



# The utilization of aerosol therapy in mechanical ventilation patients: a prospective multicenter observational cohort study and a review of the current evidence

Shan Lyu<sup>1#</sup>, Jie Li<sup>2#</sup>, Limin Yang<sup>3</sup>, Xiaoliang Du<sup>4</sup>, Xiaoyi Liu<sup>5</sup>, Libo Chuan<sup>6</sup>, Guoqiang Jing<sup>7</sup>, Zhenyan Wang<sup>8</sup>, Weiwei Shu<sup>9</sup>, Chunjuan Ye<sup>10</sup>, Qionglan Dong<sup>11</sup>, Jun Duan<sup>12</sup>, James B. Fink<sup>2,13</sup>, Zhancheng Gao<sup>14</sup>, Zongan Liang<sup>15</sup>; on behalf of Respiratory Care Committee in Chinese Thoracic Society

<sup>1</sup>Department of Critical Care Medicine, Peking University People's Hospital, Beijing, China; <sup>2</sup>Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, IL, USA; <sup>3</sup>Department of Respiratory Care, Zhejiang University School of Medical Sir Run Run Shaw Hospital, Hangzhou, China; <sup>4</sup>Department of Neurosurgical, Tongji Medical College of Huazhong University of Science and Technology Tongji Hospital, Wuhan, China; <sup>5</sup>Department of Critical Care Medicine, Dazhou Central Hospital, Dazhou, China; <sup>6</sup>Intensive Care Unit, the First People's Hospital of Yunnan Province, Kunming, China; <sup>7</sup>Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, China; <sup>8</sup>Department of Critical Care Medicine, Peking University International Hospital, Beijing, China; <sup>9</sup>Department of Critical Care Medicine, Yongchuan Hospital of Chongqing Medical University, Chongqing, China; <sup>10</sup>Department of Surgical Intensive Care Unit, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; <sup>11</sup>Department of Critical Care Medicine, the Third People's Hospital of Mianyang, Mianyang, China; <sup>12</sup>Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China; <sup>13</sup>Aerogen Pharma Corp, San Mateo, CA, USA; <sup>14</sup>Department of Respiratory and Critical Care Medicine, Peking University People's Hospital, Beijing, China; <sup>15</sup>Department of Respiratory and Critical Care Medicine, West China Medical Center, Sichuan University, Chengdu, China

**Contributions:** (I) Conception and design: S Lyu, J Li, Z Gao, Z Liang; (II) Administrative support: Z Gao, Z Liang; (III) Provision of study materials or patients: S Lyu, L Yang, X Du, X Liu, L Chuan, G Jing, Z Wang, W Shu, C Ye, Q Dong, J Duan; (IV) Collection and assembly of data: S Lyu; (V) Data analysis and interpretation: S Lyu, J Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Prof. Zongan Liang. Department of Respiratory and Critical Care Medicine, West China Medical Center, Sichuan University, 37 Guo Xue Street, Chengdu, China. Email: liang.zongan@163.com; Prof. Zhancheng Gao. Department of Respiratory and Critical Care Medicine, Peking University People's Hospital, No. 11 Xizhimen Nandajie Beijing, China. Email: zcgao@bjmu.edu.cn.

**Background:** Aerosol delivery via mechanical ventilation has been reported to vary significantly among different intensive care units (ICU). The optimal technique for using each aerosol generator may need to be updated with the available evidence.

**Methods:** A 2-week prospective multicenter observational cohort study was implemented to record aerosol delivery for mechanically ventilated adult patients in Chinese ICUs. Our data included the type of aerosol device and its placement, ventilator type, humidification, and aerosolized medication administered. A guide for the optimal technique for aerosol delivery during mechanical ventilation was summarized after a thorough literature review.

**Results:** A total of 160 patients (105 males) from 28 ICUs were enrolled, of whom 125 (78.1%) received aerosol therapy via invasive ventilation. Among these 125 patients, 53 received ventilator-integrated jet nebulizer, with 64% (34/53) of them placed the nebulizer close to Y piece in the inspiratory limb. Further, 56 patients used continuous nebulizers, with 84% (47/56) of them placed the nebulizer close to the Y piece in the inspiratory limb. Of the 35 patients who received aerosol therapy via noninvasive ventilation, 30 received single limb ventilators and continuous nebulizers, with 70% (21/30) of them placed between the mask and exhalation port. Only 36% (58/160) of the patients received aerosol treatments consistent with optimal practice.

**Conclusions:** Aerosol delivery via mechanical ventilation varied between ICUs, and only 36% of the

patients received aerosol treatments consistent with optimal practice. ICU clinicians should be educated on the best practices for aerosol therapy, and quality improvement projects aim to improve the quality and outcome of patients with the optimal technique for aerosol delivery during mechanical ventilation are warranted.

**Keywords:** Inhalation therapy; mechanical ventilation; a follow-up study

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## Introduction

Aerosol therapy delivers medications directly into the lung. Aerosol therapy has many advantages compared with systemic administration, including targeted delivery into the lung, faster response, and fewer systemic adverse effects (1). These differences have resulted in the broad use of aerosol therapy in intensive care units (ICUs) (2,3). A considerable proportion of ICU patients require artificial airway and mechanical ventilation, unlike outpatient or general unit patients, which introduces more factors that impact aerosol deposition, including the types of aerosol generator (4-6), the position of the aerosol generator in the ventilator circuit (5,7,8), mechanical ventilation settings (8-11), humidification (4,11-13), reservoirs (14-16), and inspiratory synchronization of aerosol generation (17-20). Substantial efforts have been made to understand these variables and to improve the efficiency of aerosol delivery to the lungs and minimize loss, including aerosol deposition in the ventilator circuits and artificial airways (21,22).

In 2011, Ehrmann *et al.* (23) conducted an international survey with 1,192 responses from 70 countries on aerosol therapy during mechanical ventilation. Aerosol therapy was found to vary in different institutions, and a knowledge gap among clinicians about how to administer aerosol delivery via mechanical ventilation was discovered. However, with fewer than 9% of the participants reporting from Asia (23), detailed information about Chinese ICUs remains mostly unknown. In 2014, Zhu *et al.* conducted a nationwide survey on aerosol therapy in mainland China, but their focus was on spontaneously breathing patients rather than mechanically ventilated patients (24). They found a considerable proportion of physicians and nurses who specialized in pulmonary and critical care medicine lacked knowledge on the correct use of different inhalers. As such, the Respiratory Care Committee in the Chinese Thoracic Society published two consensus documents to guide

clinicians for optimizing aerosol therapy for spontaneously breathing patients (25) and for mechanically ventilated patients (26). Last year, Zhang *et al.* (27) carried out an online survey of Chinese respiratory care practitioners and found substantial heterogeneity among institutions, and many practices not following the consensus. However, these findings need to be cautiously interpreted due to participants' recall bias. The clinical practice of aerosol therapy for Chinese ICU patients, reported in real time, is still unknown.

In the 2-week cross-sectional study conducted by Ehrmann *et al.* (28), it was found that the findings from aerosol studies were not consistently translated into clinical practice. The participating centers were predominantly located in Europe (65 of 81), with only 4 Asian ICUs in the study. To compare with the clinical practices of international peers, we translated the data collection form used by Ehrmann (with permission). The objective of this study was to identify the current practices of aerosol therapy for mechanically ventilated patients in Chinese ICUs and to recognize the gaps between clinical practice and actual practice using the best evidence. Moreover, we sought the current optimal evidence (*Tables S1-S3*) of aerosol delivery via mechanical ventilation to summarize the recommendations (*Tables 1,2*), to help update the consensus in the next steps. This article is presented following the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-1313>).

## Methods

This study is a prospective multicenter observational cohort study. It was registered on ClinicalTrials.gov (NCT03597334) and was conducted by the Respiratory Care Committee of the Chinese Thoracic Society. Recruitment advertisement was posted on the official social

**Table 1** The optimal placement of jet nebulizer, vibrating mesh nebulizer and pMDI during invasive and noninvasive ventilation

Ventilation type	Ventilator	Nebulizer type	Nebulizer optimal position
Invasive ventilation with bias flow	Dual limb ventilator	Jet neb-ventilator integrated breath synchronized	Close to Y piece in the inspiratory limb, or between Y piece and patient airway
		Jet neb-continuous	Inlet or outlet of humidifier
		Vibrating mesh nebulizer	Inlet or outlet of humidifier
		pMDI with spacer	Close to Y piece in the inspiratory limb, or between Y piece and patient airway
Noninvasive ventilation	Dual limb ventilator	Jet neb-ventilator integrated	No evidence
		Jet neb-continuous, vibrating mesh nebulizer	Between mask and Y piece
	Single limb ventilator	Jet neb-continuous, vibrating mesh nebulizer, pMDI with spacer	Between mask and fixed leak exhalation port

neb, nebulizer; pMDI, pressurized metered dose inhaler.

**Table 2** Optimal practice of using pMDI, humidification and expiratory filter during aerosol therapy

Practice	Optimal practice
Use of pMDI	Combined use of spacer
Humidification	
Active humidifier	Do not turn it off for aerosol administration
HME	Remove from between neb and patient during aerosol treatment
Expiratory filter	Should be in the expiratory limb during aerosol treatment
	Monitor expiratory resistance and change the filter as needed

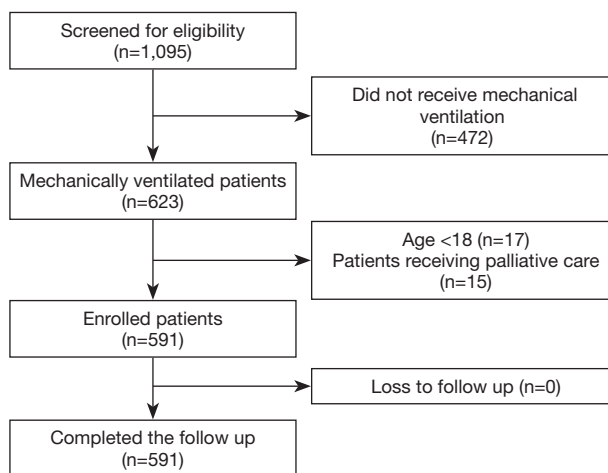
pMDI, pressurized metered dose inhaler; HME, heat moisture exchanger.

media (WeChat App, Tencent, Hangzhou, China) of the Respiratory Care Committee of the Chinese Thoracic Society and centers were enrolled voluntarily. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the leading hospital (Peking University People's Hospital, IRB approval No. 2018PHB058-01). Additional ethical approvals were gained at each participating institution if required by the participating hospital. Written informed consent was obtained from patients or legal surrogates in all participating ICUs.

