

available indicating that the relation between the wedge position of the bronchoscope and the volume of the lavaged lung segment will be constant, when the same size instrument is used in different age groups. In addition, the volume needed to fill the bronchi is poorly defined and may be too small to sample material from the alveolar space when the absolute volume for BAL is small.

In our study<sup>2</sup> we showed that by excluding the first (bronchial) BAL sample of a weight-adjusted BAL, one will obtain constant fractions of the epithelial lining fluid in children aged 3–15 years. The absolute concentrations of both urea and albumin were remarkably constant throughout the age range studied. Other BAL protocols may be equally successful, but there are currently no published reference data in children without lung disease for BAL constituents with a BAL protocol using fixed lavage volumes. We would welcome studies that compare different methods to sample BAL in children, as they could help us to understand whether differences in lavage protocol are of practical importance. As none of the current approaches offers a perfect solution and weight-adjusted protocols have been used in all age groups,<sup>1,3,4</sup> we suggest the use of a weight-adjusted BAL in children at this time.

As Prof. Zach has pointed out, the choice of the bronchoscope in clinical practice is sometimes dictated by factors other than the size of the individual. Whenever possible, we recommend not using small bronchoscopes in big children. A small bronchoscope certainly compromises the patency of the airway less than a large scope; however, it is our experience that BAL of the small generations of bronchi favors airway collapse and is associated with a low BAL recovery, which is another confounding factor that needs to be considered.

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## To the Editor: Theophylline in Acute Asthma

I commend Goodman et al.<sup>1</sup> for attempting to determine the efficacy of theophylline (aminophylline) in the treatment of children suffering from acute asthma, using a meta-analysis. They included 6 studies in their analysis, one of which was ours (Carter et al.).<sup>2</sup> They point out the shortcomings of the studies, including small sample sizes, which led to a low power to detect clinically relevant differences in outcome measures, lack of reporting of the variance in some outcome measures, and not reporting a sample size determination. Our study was guilty of these problems, but I would like to clarify some issues.

We did estimate a sample size before beginning our study, but we did not report this in the paper. Using an estimated standard deviation (SD), we determined that we would require about 15 patients per group to detect a difference in forced expiratory volume in 1 second (FEV<sub>1</sub>) of 15% of the predicted value between the two groups (aminophylline vs. placebo). The actual SD from the study data exceeded our estimated SD, and we did not achieve the desired sample size due to time constraints and patient dropout. Thus, as Goodman et al. note, our study had a low power and was at risk of a type II error. However, we addressed this concern in our discussion section and stated “There was a 78% chance of detecting a difference in FEV<sub>1</sub> of 20% of the predicted value between the 2 groups at the 36-hour time point.” We then went on to discuss the clinical relevance of this statement.

While we did not report the variances of the clinical scores, we certainly had this information filed away. Although Goodman et al. correctly point out that this information should have been available, I contend that they could have tried to obtain it for their meta-analysis. They included only 6 studies and could have contacted myself as well as the other authors to obtain data that were not reported in the studies but were integral to a complete meta-analysis.

I question whether the study by Pierson et al.<sup>3</sup> should have been included in the analysis. In that study, at 24 hours post treatment all 11 patients in the aminophylline group had serum theophylline concentrations below 7.5 µg/ml, and 8 of the 11 patients had concentrations less than 5 µg/ml. These low serum theophylline concentrations make it difficult to ascribe any treatment effect to theophylline. It is interesting that of all the studies included in the meta-analysis, this was the only one that claimed a significant improvement with theophylline.

Finally, the drawbacks of these 6 studies are manifestations of a ubiquitous problem affecting today's clinical trials—the lack of multi-center cooperation. For the most part, clinical trials are time consuming, poorly funded, and take longer than expected to complete. This was certainly true of our study. If we had combined our efforts with several other centers, we could have completed the

study sooner, enrolled many more patients, and hopefully been able to provide more conclusive results. Then, perhaps, a meta-analysis would not have been necessary. However, without funding from voluntary health organizations, or financial support from drug companies, it is difficult to coordinate and carry out multi-center clinical trials. In addition, with multi-center trials there is debate on who should get credit for the publication, making them unattractive to junior investigators and especially Fellows, who are required to be a first author on a paper before they can sit for the subspecialty boards. In the future we must overcome these obstacles if we wish to deal conclusively with clinical questions. During the past several decades we have seen the randomized controlled clinical trial become the gold standard for assessing therapeutic effects. Now we must go one step further and strive for multi-center cooperation. Once that is achieved the need for meta-analyses will diminish.

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## Reply to Dr. E.R. Carter's Letter

Dr. Carter's letter identifies many of the problems encountered when conducting clinical trials. Studying theophylline efficacy in children is further complicated by the ethical and logistical issues in pediatric research. Moreover, funding for theophylline trials is difficult to

obtain given the drug's declining commercial value. In the face of these obstacles, Carter et al.<sup>1</sup> should be commended for conducting a well-designed study that challenged an established clinical practice.

Dr. Carter points out that their study presented a post hoc power calculation based upon the observed variances of the FEV<sub>1</sub>. The observed variances were higher than those used in the original, though unreported, power calculations resulting in an underpowered study. As suggested in our paper,<sup>2</sup> the use of pilot studies to estimate standard deviations and the enrollment of more subjects than suggested by power calculations will increase the likelihood that a clinical trial will have adequate statistical power. It is gracious of Dr. Carter to offer the variances associated with his clinical scores. Many investigators are not so forthcoming. For this particular measure, the effect difference is not large enough to be of clinical importance regardless of the P value.

We agree that the inclusion of Pierson's study in the pooled results for spirometric measures is arguable. For this reason, we noted in the paper that our findings were robust to the exclusion of Pierson's data.

Though the barriers to clinical research are widely recognized, it seems unlikely that the research environment will improve in the near future. Meta-analysis will always stand second best to large and well-designed clinical trials. Given the rarity of such studies, researchers may want to consider the eventuality of meta-analysis, when selecting clinical measures and reporting their results.

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