“Opportunist” mycobacterial infections

We were greatly impressed by the Joint Tuberculosis Committee guidelines on the management of opportunistic mycobacterial infections.1 We do, however, wonder why the word “opportunist” has been used to describe the mycobacteria, other than the M tuberculosis complex, that cause human disease. All mycobacteria causing disease, even the M tuberculosis complex, are opportunists. Thus, the latter are often spoken of as causing opportunistic disease in HIV positive persons. Since the causative role of these other mycobacteria in human disease was established in the middle of the 20th century, a wide range of collective nouns has been applied to them—apocalyptic, anonymous, MOTT (mycobacteria other than tuberculosis), nontuberculous, and tuberculoid—as well as opportunist.

The distinguishing feature of almost all mycobacteria other than members of the M tuberculosis complex is that they live freely in the environment. For this reason the expression “environmental mycobacteria” has been in widespread use in recent years. May we argue that, pass very briefly over the evidence base for the use of antibiotics in this common and important clinical situation, citing only one original study, one review, and one meta-analysis to justify the statement that “antibiotics benefit the host by shortening the duration of symptoms of acute bronchitis”. For such an important and fundamental cause of morbidity in primary care there is an extraordinary dearth of studies to inform evidence-based decision making. The published studies are small, variable in quality, and use various antibiotics, dosage regimens, and outcome measures. In the quoted meta-analysis by Fahey et al of randomised controlled trials comparing antibiotics with placebo, only nine studies investigating a total of 700 randomised patients were found for analysis. Only six of these studies were suitable for the analysis of some of the key outcomes. The authors’ conclusion that antibiotic treatment has no effect on the resolution of acute cough was subsequently criticised.2

Although the clinical improvements analysed in the antibiotic-treated group failed to reach statistical significance, quite narrowly for some outcomes, the results did favour antibiotics for an effect on both resolution of cough and clinical improvement at the 25% of patients in our studies in whom the GP stated that antibiotics were definitely needed. The GP considered that antibiotics were necessary to 25% of patients in our studies in whom the GP stated that antibiotics were definitely clinically indicated than the 75% of patients consulting with acute bronchitis who are actually given antibiotics. We agree with Dr Thomas that the challenge is identifying that small group of patients in whom antibiotics are clinically indicated and it is here that further research is indicated, along with clearly described illness definitions and clinically relevant end points.


3 Canes CJ. Data do not justify study’s conclusions. BMJ 1998;317:1017.

4 Shakespeare TP, Boulté BC. Too few subjects were studied for useful conclusions to be drawn. BMJ 1998;317:1017.


Antibiotic prescribing in the community

Macfarlane et al present a comprehensive and thorough review of the multiplicity of factors affecting therapeutic decision making by general practitioners for patients presenting with acute lower respiratory tract symptoms. They do, however, pass very briefly over the evidence base for the use of antibiotics in this common and important clinical situation, citing only one original study, one review, and one meta-analysis to justify the statement that “antibiotics benefit the host by shortening the duration of symptoms of acute bronchitis”. For such an important and fundamental cause of morbidity in primary care there is an extraordinary dearth of studies to inform evidence-based decision making. The published studies are small, variable in quality, and use various antibiotics, dosage regimens, and outcome measures. In the quoted meta-analysis by Fahey et al of randomised controlled trials comparing antibiotics with placebo, only nine studies investigating a total of 700 randomised patients were found for analysis. Only six of these studies were suitable for the analysis of some of the key outcomes. The authors’ conclusion that antibiotic treatment has no effect on the resolution of acute cough was subsequently criticised.1

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Genetic susceptibility to COPD

We read with interest the report by Yim et al of a failure to observe an association between polymorphisms of the microsomal epoxide hydrolase (mEPHX) gene and chronic obstructive pulmonary disease (COPD). This contrasts with the findings of earlier studies.

There is debate in the literature on the place of association studies in the investigation of late onset complex disorders. Failure to replicate an initial report of a positive association is common and it is important that the reasons for this are established.

The authors correctly state that their failure to replicate the results of earlier studies may be a reflection of the marked racial differences in the frequency of the mEPHX gene within their population. However, their study also lacks power. Given, for example, their reported frequency of 75% for the wild type homozygous exon 3, a sample size of 80 subjects would only be able to detect a difference of 22% (e.g. 75% versus 53%) between the case and control groups (two tailed p value = 0.05, power = 0.8).

Phenotypic heterogeneity is a problem in the genetic dissection of complex traits and hampers comparisons between studies. The authors are rigorous in their spirometric criteria used to define cases. However, their COPD group also includes never smokers and those with minimal pack-year histories. It is not restricted to adult onset disease, potentially containing chronic asthmatics.

This phenotypically heterogeneous group could reduce the likelihood of demonstrating an association. The calculation of phenotypic “scores” is one solution to the clinical diversity which the label “COPD” describes.

Finally, the importance of age and sex matching cannot be understated, not only because controls may develop disease, but also to minimise the effects that will occur to the gene pool of the population ages. We would therefore urge caution before abandoning a role for this candidate gene in this population. Further studies in extended populations with rigorously matched controls are clearly needed.

C RUSE
Department of Medicine, University of Leicester, Glenfield Hospital, Leicester, UK

S G PARKER
Sheffield Institute for Studies on Ageing, University of Sheffield, Northern General Hospital, Sheffield, UK

P BURTON
Department of Epidemiology and Public Health, University of Leicester, Leicester, UK

A WARDLAW
Institute for Lung Health, University of Leicester, Glenfield Hospital, Leicester, UK

Correspondence to: Dr C Ruse


AUTHORS’ REPLY
We thank Dr Ruse and colleagues for their interest and comment on our study. They mentioned three points: (1) sample size, (2) the possibility of including asthmatic patients in the COPD groups, and (3) failure of age and sex matching between the disease and control groups.

We agree with them that our sample size was not large enough to detect small differences between the two groups (COPD 83, control 76). The strict criteria used in our study to select patients with disease or healthy smokers made our sample size smaller.

They suggested that the possibility that we may have included asthmatic patients in the COPD groups because of the minimal smoking history in some patients. It is well known that there are risk factors for developing COPD other than smoking history such as environmental tobacco smoking (passive smoking), ambient air pollution, and occupation. It is therefore possible for non-smokers to develop COPD. Although we vigorously excluded patients with minimal asthmatic features in order to select a phenotypically homogeneous group, it is true that some patients with chronic asthma cannot be differentiated from patients with COPD by any method.

Gene frequencies do not vary according to sex in the general population and the lack of sex matching in our study may not influence the result. When we excluded six women from the COPD group the result was the same. Although we adjusted for the effect of age by stratification, it is clear that an age matched control group would have been better. The first and only study which suggested the role of genotypes of microsomal epoxide hydrolase (mEPHX) in the pathogenesis of COPD also lacked age and sex matching because the control group was anonymous.

We agree with Dr Ruse and colleagues that further large scale rigorously matched case control studies are needed to clarify the role of this candidate gene in the pathogenesis of COPD.

J-J YIM, G Y PARK, C-T LEE, W F KIM, S K HAN, Y-S SHIM, C-G YOO
Department of Internal Medicine, Lang Institute and Clinical Research Institute, Seoul National University College of Medicine, Seoul 110-744, Korea

Correspondence to: Dr C-G Yoo


AUTHORS’ REPLY We appreciate the comment not. The suggestion by Y oshikawa
Weinberg equilibrium but those of exon 3 are
cities of mEPHX in exon 4 are in Hardy-
the fact that in our study
agree that further explanation is needed for
bility of overestimating the frequency of
mEPHX exon 3 can be misclassified as a
exon 3 amplified with an anti-
PCR product of exon 3 amplified with an antisense primer outside the original one we
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susceptibility to chronic obstructive pulmonary
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Gamma-glutamyltransferase
1 Yoshikawa M, Hiyama K, Ishioka S, et al. Microsomal epoxide hydrolase genotypes and
chronic obstructive pulmonary disease in Japa-
2 Noonan M, Chervinsky P, Busse WW, et al. Flutica-
sone propionate reduces oral prednisone use while it improves asthma control and quality
3 Chrousos GP, Harris AG. Hypothalamic-
pituitary-adrenal axis suppression and inhaled corticosteroids therapy. Neuroimmunomodulation
AUTHORS’ REPLY We thank Dr Honour for his valuable comments. We are currently in
the process of re-analysing our samples by an HPLC method as suggested by him, but we
have had problems finding a laboratory able to perform the HPLC measurements with the
required quality. We would like to respond as soon as the data are available.

Ronald J Meijer, HUB A M Kerstjens
Department of Pulmonary Diseases, University Hospital Groningen, 9700 RB Groningen, The Netherlands
email: h.a.m.kerstjens@int.unigo.nl

Correspondence to: Dr H A M Kerstjens.

Letters to the editor

Fluticasone in asthma

The paper by Meijer et al compares the effects of inhaled fluticasone propionate (2 mg and 0.5 mg daily) and oral steroids (prednisolone 30 mg daily) in patients with mild to moderate asthma. Many patients with severe asthma are dependent upon corticosteroids, although inhaled steroids can effectively replace oral prednisolone.

The biological effects of oral versus inhaled steroids can be compared in terms of lung function, airway responsiveness, and blood eosinophil number and activity, but suppression of the hypothalamic-pituitary-adrenal (HPA) axis is very difficult to assess. Prednisolone is so chemically similar to cortisol that most analytical methods (particularly radioimmunoassay, as used by Meijer et al) cannot distinguish between the two steroids. Although the authors attempted to overcome this problem, the correction of the measured level of cortisol for a potential cross reaction with prednisolone is not valid. If there is any possibility of cross reaction from other steroids, cortisol assays are only specific if performed using high performance liquid chromatography or mass spectrometry.

It is therefore incorrect for the authors to conclude that cortisol levels after 30 mg oral prednisolone were comparable to those after inhaled fluticasone in a dose of 2 mg/day. The paper did not describe the precise dosages and timings for fluticasone or prednisolone administration and these could have large effects on 08.00 hour serum cortisol concentrations. The increased systemic effect of prednisolone compared with fluticasone is strongly supported by the significantly higher serum ECP level and blood eosinophil count.

Many papers on the function of the HPA axis in the context of safety of oral and inhaled steroids fail to take account of the normal function of the axis, the way in which the axis is perturbed by exogenous steroids, and the best methods for testing the axis, particularly when patients are also taking oral corticosteroids. Care should be taken at the outset to select analytical methods appropriate to the design of such studies to avoid misinterpretation.

John W Honour
Reader in Steroid Endocrinology, University College London Hospital, London W1P 6DB, UK
email: john.honour@uclh.org

1 Meijer RI, Kerstens HAM, Arends LR, et al. Effects of inhaled fluticasone and oral pred-

1 Yoshikawa M, Hiyama K, Ishioka S, et al. Microsomal epoxide hydrolase genotypes and
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morphic genotypes for microsomal epoxide
hydrolase and susceptibility to emphysema.

4 Benhamou S, Reinikainen M, Bouchardy C, et al. Genetic suscepti-
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Fluticasone in asthma

JOHN W HONOUR

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