in animal studies has been shown to result in neuronal damage in wake promoting structures or disturbance in sleep architecture.22 23 Notwithstanding, one can also look at the issue of sleep hypoxaemia and daytime sleepiness from other angles. Why was desaturation more severe in the sleepy group despite similar AH? Can the daytime sleepiness in those OSA individuals be a reflection of an overall propensity to sleep2 21 with diminished ventilatory response during nocturnal sleep, hence greater oxygen desaturation? Apart from hypoxaemia, is there any role for hypercarbia, the parameter in oblivion which is expected to be there any role for hypercarbia, the para-

may have very different consequences in the study sample demarcates clearly in the study sample in phenotypes and their underlying tions in phenotypes and their underlying encounter, subjects would have a wide authors' stated hypothesis. In our daily selected for the purpose of addressing the researchers speculate on, and attempt to questions than it can answer. While 940

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Antibiotics at COPD exacerbations: the debate continues

Jadwiga A Wedzicha

The course of chronic obstructive pulmonary disease (COPD) is affected by the presence of exacerbations that are episodes of worsening of respiratory symptoms commonly triggered by airway infections, including respiratory viruses and airway bacteria.1 COPD exacerbations have important adverse effects on health status2 and mortality3 and affect the course of the disease.4 Thus there is considerable interest in the effectiveness of interventions used both to treat exacerbations and prevent further events.

Exacerbations are usually treated with oral corticosteroids and/or antibiotics depending on exacerbation severity and the nature of the symptoms. There is now considerable evidence for benefit of a course of oral corticosteroids at exacerbation1 6 and also for antibiotics when two of the three symptoms of increased dyspnoea, sputum volume and purulence are present.7 However, there is still some controversy concerning the role of antibiotics at COPD exacerbation, especially in studies performed in primary care8 where generally patients with milder disease have been recruited. There is now clear documentation of the involvement of bacteria at exacerbations with increased bacterial detection and load,9 while bacterial strain changes have also been associated with development of exacerbations.10 Eradication of bacteria in the airways with antibiotics prescribed at exacerbation has been linked to exacerbation recovery and reduction in airway inflammatory markers.11 Some of the controversy regarding

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antibiotics relates to the fact that patients with COPD show lower airway bacterial colonisation (LABC) in the stable state, and increased LABC is associated with greater airway inflammation and exacerbation frequency.

There are a number of reasons for the observed variation in outcomes seen with antibiotic trials at COPD exacerbations. A number of different outcomes have been utilised in clinical trials, including exacerbation lengths and recovery, symptom recovery, time to the next exacerbation, treatment failure and mortality. Often patients with COPD recruited into trials have been markedly heterogeneous with respect to lung function, stable treatment, comorbidity and exacerbation frequency. Outcomes from antibiotic studies have been measured mainly in the short term, and there is relatively little information on longer term outcomes. In a further analysis from the MOSAIC trial of the antibiotic moxifloxacin versus standard therapy at exacerbations, Wilson et al showed that the response to moxifloxacin was worse in the short term (up to 10 days) in patients with coexistent cardiac disease. In contrast, when exploring longer term outcomes up to 9 months after the study onset, response to moxifloxacin was greater in older patients who were aged over 65 years and in those with higher exacerbation frequencies. Thus the benefit of antibiotics are more pronounced in frequent exacerbators and this is consistent with the fact that these patients show a higher airway bacterial load in the stable state.

Further information on longer term outcomes with antibiotic therapies at COPD exacerbations is now available. Roede and colleagues report on the longer term outcomes of antibiotic therapy in a population based cohort from the Dutch PHARMO database (see page 968). This database includes pharmacy dispensing records from community pharmacies and secondary care on 2 million residents in The Netherlands. Patients with airway obstruction who had medication dispensed for airway disease were included if aged over 50 years to exclude patients with asthma as far as possible. Exacerbations were detected from courses of oral corticosteroids prescribed, as it can be assumed that these are prescribed usually for exacerbation events. Events where antibiotics were prescribed without oral corticosteroids were excluded as there was no information on the diagnostic nature of this episode. A minimum interval between individual steroid courses was taken as 3 weeks to avoid confusion over relapsed and new exacerbations. The novel aspect of this study was that the authors not only followed the patients from the initial exacerbation to the next or second event, but also from the second to the third exacerbations. The main comparisons were between exacerbations treated with oral corticosteroids alone and those treated with steroids combined with a course of antibiotics. Results showed that the time to the next/second exacerbation was longer when corticosteroids were combined with antibiotics rather than corticosteroids alone, and a similar result, although more pronounced effect, was found between the second and third exacerbation. There was also a reduction in all cause mortality in the oral corticosteroid and antibiotic group followed after the first exacerbation, although the authors are rightly cautious in suggesting a survival benefit as the cause of death was not known in the majority of the cases.

This study suffers from the usual disadvantages of being a large database study without information on spirometry to adequately classify the patients. The two exacerbation treated groups were also well matched for age, gender and comorbidity, although patients given both antibiotics and corticosteroids at exacerbation had a greater number of stable medications dispensed with fewer hospital admissions. Thus if these were a more severe patient group based on prescribed therapies, one would expect them to have shorter times to next exacerbations and this would tend to decrease the size of the treatment effect. On the other hand, long term bronchodilators and inhaled corticosteroids can all reduce exacerbation frequency in patients with COPD thus increasing the time to the next exacerbation. Exacerbations where antibiotics were used on their own were excluded, with the result that the overall study cohort exacerbation frequency was reduced.

These results describe the longer term consequences of using antibiotics in COPD exacerbations. Although we assume that antibiotics at exacerbations reduce the airway bacterial load and thus the inflammatory load at the particular exacerbation, a single course of antibiotics may also have a significant effect on the degree of LABC in the subsequent stable phase. If LABC is reduced by the first antibiotic course, then this reduction in load may enhance the benefit of antibiotics on subsequent exacerbations, although any potential mechanism leading to this observation needs further study. In this study, the class of antibiotics used did not have any effect on the outcomes, but therapy specific for the colonising or infecting bacteria may show greater benefit. On the other hand, there may be other explanations for the effects observed. As many exacerbations are triggered by respiratory viral infections, it is possible that use of oral steroids alone can increase the chance of secondary bacterial infection at an exacerbation and antibiotic therapy prevents this occurring with improved outcome. Patients prescribed antibiotics at exacerbation usually have increased sputum purulence and volume and it is also possible that symptoms related to sputum prompt patients to seek treatment for their exacerbation early after onset or commence self-management resulting in better outcomes. The study by Roede and colleagues shows that patients treated with steroids and antibiotics had more stable medications dispensed, including inhaled corticosteroids. In a recent study, patients prescribed an inhaled corticosteroid in addition to a long acting β agonist had a greater requirement for antibiotics at exacerbation than patients taking a long acting anticholinergic bronchodilator alone. This suggests that an individual patient’s stable medication may have differential effects on the character of their exacerbation and this in turn affects the nature of the therapy prescribed.

It is now clear that COPD exacerbations are complex events, occurring in patients with wide variation of disease severity, exacerbation susceptibility, underlying LABC and airway inflammation. They are associated with a number of interacting causative factors and the character of an exacerbation may be modulated by the nature of the patient’s stable medication. Thus future clinical trials of exacerbation therapy must be performed in carefully phenotyped patients with COPD with assessment of both stable and exacerbation airway microbiology, using validated outcomes and longer term follow-up. Meanwhile, I believe we have now generated more questions to be answered about the use of antibiotics and oral corticosteroids either alone or in combination to treat COPD exacerbations. The antibiotic debate will continue for some time to come.

Competing interests: None declared.
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Wheezing phenotypes

Louis I Landau

There are increasing reports of excellent data on wheezing phenotypes in early childhood. Despite some contradictory findings, generally based on differences in definitions used or ages studied, the findings are gradually providing valuable perspectives towards understanding this very common symptom. It is clear that much of respiratory disease throughout life is programmed during fetal life and the early years after birth. The patterns differ between developing and developed countries, apparently related to differences in microbial exposure, diet and exposure to cigarette smoke. The outcomes are probably mediated through the effects of these agents, timing of these exposures being critical, on airway development and maturation of the immune system. The airways may be structurally smaller due to abnormalities of the wall size, function of the smooth muscle or increased thickness of the mucosa. Abnormal maturation of the immune system influences the response to both allergens and microbes promoting either hypersensitivity or tolerance.

Cough and wheeze are very common symptoms in the early years of life with more than 60% coughing and more than 30% wheezing in the first year. Wheeze is a cardinal symptom of asthma but, in the first year of life, more than half is likely to be due to causes other than asthma such as congenitally small airways, bronchiolitis, cystic fibrosis, congenital heart disease, aspiration syndromes, social disadvantage and chronic neonatal lung disease.

A predisposition to wheeze is seen with small airways related to factors such as male gender and exposure to maternal smoking. It is more likely at this age due to a lack of collateral ventilation, a weak chest wall with reduced tethering of the airways, increased smooth muscle in the peripheral airways (particularly in premature infants) and an immature immune system.

There have been many genes associated with asthma prevalence, severity or response to drugs, although no single gene accounts for more than 10% of the asthma phenotype. Those identified generally relate to β2 receptor activity, immune maturation or function and leucotriene metabolism.

Prospective longitudinal studies commencing before birth such as those from Tucson, Melbourne, Perth and Bristol have been reported; a follow-up from this last study by Henderson and colleagues is included in this issue of Thorax (see page 974). They have defined four or more patterns of preschool wheezing: early transient (first year only), late transient (second or third year), persistent (from first year to beyond 6 years) and late onset (commencing after 5 years). Better information on these phenotypes has been obtained with measurements of lung function in this age group for forced expiratory flows using the rapid thoracic compression technique, tidal breath analysis, interrupter resistance measurements, multiple breath gas washout and lung volumes, exhaled nitric oxide, analysis of induced sputum and airway hyper-responsiveness. Those with early transient wheezing have been found to have low flow rates and airway hyper-responsiveness before the onset of symptoms associated with male gender and maternal smoking. Other triggers are being sought. One manifestation of this pattern is bronchiolitis in the...
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