

While manufacturers may use our guidelines as a basis for computer interpretation of results, all tests should ultimately be read by appropriately trained personnel.

We hope the readers of the recent American Thoracic Society/ European Respiratory Society guidelines on lung function will agree that it represents a general consensus even though it was not unanimous. We are confident they will understand that it is only with an integrated interpretation of clinical and functional data by physicians that we may be of help and not harm to our patients.

R. Pellegrino*, V. Brusasco#, R.O. Crapo[¶], G. Viegi⁺, J. Wanger[§], P. Gustafsson[†], M.R. Miller^{**}, R.T. McKay^{###}, R. Casaburi^{¶¶}, N. McIntire⁺⁺, O.F. Pedersen^{§§}, F. Burgos^{††}, R. Jensen^{¶¶} and D. Navajas^{***}

*Azienda Ospedaliera S. Croce e Carle, Cuneo, #Università degli Studi di Genova, Genova, ⁺CNR Institute of Clinical Physiology, Pisa, Italy, [¶]LDS Hospital, Salt Lake City, UT, [§]Pharmaceutical Research Associates, Inc., Lenexa, KS, ^{###}Occupational Medicine, Cincinnati, OH, ^{¶¶}Harbor UCLA Medical Center, Torrance, CA, ⁺⁺Duke University Medical Center, Durham, NC, USA, [†]Queen Silvias Children's Hospital, Gothenburg, Sweden, ^{**}University Hospital Birmingham NHS Trust, Birmingham, UK, ^{§§}University of Aarhus, Aarhus, Denmark, ^{††}Hospital Clinic Villarroel, and ^{***}Lab Biofisica I Bioingeniería, Barcelona, Spain.

REFERENCES

- 1 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
- 2 Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003; 58: 388–393.
- 3 Olive JT, Hyatt RE. Maximal expiratory flow and total respiratory resistance during induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis* 1972; 106: 366–376.
- 4 Gibbons WJ, Sharma A, Loughheed D, Macklem PT. Detection of excessive bronchoconstriction in asthma. *Am J Respir Crit Care Med* 1996; 153: 582–589.
- 5 Guerry-Force ML, Müller NL, Wright JL, *et al.* A comparison of bronchiolitis obliterans with organizing pneumonia, usual interstitial pneumonia, and small airways disease. *Am Rev Respir Dis* 1987; 135: 705–712.
- 6 Hyatt RE, Okeson GC, Rodarte JR. Influence of expiratory flow limitation on the pattern of lung emptying in man. *J Appl Physiol* 1973; 35: 411–419.
- 7 Rodarte JR, Hyatt RE, Cortese DA. Influence of expiratory flow on closing capacity at low expiratory flow rates. *J Appl Physiol* 1975; 39: 60–65.
- 8 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Standardized lung function testing. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.

DOI: 10.1183/09031936.06.00018506

Risk factors of frequent exacerbations in difficult-to-treat asthma

To the Editors:

We read with interest the recent paper by TEN BRINKE *et al.* [1], which describes the prevalence of comorbidities in “difficult-to-treat” asthmatics and the association with recurrent exacerbations. This adds to other papers examining these factors in similar populations but reached some differing conclusions, which we felt merit further discussion.

The study involved 136 patients initially; however, only 63 patients were included in the main analysis. A total of 54 patients were excluded because of their continuous use of oral steroids as the authors reported that defining an exacerbation was difficult in this group. We are unclear why this could not have been defined as the requirement for an increase in oral steroid above the usual maintenance dose. This would have increased the number of patients in the study and included those with more severe disease. The reader can only assume that the remaining 29 patients are those with two exacerbations in a year and, thus, the “study population” of 136 seems a little misleading, and rather selected, when the number of subjects analysed was 63.

The definition of difficult-to-treat asthma was made on the basis of treatment requirements and persistent symptoms. Two published systematic evaluation protocols, performed independently in populations defined in this way, have shown that a significant proportion of patients have unidentified or alternative diagnoses [2, 3]. When these are identified and managed, it results in a significant proportion of these patients becoming straightforward to manage [2, 3]. If this important differentiation was not made prior to this study, then a significant proportion of patients entered in this study may not have had persisting symptoms due to asthma.

Another issue, which does not seem to be addressed, is poor adherence. Both recent systematic protocol studies in difficult asthmatics assessed adherence to systemic steroids, and found that 32% [3] and 56% [2] were nonadherent. Using 6-monthly prescription refill records, 45% of patients attending the Belfast Difficult Asthma Clinic (Belfast, UK) were filling <50% of their prescribed combination inhaler (personal communication, J. Gamble, A. Lazenbatt, L.G. Heaney, Regional Respiratory Unit, Belfast City Hospital, Belfast, UK), despite reporting they

were adherent with therapy. Thus, nonadherence appears to be prevalent in difficult asthma, and self-reported adherence and physician assessment are known to be unreliable [4, 5].

The study by TEN BRINKE *et al.* [1] reported an association between exacerbation and reflux (odds ratio (OR) 4.9), but a definition based on the presence of reflux on pH profiling or severe reflux symptoms with response to treatment was used. Only 39 of the initial 136 patients underwent 24-h pH monitoring. It is well documented that the absence of reflux symptoms is not an accurate predictor of the absence of this condition, since many asymptomatic patients will have "silent" reflux [6]. TEN BRINKE *et al.* [1] highlight this in their discussion, with only 36% of the patients who underwent 24-h pH measurement reporting symptoms of reflux, but 77% of these had reflux using objective pH criteria. Therefore, it seems surprising that, in the other subjects, the presence or absence of reflux were accepted on clinical grounds alone. Debate exists as to whether the treatment of this condition actually has any bearing on asthma control [7, 8], and the study by TEN BRINKE *et al.* [1] does not appear to add significantly to this debate.

The association of respiratory infection (OR 6.9) as defined by "episodes of increased dyspnoea, cough and purulent sputum for which the attending physician or respiratory specialist had prescribed a course of antibiotic drug" is difficult to interpret [1]. We accept that objectively capturing all infective episodes with, for example, bacteriological, radiological or haematological markers is difficult, but the criteria used would seem to capture all other exacerbations, which may be independent of infection.

This paper by TEN BRINKE *et al.* [1] adds to other studies looking in detail at this difficult group of patients, but has reached some differing conclusions regarding exacerbating factors. This patient group with difficult-to-manage asthma requires a detailed systematic analysis to identify those subjects with other comorbidities, which, when managed, make persisting symptoms easier to control. The first question to be addressed is "Are all the symptoms due to asthma?" and, secondly, "Is the subject taking their medication?" (supported by objective measurement). At this stage, exacerbating factors should be explored, but, in order to advance the debate about the relationship between these factors and difficult asthma, groups studying in this area need to agree and apply standard assessment protocols and definitions, so that meaningful comparisons between studies can be made.

C. Butler and L.G. Heaney

Regional Respiratory Centre, Belfast City Hospital, Belfast, UK.

REFERENCES

- 1 ten Brinke A, Sterk PJ, Masclee AA, *et al.* Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005; 26: 812–818.
- 2 Heaney LG, Conway E, Kelly C, *et al.* Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003; 58: 561–566.
- 3 Robinson DS, Campbell DA, Durham SR, Pfeiffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22: 478–483.
- 4 Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? *Ann Allergy Asthma Immunol* 1997; 79: 177–187.
- 5 Cochrane G, Horne R, Chanaz P. Compliance in asthma. *Respir Med* 1999; 93: 763–769.
- 6 Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med* 2000; 162: 34–39.
- 7 Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. *Thorax* 2001; 56: 198–204.
- 8 Leggett JJ, Johnston BT, Mills M, Gamble J, Heaney LG. Prevalence of gastroesophageal reflux in difficult asthma: relationship to asthma outcome. *Chest* 2005; 127: 1227–1231.

DOI: 10.1183/09031936.06.00022606

From the authors:

C. Butler and L.G. Heaney raise several important points regarding our recent report [1], which identified risk factors of frequent exacerbations in difficult-to-treat asthma. First, they questioned why we excluded patients on oral corticosteroids from the analysis. In our clinic, and in most other pulmonary clinics, it is common practice to taper oral corticosteroids to the lowest possible dose whenever possible, and to increase the dose no more than strictly necessary in case of the worsening of asthma symptoms. This is a continuing process, mostly initiated by the patients themselves, without interference of a pulmonologist. We chose not to include patients on oral corticosteroids, because we felt that initial exacerbations could not be distinguished clearly from temporary deteriorations in symptoms.

C. Butler and L.G. Heaney also question the appropriateness of our definition of difficult-to-treat asthma. We adapted the European Respiratory Society Task Force definition of difficult asthma, *i.e.* "failure to achieve asthma control when maximally recommended doses of inhaled therapy are prescribed for at least 6–12 months" [2]. Our patients were symptomatic despite the regular use of high doses of inhaled corticosteroids combined with long-acting bronchodilators. They were non-smokers, and had a limited smoking history of <10 pack-yrs. They were only included in our study if they had been previously assessed and treated by a respiratory specialist, and closely supervised by the same specialist for ≥1 yr. We assumed that this was a long enough period to exclude unidentified or alternative diagnoses. Our patients have now been followed for another 5 yrs, and there was only one patient in whom the diagnosis of asthma was ultimately rejected; this patient suffered from chronic embolic syndrome presenting as recurrent severe wheezy attacks. More aggressive treatment of comorbid factors, such as chronic rhinosinusitis or gastro-oesophageal reflux, resulted in a better asthma outcome in ~20% of the patients.