

LETTERS TO THE EDITOR

Risk factors for death from asthma

Guite and colleagues¹ recently attempted to identify risk factors for certain causes of death among patients admitted to hospital with asthma. The data were originally collected for a different purpose,² however, and problems of data quality and completeness limit the conclusions that can be drawn from this analysis.

The current study is based on follow up of 2242 (68%) of the original cohort of 3292 patients. An expert panel identified 22 patients who died from asthma, 14 from chronic obstructive pulmonary disease (COPD) and other respiratory diseases, and 14 from cardiovascular diseases.² In the paper by Guite *et al*¹ the numbers of cases have changed significantly with 29 deaths from asthma, 21 from COPD, and 21 cardiovascular deaths. Because both papers relied on the same expert panel, these discrepancies raise fundamental questions about the interpretation of this paper.

The fact that drugs are prescribed to patients who differ according to baseline risk poses an extraordinary methodological challenge to any epidemiological study. Guite and colleagues¹ concluded that "ipratropium bromide is associated with increased risk of death from asthma even after adjustment for a range of markers of COPD." Even after including extra deaths not identified by the expert panel as asthma deaths and controlling for a marker of COPD co-morbidity but for no markers of asthma mortality, the 95% confidence interval for the odds ratio for ipratropium bromide and death from asthma is extremely imprecise (1.2 to 11). Reducing the number of cases to the original 22 asthma deaths identified by the expert panel and controlling for validated markers of asthma mortality would only further degrade the precision of this estimate.

Boehringer Ingelheim has marketed ipratropium bromide for 25 years and its impressive safety profile has been firmly established by hundreds of randomised, controlled studies and epidemiological studies evaluating tens of thousands of patients. Limitations of the current data—understandable from the fact that the study was not originally designed to meet this challenge—preclude them from providing a reliable empirical basis for suggesting an adverse effect of ipratropium.

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1 Guite HF, Dundas R, Burney PGJ. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999;54:301-7.

2 Guite HF, Burney PGJ. Accuracy of recording deaths from asthma in the UK: the false negative rate. *Thorax* 1996;51:924-8.

AUTHORS' REPLY We understand the concern that representatives of Boehringer Ingelheim have expressed about the interpretation of our paper¹ which finds an association between prescription of ipratropium and death among asthmatic patients. In the paper we were also cautious about the interpretation and stated that "the ratio of information to cases is high and therefore results should be regarded as preliminary and should be tested in a larger study".

There are, however, a number of issues that deserve additional comment. They state that this study was not originally designed to address cause of death among patients admitted to hospital for asthma. The original study plan was always to conduct such a study. Our first report of the cohort² described the identification of the cohort and established the accuracy of classification of cause of death. The focus of this paper on establishing the accuracy of recording of cause of death on the death certificates by an expert panel explains why only 22 deaths were discussed. Seven further patients who were certified as having died from asthma were not reviewed by the expert panel as there was insufficient further information on which to base a different opinion other than that given on the death certificate (table 1).² However, the high specificity of the diagnosis on the death certificates that were studied leads us to believe that assigning these seven deaths to death from asthma, as on the certificate, is reasonable. As we are concerned with deaths from any cause, this is not a critical issue.

Lanes and Wilson assume that the cohort consisted of 3292 people, but this refers to all admissions including re-admissions. The cohort consisted of 2382 individuals, as stated in both papers,^{1,2} and follow up information was available for 2242 (94%).

They are concerned that the risk estimates might be confounded by the severity of the disease. Although this is possible, we believe that their argument is misdirected. Most studies of asthma deaths have looked at death due to asthma as defined on the death certificate and have adjusted for severity using proxy measures. These measures have most often been related to health service use and have included admissions to hospital for asthma, use of oral steroids, and use of more than two asthma medications. Our study was different in that it looked at death from all causes in a cohort of patients, all of whom had been admitted to hospital for asthma. To this extent all the patients came from a single stratum of severity. Further stratification in terms of asthma severity makes little difference. We defined "clinically severe asthma" as any history of drowsiness as a result of asthma, loss of consciousness, respiratory arrest, mechanical ventilation, or admission to the ITU for asthma treatment. Taking the results in table 2¹ which shows the association between death and five risk factors and further stratifying by the presence of "clinically severe asthma", we lose one observation in whom severity could not be determined. The odds ratio associated with taking ipratropium or Duvent changes from 2.9 (95% CI 1.2 to 7.0) to 2.7 (1.1 to 6.7) on losing this case, and to 2.7 (1.1 to 6.6) on adjustment for "clinically severe asthma".

