

# Contents

<i>List of contributors</i>	<i>vii</i>
<i>Preface</i>	<i>ix</i>
<b>Part 1 Genetics, screening and diagnosis</b>	
1 Genetic predisposition and susceptibility to chronic obstructive pulmonary disease <i>Bippen D Patel and David A Lomas</i>	3
2 Identification of the individual at risk, the utility of opportunistic screening in the primary healthcare setting and the place of spirometry <i>David Bellamy</i>	13
3 The importance of achieving diagnostic accuracy <i>Robert A Stockley</i>	21
<b>Part 2 Evidence and opinion for medical intervention</b>	
4 Current thinking on the nature of exacerbation and the time course and recovery of exacerbations of COPD <i>Jadwiga A Wedzicha and Terence AR Seemungal</i>	33
5 Scientific evidence and expert clinical opinion for the selection and use of bronchodilators: clinical decision making in the individual patient <i>Philip S Marino and Philip W Ind</i>	43
6 Scientific evidence and expert clinical opinion for selection and use of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease <i>P Sherwood Burge</i>	65
7 Scientific evidence and expert clinical opinion for selection and use of novel therapies: clinical decision making in individual cases <i>Elizabeth E Gamble and Neil C Barnes</i>	75
<b>Part 3 Evidence and opinion for surgical intervention</b>	
8 Lung volume reduction surgery and lung transplantation for COPD <i>John H Dark</i>	81
<b>Part 4 Evidence and opinion for managing disability and progressing rehabilitation</b>	
9 A strategy for the management of disability and the reduction of handicap in COPD <i>Michael DL Morgan and Michael C Steiner</i>	99

**viii** Contributors

C Mike Roberts MD FRCP, Consultant Physician, Chest Unit, Whipps Cross University Hospital, London

Terence AR Seemungal MBBS MSc MRCP, British Lung Foundation Fellow, Academic Department of Respiratory Medicine, St Bartholomew's Hospital, London

Michael C Steiner, MRCP, Research Fellow, Department of Respiratory Medicine and Thoracic Surgery, Glenfield Hospital, Leicester

Nicola Stevenson MRCP, Clinical Research Fellow, Department of Medicine, University Hospital Aintree, Liverpool

Robert A Stockley MD DSc FRCP Professor of Medicine, Department of Medicine, University of Birmingham at Queen Elizabeth Hospital, Birmingham

Jadwiga A Wedzicha MA MD FRCP, Professor of Respiratory Medicine, St Bartholomew's and the Royal London School of Medicine, St Bartholomew's Hospital, London

**Table 5.4** Comparison of anticholinergic drugs with inhaled short- and long-acting  $\beta_2$  agonists

Study	n	Comparison	Baseline $FEV_1(l)$	$\Delta FEV_1 (ml)$	Symptom scores	Comments
Combivent Aerosol Study 1994	534	Ipra (21 $\mu g$ qds)	1.0	303	No significant difference between groups	DBRCT 12-week study
		Salb (100 $\mu g$ qds)	1.0	305		
		Ipra + Salb	1.0	373*		
Rennard <i>et al.</i> 1996	1445	Ipra vs $\beta_2$ agonist+	1.0	28*	No significant difference between groups	Meta-analysis of 7 clinical trials
			1.0	1		
Cazzola <i>et al.</i> 1998	16	Oxi (200 $\mu g$ )		230 <sup>P</sup>	-	
		Efm (24 $\mu g$ )	1.06	340 <sup>P*</sup>	-	Single dose study
		Sm (50 $\mu g$ )		270 <sup>P</sup>	-	
		Placebo		50	-	
Mahler <i>et al.</i> 1999	411	Ipra (36 $\mu g$ qds)	1.16	100 <sup>P</sup>	Significant decrease in nighttime SOB in sm group	DBRCT 12-week study
		Sm (42 $\mu g$ bd)	1.28	180 <sup>P*</sup>		
		Placebo	1.30	25		

KEY

- Ipra – ipratropium
- Oxi – oxitropium
- Salb – salbutamol
- Sm – salmeterol
- Efm – eformoterol

DBRCT – Double-blind randomised control trial  
 + – salbutamol or metaproterenol (oriprenaline)  
<sup>P</sup> – statistically significant vs placebo  
 \* – statistically significant vs other treatment groups  
 SOB – shortness of breath

