put together by Alex Yartsev: Sorry if i used your images or data and forgot to reference you. Tell me who you are.
aleksei.igorevich@gmail.com

Steroids and Bronchodilators for COPD

COPD defined as "irreversible airflow limitation"
Diagnosis rests on spirometry findings:
= FEV1/FVC is less than 70% of predicted
mild COPD = FEV1 still over 80%,
moderate COPD = FEV1 between 30% and 80%
severe COPD = FEV1 below 30%

Bronchodilators:

General guidelines:

- Training in inhaler technique is essential.
- On average, 80% of inhaled drug will settle on the oropharynx mucosa
- Which drugs you use depends on individual response.
- Use long-acting drugs where possible. (**i.e salmeterol**)
- Use of two or three drugs together is better than either one used alone.
- This is especially true for a [B2-agonist + anticholinergic] combo
  BUT: polypharmacotherapy is expensive.
  THUS: Use just one drug when side effects are not the limiting factor:
  i.e increase the dose of whatever they are already on.

IN BRIEF:
- **Use long-acting ones**
- **Use one drug unless limited by side-effects**
- **Beta 2 agonist + ipratropium = best combination ever!**
- **Avoid theophylline unless you have a good reason to use it**
- **Steroids only for far gone symptomatic COPD**
- **NEVER give chronic oral steroids**

Beta-2-agonists: Eg. salbutamol (short) terbutaline, salmeterol (long acting)

Action: impersonate noradrenaline at the beta-2 receptor. Dose response is log-linear: doubled effect is achieved only by a 10-fold increase in dose

Effects: bronchodilatation, enhancement of mucociliary clearance, inhibition of cholinergic transmission, enhances vascular integrity and inhibits mast cell mediator release. Last from minutes to 12 hour

Side effects: Tremor, tachycardia, vasodilation, hyperglycaemia, hypokalaemia, hypomagnesaemia.

Indication: **Use as needed with mild COPD** (FEV1 >80%); **Use regularly with severe COPD** (FEV1 <80%)

Anticholinergics: eg. Ipratropium (Atrovent), tiotropium, oxitropium (long acting)

Action: competitive muscarinic acetylcholine receptor antagonists. Most potent at inhibition of bronchial receptors less so of salivary receptors, and minimal effects on cardiac and urinary bladder receptors

Effects: bronchodilation; lasts about 2-4 hrs

Side effects: dry mouth due to effects on the salivary glands. Otherwise systemic effects are negligible with an inhaled dose (sometimes: palpitations, nervousness, anxiety, headache, nausea)

Indication: **Use as needed with mild COPD** (FEV1 >80%); **Use regularly with severe COPD** (FEV1 <80%)

Methylxanthines: theophylline (Oral formula), aminophylline (Intravenous formula)

Action: poorly understood, probably involves competitive inhibition of adenosine receptors

Effects: bronchodilation, improves diaphragmatic contraction, increases rate of mucociliary clearance, increases rate and force of cardiac contraction, lowers blood pressure, increases rate of urine production, increases renal blood flow, and has some anti-inflammatory effect.

Side effects: nausea and diarrhoea at high therapeutic levels; cardiac arrhythmias and fits when plasma concentration exceeds recommended range. Normal doses produce some caffeine-like CNS stimulation.

Indication: **Use when aerosol therapy is impossible or unavailable or the patient is refractory to inhaled bronchodilators.** Because of potential toxicity, inhaled bronchodilators are preferred when available. **Avoid using in liver disease. It interacts with anti-epileptic drugs, allopurinol, erythromycin, cimetadine.**

Inhaled corticosteroids: beclomethesone, budesonide, fluticasone and others.

Action: combine with intracellular receptors, produce many effects (eg. inhibit phospholipase A2, suppress immune system, etc etc)

Effects: **DO NOTHING TO STOP RESPIRATORY FUNCTION FROM DECLINING.**
Reduce frequency of exacerbations, improves respiratory function (sometimes)

Side effects: Hoarseness, mouth candida infections, Cushings syndrome with prolonged use.

Indication: **ONLY ever use these when the patient has moderate to severe SYMPTOMATIC COPD, OR when the patient regularly presents with acute exacerbations**
ALSO you need to demonstrate that there is a benefit:
THUS do a trial of 6 weeks to 3 months, with regular spirometry. If FEV1 / FVC improves, continue.

Oral corticosteroids: useless and dangerous.

a side effect of long-term treatment with systemic glucocorticosteroids is **steroid myopathy** which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.

OTHER PHARMACOTHERAPY for COPD

Vaccines. Influenza vaccines can reduce serious illness and death in patients with COPD by approximately 50%
- should be given once (in autumn) or twice (in autumn and winter) each year

alpha1-Antitrypsin augmentation therapy. Young patients with severe hereditary $_1$-antitrypsin deficiency and established emphysema may be candidates for $_1$-antitrypsin augmentation therapy.
- However, this therapy is very expensive and is not available in most countries.

Antibiotics: not recommended other than in treating infectious exacerbations of COPD and other bacterial infections

Mucolytic (mucokinetic, mucoregulator) agents. (ambroxol, erdosteine, carbocysteine, iodinated glycerol):
- overall benefits seem to be very small. Very few patients will benefit (NNT very large)

Antioxidant agents. Antioxidants, in particular *N*-acetylcysteine, have been shown to reduce the frequency of exacerbations.
- could have a role in the treatment of patients with recurrent exacerbations, but jury is still out.

Immunoregulators (immunostimulators, immunomodulators). One study only, crap evidence.
- decrease the severity (though not in the frequency) of exacerbations - but these results have not been duplicated.

Antitussives. Cough has a significant protective role. NEVER USE ANTITUSSIVES!

Vasodilators. inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-balance and thus is contraindicated.

Narcotics. Narcotics are contraindicated in COPD because of their respiratory depressant effects and potential to worsen hypercapnia. Clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects. Codeine and other narcotic analgesics should also be avoided.

Others. Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupuncture, homeopathy) have not been adequately tested in COPD patients and thus cannot be recommended with a straight face.

Managing stable COPD: data from RCTs

COPD requires a stepwise increase in treatment, depending on the severity of the disease.

1. **EDUCATION**: improves ability to cope with illness
   Also improves chances of smoking cessation
   Also helps patient recognise and cope with acute exacerbations
2. **SMOKING CESSATION** reduces rate of decline in lung function
3. **EXERCISE:** All patients with COPD benefit from exercise training programs,
   Improves exercise tolerance and symptoms of dyspnea and fatigue
4. **HOME OXYGEN: > 15 hrs per day:** increases survival if chronic respiratory failure.
5. **PHARMACOTHERAPY** to improve symptoms: **DOES NOT MODIFY DISEASE PROGRESSION**
   - **Bronchodilators** = central to symptom management
     - Beta-2-agonists
     - Anticholinergics
     - Theophylline
   - **Avoid corticosteroids** unless
     - Documented spirometric response to steroids
     - <50% FEV1/FVC and repeated exacerbations
   - **AVOID CHRONIC STEROIDS:** unfavourable risk-vs-benefit ratio

TABLE 8. THERAPY AT EACH STAGE OF COPD

Stage	Characteristics	Recommended Treatment	
All		Avoidance of risk factors Influenza vaccination	
0: At risk	Chronic symptoms (cough, sputum) Exposure to risk factors Normal spirometry		
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without symptoms	Short-acting bronchodilator when needed	
II: Moderate COPD	IIA $FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response
	IIB $FEV_1/FVC < 70\%$ $30\% \leq FEV_1 > 50\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation	Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or presence of respiratory failure or right heart failure	Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments	