The analysis by cause of death is a sub-analysis and is probably less relevant to the general argument. It was, however, of some interest that the excess mortality among those taking ipratropium was found for all major causes of death.

Our own view remains, as stated in the paper, that the most likely source of confounding is with concurrent COPD. We have good reason to believe that this is associated with a particularly bleak outlook for the patients and is likely to be associated with prescription of ipratropium. The analysis of the data did not, however, support this view (table 4) and the elevated risk seemed to persist on adjusting for different markers of COPD, regardless of the certified "cause of death".

Prescribing decisions need to be taken with an overall view of costs and benefits and we would not feel that the data produced in our paper necessarily warrant a change in prescribing in those cases where there is clear clinical benefit to be obtained from the use of ipratropium. An excess death rate that is estimated to be two to three times that on other regimens does, however, in our opinion need to be taken seriously and further work must be done to assess whether the observed association is real and, if so, how it might be explained.

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2 Guite HF, Burney PGJ. Accuracy of recording deaths from asthma in the UK: the false negative rate. *Thorax* 1996;51:924-8.

Nebulised taurolidine and *B cepacia* bronchiectasis

We have already reported a unique case of bronchiectasis with chronic colonisation by UK epidemic (ET12) *Burkholderia cepacia* in a previously well woman which developed following an acute infection acquired from her two *B cepacia* colonised children with cystic fibrosis.¹ This has intermediate sensitivity to only co-trimoxazole and ceftazidime and, despite several intravenous courses of these antibiotics, the patient has remained chronically colonised for more than four years. We have therefore looked for other antibiotics which may have action against this multidrug resistant pathogen. Taurolidine acts by disrupting the cell wall, diminishing bacterial adherence, and neutralising toxins.² It has good in vitro anti-*B cepacia* activity (MIC 0.4 mg/ml) but is currently used as an antiseptic peritoneal lavage solution. We gave nebulised taurolidine to our non-cystic fibrosis patient in a randomised, double blind, placebo controlled, crossover fashion ("n-of-1 trial") to assess its effect on her chronic respiratory *B cepacia* colonisation (primary outcome measure), spirometric tests, and inflammatory markers (serum and sputum concentrations of interleukins 6 and 8, C

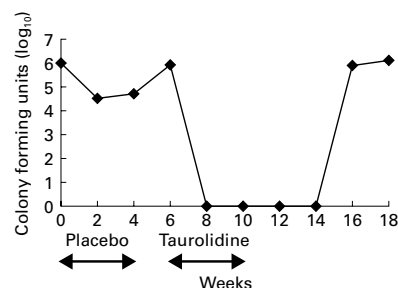


Figure 1 Effect of treatment with taurolidine on colonisation with *Burkholderia cepacia* in a non-cystic fibrosis patient.

reactive protein, total white cell count, erythrocyte sedimentation rate) (secondary outcome measures). She was given 4 ml 2% taurolidine twice daily in the active arm and 4 ml 0.9% saline twice daily in the placebo arm, each for four weeks separated by a two week washout period. Every two weeks sputum counts of *B. cepacia* (colony forming units/ml) were determined by two independent microbiologists blinded to each others' results; concordance between them was >95%. A bioassay was performed on the sputum by agar diffusion to confirm that taurolidine was no longer active.

The study was approved by the local ethics committee and the patient gave her informed consent.

B. cepacia disappeared from the sputum during the taurolidine arm and did not reappear until four weeks after cessation of treatment. There was no change in the placebo arm (fig 1). The only side effects noted during taurolidine treatment were transient mild pharyngitis and cough. There was no difference in spirometric parameters or inflammatory markers between the active and control arms. No changes in medication occurred during the trial.

UK epidemic (ET12) *B. cepacia* is innately resistant to many antibiotics and therefore the discovery of a different antimicrobial agent that has activity against this organism is important. Whilst a pilot study of taurolidine in patients with cystic fibrosis suggested that it may reduce colony counts,³ in a formal double blind placebo controlled crossover trial the results were disappointing.⁴ However, in our non-cystic fibrosis patient *B. cepacia* disappeared from the sputum within two weeks of commencement of treatment and remained absent for two weeks after treatment stopped. Dilutional studies showed no taurolidine activity in the sputum samples so recurrence of the organism in sputum after cessation of treatment may reflect recolonisation from her children or spread of residual colonisation in her upper respiratory tract. The apparent difference between the effect of taurolidine in this formulation in our patient and in patients with cystic fibrosis raises interesting questions as to the mechanisms by which *B. cepacia* survives in subjects with cystic fibrosis. These include the presence of a biofilm⁵ and intracellular survival of organisms allowed by the defective CFTR protein.⁶

The current formulation of taurolidine uses povidone as a solubilising agent which may cause an unpleasant taste. Furthermore, taurolidine is only available as a 2% solution. We believe this agent may have a part to play in *B. cepacia* infections in patients both with and without cystic fibrosis, and reformulation of taurolidine and its derivatives to allow a higher concentration to be delivered may

improve its efficacy in patients with cystic fibrosis.

