unanswered questions are—at which stage to start and what dose to use? Randomised trials in these areas are badly needed. They will require large numbers, enthusiasm from respiratory clinicians, and are likely to need public rather than pharmaceutical industry funding.

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References

1 **Burge PS**, Lewis SA. So inhaled steroids slow the rate of decline of FEV_1 in patients with COPD after all? *Thorax* 2003;**58**:911–3.
2 **Burge PS**, Calverley PMA, Jones PW, *et al*. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;**320**:1297–303.
3 **Vestbo J**, Sorensen T, Lange P, *et al*. Long-term effects of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;**353**:1819–23.
4 **Pauwels RA**, Lofdahl C, Laitinen LA, *et al*, for the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;**340**:1948–53.
5 **The Lung Health Study Research Group**. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902–9.
6 **Calverley PMA**, Pauwels R, Vestbo J, *et al*, for the TRISTAN Study Group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;**361**:449–56.
7 **Szafranski W**, Cukier A, Ramirez A, *et al*. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;**21**:74–81.

Delays in diagnosis of OSAHS

We very much enjoyed the first paper in the review series on sleep and admired Stradling and Davies's honest appraisal of the current difficulties in defining disease and the lack of a relationship between symptoms and the results of investigations.[1] One of the problems of truly determining the size of the health burden associated with the obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is that much of the burden may occur before the diagnosis is made. Others have shown how use of hospital resources and use of cardiovascular medication is high in those with undiagnosed obstructive sleep apnoea.[2 3] We administered a questionnaire to 166 consecutive patients with diagnosed OSAHS on continuous positive airway pressure treatment and asked them to identify how long they could recall having symptoms at the time of diagnosis. In 155 cases (93.4%) someone had previously complained of the patient's loud snoring and first mention of this had been made a median of 12 years (range 2–52) before diagnosis of OSAHS. In 84.3% of respondents excessive daytime sleepiness had been present for a median of 8 years (range 0.5–62) and 133 patients (80.1%) reported that their bed partner had witnessed apnoeas a median of 8 years (range 1–49) before diagnosis. We also found that, of the 119 (71.7%) who were drivers, 26 (21.8%) reported at least one or more automobile crashes in the previous 5 years, with seven respondents having had two and one having had four.

These results suggest a lack of awareness of sleep related breathing disorders among the general population and probably among health professionals. The delay in diagnosis is likely to have significant effects on morbidity, and in recent preliminary work it has been shown that those with OSASHS have structural changes in brain morphology compared with healthy controls.[4] In addition to the health and quality of life benefits to the individual to be gained by prompt diagnosis, there are also economic aspects in favour of prompt diagnosis and treatment[5 6] and early benefits in terms of driving performance.[7]

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References

1 **Stradling JR**, Davies RJO. Sleep · 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology and natural history. *Thorax* 2004;**59**:73–8.
2 **Kryger MH**, Roos L, Delaive K, *et al*. Utilisation of health care services in patients with severe obstructive apnoea. *Sleep* 1996;**19**:S111–6.
3 **Otake K**, Delaive K, Walld R, *et al*. Cardiovascular medication use in patients with undiagnosed obstructive sleep apnoea. *Thorax* 2002;**57**:417–22.
4 **Morrell M**, McRobbie D, Quest R, *et al*. Changes in brain morphology associated with obstructive sleep apnoea. *Sleep Med* 2003;**4**:451–4.
5 **Pelletier-Fleury N**, Meslier N, Gagnadoux F, *et al*. Economic arguments for the immediate management of moderate to severe obstructive sleep apnoea syndrome. *Eur Respir J* 2004;**23**:53–60.
6 **Douglas NJ**, George CFP. Treating sleep apnoea is cost effective. *Thorax* 2002;**57**:93.
7 **Turkington PM**, Sircar M, Saralaya D, *et al*. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea/hypopnoea syndrome. *Thorax* 2004;**59**:56–9.

Prophylactic antibiotic treatment of bronchiectasis with azithromycin

Once a treatable cause of bronchiectasis such as hypogammaglobulinaemia has been excluded, management largely involves physiotherapy and treatment of infective exacerbations with appropriate antibiotics.[1] In a proportion of patients this is not adequate to prevent frequent infective exacerbations. Prophylactic antibiotic treatment can be used to try to prolong the exacerbation free period. This may be administered orally, via a nebuliser, or using a cyclical regimen of intravenous antibiotics. Prophylactic treatment may be problematic due to side effects and development of antibiotic resistance.[2] Macrolide antibiotics exhibit immunomodulating properties. Long term, low dose erythromycin has been shown in diffuse panbronchiolitis, a disease with some similarities to idiopathic bronchiectasis, to be effective in controlling chronic suppurative airways disease.[3] Recently published research has shown benefits of long term azithromycin treatment in patients with cystic fibrosis.[4] These results led us to consider using azithromycin as prophylaxis in patients with non-cystic fibrosis bronchiectasis with frequent infective exacerbations.

