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The editors will decide as before whether to also publish it in a future paper issue.

Authors’ reply

We thank Dr Wildman for his letter suggesting a further possible reason for the variation in outcome in that we reported for the acute care of COPD patients in different hospital centres. In a further unpublished multiple regression analysis of the RCP/BTS 2001 audit we found that 26% of the variation in the outcome of death at 90 days following admission could be accounted for by factors measured in the study—indeed the included patient characteristics such as performance status and resource and organisational issues, as described in our paper.1 Dr Wildman suggests that individual clinicians might vary in determining admission to the ITU for COPD patients in respiratory failure, and suggests that respiratory physicians need to be advocates for their patients in this arena.

Attitudes and beliefs in what might be achieved are important but are difficult to measure in clinical practice. They might account for some of the variation in outcome but, if so, the therapeutic nihilism would have to vary systematically between whole hospitals and not just a factor in our study. Admission to the ITU depends on more than the individual attitude of the referring doctor. A lack of availability of beds may raise thresholds, and an institutional nihilism within the ITU may lead to rejection of suitable patients.

Perrin et al2 reported a study in which questionnaires regarding initiation of mechanical ventilation in end stage COPD patients were completed by 350 doctors subdivided by specialty (intensivists, respiratory specialists and other physicians). As in the paper by Wildman et al,3 there was considerable individual variation in decision making but no overall difference between the three types of specialist studied. However, no analysis by hospital or trust was made to identify local patterns. We believe all respiratory physicians will share Dr Wildman’s call that referring physicians should be advocates for their patients, and this has to be matched by a willingness of the ITU staff to accept such patients and the availability of beds within an ITU/HDU to accommodate them. Perrin’s paper provides hope of a generic match although individual disagreements may still occur. It is, however, not only admission to the ITU that matters, as in many hospitals non-invasive ventilatory support is provided on general wards by respiratory units without input from intensivists.

In the BTS/RCP 2003 national audit of the acute care of COPD patients, 95% of all acute admitting sites have now registered to participate and data collection is nearing completion. Within the clinical data gathering there is a question that attempts to document clinical decision making when a patient eligible for ventilation on blood gas criteria does not receive ventilatory support. In addition, data on available resources such as ITU beds, bed occupancy, and numbers of ITU candidates transferred off site will be recorded. We may be in a position to shed further light on the issues of individual versus institutional nihilism or rationing in due course.

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References


Do inhaled corticosteroids slow FEV1 decline in COPD after all?

I question the findings of the meta-analysis by Sunderland et al1 and the content of the associated editorial by Burge and Lewis.2 The meta-analysis has drawn from available long term data from randomised controlled studies (RCTs) of inhaled corticosteroids (ICS) in chronic obstructive airways disease (COPD). The whole purpose of meta-analysis is to analyse such data systematically to answer a question. This study seems to use the data selectively to demonstrate an effect. Another recent meta-analysis—in my opinion properly conducted—drew on the same studies and reached the opposite conclusion.3 The fact is that four long term, adequately powered RCTs have examined the effect of ICS, some of these studies failed to show a benefit of ICS on the primary outcome measure of decline in forced expiratory volume in

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References


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1 second (FEV1). There may be a subset of people in whom the exacerbation rate is reduced, which was a secondary outcome in some of these studies.

In any case, as the authors point out, an annual difference of 7.7–9.9 ml in FEV1 decline compared with placebo is of “debatable clinical importance”. It is hardly something to shout about, as occurred following this publication (probably egged on by the editorial) which was quoted in the GP press as suggesting that current widespread ICS use (albeit “off-label”) was now clinically justified.

Another major problem with this study is that it does not analyse harm. For example, the largest RCT showed a significant reduction in bone mineral density of the lumbar spine and femur in patients receiving inhaled triamcinolone. People with COPD likely to receive ICS are frail and have poor mobility, so this finding raises particular concern as they are more likely to fall and falls could result in fracture. Even if inhaled triamcinolone is not used in the UK, fluticasone is. Fluticasone has been the subject of particular cautionary advice because of its ability to cause systemic effects at high doses. If there is indeed a marginal clinical benefit from using these drugs, I think these people deserve a better assessment of risk and benefit than was presented in this meta-analysis and the accompanying editorial.

The editorial claimed that it is no longer ethical to do more long term trials: surely the conclusion is the opposite? We need better data to justify the widespread use of ICS in COPD.