- Clark CJ & Boyd G (1980). Combination of aminophylline (PhyllocontinContinuous tablets) and salbutamol in the management of chronic obstructive airways disease. *British Journal of Clinical Pharmacology* **9**, 359–64
- Combivent Inhalation Aerosol Study Group (1994). In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest* **105**, 411–419
- Current Best Practice for Nebuliser Treatment (1997). The Nebuliser Project Group of the British Thoracic Society Standards of Care Committee. *Thorax* **52**, S49–S52
- Cushley MJ, Tattersfield AE, Holgate ST (1984). Adenosine-induced bronchoconstriction in asthma. Antagonism by inhaled theophylline. *American Review of Respiratory Disease* **129**, 380–384
- Dahl R, Greefhorst APM, Nowak D *et al.* (2000). Comparison of the efficacy and safety in inhaled formoterol and ipratropium in patients with COPD. *American Journal of Respiratory & Critical Care Medicine* **161**, A489
- Donohue J, Emmett A, Rickard K, Knobil K (1999). Salmeterol is effective bronchodilator therapy for all stages of COPD. *American Journal of Respiratory & Critical Care Medicine* **159**, A817
- Dowling RB, Johnson M, Cole PJ, Wilson R (1999). Effect of fluticasone propionate and salmeterol on *Pseudomonas aeruginosa* infection of the respiratory mucosa in vitro. *European Respiratory Journal* **14**, 363–369
- Dowling RB, Rayner CF, Rutman A *et al.* (1997). Effect of salmeterol on *Pseudomonas aeruginosa* infection of respiratory mucosa. *American Journal of Respiratory & Critical Care Medicine* **155**, 327–336
- Dullinger D, Kronenberg R, Niewoehner DE (1986). Efficacy of inhaled metaproterenol and orally-administered theophylline in patients with chronic airflow obstruction. *Chest* **89**, 171–3
- Fagon JY & Chastre J (1996). Severe exacerbations of COPD patients: the role of pulmonary infections. *Seminars in Respiratory Infections* **11**, 109–18
- Friedman M (1996). A multicenter study of nebulised bronchodilator solutions in chronic obstructive pulmonary disease. *American Journal of Medicine* **100**, 30S–39S
- Friedman M, Witek Jr TJ, Serny CW, Flanders J, Menioge SS, Wilson JD (1996). Combination bronchodilator therapy is associated with a reduction in exacerbations (E) of COPD. *American Journal of Respiratory & Critical Care Medicine* **153**, A126
- Guyatt GH, Townsend M, Pugsley SO *et al.* (1987). Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. *American Review of Respiratory Disease* **135**, 1069–1074
- Jones PW & Bosh TK (1997). Quality of life changes in COPD patients treated with salmeterol. *American Journal of Respiratory & Critical Care Medicine* **155**, 1283–1289
- Imhof E, Ehasser S, Karrer W *et al.* (1993). Comparison of bronchodilator effects of fenoterol/ipratropium bromide and salbutamol in patients with chronic obstructive lung disease. *Respiration* **60**, 84–88
- LeDoux EJ, Morris JF, Temple WP, Duncan C (1989). Standard and double dose ipratropium bromide and combined ipratropium bromide and inhaled metaproterenol in COPD. *Chest* **95**, 1013–1016
- Littner MR, Howite JS, Tashkin DP *et al.* (2000). Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva). in stable chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* **161**, 1136–1142

# Scientific evidence and expert clinical opinion for the selection and use of novel therapies: clinical decision making in individual cases

*Elizabeth E Gamble and Neil C Barnes*

## **Introduction**

Considering drug treatment choices in the future, one needs to consider the main problems in chronic obstructive pulmonary disease (COPD): the heterogeneity of the disease and the clinical effectiveness of currently available therapies. The main problems in COPD are the continuing symptoms of shortness of breath, the risk of exacerbations of the disease and the increased mortality (American Thoracic Society 1995). The risk of mortality is related to the impairment in lung function as measured by the forced expiratory volume in 1 second (FEV<sub>1</sub>) (Anthonisen *et al.* 1986). The only therapeutic manoeuvres, which have been shown to have a major effect on mortality, are cessation of smoking (Anthonisen *et al.* 1994) and oxygen therapy in hypoxic patients with cor pulmonale (Nocturnal Oxygen Therapy Trial Group 1980; Medical Research Council Working Party 1981). Smoking cessation slows the accelerated decline in FEV<sub>1</sub> and therefore decreases mortality and decreases the risk of disease exacerbation. Other therapies have not been shown to decrease mortality, although they may have a small but, in the context of the disease, clinically useful effect on symptoms and disease exacerbations. Long-acting  $\beta_2$  agonists and anticholinergic drugs produce improvements in symptoms (O'Donnell *et al.* 1999; Lotvall 2000) and there is the theoretical possibility that long-acting  $\beta_2$  agonists may have a beneficial effect on exacerbations of COPD (Kips 2000). Inhaled steroids decrease exacerbations of COPD in patients with more severe disease, but the effect on pulmonary function and symptoms is at best modest (Burge *et al.* 2000).

## **Pathology**

Against this background, any drug that had a beneficial effect on symptoms, preventing exacerbations or slowing the rate of decline of FEV<sub>1</sub> and therefore the risk of mortality, would be of benefit. There are several problems associated with developing a drug that would have such a beneficial impact. It is now clear from a number of studies that, in patients with COPD but no features of asthma, the inflammatory profile is quite distinct from that of asthma. In asthma there is an increase in CD4<sup>+</sup> T cells, eosinophils and thickening of the basement membrane with