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Effect of salmeterol on airway eosinophils

Dente *et al*¹ used the examination of induced sputum cell counts (as well as sputum eosinophil cationic protein (ECP), blood eosinophils and serum ECP) to examine the inhibitory effects of a single dose of placebo and salmeterol on allergen induced inflammatory (as well as asthmatic) responses. They performed a crossover randomised study in 11 subjects who had two allergen challenges four weeks apart and found that salmeterol inhibited the allergen induced increases in sputum eosinophils but had no effect on the other inflammatory parameters.

The results differ from the negative results reported by us² and Dante *et al*³ attribute this to differences in study design. We agree with this explanation but not for the reasons given. Their study design has a major flaw in the use of only one baseline measurement to investigate two distinct interventions four weeks apart. The time of baseline measurements in relation to the randomised crossover design study was not given; we presume that it was at some appropriate point before the first allergen challenge. It will therefore be relevant only for half of the subjects. This design therefore ignores a basic rule of the randomised crossover trial—namely, to provide evidence that the baseline measurements of the outcome of interest before each challenge are similar. The absence of a baseline measurement is even more crucial in their study because there was a wide variation in the baseline proportion of sputum eosinophils and the randomisation of subjects was not performed after stratification for this. Therefore the claim cannot be made that sal-

meterol prevents sputum eosinophilia because there were no baseline measurements in at least half of the subjects to prove or disprove this assumption.

The authors suggested that differences between their results and ours may be due to the fact that we performed five allergen challenges and four hypertonic saline inductions for each allergen and say that "this could have resulted in a progressive increase in airway inflammation in each subject during the progression of the study, leading to a more persistent eosinophilic inflammation and consequently to the low repeatability reported by these authors in sputum eosinophil percentages measured before each allergen challenge".¹ Although a small change in airway inflammation can be induced by repeated hypertonic saline challenges,³ this statement has three inaccuracies. Firstly, in our study the repeated allergen challenges did not lead to a progressive sputum eosinophilia as can be clearly seen in fig 4 which shows individual values of sputum eosinophils before and after each intervention. Secondly, the authors incorrectly translated the baseline period variations in sputum eosinophils as "low repeatability". This was not a repeatability study but an intervention study. Repeatability refers to, and reflects, the amount of error, both random and systematic, inherent in any measurement.⁴ Our study shows that the method of sputum examination we used is responsive to longitudinal changes, whether occurring by regression to the mean or after an intervention. Finally, the study by Holz³ refers to the effect of repeated inductions on neutrophils and not eosinophils, a point which is irrelevant to the interpretation of the results of our study.

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AUTHORS' REPLY In their letter Dr Pizzichini and colleagues disagree with our conclusion that salmeterol prevents allergen induced sputum eosinophilia. We do not agree with their opinion.

In the results section of our study it is clearly stated that comparison of sputum eosinophils, as well as other parameters, was made between measurements performed after allergen challenge following pretreatment with placebo or salmeterol. Our conclusions were made on the basis of this comparison and not by evaluating differences from baseline as is commonly used in other models in other studies.¹ Only one baseline measurement was performed for several reasons: (1) it showed good reproducibility for sputum cell counts in two samples collected under similar

conditions²; this assumption is used to consider unchanged cell counts in sputum in two tests with hypertonic saline performed under the same conditions except for allergen challenge or premedication as intervention; (2) it is a good rule to perform only a few challenge tests as it is less likely that the characteristics of the subjects will change if they are examined over a short period of time than when they have to perform many tests over a longer period of time. We have previously reported an influence of the shortness of the time interval between two subsequent allergen challenges.³ Moreover, the number of subjects in our study was adequate to study a difference in sputum eosinophils due to an intervention, as calculated by power analysis, but the number was too small to permit stratification for sputum eosinophils in the baseline evaluation.

In the second part of their letter Pizzichini *et al* quote from our paper that differences between their results and ours may be due to the large number of challenges that each patient performed in their study. Our sentence refers mostly to the large number of allergen challenges. In fact, if a lot of allergen challenges are performed over a short time there will probably be a worsening of asthma symptoms and late asthmatic response, and consequently an increase in the airway inflammation. If the large number of allergen challenges is performed over a longer period of time with an adequate interval between subsequent allergen challenges, there is a greater probability that different conditions will occur as a result, for example, of respiratory infections or allergen exposure, and consequently a poorer repeatability is likely.

