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**Why Conventional Exhaled Breath Condensate pH Studies Cannot Provide Reliable Estimates of Airway Acidification**

To the Editor:

In a recent article in CHEST (February 2011), the failure of Liu et al.\(^1\) to confirm earlier reports of decreased exhaled breath condensate (EBC) pH among patients with asthma\(^2\) is disappointing but may have been inevitable because of some fundamental misconceptions in conventional EBC pH studies. Although EBC acidification is used to detect acidification of airway lining fluid (ALF), ALF pH cannot be estimated from EBC pH unless the buffer capacities of ALF and EBC are also known. It is likely that the principal buffers in ALF are nonvolatile and similar to those in plasma, primarily proteins and phosphates. In contrast, NH\(^4\)/NH\(^3\) usually accounts for ~90% of buffering in EBC.\(^3,4\) Most of this volatile constituent is derived from the diffusion of gaseous NH\(^3\) from saliva into exhaled air, and it is associated with the equilibration of CO\(_2\)/bicarbonate (HCO\(_3\)\(^-\)) at ambient PCO\(_2\).\(^3,4\) Unfortunately, the relatively high concentrations of NH\(^3\)/NH\(^4\) and CO\(_2\)/HCO\(_3\) found in most EBC samples overwhelm any effects that metabolic acids in the miniscule amounts of ALF present in EBC can have on EBC pH. It has been argued that because changes in NH\(^3\) concentration may have a relatively modest effect on EBC pH, they can be ignored.\(^3\) This is patently incorrect because changes in buffer concentrations typically have modest effects on pH but have profound effects on buffer capacity. The buffer capacity of EBC must increase with NH\(^3\)\(^+\), thereby reducing any impact that ALF acids have on EBC pH.

Conventional EBC pH studies also fail to consider or measure the dilution of ALF by condensed water vapor, which is large and variable (~5,000-20,000 fold). The effect of nonvolatile acids in ALF on EBC pH will obviously be less when the dilution is increased. In view of the dominance of oral NH\(^+\) on EBC pH, investigators should measure specific ions in EBC (e.g., lactate), indicating metabolic acids from the ALF. Furthermore, sensitive anion measurements should be routinely made to estimate salivary contamination.\(^5\) Some low EBC pH values that have been reported may reflect acid reflux, suggesting that gastric markers should be utilized. Efforts to remove CO\(_2\) by bubbling argon through the EBC\(^6,7\) are unwise because measurements are not made of the effects of purging on CO\(_2\), NH\(^3\)/NH\(^4\), water, or other volatile constituents. Unless these problems are addressed, it is unlikely that EBC pH will ever become a reliable indicator of pulmonary airway acidosis or inflammation. The expenditure of additional time and scarce resources on conventional EBC pH measurements would, therefore, seem unjustified.

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**Probiotics in United Airways Disease**

To the Editor:

I read with great interest the article by Forsythe\(^1\) in a recent issue of CHEST (April 2011). The author reports that probiotics are not shown to be beneficial in the treatment of asthma. This holds true for the preventive effect, but not the therapeutic effect, of probiotics. I agree with the author that clinical trials have not shown beneficial effects of probiotics in patients with asthma. But, at the same time, children having comitant asthma and allergic...
rhinitis (AR) have benefited from probiotics treatment, as shown in some trials.

In one trial, researchers found that the time free from episodes of asthma/rhinitis was longer and the cumulative number of asthma and rhinitis episodes was lower in the probiotics group. In another trial, researchers found improvement in the pulmonary function, a significant increase in peak expiratory flow rate, and decreases in the clinical symptom scores for asthma and AR in the patients treated with probiotics compared with the control group. The beneficial effects of probiotics treatment in patients with both asthma and AR (but not asthma alone) can be explained by the fact that probiotics treatment has consistently been shown in clinical trials to be beneficial in patients with AR. In a systematic review by our group, we also found that probiotics intake with both asthma and AR (but not asthma alone) can be explained by the fact that probiotics treatment has consistently been shown in clinical trials to be beneficial in patients with AR. In a systematic review by our group, we also found that probiotics intake improved the quality-of-life score (standardized mean difference, $-1.17; 95\% CI, -1.47$ to $-0.86; P < .0001)$ and decreased the number of episodes per year in patients with AR. This has important clinical as well as therapeutic implications if we consider the concept of united airways disease or allergic rhino-bronchitis. Increasing evidence shows a close link between the upper and lower airways and suggests rhinitis may have an important impact on asthma. The result of any common inflammatory process can explain some of the complex interactions among rhinitis, sinusitis, bronchial hyperresponsiveness/asthma, and viral infections. Moreover, evidence that treatment of rhinitis benefits patients with asthma has recently provided further support for the hypothesis.

To conclude, though current evidence does not show probiotics to be beneficial in asthma, it would be premature to say at this stage that probiotics are not beneficial in the treatment of asthma. I hope that future trials will try to answer the many unresolved questions (eg, beneficial effect of any particular strain of bacteria, subgroup of population showing the benefit, actual molecular mechanism, effectiveness of larger dose of probiotics if smaller dose is not effective, etc.) before any firm conclusions are made.

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Response

To the Editor:

I thank Dr Das for the interesting points raised in his letter. I should state at the outset that my recent article in CHEST in no way meant to discount the potential for probiotic therapy in asthma. Dr Das rightly highlights the association between rhinitis and asthma. Rhinitis may contribute to inflammation of the lower airway, is an independent risk factor for the development of asthma, and is associated with poor control of the disease. Thus, the benefits derived from probiotic treatment in rhinitis may lead to asthmatic symptom improvement in patients with both disorders, just as the indirect benefits of probiotics may be derived from the reduction in respiratory infections known to exacerbate asthma.

However, the fact remains that there is no evidence of direct therapeutic or preventive effects of probiotic treatment in asthma alone. Indeed, in one of the probiotic trials highlighted by Dr Das, the authors themselves reach the conclusion that “long-term consumption of fermented milk containing a specific *Lactobacillus casei* may improve the health status of children with allergic rhinitis but appear to do not [sic] exercise significant effect in children with asthma.”

Studies that indicate the beneficial effects of probiotics in patients with allergic rhinitis are in line with data from clinical trials that demonstrate positive effects in other allergic conditions such as atopic dermatitis, making the lack of evidence of direct preventive or therapeutic effects of probiotics in asthma all the more conspicuous. This interesting disparity in therapeutic effects of current probiotic treatment strategies between asthma and other allergic disorders deserves further investigation. Unfortunately, there remains the possibility that this may have more to do with differences in the pathophysiology of the human diseases than an incorrect choice of probiotic strain or dose.

Simply conducting more clinical trials with candidate probiotic strains based on vague or poorly understood immunomodulatory parameters will have limited chances for success. However, given the evidence that probiotic treatment can modulate immune responses in the lung and, in particular, the encouraging indications that microbial stimulation of the gut can enhance the regulatory response in the airway, I agree wholeheartedly with the need for more research aimed at understanding the mechanisms underlying the beneficial effects of probiotics. In particular, identification of the key immunoregulatory components of bacteria, and evidence that results obtained in animal models translate into human models, will be critical to the selection of strains and treatment strategies that are most likely to meet with success in preventing or treating asthma.

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