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Ethics of placebo controlled studies of inhaled steroids for COPD

The meta-analysis by Sutherland et al of the effect of inhaled corticosteroids on the progression of airflow limitation in patients with chronic obstructive pulmonary disease (COPD) found a small improvement in forced expiratory volume in 1 second (FEV1) of 7.7–9.9 ml/year (95% CI −1.2 to 1.2) which is similar to the results of the meta-analysis performed by Highland et al (5 ml/year (95% CI −1.1 to 1.2)) using a very similar data set. The meta-analyses employed slightly different study selection criteria and analytical techniques, and questioned the clinical significance of such small differences in FEV1. The selected primary studies suffered from potential drop-out bias and significant selection bias. All of the studies were subjected to meta-analyses excluded patients with a bronchodilator response. Studies of asthma and COPD as separate entities are limited because asthma and COPD (observed in cross-section) represent a continuum, and the small number of available prospective observations indicates that asthma and COPD are sometimes different clinical manifestations of the same underlying aetiology evolving over time. Given all the uncertainties, questions and limitations which Burge concluded (correctly in my opinion) that “additional studies are needed to evaluate the effects on quality of life, risk for systemic side effects, dose–response relationships in corticosteroid-responsive patients, and the economic effect of inhaled corticosteroids”. On the other hand, in an editorial accompanying the paper by Sutherland et al, Burge and Lewis state: “It is no longer ethical to do more long term placebo controlled studies [of inhaled corticosteroids in COPD]”. Given the uncertainties, questions and limitations which Burge and Lewis acknowledged, I was puzzled by this statement and would like to ask them why they reached this conclusion.

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2 Burge PS, Lewis SA. Inhaled steroids slow the rate of decline in FEV1 in patients with COPD after all. Thorax 2003;58:911–3
6 Burge PS, Lewis SA. Inhaled steroids slow the rate of decline of FEV1 in patients with COPD after all? Thorax 2003;58:911–3

Authors’ reply

To make randomised controlled studies ethical, the investigator must believe that neither treatment is known to be superior to the other. If the trial is to be placebo controlled, the investigator must believe that no non-approved treatment is known to be of benefit to the patient. Both Drs Duerden and Hahn want more placebo controlled trials of inhaled cortico-
steroids (ICS) in COPD before they recommend their use. He claimed that ICS were of established benefit in reducing exacerbations of COPD, so any future placebo controlled study would need to be in patients without a history of exacerbations. As exacerbations are associated with disease severity, and as about 80% of patients with an FEV1 <50% predicted have at least one exacerbation over a 3 year period, any trial would need to be in those with early disease. The Copenhagen City Lung Study found that inhaled budesonide 800 µg/day had no benefit if start in a population of smokers of similar age with a reduced FEV1/FVC ratio, the majority of whom had an FEV1 above 80% predicted. This leaves the group with an FEV1 between 50% and 80% predicted, many of whom have not been identified by their medical practitioners. This was the group included in the EUROSCOP and Lung Health 2 studies, where the results included in the meta-analysis were the most divergent, probably because of the relatively low dose of ICS used in the Lung Health study. The symptomatic patient with more severe disease, the combination of a long acting β agonist and an ICS has been shown to be superior to either alone and is now the treatment of choice.

This leaves the symptomatic population in whom a decline in FEV1, is the only practical outcome measure. No randomised study using an intention to treat analysis has shown a reduction in FEV1 from assessment to treatment in any disease, including ICS in asthma, although several studies have shown an improvement in FEV1 with ICS in COPD. Our editorial tried to explain why changes in FEV1, did not show a benefit in patients with COPD. Patients with progressive disease are likely to be given ICS by their clinicians outside any trial, reducing the power of any study.

Any treatment should weigh the potential risks against any benefit. Dr Duerden wants a better analysis of the risks of ICS in patients with COPD, particularly related to bone loss, and points out the reduced bone mineral density in the triamcinolone group in the Lung Health 2 study. The reported results are in 359/412 of a convenience sample who had three measurements of bone density. After 3 years the lumbar spine density reduced from 0.988 to 0.983 g/cm2, and the femoral neck from 0.762 to 0.747 g/cm2 in the triamcinolone group. EUROSCOP studied bone density measurements in 194 subjects’ and showed very small changes which were significantly less at the lumbar spine and femoral neck in the budesonide group (0.04%/year v 0.36%/year in the placebo group). Randomised controlled studies are probably not the best method for assessing the extent of long term adverse effects, but the evidence from the randomised studies to date shows that the risks are relatively minor compared with the risks of death from the natural progression of the disease. Introducing ICS at an earlier stage may alter the risk/benefit ratios. The adverse effects on the bones are probably best studied in asthmatics of whom many are already taking long term ICS in equivalent doses.