Patients attending the outpatients department between February 1999 and April 2002 who fulfilled the following criteria were considered for azithromycin prophylaxis:

- bronchiectasis defined by CT scan;
- any causal condition had been treated if possible;
- general management optimised;
- >4 documented infective exacerbations requiring oral or intravenous antibiotic treatment during the last 12 months;
- *Pseudomonas aeruginosa* respiratory infection, if present, had not responded to nebulised antibiotic prophylaxis or this had not been tolerated;
- failure to control chronic symptoms.

Exclusions included allergy to macrolides and abnormal liver function tests. The dosing schedule was 500 mg once daily for 6 days, 250 mg once daily for 6 days, then 250 mg on Monday/Wednesday/Friday of each week. A safety blood examination was organised 1 month after starting treatment. The patients were fully reviewed at least 4 months after commencement of azithromycin prophylaxis and lung function tests repeated. Sputum culture results before and after starting prophylaxis were noted. Statistical analysis was performed using a paired *t* test and non-parametric Wilcoxon test.

Thirty nine patients were studied. Fifteen had idiopathic bronchiectasis and the remainder consisted of 13 with post childhood infections, five with primary ciliary dyskinesia, five with common variable immunodeficiency, and one with Young's syndrome. Their mean (SD) age was 51.9 (16.1) years (range 18–77) with a 2:1 female predominance. All patients had had more than four documented exacerbations during the previous 12 months. Six patients stopped taking the azithromycin prophylaxis because of side effects: abnormal liver function tests (n = 2), diarrhoea (n = 2), rash (n = 1), and tinnitus (n = 1). All occurred during the first month of treatment. Other side effects experienced were mild and mainly gastrointestinal. Five patients were on long term oral corticosteroids with no change in dosage, in two new inhaled corticosteroids were introduced, and one patient was given a short 7 day reducing course of oral corticosteroids. The mean (SD) length of time taking azithromycin, excluding those who stopped because of side effects, was 20 (10.1) months (range 4–38). Twenty six patients are continuing with the prophylaxis at the present time; in the other seven treatment was discontinued because of improvement in their condition.

Sputum culture results (all bacteria isolated) before commencement showed no growth (n = 13), *Pseudomonas aeruginosa* (n = 8), *Staphylococcus aureus* (n = 6), *Haemophilus influenzae* (n = 6), *Streptococcus pneumoniae* (n = 3), *Stenotrophomonas maltophilia* (n = 2), *Morexella catarrhalis* (n = 1), not done (n = 4). After 4 months the results were no growth (n = 18), *P aeruginosa* (n = 5),

Table 1 Change in symptoms while taking azithromycin prophylaxis

	Mean	SD	SE	p value
Sputum volume	1.6	0.8	0.14	<0.001
Sputum colour	2.1	0.7	0.13	<0.001
Sputum consistency	2.5	0.6	0.11	0.006
Cough	2.4	0.7	0.12	0.001
Fatigue	2.1	1.0	0.18	0.001
Exercise tolerance	3.8	0.9	0.16	0.002
Wheeze	2.6	0.8	0.14	0.011
Breathlessness	2.3	0.7	0.13	0.002

Symptoms scored on a 5-point scale: 1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms.

S aureus (n = 1), *S pneumoniae* (n = 1). not done (n = 10). In three patients who had cultured *P aeruginosa* before starting azithromycin prophylaxis the organism was not recultured at follow up.

In the 33 patients completing at least 4 months treatment there was a statistically significant reduction in infective exacerbations requiring oral antibiotics from a mean of 0.71 per month to 0.13 per month ($p<0.001$). There was also a reduction in the requirement for intravenous antibiotics from a mean of 0.08 courses per month to 0.003 courses per month ($p<0.001$). Subgroup analysis of patients with *P aeruginosa* isolated before starting azithromycin prophylaxis showed no difference compared with all patients included ($p = 0.22$). Twenty five patients had lung function tests before and after at least 4 months of treatment (range 4–20 months). There was an improvement in all lung function parameters but the improvement in carbon monoxide transfer factor (TLCO) was the only one to reach statistical signficance ($p = 0.01$).

Symptom data were collected from 32 patients and scored on a 5-point scale (table 1). Statistical analysis using a non-parametric Wilcoxon test showed that there was a significant improvement in all symptoms.

The mechanism by which azithromycin reduces the number of infective exacerbations and chronic symptoms is unknown, but it is likely to be multifactorial. It may be due to downregulation of the host immune response by azithromycin, so decreasing host mediated tissue damage as postulated in the vicious circle hypothesis. It might also benefit patients by reducing bacterial load and therefore the stimulation for neutrophilic inflammation, or by influencing the pathogenic mechanisms of bacteria. Macrolide antibiotics have also been shown to reduce mucus secretion.[1 5]

Currie *et al* compared high dosage amoxicillin with placebo over an 8 month period and found a greater reduction in the volume of purulent sputum between exacerbations in the amoxicillin group (to 20% of pretreatment volume) than in the placebo group, but did not demonstrate any reduction in infective exacerbations.[6] The superior findings of our study suggest that the anti-inflammatory effects of azithromycin were important in achieving the results obtained. This study was performed with patients who were sufficiently unwell to preclude consideration of a placebo group. The patients therefore acted as their own controls. The results are sufficiently impressive to encourage the design of a randomised study, either enrolling less sick patients and having a placebo comparator or using a comparator antibiotic without immunomodulating properties.

