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From the authors:

We thank K.C. Chang and C.C. Leung for their interest in our meta-analysis [1] and we welcome their comments.

As our respectful colleagues acknowledged, a well-designed and carefully performed meta-analysis is graded at the highest level of scientific quality by evidence-based movement [2]. It has been stated that a systematic review “faithfully summarizes the evidence from all relevant studies on a topic, and it does so concisely and transparently” [3]. Thus, meta-analyses are consistently used as the basis for a grade A recommendation in clinical practice guidelines, including those dealing with antimicrobial therapy [4]. Convinced by the principles of evidence-based medicine, we attempted to perform several meticulous meta-analyses in the field of antimicrobial treatment for acute bacterial exacerbations of chronic bronchitis (ABECB) [1, 5], as well as for other lower respiratory tract infections [6, 7].

We are aware that simple pooling of data is not sufficient to ensure the internal validity and, therefore, the generalisability of the findings of a meta-analysis [8]. Thus, we have critically appraised the evidence derived from systematic reviews [9]. For example, in our meta-analysis of the various antimicrobials for ABECB, we insisted on assessing its potential limitations [1]; a great proportion of the Discussion section is devoted to this. We emphasised that “antimicrobial resistance is a moving target and only data from local surveillance studies on this major clinical and public health problem provide information that helps the clinician in decision making regarding the choice of the appropriate antibiotic for a given patient with ABECB” [1]. In addition, in table 1 of the manuscript we carefully listed the characteristics of the subjects included in the individual randomised controlled trials, in order to help the reader determine

whether its findings are applicable to his/her patient population [1]. Taking these issues into consideration, we believe that clinicians will find our meta-analysis results valuable while treating patients with ABECB.

Finally, we agree with K.C. Chang and C.C. Leung that several concerns have arisen regarding the usage of fluoroquinolones for the treatment of patients with lower respiratory tract infections in areas with endemicity of tuberculosis [10]. Actually, it could be argued that this fact further underscores the usefulness of the present meta-analysis. Indeed, if clinicians acknowledge that fluoroquinolones are equivalent to macrolides or amoxicillin/clavulanate for the treatment of patients with acute bacterial exacerbations of chronic bronchitis in terms of their short period of effectiveness, they may prefer to use macrolides or amoxicillin/clavulanate rather than fluoroquinolones in areas with endemicity of tuberculosis.

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STATEMENT OF INTEREST

None declared.

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Nebulised corticosteroid and amphotericin B: an alternative treatment for ABPA?

To the Editors:

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disease that results from a hypersensitivity response to *Aspergillus fumigatus* [1]. It occurs in asthmatic and cystic fibrosis (CF) patients, with a prevalence among CF patients recently estimated at 7.8% [1]. The natural course is characterised by acute exacerbations, which can be life-threatening [2], and progressive, irreversible, lung damage leading to long-term pulmonary fibrosis if the disease is not well controlled [1].

Therapy for ABPA has two main targets. The first is the attenuation of the inflammation and immunological activity, for which oral corticosteroids are the mainstay of therapy [1]. The second is the attenuation of the antigen burden arising from fungal colonisation of the bronchial tree, for which only itraconazole has shown limited evidence of its usefulness [1]. However, long-term systemic corticotherapy predisposes to diabetes, osteopaenia, infections and growth retardation, especially in patients with CF, while itraconazole is associated with several drug interactions, suppression of adrenal glucocorticoids synthesis when associated with inhaled budesonide [3], and hepatic toxicity [4, 5]. After one of our patients experienced serious side-effects while treated for ABPA with oral corticosteroids, it was decided that a different drug regimen should be used for this disease. We report herein three cases of CF patients with ABPA successfully treated by the association of nebulised budesonide (Nbud) and nebulised amphotericin B (NampB): three children of 7, 12 and 13 yrs of age affected by CF with $\Delta 508$ mutation, two of whom were chronically infected with *Staphylococcus aureus* and one with *Pseudomonas aeruginosa*. The oldest child had developed diabetes.

The three cases benefited from a treatment that associated chest physiotherapy, aerolised recombinant DNase, inhaled aminoglycosides and regular outpatient intravenous antibiotic therapy through a central catheter. In a context of well-controlled disease, these patients developed wheezing dyspnoea, chest pain, new infiltrates on chest radiography and decreased pulmonary function. Additional studies demonstrated peripheral blood eosinophilia, an increase in total serum immunoglobulin (Ig)E and specific IgE, and precipitins to *A. fumigatus*. The diagnosis of ABPA was established according to the Cystic Fibrosis Foundation Consensus Conference [1].

Cases 1 and 2 benefited from two successive treatments. First, they received an association of Nbud (1 mg twice a day) and

oral itraconazole (400 mg daily) for almost 1 yr. Their clinical status improved but due to the lack of improvement of proximal obstruction, hypoxaemia and the persistence of high levels of precipitins and serum IgE antibodies to *A. fumigatus*, itraconazole was changed to NampB (5 mg twice a day), while maintaining Nbud at the same dose. Due to a dramatic response in serological status for both cases, case 3 benefited directly from the association of Nbud and NampB. The three children presented a good clinical, biological and functional response to this treatment, from the 6th month on, with improvement of hypoxaemia and forced expiratory volume in one second, net reduction of blood eosinophilia, total and specific serum IgE antibodies to *A. fumigatus* and a disappearance of precipitins to *A. fumigatus*.

To our knowledge, the three cases reported herein are the first cases of ABPA to have benefited from the association of Nbud and NampB. Previous articles have shown the usefulness of inhaled corticosteroids in ABPA but always as a means of discontinuing an oral corticotherapy [6]. Another study has failed to support these findings; however, the dose of inhaled corticosteroids was very low [7]. A recent article reviewed antifungal therapies in the treatment of ABPA, and NampB showed good results for two patients but always in association with oral prednisone [4]. However, our findings support the fact that ABPA can be treated without systemic corticosteroids in patients with CF. The association of Nbud and NampB resulted in a complete clinical remission of ABPA and a substantial improvement of all biological and functional parameters. Cases 1 and 2 first received Nbud associated with itraconazole and showed a good but incomplete response. Then the switch from itraconazole to NampB allowed a complete cure of ABPA. Case 3 benefited straight away from the association of Nbud and NampB, and showed a quick and complete cure. Moreover, none of the cases have shown any side-effects.

This new treatment is two-fold: Nbud decreases the inflammation and immunological activity, while NampB decreases the antigenic load of *A. fumigatus*. The use of nebulised drugs greatly limited the toxicity of the treatment.

In conclusion, we think the association of nebulised budesonide and nebulised amphotericin B is a safe and efficacious treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. We also feel that this nebulised treatment could greatly benefit asthmatic patients with allergic bronchopulmonary aspergillosis, as its long-term side-effects