happen, and most medical schools are following advice from Public Health England to determine how to proceed.

Despite widespread panic and uncertainty, the medical community must ask itself what history has taught us about medical education during pandemics. To answer this question, we reflect on the effects of severe acute respiratory syndrome (SARS) on medical education in China at the turn of the century.[1] Some Chinese medical schools officially cancelled formal teaching on wards and their exams were delayed, hindering the education of medical students in the face of the newly emerging epidemic.[1] Similarly, in Canada, the impact of the SARS restrictions led to the cessation of clinical clerkships and electives for students for up to 6 weeks.[2] The Canadian national residency match felt the effect of these limitations, particularly because electives are one of the most crucial factors determining allocation.[1]

Despite the challenges posed by the SARS epidemic, several resourceful initiatives were implemented, leading to progress in medical education. In one Chinese medical school, online problem-based learning techniques were implemented to complete the curricula; these methods proved incredibly popular, to the extent that they were applied in subsequent years. These impressive feats illuminate how even in times of distress, solace can always be found. We are waiting to see what ingenuities for medical education will emerge in the face of the COVID-19 pandemic.

See Online for appendix

We declare no competing interests.

*Hanad Ahmed, Mohammed Allaf, Hussein Elghazaly
ha1g14@soton.ac.uk

Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK

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See Online for video

The INHALE trial: multiple reasons for a negative result

The INHALE trial, a Bayer-sponsored phase 3 trial in critically ill patients with pneumonia caused by Gram-negative bacteria by Michael Niederman and colleagues,[1] did not find aerosolised amikacin as an adjunctive therapy to intravenous antibiotics to be superior to intravenous antibiotics alone. The study design, the doses of amikacin, and the technique of nebulisation are all likely to explain this negative result.

The main trial inclusion criterion was pneumonia caused by, or showing two risk factors for, a multidrug-resistant, Gram-negative bacteria. The presence (or the risk) of a multidrug-resistant pathogen infecting the lungs was justification for administering two intravenous antibiotics in both the amikacin treatment group and the placebo group.[2] Antimicrobial bitherapy is not superior to monotherapy in ventilator-associated pneumonia caused by non-resistant, Gram-negative bacteria.[3] In the IHNALE trial,[1] 49% of identified pathogens were not multidrug-resistant and a treatment success of 77% in the placebo group reflected the high efficiency of intravenous bitherapy. Therefore, an additional benefit from aerosolised amikacin could not be reasonably expected.

The pulmonary drug delivery system used in the INHALE trial increases the respirable mass[4] but markedly lengthens the time of nebulisation by restricting aerosol generation to the inspiratory phase (appendix). With the pulmonary drug delivery system, the authors previously reported that nebulisation of amikacin at a dose of about 12 mg/kg per day requires two 60 min nebulisations. With a non-synchronised mesh nebuliser, nebulisation of amikacin at 25 mg/kg per day took only 30–45 min thanks to the bolus effect (video).[5] With the pulmonary drug delivery system, nebulisation of amikacin at the high doses recommended to treat multidrug-resistant, ventilator-associated, Gram-negative pneumonia (40 mg/kg/day)[6] would have been unfeasible, requiring two 3·5 h nebulisations per day. Prolonging nebulisation time beyond 60 min should be avoided as heating and humidification of the inspired gas are interrupted during aerosol delivery.[7]

Amikacin is a concentration-dependant antibiotic and the administration of about 6 mg/kg twice daily, as in the INHALE trial, is suboptimal. In 28 patients with ventilator-associated pneumonia treated by nebulised amikacin, amikacin tracheal concentrations were found to be 25 times higher and epithelial lining fluid concentrations were found to be four times higher than the minimum inhibitory concentration of multidrug-resistant, Gram-negative bacteria.[4] These concentrations were interpreted as reflecting high amikacin distal lung deposition and justified the administration of 12 mg/kg per day in the INHALE trial. Interestingly, epithelial lining fluid concentrations of tobramycin in ventilated sheep receiving a single nebulisation were 100 times greater than interstitial space fluid concentrations measured by microdialysis.[8] These data are highly suggestive of a massive bronchial contamination of the fiberscope and the bronchoalveolar lavage; therefore, elevated epithelial lining fluid concentrations of a nebulised drug can be considered an artefact.[9] Finally, the insufficient optimisation of ventilator settings during the nebulisation could have further reduced amikacin distal lung deposition by potentiating the impaction of aerosolised particles on bronchial walls. In the INHALE trial, lung tissue amikacin concentrations were likely to be below the minimal inhibitory concentrations of causative pathogens, explaining the trial failure.

