# Chronic Obstructive Pulmonary Disease

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## Definition

- COPD is characterised by **airflow limitation** that is **not fully reversible**
- The **airflow limitation** is usually both **progressive** and **associated with an abnormal inflammatory response of the lungs to noxious particles and gases**

## How common is COPD now?

- **Currently 5th leading cause of death worldwide** (4th in economically developed countries)
- **By 2020, COPD will become the 3rd leading cause of death worldwide** (Global Burden Of Disease Study)

## COPD: A LEADING CAUSE OF MORTALITY

- In 2003 in the UK 30,000 people died from COPD[1]
- COPD is the 3rd leading cause of death in Europe; 4th leading cause of death worldwide[2]
- Nearly 3 times more patients died from COPD than colon cancer in England and Wales in 1999[3]
- 20 deaths from COPD for every one with asthma

1. Shahab et al. Thorax 2006;61:1043-47
2. Murray and Lopez. Global burden of disease, 1996
3. National Office of Statistics, 1999

## Spirometry coupled with a good history

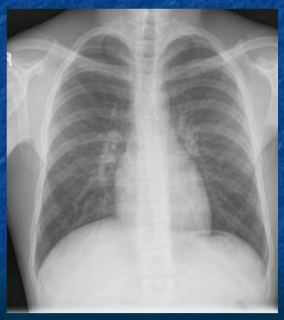
The cornerstone of diagnosing COPD

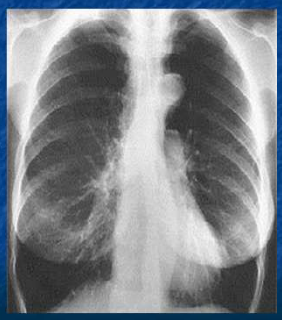
¾ of the lungs empty in 1 second; FEV1/FVC<70%

- COPD: This emptying is delayed and incomplete:: the lungs are nowhere near 75% empty after 1 second
- This brings FEV1/FVC <0.7