There is a striking difference between the way that cardiac and respiratory physicians greet new treatments whose individual effects are present but relatively minor. There has been a meaningful balance of cardiac deaths attributed to the combination of several treatments with modest individual effects. This has resulted in more smokers living to develop significant COPD. It is likely that improvements in the quality and quantity of life in patients with COPD will come from a combination of treatments, among which ICS have a place. The main
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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1 Burge PS, Lewis SA. So inhled steroids slow the rate of decline of FEV1 in patients with COPD after 8 years (range 0.5–62) and 133 patients (84.3% of respondents excessive daytime sleepiness in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353:1819–23.


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 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 large are 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 of 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 apnoea 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 OASHS 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 treatment5 and early benefits in terms of driving performance.6

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References


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.2 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 as an intravenous or 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.

2Sputum culture results (mixed 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), Stentrophononas maltophilia (n = 2), Moraxella catarrhais (n = 1), not done (n = 4). After 4 months the results were no growth (n = 18), P aeruginosa (n = 5),...
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 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 0.03 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 significance (p = 0.01).

Symptom data were collected from 32 patients and scored on a 5-point scale (1 = large decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = large increase in symptoms).

Table 1 Change in symptoms while taking azithromycin prophylaxis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean (SD)</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum volume</td>
<td>1.6 (0.8)</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum colour</td>
<td>2.1 (0.7)</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum consistency</td>
<td>2.5 (0.6)</td>
<td>0.11</td>
<td>0.006</td>
</tr>
<tr>
<td>Cough</td>
<td>2.4 (0.7)</td>
<td>0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.1 (1.0)</td>
<td>0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Exercise tolerance</td>
<td>3.8 (0.9)</td>
<td>0.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Wheeze</td>
<td>2.6 (0.8)</td>
<td>0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>2.3 (0.7)</td>
<td>0.13</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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

Early life antibiotics and asthma

Cullinan et al. 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 3 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 causal role in promoting the asthma phenotype 30 years ago when both the prevalence of asthma and antibiotics 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.

References


Recurrent 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 progressed to respiratory failure. The clinical picture included severe hypoxaemia, increased white blood cell count, raised C-reactive protein, and reduced carbon monoxide...
Acute respiratory failure was attributed to inhalation of the waterproofing spray in view of the sudden occurrence of symptoms following exposure, the diffuse ground glass opacities without other abnormalities on the CT scan, and the absence of any other detected cause. In particular, BAL fluid was sterile for bacteria, mycobacteria, viruses and fungi. Serological tests for chlamydia and mycoplasma were performed on two patients and were negative. A nasal swab for influenza was performed on one patient and was negative.

We were, however, surprised that the patients used three different spray brands. Waterproofing sprays contain three types of components—a propellant gas (propane butane), a waterproofing agent (fluorocarbon resin), and a solvent. It appeared that the manufacturer of the fluorinated resin changed during the summer of 2002 (for the three brands) and that the isopropanol solvent had to be replaced with a heptane solvent. Consumers started complaining of the spray. One untreated patient developed a pulmonary fibrosis during a German outbreak in the 1980s and one death was reported in Japan in the 1990s.

Following these outbreaks serious suggestions were proposed to explain these intoxications. In our opinion, the most likely explanation for the present outbreak is that the heptane solvent, which is more volatile than the previous one (isopropanol), allows the mist containing the new fluorinated resin to spread further in the tracheobronchial tree and to reach the alveoli where it might produce reactive metabolites inducing an alveolitis. However, the exact chemical reaction remains unknown. Because of the potentially lethal aspect of these intoxications and the possibility of new outbreaks, we consider that more research is needed on the effect of mist particle size and large analytical epidemiological studies are required to investigate this phenomenon further.