We suggest that future randomised controlled trials exclusively include

patients with ventilator-associated pneumonia caused by documented multidrug-resistant, Gram-negative bacteria; compare intravenous bitherapy with and without a once daily nebulisation of amikacin at 40 mg/kg per day; deliver aerosol using a non-synchronised mesh nebuliser; and optimise ventilator settings during nebulisation.

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*Jean-Jacques Rouby, Antoine Monsel, Stephan Ehrmann, Adrien Bouglé, Pierre-François Laterre

jjrouby@invivo.edu

Multidisciplinary Intensive Care Unit (J-JR, AM), and Cardiology Institute (AB), Department of Anaesthesiology and Critical Care, La Pitié-Salpêtrière Hospital, Assistance Publique Hôpitaux de Paris, Medicine Sorbonne University, Paris 75013, France; Médecine Intensive Réanimation, Centre d'Investigation Clinique INSERM 1415, CHRU Tours, Tours, France (SE); Centre d'étude des pathologies respiratoires, INSERM U1100, University of Tours, Tours, France (SE); and Saint Luc Clinical Coordinating Center, Department of Critical Care Medicine, St Luc University Hospital, Catholic University of Louvain, Brussels, Belgium (P-FL)

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Authors' reply

Jean-Jacques Rouby and colleagues have commented on the negative result of our study of inhaled amikacin as adjunctive therapy for mechanically ventilated patients with Gram-negative pneumonia.[1] They have concluded that errors in trial design and the specifics of the inhalation device, the pulmonary drug delivery system, account for these findings. The authors suggest that future trials could be positive if they used a different method and followed specific recommendations, most of which are not proven to be superior for drug delivery or practical for trial design.

Our trial included patients suspected of having Gram-negative pneumonia, which was confirmed in 508 (70%) of 725 enrolled patients. Of the 508 patients, 238 (47%) did not have multidrug-resistant pathogens present.[1] Rouby and colleagues recommend that only those individuals with proven multidrug-resistant pneumonia be included in future trials, but we found the outcome to be the same irrespective of whether the pathogen was multidrug-resistant or not.[1] In addition, if only those people with confirmed multidrug-resistant infections were included, patients would probably not be enrolled as early in the course of illness, as enrolment in our study was on the basis of clinical risks for multidrug-resistant Gram-negative pneumonia.

Rouby and colleagues believe that with a survival rate of 77% (196 of 253 patients) in the placebo group, little benefit could be expected from the inhaled therapy. Although inhaled therapy might not improve survival, there could be a benefit with use of a different endpoint. We considered whether inhaled amikacin could shorten the duration of systemic therapy, as suggested in a previous study, but we saw no effect.[1,2] This endpoint might be reconsidered in the future, now that the durations of therapy for ventilator-associated pneumonia are shorter than during the time of our study (median of 18 days).

Rouby and colleagues claim that they could deliver amikacin much more effectively without the pulmonary drug delivery system using a proposed methodology with no data showing better delivery to the site of lung infection. The pulmonary drug delivery system was designed to aerosolise amikacin within the respirable range of less than 5 µm, in order to maximise delivery to the deep lung. As shown by Luyt and colleagues,[3] this system achieves high amikacin concentrations in epithelial lining fluid and tracheal secretions from the site of infection. This method aerosolises the drug during the first 75% of the inspiratory cycle, optimising the delivery to provide 50% of a nominal nebuliser dose to the lung. The deposition is much higher than with conventional vibrating mesh nebulisers, which deliver approximately 18% of the nominal dose, and jet nebulisers, which deliver only 10%. With placement close to the airway, the last 25% of the inspiratory cycle pushes the aerosol deep into the lung without wasting the aerosolised drug in the ventilator circuit. The pulmonary drug delivery system can deliver the same 50% of nominal dose to either intubated or extubated patients, maintaining a consistent dose throughout the course of therapy, with no effect of humidification on the delivered dose.