- **Spirometry: How fast do the lungs empty?**

## Consequences of airflow obstruction

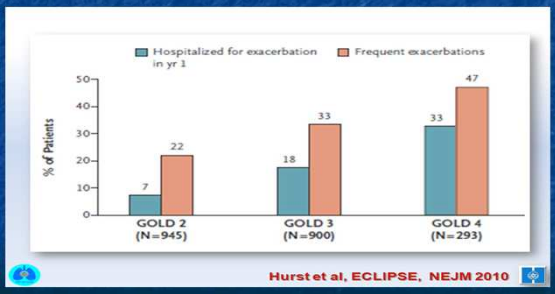




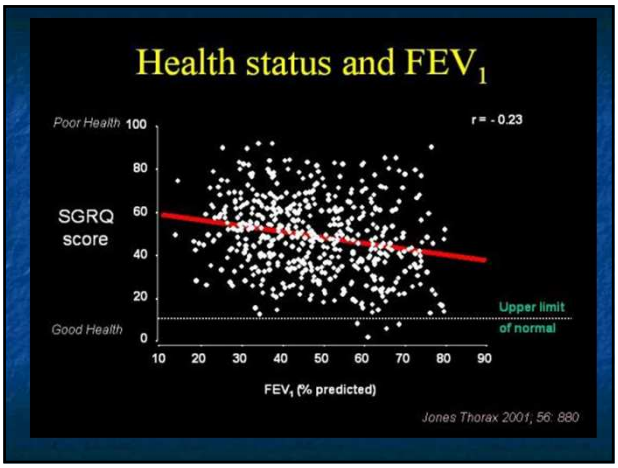
## Classifying COPD: GOLD and NICE

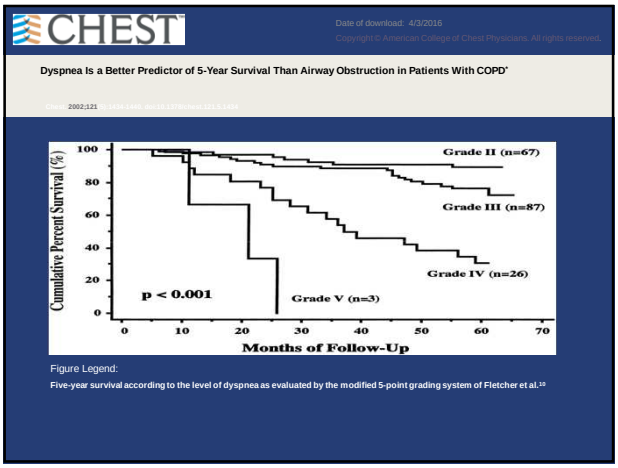
| Post-bronchodilator $FEV_1/FVC$ | $\%FEV_1$ predicted | GOLD (2014) Post-bronchodilator | NICE (2010) Post-bronchodilator |
|---|---|---|---|
| <0.7 | ≥80% | Stage 1 - Mild | Mild* |
| <0.7 | 50–79 | Stage 2 - Moderate | Moderate |
| <0.7 | 30–49 | Stage 3 - Severe | Severe |
| <0.7 | <30 | Stage 4 - Very severe | Very severe** |

## Relationship between GOLD staging with exacerbations and hospitalization




## Both have the same %FEV1 predicted


Health status and FEV1
Poor Health
Good Health
SGRQ score
r = - 0.23
Upper limit of normal
FEV1 (% predicted)
Jones Thorax 2001; 56: 880


CHEST
Date of download: 4/3/2016
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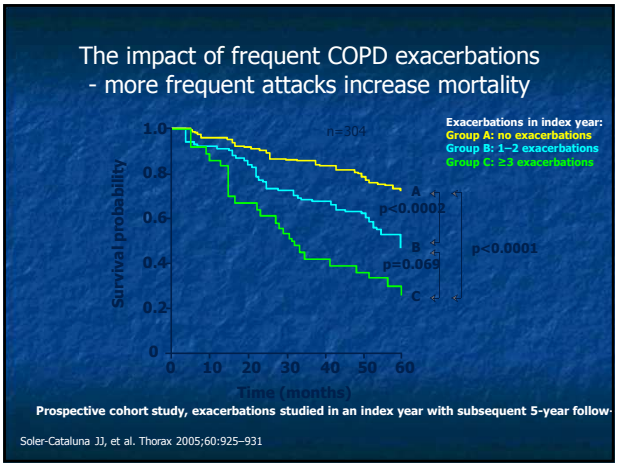
Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD*
Grade II (n=67)
Grade III (n=87)
Grade IV (n=26)
Grade V (n=3)
p < 0.001
Cumulative Percent Survival (%)
Months of Follow-Up
Figure Legend:
Five-year survival according to the level of dyspnea as evaluated by the modified 5-point grading system of Fletcher et al.[3]


The impact of frequent COPD exacerbations
- more frequent attacks increase mortality
n=304
Exacerbations in index year:
Group A: no exacerbations
Group B: 1–2 exacerbations
Group C: ≥3 exacerbations
Survival probability
p<0.0002
p=0.069
p<0.0001
Time (months)
Prospective cohort study, exacerbations studied in an index year with subsequent 5-year follow-
Soler-Cataluna JJ, et al. Thorax 2005;60:925–931

## Predicting mortality in COPD: BODE index

- B: Body mass index (BMI > 21)
- O: Obstruction to airflow
- D: Dyspnoea index
- E: Exercise capacity

- ***The BODE index (a 10 point scale) predicted mortality and prognosis more accurately than the FEV1 alone*** *(Celli et al; NEJM 350; 1005-1012)*

## Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index

**Table 2.** Variables and Point Values Used for the Computation of the Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*

