Editorial

Precision medicine and aerosolization in mechanically ventilated adults

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Provenance: This is an invited Editorial commissioned by the Section Editor Dr. Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comments on: van Meenen DM, van der Hoeven SM, Binnekade JM, *et al.* Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation: A Randomized Clinical Trial. JAMA 2018;319:993-1001.

Submitted Jun 25, 2018. Accepted for publication Jul 05, 2018.
doi: 10.21037/jtd.2018.07.64
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.64

The use of nebulized drugs in critically ill patients is increasing, but little is known about the safety and efficacy of this strategy. Modern medicine implements strategies based on evidence, and the highest levels of evidence are obtained in randomized clinical trials. Therefore, van Meenen *et al.* (1) should be congratulated for their design of a multicentre randomized clinical trial to compare two different strategies of management: on-demand nebulization (that is, nebulization based on the physician's clinical judgment) with N-acetylcysteine (a mucolytic) or salbutamol (a β-agonist), versus routine nebulization scheduled four times per day, regardless of patients' clinical situation. The lack of masking was inherent in the protocol itself and although it may represent a limitation, it could not be obviated. The study was designed as a non-inferiority study. The primary outcome was the number of ventilation-free days within 28 days of inclusion; secondary outcomes were ICU and hospital length of stay and mortality, pulmonary complications (among them ventilator-associated pneumonia) and nebulization-related adverse events. The results can be summarized as follows: the on-demand nebulization strategy achieved similar results to routine nebulization, and adverse events were notably higher in the routine nebulization group. Another interesting finding was that nearly two-thirds of subjects in the elective arm did not have a condition requiring aerosolization.

One of the features of the respiratory system that distinguishes it from the other systems in the human body is that it is in permanent contact with the atmosphere, and is therefore exposed both to changes in temperature and humidity and to allergens and microorganisms. In intubated patients, this feature is enhanced. The upper airways act as a protective physical and functional barrier, by heating the inspired air and humidifying it; the hairs of the nostrils prevent the passage of impurities and microorganisms. These safety mechanisms minimize deleterious effects but are absent in intubated subjects. Many patients in the ICU setting need intubation, which, in addition to their poor nutritional state, immunological impairment and systemic infections, makes them particularly susceptible to lower airway insults. The respiratory system has another defence mechanism: the mucous layer barrier that protects the bronchial epithelium by capturing and cleaning impurities and microorganisms and helping to maintain homeostasis.

The decision to bypass the upper airways is not to be taken lightly. However, the route created by the tracheal tube provides a direct opportunity to intervene in or modify conditions in the lower airway: physical conditions can be regulated by the ventilator, and infections can be prevented by applying bundles or by limiting sedation.

Nonetheless, these techniques have some limitations and two major problems in particular may appear: difficulties in mucus drainage (leading to the creation of mucous plugs) and bronchial hyperresponsiveness, which may develop as a consequence of small airway stimulation. These issues may be treated or prevented with tracheal nebulizations of mucolytic agents and/or β-agonists.

The protective mucous layer that lines the bronchial epithelium has two phases (2): the gel phase, in contact with the airway lumen, and the sol phase, in contact with the upper part of the bronchial epithelium where the bronchial cilia are included. The characteristics of the layers are very different; although they are in contact, they do not mix. The viscous mucus layer lies on top of a less viscous periciliary fluid in which the cilia beat. It is not yet known how the mucus forms above the periciliary space, but it is probably via a combination of capillary action through the periciliary space upon secretion and the subsequent inability of the newly hydrated and cross-linked macromolecules to penetrate the dense cilia cover. The ciliary beat produces a wave in the sol phase and it is the motion of this layer that causes the movement of the upper layer (the gel phase). Mucolytics have been widely used for patients with COPD, with controversial results (3). In some cases, ambroxol administered orally has shown a certain synergistic effect with antibiotics (4). On the whole, mucolytics have been used to prevent exacerbations (5-8). There is no evidence to support previous theories that attributed the beneficial effect of these drugs to their capacity to cross the bronchial epithelial cells to reach the airway lumen and thus affect directly the gel phase of the mucus; In fact, the effect of these drugs is more likely to be due to the changes occurring in the gel phase of the mucus which interfere with microorganism development and biofilm creation. In van Meenen *et al.*'s study (1), the drug (N-acetylcysteine) reaching the respiratory tract through the airway may not need to cross the bronchial epithelium to reach the gel phase of the mucus layer; it may do so via its capacity to hydrolyse and break the disulphide bonds in mucin (9). In any case mucolytic drugs may sometimes have a beneficial effect. Aerosol therapy with bronchodilators is often prescribed (10), and it has been reported that one fifth of ventilated patients receive this treatment at some time (10,11). The rationale behind it is the prevention and treatment of airway problems resulting from an increase in viscosity of the bronchial secretion, impaired clearance, stasis, atelectasis, and infection.

The efficacy and effectiveness of this therapeutic approach is controversial. Some authors (12-14) but not others (15) have found that N-acetylcysteine offers some benefit regarding the characteristics of sputum. Certain side effects have been observed after mucolytic therapy (especially N-acetylcysteine), in particular the increase in inspiratory airway resistance due to bronchoconstriction (9,16,17). Moreover, some authors have found that instillations of N-acetylcysteine may induce cough or bronchospasm which can persist for up to 2 hours (12,18). The evidence that reducing the concentration of the nebulized drug can influence peak and plateau airway pressures is weak (15,18).

These side effects can be reduced either by adding bronchodilators to the aerosol or by the administration of antimuscarinic drugs. However, these treatments may increase the heart rate. In special situations, such as cardiac diseases, the addition of β-agonists to the aerosol or the administration of atropine may be relatively contraindicated. In other situations, the increase in cardiac output can contribute to worsening patients' V/Q mismatch. Finally, nebulization may eventually have a drag effect on the micro-organisms anchored on the gel phase of the mucus layer and may contribute to their spread throughout the airways, thus favouring lower airway infection.

Another interesting observation is that two-thirds of patients used jet nebulizers and one-third mesh nebulizers, in accordance with general use in antimicrobial aerosolization (19-21). This is not a minor issue, because these devices deliver particles of different size. Indeed, jet nebulizers are suboptimal for treating alveolar conditions such as pneumonia, and are more suitable for treating conditions associated with the proximal airways. Interestingly, as reflected in Table 2 (1), length of stay was 50% (7 days) longer in the jet nebulized arm than in the mesh device arm.

Precision medicine is defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" (22). The final objective of precision medicine is to "improve clinical outcomes for individual patients while minimizing unnecessary side effects for those less likely to respond to a given treatment" (23). This concept of precision medicine, however, is not entirely novel; in medical practice it has always been the physician's task to manage patients individually towards better outcomes (24). Thus, it does not seem advisable to follow the concept that "one size fits all".

van Meenen *et al.*'s report has four major implications: (I) aerosolization should not be implemented as standard practice in mechanically ventilated adults, and needs to be customized as part of a personalized strategy; (II) its effects in the subset of patients with pneumonia were different from those in other cohorts; (III) evidence from non-intubated subjects cannot be transferred to the ventilation scenario, as consistently reported with aerosolized antibiotics (25-27); (IV) medical education and standardization of nebulization procedures in mechanical ventilated subjects are needed. As in sepsis management (28), implementation of precision medicine with a highly individualized approach is required.

Classical medical principles, aware of physicians' limitations, advise prudence in therapeutic decisions: "Primum non nocere". At medical schools, students are taught that prevention is better than cure, but attempts at prevention must not entail other dangers. van Meenen *et al.*'s study seems to advocate Primum non nocere and treating the treatable traits when possible!

Acknowledgements

Supported in part by CIBERES CB06/06/036, Instituto de Salut Carlos III, Madrid, Spain.

Footnote

Conflicts of Interest: J Rello has served as a consultant for BAYER and has received research grants from BAYER. C Domingo has no conflicts of interest to declare.

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Cite this article as: Rello J, Domingo C. Precision medicine and aerosolization in mechanically ventilated adults. J Thorac Dis 2018;10(Suppl 26):S3111-S3114. doi: 10.21037/jtd.2018.07.64

