Correspondence

And The Beat Goes On

To the Editor:

DOT Works and is Essential
DOT Works but is Obtrusive
DOT Doesn't Work

Ever since the directly observed therapy (DOT) strategy was endorsed by the World Health Organization (1), it has been a beacon of controversy.

Even though it is virtually intuitive that administering (the original term, although not immortalized by an acronym, was *directly administered therapy*) or observing drug taking ensures adherence, it has engendered controversy. The reasons behind the controversy, however, are not considered in Jasmer's analysis (2) or Burman and Reeves' editorial (3) essentially. DOT does not equal DOT, depending on the specific program. Zwarenstein (4), in an article considered the main detractor of DOT, reported 50% compliance with DOT, yet it is widely acknowledged that this was a poor program.

Recently, at the New Jersey Medical School National TB Center, we teased out exactly what component of the commonly used activities in TB control was most effective in curing patients (5). Employing a fortuitous stepwise change in program components over time, we showed in successive cohorts of patients using self-administration, self-administration with selective DOT, universal DOT alone, and DOT plus case management that *only* the addition of case management to DOT raised level of treatment completion and care from 50% to almost 90% (case management is an overarching system merging quality service with accountability for program performance) (6). The key concept is that observing medication taking along with accountability of staff for program components is the successful ingredient.

The San Francisco program as described (2) does not just observe patients, but does so in a meaningful, responsible manner (e.g., case management). It is time to ascribe its success to this modality combined with DOT. Simply put, case management is connecting the "dots" of a patient's journey through TB care from many different aspects: child care to social service to transportation and other medical services needed. Enablers and incentives in a program cannot happen by themselves: a responsible, accountable person needs to manage and coordinate these services for the patient.

Conflict of Interest Statement: L.B.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.T.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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From the Authors:

We appreciate the comments of Drs. Reichman and Mangura regarding our study of directly observed therapy (DOT) for tuberculosis patients in San Francisco (1). As we stated in our Methods section, DOT in our study involved more than simply observing patients taking their antituberculosis medications. Patients received so-called enhanced DOT in which enablers and incentives such as travel vouchers, food, and housing assistance were utilized to promote adherence (2). While enablers and incentives enhance completion of treatment, it cannot be overstated that successful tuberculosis care requires establishing trust and credibility with each patient. Necessary components include staff commitment as well as a respectful, tolerant, and compassionate approach. Experience and skill in working with patients who are marginalized or from different cultures are also important in addressing individual psychosocial needs.

We agree that this individualized focus on a patient's specific needs, referred to as "case management" by Dr. Reichman, is critical for the success that we found in our DOT program. A patient-centered approach based on each patient's specific social circumstances is an integral component of DOT.

Conflict of Interest Statement: R.M.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.L.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Should We Start Considering Surfactant for Atelectasis?

To the Editor:

We read with great interest the article by Dr. van Kaam and colleagues (1) on the potential role of exogenous surfactant and reduction of atelectasis in prevention of pneumonia. Their findings share the same direction with our clinical data (2), and although the extrapolation of these results to humans is quite complex, they offer a stimulating background for the pathways connecting atelectasis, pneumonia, and surfactant.

We recently monitored bronchoalveolar lavage (BAL) fluid alterations prior to, during, and after atelectasis in eight mechanically ventilated patients with previously normal lungs (2). BAL of the involved atelectatic area revealed quantitative and qualitative alterations of the surfactant system (decreased total phospholipids, reduced large aggregates fraction, reduced fraction of phosphatidylcholine) and permeability defects (increased total protein and albumin), as well as findings compatible with local inflammatory reaction (increased neutrophils, reduced alveolar macrophages, and increased platelet-activating factor (PAF) and PAF-acetylhydrolase levels). We also found a significant reduction of proteins in the 30,000 $\times$ *g* BAL subfraction suggesting a decrease in SPA, a finding potentially related to impairment of pulmonary immune function. Within 48 to 72 hours after resolution of atelectasis, capillary–alveolar membrane permeability and inflammation markers returned to pre-atelectasis values, but surfactant alterations persisted, indicating prolonged alveolar II cell injury. The degree of the above BAL fluid alterations correlated with the duration of atelectasis, and in some long-standing cases of atelectasis, there was significant overlap with ventilator-associated pneumonia (VAP) (2).