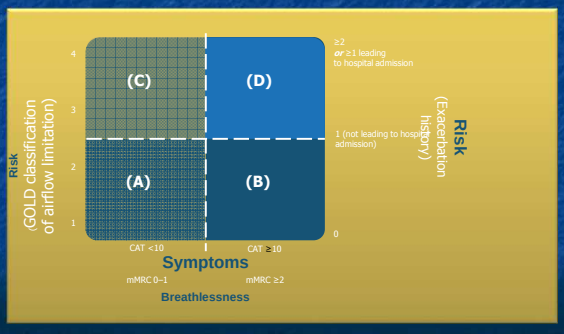
| Variable | Points on BODE Index | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| $FEV_1$ (% of predicted)† | ≥65 | 50–64 | 36–49 | ≤35 |
| Distance walked in 6 min (m) | ≥350 | 250–349 | 150–249 | ≤149 |
| MMRC dyspnea scale‡ | 0–1 | 2 | 3 | 4 |
| Body-mass index§ | >21 | ≤21 | | |

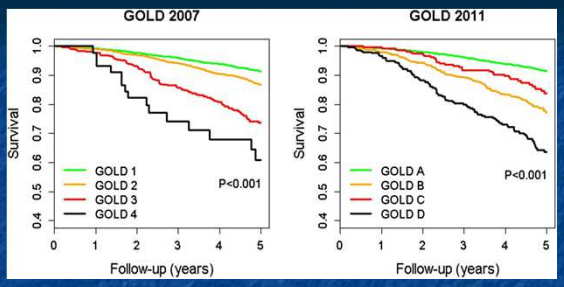
* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. $FEV_1$ denotes forced expiratory volume in one second.
† The $FEV_1$ categories are based on stages identified by the American Thoracic Society.
‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Celli, B. R. et al. N Engl J Med 2004;350:1005-1012

The NEW ENGLAND JOURNAL of MEDICINE

## Revised GOLD classification system



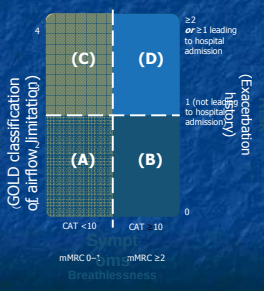



Group B: 3 year mortality from Cardiac Disease: 10.6%

Group C: 3 year mortality from Cardiac Disease: 3.8%

(Lange et al Am J Resp Crit Care Med 2012

## Principles of managing COPD




- Make a diagnosis: History and spirometry
- Control of symptoms
- Reduce exacerbations
- Address co-morbidities

## COPD is a risk factor for cardiovascular death

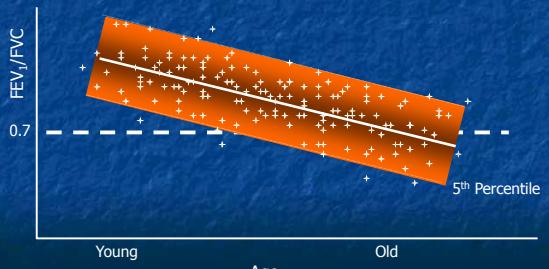
- For every 10% decrease in FEV1, cardiovascular mortality increases by 28%; all cause mortality increases by 14% ***Sin et al; Proc Am Thoracic Society 2005; 2 (1): 8-11***
- **Having COPD is a powerful independent risk factor for coronary artery disease**
- **The breathlessness in mild COPD could be due to cardiac disease (Check ECG, BNP etc)**

## What defines COPD? FEV1/FVC<0.7?

- As people get older, the elastic recoil of the lungs gets less i.e. they deflate more slowly but this is physiological
- This could bring the FEV1/FVC ratio <0.7
- Risks falsely classifying elderly people as having COPD
- **Lower limit of normal of FEV1/FVC** i.e. bottom 5% of a healthy non smoking population in terms of FEV1/FVC ratio (1.645 SDs below the predicted value)

## Relationship between FEV1/FVC and age

**We can misclassify «normals» as having COPD or miss other causes of SOB e.g. Cardiac disease**




(Hardie, Phoney Data, 2008)

## FEV1/FVC ratio v LLN

- Study of 7879 participants, aged 40–95 years, no diagnosis of asthma: underwent spirometry data.

