Prim Care Respir J 2013; **22**(3): 261-270

Primary Care
RESPIRATORY JOURNAL
www.thepcrj.org

EDITORIALS

Long-term antibiotics in COPD: more benefit than harm?

*Marc Miravitlles[1]

[1] Pneumology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain.

*Correspondence: Dr Marc Miravitlles, Servei de Pneumologia, Hospital Vall d'Hebron, P. Vall d'Hebron 119-129, 08035 Barcelona, Spain
Tel: +34932746083 Fax: +34932746157
E-mail: mmiravitlles@vhebron.net

See linked article by James *et al*. on pg 271

Chronic obstructive pulmonary disease (COPD) is characterised by recurrent episodes of exacerbations defined by an acute increase in respiratory symptoms. These exacerbations are the main cause of medical visits and mortality, particularly so in severe COPD, and therefore prevention of these episodes is one of the major goals in the management of COPD.[1]

With this objective in mind, in the early 1970s some studies on the use of long-term antibiotics in patients with chronic bronchitis and frequent infective exacerbations were conducted. Most of these studies were characterised by small sample sizes and important flaws in their design.[2] Although they showed a small reduction in exacerbations in general, a growing concern for the development of bacterial resistance emerged. With the development of new and more effective inhaled medications for COPD, this strategy of treatment was generally abandoned and no further trials were conducted until recently.

Current guidelines recommend the use of long-acting bronchodilators and (corticosteroid) anti-inflammatories, together with non-pharmacologic measures such as pulmonary rehabilitation in order to prevent COPD exacerbations.[1] However, some (or most) of these exacerbations have an infectious origin, and bronchodilators and anti-inflammatories never fully prevent these episodes in COPD patients who are chronically infected and may have associated bronchiectasis. In fact, some evidence suggests that the use of inhaled corticosteroids (ICS) might even be a risk factor for increased bacterial load in the airways of such patients,[3] and that this relates to the observed increased risk of pneumonia.[4]

Patients with COPD may present different clinical phenotypes, and therefore not only treatment[5] but also prevention of exacerbations[6] may be different according to the phenotype. Those patients with frequent bacterial exacerbations characterised by dark sputum and who often have bronchiectasis when studied by computed tomography (CT) scanning constitute a particular phenotype – the "infective phenotype".[7] Those patients who, despite optimal management, continue to present bacterial exacerbations may require complementary treatment directed to control and (if possible) eradicate bacterial infection in the airways.

The frequency of current use of long-term antibiotics for the prevention of exacerbations of COPD in clinical practice is unknown. In this issue of the *PCRJ*, James *et al*. investigated the use of this therapy in the UK through a retrospective cohort study of a large primary care database between 2000 and 2009.[8] The results demonstrate that long term antibiotics were seldom used (only 567 patients out of 92,576; 0.61%) and interestingly tetracyclines and penicillin were the most widely used antibiotics, followed by macrolides. These results suggest that the choice of antibiotic was more influenced by the old chronic bronchitis studies than by new evidence on the use of macrolides in cystic fibrosis or bronchiectasis. However, the use of macrolides increased after 2005, which suggests an influence from more recent studies in patients with chronic respiratory diseases. Interestingly, this is the first study to provide an estimate of the prevalence of use of this type of therapy for COPD in the community, and the results indicate that the use of long-term antibiotics until 2009 in the UK was marginal. It will be interesting to see if there has been any increase after the publication of new studies with pulsed moxifloxacin[9] or with macrolides during the last 5 years.[10,11] These studies have been conducted in large, well defined populations and, in general, have provided positive results in the prevention of exacerbations when using long-term antibiotics on top of the usual medication for COPD.

Despite the positive results in the prevention of exacerbations in patients with COPD, it has to be remembered that long-term treatment with antibiotics, and particularly with macrolides, is associated with significant side effects and the risk of development of bacterial resistance,[11,12] affecting not only the treated patients but also adversely affecting community macrolide resistance as well.[13] In this context it has to be considered a very positive result that only 0.61% of COPD patients in the UK were receiving this therapeutic alternative.[8] Nevertheless, it is clear that a small subpopulation of patients with COPD may benefit from this approach. The real challenge is to provide this treatment to the right patient and prevent the excessive use of long-term antibiotics in the community. Most guidelines do not recommend the use of long-term antibiotics based on a negative evaluation of the possible benefit and harm, but they fail to consider the selected population in which benefit may clearly exceed the harm.[1] The recent Spanish guidelines for COPD suggest that long-term treatment with macrolides can be considered in patients with severe COPD and frequent exacerbations or hospital

admissions, despite optimal pharmacologic and non-pharmacologic treatment, and always with an accurate clinical and bacteriological control in reference centers.[14] This recommendation concurs with that expressed by other experts in recent reviews on this type of therapy.[12,15]

Treatment with long-term antibiotics is a clear example of a necessary collaboration between primary and secondary care. Primary care physicians must be alert to the possibility and identify those patients who could potentially benefit from this therapy, and secondary care must assess the patients' suitability, optimising baseline treatment, investigating the presence of bronchiectasis and possible chronic bronchial infection – including the patterns of resistance to antibiotics to the identified microorganisms – and evaluating heart and liver function before long-term treatment with macrolides can be indicated.

However, some questions must be addressed before a broader recommendation on the use of long-term antibiotics in COPD can be made. It is not clear which is the best antibiotic, whether it is better to use the same drug or rotate different antibiotics, which is the best dose for macrolides and, once started, what the duration of treatment should be. For all these reasons the use of long-term antibiotics in COPD must be restricted to a very selective subgroup (or phenotype) of patients with close supervision by primary and secondary care.

Conflicts of interest Marc Miravitlles has received speaker fees from Boehringer Ingelheim, Pfizer, AstraZeneca, Bayer Schering, Novartis, Talecris-Grifols, Takeda-Nycomed, Merck, Sharp & Dohme and Novartis, and consulting fees from Boehringer Ingelheim, Pfizer, GSK, AstraZeneca, Bayer Schering, Novartis, Almirall, Merck, Sharp & Dohme, Talecris-Grifols and Takeda-Nycomed.

Commissioned article; not externally peer-reviewed; accepted 5th July 2013; online 21st August 2013

http://dx.doi.org/10.4104/pcrj.2013.00074
Prim Care Respir J 2013; **22**(3): 261-262

References

1. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. *Am J Respir Crit Care Med* 2013;**187**:347-65. http://dx.doi.org/10.1164/rccm.201204-0596PP
2. Staykova T, Black PN, Chacko EE, Poole P. Prophylactic antibiotic therapy for chronic bronchitis. Cochrane Review. Published online: 21 Jan 2009. http://dx.doi.org/10.1002/14651858.CD004105
3. Garcha DS, Thurston SJ, Patel ARC, *et al*. Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012;**67**: 1075-80. http://dx.doi.org/10.1136/thoraxjnl-2012-201924
4. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease. *JAMA* 2009;**169**:219-29.
5. Bafadhel M, McKenna S, Terry S, *et al*. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;**186**:48-55. http://dx.doi.org/10.1164/rccm.201108-1553OC
6. Miravitlles M, Soler-Cataluña JJ, Calle M, Soriano J. Treatment of COPD by clinical phenotypes. Putting old evidence into clinical practice. *Eur Respir J* 2013;**41**:1252-6. http://dx.doi.org/10.1183/09031936.00118912
7. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype? *Respir Med* 2013;**107**:10-22. http://dx.doi.org/10.1016/j.rmed.2012.10.024
8. James GD, Petersen I, Nazareth I, Wedzicha JA, Donaldson GC. Use of long-term antibiotic treatment in COPD patients in the UK: a retrospective cohort study. *Prim Care Respir J* 2013;**22**(3):271-7. http://dx.doi.org/10.4104/pcrj.2013.00061
9. Sethi S, Jones PW, Theron MS, *et al*. for the PULSE Study group. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010;**11**:10. http://dx.doi.org/10.1186/1465-9921-11-10
10. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008;**178**:1139-47. http://dx.doi.org/10.1164/rccm.200801-145OC
11. Albert RK, Connett J, Bailey WC, *et al*. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011;**365**:689-98. http://dx.doi.org/10.1056/NEJMoa1104623
12. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular detah. *N Engl J Med* 2012;**366**:1881-90. http://dx.doi.org/10.1056/NEJMoa1003833
13. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med* 2013;**1**:262-74. http://dx.doi.org/10.1016/S2213-2600(13)70038-9
14. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al*. Spanish COPD guidelines (GesEPOC). Pharmacological treatment of stable COPD. *Arch Bronconeumol* 2012; **48**:247-57. http://dx.doi.org/10.1016/j.arbres.2012.04.001
15. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J* 2013;**42**:239-51. http://dx.doi.org/10.1183/09031936.00136712

Asthma prevalence and humoral immune response in Somali immigrants in the US: implications for the hygiene hypothesis

*Christopher C Butler[1], Nicholas A Francis[1]

[1] Institute of Primary Care and Public Health, Cardiff University, Cardiff, UK

*Correspondence: Professor Chris Butler, Professor of Primary Care Medicine, Director of Institute of Primary Care and Public Health, Cardiff University, School of Medicine, 5th Floor, Neuadd Meirionnydd, Heath Park, Cardiff CF14 4XN, UK
Tel: +44 (0)29 2068 7168 Fax: +44 (0)29 2068 7219
E-mail: butlercc@cardiff.ac.uk

See linked article by Patel *et al*. on pg 278

As the social determinants of health improved,[1,2] so exposure to microbiological diversity reduced[3] and asthma prevalence increased.[4,5] The Hygiene Hypothesis suggests a causal relationship between these trends, through an effect of exposure of environmental factors (including invasive and non-invasive infections) on T-helper cells.[4,6] Children with greater exposure to infections and a wider array of microbes early on in life, according to the hypothesis, can expect to have lower rates of asthma and better