TABLE 6. DIFFERENTIAL DIAGNOSIS OF COPD

Diagnosis	Suggestive Features*
COPD	Onset in mid-life Symptoms slowly progressive Long smoking history Dyspnea during exercise Largely irreversible airflow limitation
Asthma	Onset early in life (often childhood) Symptoms vary from day to day Symptoms at night/early morning Allergy, rhinitis, or eczema also present Family history of asthma Largely reversible airflow limitation
Congestive heart failure	Fine basilar crackles on auscultation Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages Chest X-ray shows lung infiltrate or nodular lesions Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset in younger age, nonsmokers May have history of rheumatoid arthritis or fume exposure CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

* These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

TABLE 10. COMMONLY USED BRONCHODILATOR DRUGS

Drug*	Metered-dose Inhaler (μg)†	Nebulizer (mg)†	Oral (mg)	Duration of Action (h)
β_2-agonists				
Fenoterol	100–200	0.5–2.0	—	4–6
Salbutamol (albuterol)‡	100–200	2.5–5.0	4	4–6
Terbutaline	250–500	5–10	5	4–6
Formoterol	12–24	—	—	12+
Salmeterol	50–100	—	—	12+
Anticholinergics				
Ipratropium bromide	40–80	0.25–0.5	—	6–8
Oxitropium bromide	200	—	—	7–9
Methylxanthines§				
Aminophylline (SR)	—	—	225–450	Variable, up to 24
Theophylline (SR)	—	—	100–400	Variable, up to 24

* Not all products are available in all countries.
† Doses: β_2-agonists refer to average dose given up to 4 times daily for short-acting and 2 times daily for long-acting preparations; anticholinergics are usually given 3–4 times daily.
‡ Name in parentheses refers to North American generic term.
§ Methylxanthines require dose titration depending on side effects and plasma theophylline levels.

TABLE 7. STRATEGIES TO HELP THE PATIENT WILLING TO QUIT SMOKING (75)

1. ASK: Systematically identify all tobacco users at every visit.
   Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented.
2. ADVISE: Strongly urge all tobacco users to quit.
   In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS: Determine willingness to make a quit attempt.
   Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 d).
4. ASSIST: Aid the patient in quitting.
   Help the patient with a quit plan; provide practical counseling; provide intratreatment social support; help the patient obtain extratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE: Schedule follow-up contact.
   Schedule follow-up contact, either in person or via telephone.

TABLE 9. BRONCHODILATORS IN STABLE COPD

Bronchodilator medications are central to symptom management in COPD.
Inhaled therapy is preferred.
The choice between β_2-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
Long-acting inhaled bronchodilators are more convenient.
Combining bronchodilators may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator.

TABLE 13. MANAGEMENT OF SEVERE BUT NOT LIFE-THREATENING EXACERBATIONS OF COPD IN THE EMERGENCY DEPARTMENT OR THE HOSPITAL*

Assess severity of symptoms, blood gases, chest X-ray.
Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 min.
Bronchodilators:
- Increase dose or frequency.
- Combine β_2-agonists and anticholinergics.
- Use spacers or air-driven nebulizers.
- Consider adding intravenous aminophylline, if needed.

Add glucocorticosteroids oral or intravenous.
Consider antibiotics when signs of bacterial infection, oral or occasionally intravenous.
Consider noninvasive mechanical ventilation.
At all times:
- Monitor fluid balance and nutrition.
- Consider subcutaneous heparin.
- Identify and treat associated conditions (e.g., heart failure, arrhythmias).
- Closely monitor condition of the patient.

* Local resources need to be considered.

ROMAIN A. PAUWELS, A. SONIA BUIST, PETER M. A. CALVERLEY, CHRISTINE R. JENKINS, and SUZANNE S. HURD on behalf of the GOLD Scientific Committee; **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease** : NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary; Am. J. Respir. Crit. Care Med., Volume 163, Number 5, April 2001, 1256-1276

Inhaled corticosteroids and COPD **Donald Farquhar, Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK, on behalf of the ISOLDE study.** CMAJ • August 8, 2000; 163 (3)