Effect of PM10 on *H influenzae* and *S pneumoniae*

That air pollution, and specifically particles, are harmful to health is well accepted, causing direct effects such as lung inflammation resulting in exacerbations of lung and cardiac conditions and being associated with admissions for prediagnosis of myocardial infarction. In the 1960s Lauer and al showed that ambient particles stimulated the growth of *Haemophilus influenzae* in vitro, suggesting a direct effect of particles on bacteria themselves. However, it is not known whether this remains so for modern ambient particles where the sources are different.

To address this we have assessed the effect of PM10 (particles essentially less than 10 μm in diameter) on the respiratory pathogens commonly associated with acute exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia. The effect of dilutions of extracts of PM10 on the growth of *H influenzae* and *Streptococcus pneumoniae* grown in liquid broth and the effect of PM10 on microbial growth kinetics of *S pneumoniae* was assessed.

Fresh isolates of *H influenzae* and *S pneumoniae* obtained from clinical specimens and the control strains *H influenzae* NCTC 11931 and *S pneumoniae* ATCC 49619 were used. Particles were collected on a tapered element oscillating microbalance situated in central Birmingham, representative of an urban background site. To obtain a usable sample the surface of the filter was wetted and rinsed with two sequential aliquots of 0.5 ml saline using a Gilson pipette until visual inspection showed no more particles coming off the filter. The two aliquots were combined and sonicated for 2 minutes to disperse the particles and aggregates. This procedure usually gives a yield of 50–300 μg/ml particles (Donaldson, personal communication). It is not known for certain how these concentations relate to likely concentrations in the epithelial lining fluid, but this approach has been used in previous in vitro studies of inflammatory responses which have shown pro-inflammatory effects.

In the first experiment a 1:20 dilution of PM10 was made by adding 0.5 ml to 9.5 ml iso sensitiv broth (ISTA; Oxoid Ltd, Basingstoke, UK) supplemented with 5% horse blood and 20 μg/ml NAD. The same volume of normal saline was added to controls. Test and control bottles were incubated with 0.5 ml of organism suspension at a density of 0.5 McFarland. A viable plate count was performed hourly for 5 hours while incubating at 37˚C in 5% CO2 using the Miles and Misra technique. In the growth kinetic experiment equal volumes of PM10 solution and ISTA broth (supplemented with 5% lysed horse blood and 20 μg/ml NAD) were added to the first column of a sterile microtitre tray. Serial broth dilutions to a final dilution of 1:64 were performed from clinical specimens and only broth and wells for sterility checks contained PM10 alone, broth alone and inoculum alone. Organism suspension, 50 μl *S pneumoniae* ATCC 49619, was added into each test and control column of the wells and incubated at 37˚C in 5% CO2 for 5 hours. The Miles and Misra technique was used to estimate the viable count of organism in each well and the differences in log cfu/ml between test and control were plotted against serial dilutions of PM10. This test was repeated five times using the same strain to check for reproducibility.
In the first experiment the number of viable cells increased progressively and in the expected pattern over time (fig 1A and B), whether in the presence or absence of PM10 for both H influenzae and S pneumoniae. In the growth kinetics experiment the only consistent finding was an inhibition of growth at a PM10:broth medium dilution of 1:1, possibly due to the particles themselves or to dilution of the broth by the added saline. These findings suggest that the association of air pollution with hospital admissions for exacerbations of COPD and for pneumonia is probably not mediated through direct promotion of bacterial growth. If particles alone are responsible for these effects, they are likely to be mediated by particles causing lung inflammation, thus encouraging penetration and growth of bacteria in the respiratory tract. Alternatively, gaseous pollutants may be responsible for the epidemiological findings, either directly or in conjunction with particles. This interactive mechanism is supported by the association of ambient nitrogen dioxide levels with admissions for croup, and is analogous to the potentiation of the airway response to inhaled allergen by both nitrogen dioxide and ozone. Finally, it is possible that the particles have an effect on bacterial virulence and toxin production rather than growth. This possibility has not been tested here but warrants further study.

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References

CORRECTIONS

doi: 10.1136/thx.2004.020307corr1

PAPER BY HORVATH ET AL (THORAX 2003;58:68–72)

In the paper entitled “Comparison of exhaled nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia” by I Horvath, S Loukides, T Wodehouse, et al published in the January 2003 issue of Thorax (2003;58:68–72), there was an error in the labelling of fig 1. The correct version of the figure is printed here. The publishers apologise for this error.