ipratropium

- IV or PO corticosteroids

- Are Antibiotics Needed?

- Consider Non-invasive ventilation
- Consider Theophylline

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

Thank-You

Any Questions?