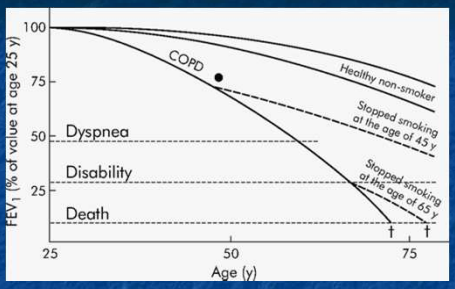
Prevalence of COPD:

- 22.2% using Fixed Ratio i.e. GOLD; FEV1/FVC <0.7
- 13.1% using LLN criteria

(Scholes et al BMJ 2014)

## Could the breathlessness in apparently mild COPD be due to cardiac disease?

- 6.4% had an FEV1/FVC < 0.70 (FEV1 100–50% predicted) yet ≥LLN; *Lamprecht et al Pulm Med 2011*
- More likely to be significantly older and male gender
- A diagnosis of heart disease observed more often than subjects with "normal" lung function (FEV1/FVC > 0.70 & FVC ≥ 80% pred.)

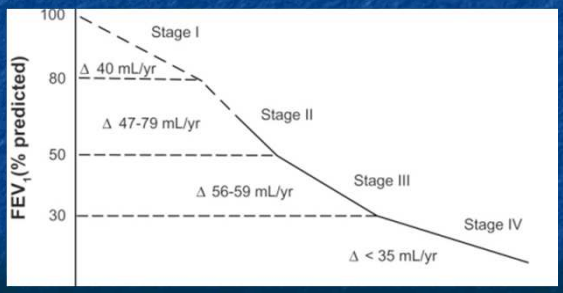



Bednarek, M et al. Thorax 2006;61:869-873

Thorax ONLINE

## The natural history of COPD

(Tantucci Int J COPD 2012)



## Distinguishing COPD from Asthma

- Smoking history: 80-90% of COPD in developed countries due to tobacco smoking
- **Presentation at advanced age, 6 times more prevalent over the age of 60** (beware younger patients with a history of illicit drug use)
- Nocturnal wakening, reactive symptoms with triggers points to asthma
- Spirometry: If lung function returns to normal following administration of a bronchodilator, then it isn't COPD (16-23% of asthma patients have irreversible obstruction)
- Peripheral eosinophilia: Asthma
- Raised IgE levels; preserved gas transfer: points to asthma

## COPD v Asthma

**Table 1.1. Similarities and distinguishing features of COPD and asthma (adapted from NICE Clinical Guidance 101, 2010)[1]**

| | COPD | Asthma |
|---|---|---|
| Patients are current smokers or have previously smoked | Usually | Possibly |
| Symptoms present in patients <35 years | Rare | Often |
| Chronic and productive cough | Common | Uncommon |
| Breathlessness | Persistent and progressive | Variable |
| Night-time waking with breathlessness and/or wheeze | Uncommon | Common |
| Day-to-day variability in presenting symptoms | Uncommon | Common |

## BACTERIAL INFECTIONS CAUSING AECOPD (common)

60% - Haemophilus influenza
Moraxella catarrhalis
Streptococcus pneumoniae
10% - Atypical Chlamydia
0-10% - Pseudomonas aeruginosa
gram(-) enteric bacilli

Newer studies include methicillin-sensitive Staph Aureus (16%) in severe AECOPD in ICU.

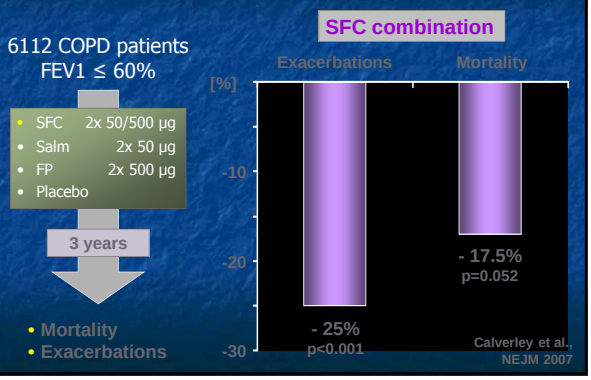
Nseir S et al, Respiration 2008

## Indications for inhaled steroids in COPD

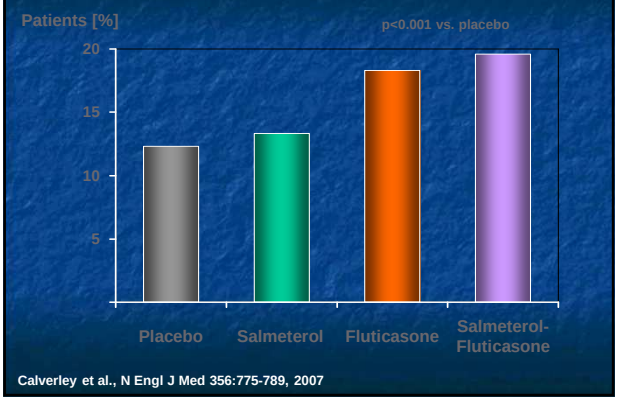
- FEV1 less than or equal to 50% predicted
- 2 or more exacerbations in 12 months
- Different from asthma where inhaled steroids are the cornerstone of management from step 2 onwards (need to use Salbutamol reliever >3 times a week)
- Oral steroids given in COPD as a 5-7 day course during acute exacerbations

## TOwards a Revolution in COPD Health

## TORCH: Salmeterol and fluticasone in COPD




## TORCH: Risk of pneumonia




Calverley et al., N Engl J Med 356:775-789, 2007

## COPD patients and Inhaled Steroids: The Risk of Pneumonia

- INSPIRE study (Seretide 500/50 v Tiotropium 18ucg) in 1323 COPD patients over 2 years
- 2 fold increase in Pneumonia events in the Seretide arm (7 v 4%; p=0.008) but overall, mortality was half in this group (4 v 8%;p=0.03)
- **Dose dependent effect:** Odds Ratio 2.5 for Pneumonia if taking >1000ucg Fluticasone daily; 1.50 for 500ucg daily)
- Pneumonia more common in patients more breathless at baseline
- Risk persists 9-12 months following cessation of Inhaled Steroid

*Am J Respir Crit Care Med 2008; (177): 19-26*

## Anticholinergic bronchodilators in COPD



## UPLIFT trial

- Randomised double blind 4 year trial *(Taskhin et al; NEJM Oct 2008)*
- 5993 COPD patients (FEV1 1.32 litres; 30% current smokers)
- Randomised to once daily tiotropium or placebo
- Improvement in quality of life/health status
- Reduced risk of COPD exacerbations by 14% (p< 0.001) and respiratory failure by 33%
- All cause mortality reduced by 16% (p=0.016) as well as respiratory and cardiac morbidity significantly (p<0.05)

## Newer anticholinergics in COPD




## Combining LABA and LAMA in COPD




## The WISDOM of withdrawing Inhaled steroids in COPD

- 12-month study; 2485 patients with a history of exacerbation of COPD (Magnussen et al NEJM 2014)
- 6 week run in: triple therapy consisting of tiotropium, salmeterol and the ICS fluticasone propionate (500 µg twice daily) during a 6-week run-in period.
- 1243 continued to receive tiotropium, salmeterol and fluticasone
- 1242 continued to receive tiotropium and salmeterol but had a stepwise reduction in the fluticasone dose every 6 weeks from a total daily dose of 1000–500 µg, then to 200 µg and finally to 0 µg (placebo)

## The WISDOM of withdrawing Inhaled steroids in COPD

- ICS withdrawal not associated with either an increased risk of exacerbation (HR 1.06 (95% CI 0.94 to 1.19)) or increased rate of exacerbations (0.95/pt/y (95% CI 0.87 to 1.04)
- ICS withdrawal was associated with a fall in FEV1 by 43 mL compared with the "continuation" group at the end of the year.
- No significant difference in Breathlessness scores or in Quality Of Life
- **If no benefit seen with ICS/LABA: withdraw and stop: replace with a LABA/LAMA bronchodilator**

## The role of oxygen in stable COPD

- **Long term oxygen therapy**: A minimum of 15 hours of oxygen a day; delivered via a concentrator; patient usually receives this via nasal prongs
- **Short burst oxygen therapy**: Oxygen delivered via cylinders : **No evidence**
- **Ambulatory oxygen therapy**: Portable oxygen devices for when the patient is out of the house

## Long term oxygen therapy reduces mortality and influences disease progression in COPD

- Report of Medical Research Council (MRC) working party; Lancet 1981; 1: 681-5
- Randomised controlled trial in 87 severely hypoxic COPD patients: LTOT (42 patients) v No oxygen (45 patients)
- 5 year survival of 41% in LTOT arm against 25% in control arm
- Also: NOTT trial group (Ann Inter Med 1980; 93: 391-8)

## When should COPD patients receive Long term oxygen therapy?

- When oxygen levels on arterial blood (PaO2) fall below 7.3 kPa (or 55mmHg) on room air on 2 separate measurements 6 weeks apart (8.0 kPa in presence of polycythaemia, heart failure, cor pulmonale)
- FEV1 should be below 1.5 litres
- Patient should have stopped smoking
- Patient must be clinically stable (free of exacerbations) during this time

## The role of mucolytics in reducing COPD exacerbations

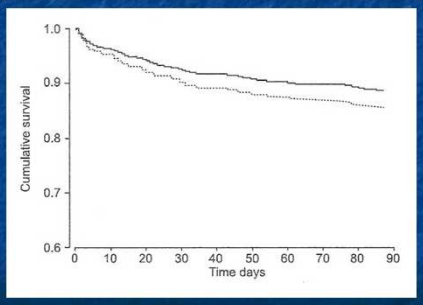
- A trial may be beneficial in COPD patients with a history of recurrent exacerbations
- **Cochrane review 2015:** 26 studies with 6233 participants: likelihood of being exacerbation-free during the study period was greater among mucolytic groups (OR) 1.75, 95% confidence interval (CI) 1.57 to 1.94)
- Need to treat 8 patients with mucolytics for a period of 10 months to keep 1 patient exacerbation free
- NAC (600mg daily) shown to **have a more beneficial effect in reducing exacerbations in those not treated with Inhaled Steroids** (Bronchus study)

## The role of mucolytics in reducing COPD exacerbations

- **Carbocisteine:** 709 COPD patients with >=2 exacerbations (The PEACE study)
- 1-year treatment with carbocysteine (1,500 mg) v placebo
- Reduced the rate of exacerbations with carbocisteine v placebo by 25% (1·01 [SE 0·06] vs 1·35 [SE 0·06]) (95% CI 0·62–0·92, p=0·004)
- No difference in exacerbation rate at 3 months
- **Erdocisteine 300mg BD for acute exacerbations** for a 7-10 day course: may improve symptoms and time course of exacerbation (Marchioni et al 1995)

## Pneumonia complicating COPD

744 CAP admissions, including 215 with COPD




Restrepo et al *Eur Respir J* 2006;28:346-351

## Influenza vaccination

- Cochrane review (*Poole et al; The Cochrane Database of Systematic Reviews 2000; Issue 3*); 4 randomised controlled trials of the inactivated flu vaccine (Range of effectiveness 30-80%)
- Significant reduction in number of early and late exacerbations in flu vaccinated subjects when compared to placebo
- Recent RCT of influenza vaccination; 125 patients; effectiveness rates of 76%: ***Chest 2004; 125: 2011-2020***

## Does the Polysaccharide 23 PPS Vaccine prevent Pneumonia in your patients?

- 47,365 persons>65 years assessed over 3 years
- 61 had pneumococcal bacteraemia; 1428 hospitalized with CAP; 3061 diagnosed with CAP in community
- 26,313 vaccinated before study commenced
- Additional 10,869 vaccinated during study period

**What were the outcomes in Vaccinated Individuals?**

- Vaccinated individuals had a 44% reduction in risk of developing bacteraemia
- Vaccinated individuals had a higher risk of hospitalization due to Community Acquired Pneumonia (OR 1.14)
- No difference in overall Pneumonia incidence

*Jackson et al; NEJM 2003 348;18:1747-1755*

## Prophylactic Antibiotics in COPD

- Azithromycin 250mg daily (Albert et al; N Engl J Med. 2011 Aug 25;365(8):689-98)
- Postulated to have anti-inflammatory effects
- 1142 COPD patients randomly assigned to receive azithromycin, at a dose of 250 mg daily (n=570) or placebo (n=572) for 1 year
- Median time to the first exacerbation: 266 days v 174 days (p<0.001)
- Frequency of exacerbations: 1.48 exacerbations per patient-year in the azithromycin group, as compared with 1.83 per patient-year in the placebo group (P=0.01),
- More chance of hearing problems in Azithromycin group (25 v 20%)
- Also, what happens after 1 year?
- Effects of antibiotic resistance in the population

## Pulmonary Rehabilitation

**Components of Pulmonary rehabilatation**

- 6-12 week program with multidisciplinary emphasis
- Exercise endurance/resistance training
- Respiratory muscle training
- Education & disease self-management
- Psycho-social support; re-enforcement of smoking cessation
- Nutritional support & interventions

## How can my COPD patient benefit from pulmonary rehabilitation?

- **Improved exercise capacity** (can walk further 6MWT distance of 49 metres) & improved work rate
- **Improved exercise endurance** (can exercise at a given work rate for longer) and efficiency
- **A decreased sensation of breathlessness at a given level of exercise**
- **An improvement in exercise tolerance** over and above adding a bronchodilator

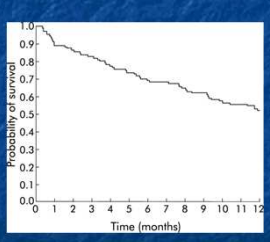
## Benefits of pulmonary rehabilitation

- **Improvement in health status and quality of life** as seen by the St George's Respiratory Questionnaire
- **Improvement in anxiety & depression**
- **Reduction in hospital days (21 to 10.4) and use of health care resources** *(Griffiths et al Lancet 2000; n=200 patients; 6 weeks of rehab with 18 visits)*
- Fewer primary care home visits (1.5 v 2.8; p=0.037); *Griffiths et al Lancet 2000*
- ?Reduction in overall exacerbations
- No proven effect on mortality

## End of Life Care in COPD

- Challenging to predict survival in COPD patients
- Fear of giving opiates/benzodiazepines to people who may not be reaching end of life
- No real evidence based guidance
- FEV1<30% predicted/LTOT therapy/BMI<21/Episodes of hospitalisation needing NIV

## The need for acute NIV as a marker of severity




- A study of 110 COPD patients admitted with acute respiratory failure needing NIV
- 1 year after discharge 79.9% had been readmitted 63.3% and 49.1% had died
- Survivors spent a median of 12% of the subsequent year in hospital

(Chu et al Thorax 2004)

## When to refer COPD patients to secondary care?

- When the diagnosis is in doubt (never really smoked, spirometry which doesn't match)
- Frequent exacerbations
- Suitability for long term oxygen therapy?
- Young people with severe disease

## Issues in COPD management

- Young people with COPD: Potential transplant candidates (life expectancy<2 years)
- Lung Volume Reduction Surgery (upper lobe predominant emphysema with reduced exercise); Endobronchial valves; coils; glue
- Young people with COPD: illicit drug abuse
- Remember: fixed doses for combination therapy