Besides optimal ventilatory management, physiotherapy, and position changes, nothing can be done to prevent or treat atelectasis in the clinical setting. Atelectasis can provoke lung injury and the atelectatic alveolar microenvironment favors the development of pneumonia. Since surfactant dysfunction represents one of the most profound characteristics of atelectasis, administration of exogenous surfactant could be a biologically plausible therapy. Moreover, recent clinical data imply that exogenous surfactant might be effective in direct lung injury (3).

Unfortunately, the situation may not be that simple. Mechanical ventilation *per se* seems to affect many aspects of the surfactant system, even when the lung is intact and modest ventilator settings are employed (4). Consequently, exogenous surfactant replacement requires the recognition of some kind of threshold that could guide its use, and the identification of specific situations (e.g., persisting atelectasis) that could justify such a costly approach in specific cases of atelectasis. Although the theoretical rationale is attractive, and experimental and early clinical data are encouraging, the road to successful clinical trials and effective clinical practice seems long.

Conflict of Interest Statement: H.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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From the Authors:

We thank Dr. Tsangaris and colleagues for their interest in our article (1). Tsangaris and colleagues analyzed the bronchoalveolar lavage (BAL) fluid obtained from atelectatic lung regions of eight mechanically ventilated patients, and found clear signs of increased permeability, inflammation and surfactant alterations (2). These changes in the BAL fluid correlated with the duration of atelectasis and showed considerable overlap with ventilator-associated pneumonia (VAP). Their findings offer important clinical support for the role of atelectasis and surfactant dysfunction in the pathogenesis of VAP.

As suggested by Tsangaris and colleagues, exogenous surfactant seems to be the next logical step in reducing the incidence of VAP in ventilated patients. However, several variables that might influence the efficacy of exogenous surfactant should be considered when designing future clinical trials. First, the surfactant dose should be sufficient to overcome possible inhibition by proteins present in the alveolar compartment. Both experimental and clinical data show that protein levels in the alveolar space are increased during VAP (1, 2). Second, the data from Tsangaris and colleagues indicate that the duration of atelectasis might be a crucial factor in the development of VAP. This finding would suggest that treatment with exogenous surfactant early in the course of disease might prove more efficacious than late selective treatment. Finally, as mentioned by Tsangaris and colleagues, the ventilation strategy applied following surfactant treatment could also affect its efficacy and preservation (3). This is also indicated by our experimental study showing that exogenous surfactant combined with an open lung ventilation strategy is more efficacious in attenuating bacterial growth and translocation than either therapy alone (1).

Exogenous surfactant may also serve as a vehicle for local administration of other agents, such as antibiotics or immunoglobulins, into the lung, which may offer additional advantages in the treatment of VAP (4, 5).

However, despite these promising experimental and clinical observational studies, we fully agree with Tsangaris and colleagues that future clinical trials are necessary to investigate the role of exogenous surfactant in the treatment of mechanically ventilated patients at risk for VAP.

Conflict of Interest Statement: A.v.K. has participated as a speaker in scientific meetings or courses organized and financed by pharmaceutical companies Boehringer Ingelheim and Nycomed, and received financial support for experimental research; R.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.H. has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (Chiesi, Abbott, Boehringer, Altana, and Draeger), and has two industry sponsored grants pending (Altana Pharma and Chiesi); A.D.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.v.I. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.L. is a member of the Advisory Board of Halas Pharma GmbH

and has shares in that same company and received a research grant from Leo Pharma for surfactant research.

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