Finally, we think that the calculation of repeatability evaluating the baseline series of data in the study by Pizzichini *et al* is correct. In fact, if similar conditions are maintained, having two or more different series of data of the same parameter is good for performing repeatability tests (as performed in our study).

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BOOK REVIEW

Acute Respiratory Distress Syndrome: A Comprehensive Clinical Approach
Russell JA, Walley KR. (Pp 356, paperback; £29.95). Cambridge: Cambridge University Press, 1999. ISBN 0 521 65410 6.

During little over three decades since its characterisation, the acute respiratory distress syndrome, alone or as a part of the multi-organ dysfunction syndrome, has grown to constitute one of the major challenges facing intensive care specialists across the globe. Within the past decade major advances in our understanding of the aetiology and pathophysiology of the condition and the introduction of new treatment modalities and management strategies have conspicuously failed to improve patient outcome significantly.

In this publication James Russell and Keith Whalley have produced an excellent pocket sized text that provides a comprehensive and up to date review of the current understanding and management of the acute respiratory distress syndrome, and which fills a valuable niche between the journals and larger reference textbooks.

The book is divided logically into concise, easy to read chapters, supported by a wealth of tables, graphs and illustrations, with each chapter individually and comprehensively referenced. All aspects of the syndrome are addressed from epidemiology through molecular biology, pathology and physiology, to resolution and recovery. Individual chapters deal with pulmonary and cardiovascular pathophysiology, mechanical ventilation and weaning, and innovative therapies. Clinical trials are reviewed and assessed in an unbiased, rational, evidence based manner, and recommendations for best practice are proposed upon the basis of available knowledge.

The major strength of the book, however, lies within the authoritative and holistic approach in those chapters pertaining to the clinical management of the patient with ARDS. The book is crammed full of useful practical advice, clinical expertise, and good common sense. I was particularly impressed with the chapters dealing with total patient care and nosocomial pneumonias, and delighted to see so many published algorithms and therapeutic guidelines. In addition, I thought that the insertion of a chapter giving a concise overview of ARDS and its management was an excellent idea. If trainees were to read no more than this, they would learn much.

There were very few things that I did not like about the book. Given the overall quality, I was disappointed with the standard of reproduction of the chest radiographs. The photomicrographs and pathology slides would have benefited by being in colour. In addition, the casual admixture of the terms “multiorgan dysfunction syndrome” and “multisystem organ failure” in chapter 13 runs against current vogue and may confuse the less experienced reader.

Nonetheless, I thought this an excellent text that should have broad appeal. It is relevant to all disciplines involved in the care of the critically ill, both as a reference text and as an easy to read manual for trainees. Furthermore, the diverse aetiologies and unpredictability of multiorgan dysfunction and acute respiratory distress syndromes make this book an invaluable reference for acute ward based staff who may become involved in the early care of this most challenging of conditions.—ML

NOTICES

ARTP Millenium Meeting

The Association for Respiratory Technology and Physiology (ARTP) Millenium Meeting will be held on 10–12 February 2000 at The Hanover International Hotel & Club, Daventry, Northamptonshire NN11 5SG, UK and will include keynote speeches on Smoking Cessation and Pulmonary Vascular Disorders and plenary sessions on Thoracic Surgery, Sleep Breathing Disorders, Exercise and Respiratory Medicine, and Allergy. There will also be poster presentations from successful submitted abstracts. The meeting has been approved for CME accreditation. For further information and registration forms contact the ARTP Secretariat on 0121 622 3644; email: uccbham@compuserve.com

Scadding-Morrison Davies Joint Fellowship in Respiratory Medicine 2000

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respiratory medicine. Applications are invited from medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade. **There is no application form** but a curriculum vitae should be submitted together with a detailed account of the duration and nature of the work and the centres to be visited, confirming that these have agreed to provide the facilities required. Please state the sum of money needed for travel and subsistence. A sum of up to £15 000 can be awarded to the successful candidate, or the sum may be divided to support two or more applications. Applications should be sent to Dr I A Campbell, Secretary to the Scadding-Morrison Davies Fellowship, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX by 31 January 2000.

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the Dr H M (Bill) Foreman Memorial Fund invite applications for grants relating to study in respiratory disease. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study respiratory disease, and also for support for clinical research abroad. Intending applicants should write for further details to Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK.