Update in the management of Asthma and COPD

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Content

- Current guidelines in asthma management
- Current guidelines in COPD management
- New treatment for COPD

Size of the problem

In the UK:

- 3 million COPD sufferers
- 2 million of those undiagnosed
- 1 death every 20 minutes from COPD
- 2000 asthma deaths per annum

Asthma Guidelines

Aim of treatment is to control the disease

- No daytime symptoms
- No night time awakening
- No need for rescue treatment
- No exacerbation
- No limitation on activity
- Normal lung function
- Minimal side effects

BTS/SIGN Guidelines (Updated 2009)

STEP 1: Mild intermittent asthma

- Inhaled SABA as required

STEP 2: Regular Preventer Therapy

- Add inhaled steroid 200-800mcg/day (BDP equivalent)

BTS/SIGN Guidelines (Updated 2009)

STEP 3: Initial Add-on Therapy

- Add LABA
- If benefit but inadequate control, increase inhaler steroid to 800mcg
- If no benefit, stop LABA and increase inhaled steroid to 800mcg. If control is still inadequate, add in LTRA or theophylline
- In selected patients, consider Symbicort as per the SMART protocol

LABA and Asthma

- LABA should not be used in Asthma without concurrent ICS
- Use of LABA alone has been linked to increased mortality

BTS/SIGN Guidelines (Updated 2009)

STEP 4: Persistent poor control

- Consider trials of
  - High dose inhaled steroid 2000mcg/day
  - Addition of a 4th drug: LTRA, Theophylline, β2 agonist tablet

STEP 5: Continuous or frequent use of oral steroid

- Use lowest dose of steroid to provide adequate control
- Maintain high dose inhaled steroid 2000mcg/d
- Consider steroid sparing agents: ciclosporin, methotrexate or oral gold
- Consider referral to a specialist centre

Remember to step down treatment

BTS/SIGN Guidelines (Updated 2009)

- Non-pharmacological therapy
- Smoking cessation
- Weight loss
- Breathing control exercises
- Immunotherapy
- Allergen avoidance

Omalizumab

- Monoclonal anti-IgE therapy
- Add-on therapy to improve asthma control in patients with severe persistent allergic asthma, who have:

i. Proven allergy to perennial aeroallergen
ii. FEV_1 <80%
iii. Frequent symptoms
iv. Multiple severe asthma exacerbations

Despite high dose ICS and LABA

Omalizumab (Cochrane Review 2006)

- 14 trials with a total of 3143 mild to severe allergic asthmatics
- Omalizumab significantly reduced free IgE compared with placebo
- Significant reduction in inhaled steroid use compared with placebo
- Significant increases in the number of participants who were able to reduce ICS by over 50% (OR 2.50)
- Patients on Omalizumab were less likely to suffer an asthma exacerbation with treatment as an adjunct to ICS (OR 0.52)

Bronchial Thermoplasty

(AIR2 Trial Jan 2010)

- Bronchoscopic procedure applying controlled thermal energy to airway wall decreasing smooth muscle
- Increased hospitalisation up to 6 weeks post procedure
- Long-term improvement in asthma-specific quality of life, fewer severe exacerbations and reduced rate of patient access to healthcare

COPD guidelines

NICE Guidelines (2004)

Breathlessness and exercise limitation

- Use short-acting bronchodilator as needed
- If still symptomatic try combined therapy with a short-acting beta2-agonist and a short-acting anticholinergic
- OR If still symptomatic use a long-acting bronchodilator (beta2-agonist or anticholinergic)

NICE Guidelines (2004)

In moderate or severe COPD (FEV1 < 50%)

- If still symptomatic consider a combination of a long-acting bronchodilator and inhaled corticosteroid;
  - **discontinue if no benefit after 4 weeks**
- If still symptomatic consider adding theophylline
- Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled
- Consider referral for surgery: bullectomy, lung volume reduction, transplantation

NICE Guidelines (2004)

Frequent Exacerbations

- Offer annual influenza vaccination
- Pneumococcal vaccination
- Self-management advice
- Optimise bronchodilator therapy with one or more long-acting bronchodilator (LABA or LAMA)
- Add inhaled corticosteroids if FEV1 ≤ 50% and >2 exacerbations in 1 yr

(NB these will usually be used with long-acting bronchodilators)

NICE Guidelines (2004)

Respiratory Failure

- LTOT assessment
  - Based on MRC(1981) and NOTT(1980) trial
  - Reduction in mortality
  - 16 hours of O2 supplementation if PaO2 < 7.4 or <8.0 if PHT, Cor pulmonale
- Short burst and ambulatory O2 therapy
- Domicillary NIV
  - Poor evidence to date
  - Currently, main indication is recurrent admission with AHRF

NICE Guidelines (2004)

- Cor Pulmonale
  - NB no evidence for use of vasodilators in secondary pulmonary hypertension
- Abnormal BMI
- Anxiety/Depression
- Palliative Care

Smoking Cessation

- Reduces rate of decline of FEV1
- Reduction in mortality

Latest Evidence

Seretide

Does combination therapy affect mortality in COPD patients?

TORCH Study

- Absolute risk reduction for death 2.6% for seretide vs placebo
- Hazard ratio was 0.825 (P=0.052)
  - N Engl J Med. 2007 Feb 22;356(8):775-89.

Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination Therapy Group (N=1533)	Comparison	Hazard Ratio (95% CI)	P Value
Mortality analysis							
No. of deaths from any cause	231	205	246	193			
Probability of death at 3 yr — %	15.2	13.5	16.0	12.6	Combination therapy vs. placebo (adjusted)*	0.825 (0.681–1.002)	0.052
					Combination therapy vs. placebo (unadjusted)	0.820 (0.677–0.993)	0.04
					Combination therapy vs. salmeterol	0.932 (0.765–1.134)	0.48
					Combination therapy vs. fluticasone propionate	0.774 (0.641–0.934)	0.007
					Salmeterol vs. placebo	0.879 (0.729–1.061)	0.18
					Fluticasone propionate vs. placebo	1.060 (0.886–1.268)	0.53
Adjusted probability of death at 3 yr — %†	12.6	10.9	13.3	10.3	Combination therapy vs. placebo	0.811 (0.670–0.982)	0.03
					Combination therapy vs. salmeterol	0.946 (0.777–1.151)	0.58
					Combination therapy vs. fluticasone propionate	0.768 (0.636–0.927)	0.006
					Salmeterol vs. placebo	0.837 (0.710–1.033)	0.11
					Fluticasone propionate vs. placebo	1.056 (0.883–1.264)	0.55
COPD-related deaths‡							
No. of deaths	91	93	106	72			
Probability of death at 3 yr — %	6.0	6.1	6.9	4.7	Combination therapy vs. placebo	0.78 (0.57–1.06)	0.11
					Combination therapy vs. salmeterol	0.77 (0.56–1.04)	0.09
					Combination therapy vs. fluticasone propionate	0.67 (0.50–0.90)	0.008
					Salmeterol vs. placebo	1.01 (0.76–1.35)	0.93
					Fluticasone propionate vs. placebo	1.16 (0.88–1.53)	0.30
Primary cause of death up to 3 yr — no. (%)							
Cardiovascular	71 (5)	45 (3)	61 (4)	60 (4)			
Pulmonary	74 (5)	80 (5)	91 (6)	61 (4)			
Cancer	45 (3)	44 (3)	51 (3)	44 (3)			
Other	23 (2)	22 (1)	30 (2)	11 (1)			
Unknown	18 (1)	14 (1)	13 (1)	17 (1)			
Efficacy analysis for exacerbation						**Rate Ratio (95% CI)**	
Annual rate							
Moderate or severe	1.13	0.97	0.93	0.85	Combination therapy vs. placebo	0.75 (0.69–0.81)	<0.001
					Combination therapy vs. salmeterol	0.88 (0.81–0.95)	0.002
					Combination therapy vs. fluticasone propionate	0.91 (0.84–0.99)	0.02
					Salmeterol vs. placebo	0.85 (0.78–0.93)	<0.001
					Fluticasone propionate vs. placebo	0.82 (0.76–0.89)	<0.001
Requiring systemic corticosteroids	0.80	0.64	0.52	0.46	Combination therapy vs. placebo	0.57 (0.51–0.64)	<0.001
					Combination therapy vs. salmeterol	0.71 (0.63–0.79)	<0.001
					Combination therapy vs. fluticasone propionate	0.87 (0.78–0.98)	0.02
					Salmeterol vs. placebo	0.80 (0.72–0.90)	<0.001
					Fluticasone propionate vs. placebo	0.63 (0.58–0.73)	<0.001
Severe (requiring hospitalization)	0.19	0.16	0.17	0.16	Combination therapy vs. placebo	0.83 (0.71–0.98)	0.03
					Combination therapy vs. salmeterol	1.02 (0.87–1.20)	0.79
					Combination therapy vs. fluticasone propionate	0.95 (0.82–1.12)	0.56
					Salmeterol vs. placebo	0.82 (0.69–0.96)	0.02
					Fluticasone propionate vs. placebo	0.88 (0.74–1.03)	0.10

* Only the primary comparison was adjusted because interim analyses were performed. Unadjusted data for the primary end point are provided for comparison.
† The adjusted probability of death was calculated with the use of a Cox proportional-hazards model.
‡ Cause of death was adjudicated by the clinical end-point committee.

Table 3. Other Efficacy Outcomes.*

Variable	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)	Comparison	Difference (95% CI)	P Value
St. George's Respiratory Questionnaire*							
No. of patients completing a validated questionnaire	1231	1232	1248	1240			
No. of patients included in the analysis†	924	980	1005	1002			
Mean baseline score	48.4	49.4	49.5	48.7			
Adjusted mean change in score averaged over 3 yr (units)	+0.2	−0.8	−1.8	−3.0	Combination therapy vs. placebo	−3.1 (−4.1 to −2.1)	<0.001
					Combination therapy vs. salmeterol	−2.2 (−3.1 to −1.2)	<0.001
					Combination therapy vs. fluticasone propionate	−1.2 (−2.1 to −0.2)	0.02
					Salmeterol vs. placebo	−1.0 (−2.0 to 0)	0.06
					Fluticasone propionate vs. placebo	−2.0 (−2.9 to −1.0)	<0.001
Postbronchodilator FEV_1							
No. of patients included in the analysis†	1261	1334	1336	1392			
Mean baseline FEV_1 (liters)‡	1.26	1.23	1.23	1.24			
Adjusted mean change in FEV_1, averaged over 3 yr (liters)	−0.062	−0.021	−0.015	+0.029	Combination therapy vs. placebo	0.092 (0.075 to 0.108)	<0.001
					Combination therapy vs. salmeterol	0.050 (0.034 to 0.067)	<0.001
					Combination therapy vs. fluticasone propionate	0.044 (0.028 to 0.061)	<0.001
					Salmeterol vs. placebo	0.042 (0.023 to 0.058)	<0.001
					Fluticasone propionate vs. placebo	0.047 (0.031 to 0.064)	<0.001

* Scores on the St. George's Respiratory Questionnaire are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant.
† Patients for whom at least one measurement was obtained after baseline were included in the analysis.
‡ Patients included in the analysis were those for whom data on the change from baseline FEV_1 were available.

Tiotr

UPLIFT Study

N Engl J Med. 2008 Oct 9;359(15):1543-54

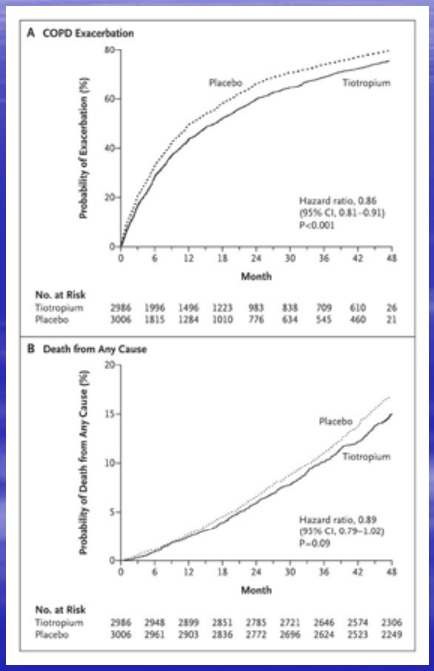
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=2986)	Placebo (N=3006)
Male sex (%)	75.4	73.9
Age (yr)	64.5±8.4	64.5±8.5
Body-mass index	26.0±5.1	25.9±5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yr)	49.0±28.0	48.4±27.9
Duration of COPD (yr)	9.9±7.6	9.7±7.4
Baseline spirometry		
Before bronchodilation		
FEV_1 (liters)	1.10±0.40	1.09±0.40
FEV_1 (% of predicted value)	39.5±12.0	39.3±11.9
FVC (liters)	2.63±0.81	2.63±0.83
Ratio of FEV_1 to FVC	42.4±10.5	42.1±10.5
After bronchodilation		
FEV_1 (liters)	1.33±0.44	1.32±0.44
FEV_1 (% of predicted value)	47.7±12.7	47.4±12.6
FVC (liters)	3.09±0.86	3.09±0.90
Ratio of FEV_1 to FVC	43.6±10.8	43.3±10.7
GOLD stage (%)†		
II	46	45
III	44	44
IV	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β_2-agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	2.3	1.9

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SGRQ St. George's Respiratory Questionnaire.
† Data were missing in this category for 2% of patients. The enrollment of three patients with stage I disease, according to criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), represented a protocol violation, but data from these patients were included in the study.
‡ Data are for 2888 patients in the tiotropium group and 2909 patients in the placebo group. Scores on the SGRQ range from 0 to 100, with lower scores indicating improvement; a change of 4 units or more is considered to be clinically meaningful.
§ This medication was used either alone or as a fixed combination.

UPLIFT Study

- Improvement in quality of life and reduction in exacerbation rate
- No significant reduction in rate of FEV1 decline



Symbicort

- Improved ability to carry out morning activities
- Symbicort / tiotropium vs tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and ADL's and reduces severe exacerbations

Welte et al Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Oct 15;180(8):741-50.

Lung Volume Reduction Surgery: What have we learnt from NETT?

N Engl J Med. 2003 May 22;348(21):2059-73

Table 3. Improvement in Exercise Capacity and Health-Related Quality of Life at 24 Months.*

Patients	Improvement in Exercise Capacity				Improvement in Health-Related Quality of Life			
	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value	Surgery Group	Medical-Therapy Group	Odds Ratio	P Value
	no./total no. (%)				*no./total no. (%)*			
All patients	54/371 (15)	10/378 (3)	6.27	<0.001	121/371 (33)	34/378 (9)	4.90	<0.001
High-risk†	4/58 (7)	1/48 (2)	3.48	0.37	6/58 (10)	0/48	—	0.03
Other	50/313 (16)	9/330 (3)	6.78	<0.001	115/313 (37)	34/330 (10)	5.06	<0.001
Subgroups‡								
Predominantly upper-lobe emphysema								
Low exercise capacity	25/84 (30)	0/92	—	<0.001	40/84 (48)	9/92 (10)	8.38	<0.001
High exercise capacity	17/115 (15)	4/138 (3)	5.81	0.001	47/115 (41)	15/138 (11)	5.67	<0.001
Predominantly non–upper-lobe emphysema								
Low exercise capacity	6/49 (12)	3/41 (7)	1.77	0.50	18/49 (37)	3/41 (7)	7.35	0.001
High exercise capacity	2/65 (3)	2/59 (3)	0.90	1.00	10/65 (15)	7/59 (12)	1.35	0.61