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References

1 **Wilson R**. Bronchiectasis. In: Gibson J, Geddes D, Costabel U, eds. *Respiratory medicine*, 3rd ed. Edinburgh: WB Saunders, 2002:1145–464.
2 **Rayner CF**, Tillotson G, Cole PJ, *et al*. Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis. *J Antimicrob Chemother* 1994;**34**:149–56.
3 **Kudoh S**. Erythromycin treatment in diffuse panbronchiolitis. *Curr Opin Pulm Med* 1998;**4**:116–21.
4 **Wolter J**, Seeney S, Bell S, *et al*. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002;**57**:212–6.
5 **Tsang KW**, Ho PI, Chan KN, *et al*. A pilot study of low-dose erythromycin in bronchiectasis. *Eur Respir J* 1999;**13**:361–4.
6 **Currie DC**, Garbett ND, Chan KL, *et al*. Double-blind randomized study of prolonged higher-dose oral amoxycillin in purulent bronchiectasis. *Q J Med* 1990;**76**:799–816.

Early life antibiotics and asthma

Cullinan *et al*[1] present interesting data on the association between exposure to antibiotics in early life and the subsequent expression of atopy and asthma. In keeping with other studies, they report a positive association between antibiotic receipt over the first 5 years of life and asthma. The association was, however, largely accounted for by prescriptions issued for respiratory illnesses, and the authors conclude that reverse causation was the likely explanation for this association.

The inappropriate use of antibiotics for respiratory symptoms caused by unrecognised asthma is the main potential confounding factor in observational studies attempting to demonstrate a causal link between antibiotic receipt and atopic illnesses. It is certainly plausible that GPs may prescribe antibiotics in children with symptoms such as cough and wheeze in early life. Suggestions of a casual link are strengthened by demonstration of an association when antibiotics were used for symptoms not associated with asthma. The earlier study by Farooqui and Hopkins[2] did, indeed, observe an association with non-respiratory use of antibiotics and asthma; in the study by Cullinan *et al* the association between non-respiratory indicated antibiotics and atopic asthma narrowly failed to reach statistical significance. The authors acknowledge that the study was only powered to show a doubling of the odds ratio for the association between early life antibiotic use and asthma, so an association remains possible in this cohort.

The most important limitation of the study, however, is the timing of the observed early life events in relation to secular changes in asthma prevalence and antibiotic prescribing, and hence the applicability of the results to modern day settings. This study observed events occurring 30 or more years ago in the parents of the Ashford birth cohort. As is well described, the prevalence of asthma has increased greatly over the last 30 years.[3] There may also have been significant increases in antibiotic prescribing over this time. The subjects in this study received an average of 3.1 and a median of 3 antibiotic prescriptions over 5 years, while we found in a recent case-control study[4] of 37 children with atopy and wheezing and 37 without either that the average and median number of antibiotic courses received during the first 5 years of life was 9.9 and 7 for wheezers and 6.3 and 5 for non-wheezers. There is also evidence of earlier prescribing of antibiotics in recent times; in our study group 89% of wheezers and 68% of non-wheezers received one or more courses of antibiotics in the first year, while in the Ashford study only 396 prescriptions were issued to 746 subjects in the first year, so a maximum of 53% children received any antibiotics.

It seems likely from the data presented that antibiotic exposure did not play a major causal role in promoting the asthma phenotype 30 years ago when both the prevalence of asthma and antibiotic prescribing to young children were significantly less than they are now, but the question of whether it may now be a significant and potentially modifiable factor remains unanswered.

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References

1 **Cullinan P**, Harris J, Mills P, *et al*. Early prescription of antibiotics and the risk of allergic disease in adults: a cohort study. *Thorax* 2004;**59**:11–5.
2 **Farooqui IS**, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998;**53**:927–32.
3 **Holgate ST**. The epidemic of allergy and asthma. *Nature* 1999;**402**:B2–4.
4 **Thomas M**, Murray CS, Simpson B, *et al*. Early life antibiotic exposure and subsequent risk of asthma: a case control study. *Thorax* 2003;**58**:iii67.

Recurrence of acute respiratory failure following use of waterproofing sprays

Between January and March 2003 six patients were admitted to hospital in the Lausanne area of Switzerland with acute respiratory failure following use of a waterproofing spray for clothes and leather. Within hours of exposure all patients developed a dry cough and rapidly progressive dyspnoea. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide