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.

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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 $\geqslant 1$ 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 $\sim$20% of the patients.

With regards to poor adherence, we agree that this can be an important exacerbating factor in patients with asthma. However, poor compliance with treatment is notoriously difficult to estimate [3]. In contrast to the UK, individual prescription records were not readily available in the Netherlands at the time of the study. Therefore, unfortunately, the (indirect) method to assess compliance as referred to by C. Butler and L.G. Heaney could not be applied.

C. Butler and L.G. Heaney are also concerned about our diagnosis of gastro-oesophageal reflux. In our study, the diagnosis of reflux was based on 24-h pH measurement (n=39) and/or on the basis of a trial with proton-pump inhibitors (n=66). The latter diagnostic test was performed in those who were too dyspnoeic to undergo a 24-h pH measurement. All other patients who had not undergone one of these diagnostic tests were considered as having no reflux, which was most likely an underestimation of the real prevalence of this comorbid factor. In our opinion, this emphasises the importance of this exacerbating factor in patients with difficult-to-treat asthma even further.

Finally, C. Butler and L.G. Heaney expressed concern about our definition of respiratory infections. We based the diagnosis of respiratory infection on symptoms (episodes of increased dyspnoea, accompanied with increased production of purulent sputum) and the prescription of a course of antibiotics by the respiratory specialist. Since healthcare providers in the Netherlands are particularly conservative when it comes to the prescription of antibiotics for respiratory diseases [4], we assumed that there was a serious suspicion of upper or lower respiratory infection. We agree that this is not a rock-hard definition, but, in our opinion, workable for the purpose of this study.

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