* Improvement in exercise capacity in patients followed for 24 months after randomization was defined as an increase in the maximal workload of more than 10 W from the patient's postrehabilitation base-line value. Improvement in the health-related quality of life in patients followed for 24 months after randomization was defined as a decrease in the score on the St. George's Respiratory Questionnaire of more than 8 points (on a 100-point scale) from the patient's postrehabilitation base-line score. For both analyses, patients who died or who missed the 24-month assessment were considered not to have improvement. Odds ratios are for improvement in the surgery group as compared with the medical-therapy group. P values were calculated by Fisher's exact test. A low base-line exercise capacity was defined as a postrehabilitation base-line maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men); a high exercise capacity was defined as a workload above this threshold.

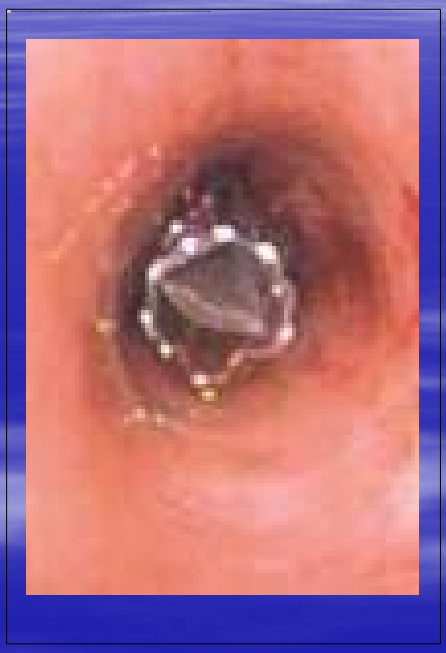
† High-risk patients were defined as those with a forced expiratory volume in one second (FEV_1) that was 20 percent or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value.

‡ High-risk patients were excluded from the subgroup analyses. For improvement in exercise capacity, P for interaction = 0.005; for improvement in health-related quality of life, P for interaction = 0.03. These P values were derived from binary logistic-regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact-score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the base-line FEV_1, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation in one minute to carbon dioxide excretion in one minute, distribution of emphysema (heterogeneous vs. homogeneous), perfusion ratio, score for health-related quality of life, and Quality of Well-Being score; age; race or ethnic group; and sex.

Bronchoscopic LVR

(Emphysis Medical)

Bronchoscopic LVRS



Bronchoscopic Lung Volume Reduction

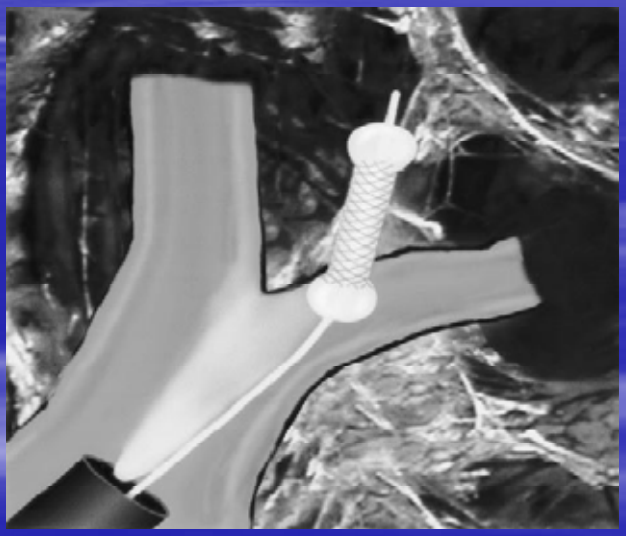
- Report of 98 patients (Multi-centre Trial)
  - RV decreased by 4.9 +/- 17.4% (p = 0.025)
  - FEV1 increased by 10.7 +/- 26.2% (p = 0.007)
  - FVC increased by 9.0 +/- 23.9% (p = 0.024)
  - 6-min walk distance increased by 23.0 + 55.3% (p = 0.001)
  - 90 day complication rate 8.4%

Wan IY, Toma TP, Geddes DM, Snell G, Williams T, Venuta F, Yim AP. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. Chest. 2006 Mar;129(3):518-26.

Airway Bypass Surgery

- Radiofrequency balloon catheter establishes a "fenestration," between central airway and hyperinflated lung
- Fenestration facilitates lung emptying, reducing end-expiratory volume without altering lung recoil *per se*
- Trials have focused primarily on patients with homogeneous disease
- EASE trial ongoing

Bronchial fenestration



Theophylline

- Bronchodilatation by PDE inhibition
- Increased FEV1 of 100ml in COPD

  Ram FS. Use of theophylline in chronic obstructive pulmonary disease: examining the evidence. Curr Opin Pulm Med. 2006 Mar;12(2):132-9
- Reduced activity of histone deacetylases (HDAC) contributes to enhanced inflammation in stable COPD
- Theophylline restores HDAC activity at low dose
- Clinical significance ? No RCT to date

Roflumilast

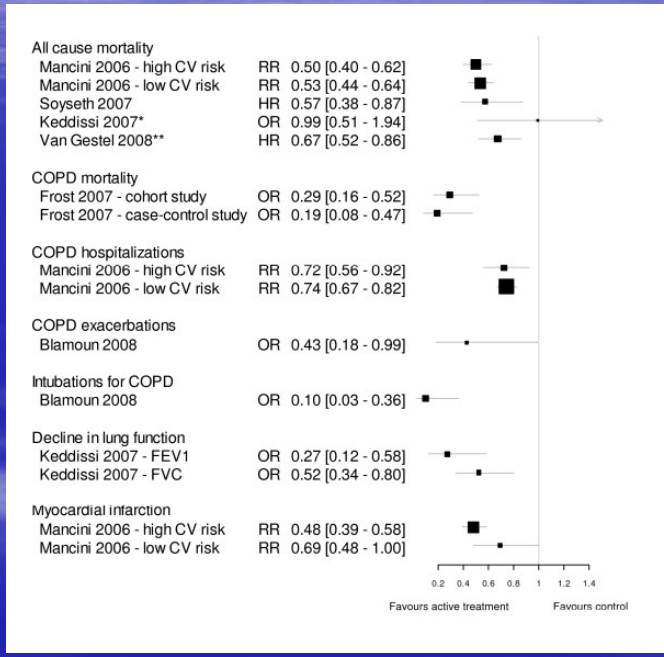
- PDE-4 inhibitor
- Recent multicentre study roflumilast (n=1537) vs placebo (n=1554)
- Pre- bronchodilator FEV1 increased by 48 mL with roflumilast vs placebo (p<0.0001)
- Rate of exacerbations per patient per year was 1.14 with roflumilast vs1.37 with placebo (reduction 17%) , p<0.0003

Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009 Aug 29;374(9691):685-94.

COPD and Statin

- Increasing evidence of benefit of statins in COPD

Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. BMC Pulm Med. 2009 Jul 12;9:32.



COPD – not just an airways disease

- "spill-over" of inflammatory mediators into the circulation leading to systemic manifestations of the disease such as skeletal muscle wasting and cachexia
- Systemic inflammation may also initiate or worsen co-morbid diseases, such as IHD, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes

Conclusion

- Important conditions
- Area of ongoing research
- Less lung orientated approach to management of COPD?