All adult patients who aged 18 and above and stayed in ICU between midnight on July 9, 2018, and midnight on July 23, 2018, who received invasive or noninvasive

ventilation and agreed to participate in this study were eligible for inclusion. Patients were excluded if they were placed on palliative care. Each patient was observed for up to 28 days or until discharge from ICU. All patients in each ICU were registered, and identification information was recorded to allow for verification by the primary investigator to avoid any patient enrollment bias or patients being missed. The primary endpoint was to identify the proportion of patients receiving aerosol treatments consistent with optimal practice. The secondary endpoints were to identify mechanically ventilated patients receiving aerosol therapy and to investigate aerosol therapy practice and side effects in various ICUs. Respiratory support, prescribed aerosol therapy (aerosol generator and placement), and adverse events were recorded for each patient daily along with the patients' demographic information. The optimal delivery guide (*Tables 1,2*) was used to assess if each patient received optimal therapy or not.

Normal distribution quantitative variables were expressed as the mean  $\pm$  standard deviation and compared with Student's *t*-test, and non-normal distribution quantitative variables were expressed as the median (interquartile) and compared using the Mann Whitney test. Qualitative variables were expressed as counts (%) and compared between the groups using the chi-square test. A 95% confidence interval (95% CI) of proportions was calculated for the main variables of aerosol therapy. Missing data were also reported in the results. A P value of less than 0.05 was considered significant. Data analysis was performed using SPSS (SPSS 23.0, Chicago, IL, USA).



**Figure 1** Flow chart.

## Results

This study was carried out with respondents representing 28 ICUs from 28 hospitals in mainland China (the centers and investigators are listed in the Appendix 1); 27 (96.4%) were teaching hospitals. The number of beds in the participating ICUs and hospitals was  $20 \pm 13.2$  and  $2,266.1 \pm 1,299.6$ , respectively. During the study period (Figure 1), 1,066 patients were screened in the ICUs, with 507 patients excluded due to the following reasons: 472 patients did not receive mechanical ventilation, 17 patients were aged under 18 years old, and 15 patients were placed on palliative care. Eventually, 591 patients receiving mechanical ventilation were enrolled. These 591 patients completed follow-ups and were analyzed. The median follow-up time for each patient was 5 days; the maximum follow-up time was 28 days. Data were complete for all 591 patients, of whom 160 (27.1%; 95% CI: 23.5–30.7%) received 4,198 aerosol treatments while in the ICU. Among the 160 patients, 125 received invasive ventilation, and 35 patients received noninvasive ventilation. Only six patients were ordered to change from aerosolized medications during the study period.

Of the 160 patients receiving aerosol therapy, the mean age was  $68.0 \pm 15.6$  years, and 65.6% (105/160) of the patients were male. The majority (76.9%, 123/160) of the patients were non-surgical, and 56.3% (90/160) had cardiopulmonary diseases. The average Sequential Organ Failure Assessment (SOFA) score of these 160 patients, when admitted to ICU, was  $5.5 \pm 2.6$ . The median length of ICU stay for these patients was 8 days. During the study

period, 57.5% (92/160) of the patients were transferred to general units, 21.9% (35/160) of them were discharged, 11.3% (18/160) of them remained in ICU after 28 days, and 9.4% (15/160) died.

The 160 patients who received aerosol therapy were older ( $68.0 \pm 15.6$  vs.  $60.0 \pm 16.8$  years,  $P < 0.001$ ) and had more cardiopulmonary comorbidities (55.4% vs. 26.5%,  $P < 0.001$ ), and a higher percentage of them were diagnosed with acute respiratory failure or acute exacerbation of chronic respiratory failure (45.8% vs. 16.1%,  $P < 0.001$ ), compared with the 431 patients who did not receive aerosol therapy. In the 28-day outcomes, patients who received aerosol therapy had a longer ICU stay {8 [4, 14] days vs. 4 [2, 10] days,  $P < 0.001$ } {median [interquartile]}, longer invasive ventilation duration {4 [1, 9] days vs. 2 [1, 4] days,  $p = 0.007$ } {median [interquartile]}, longer noninvasive ventilation duration {0 [0, 3] days vs. 0 [0, 0] days,  $P < 0.001$ } {median [interquartile]}, and a higher percentage of them were discharged against medical advice (20.8% vs. 9.5%,  $P < 0.001$ ), compared with patients who did not receive aerosol therapy.

### *Aerosol therapy practice during invasive ventilation*

All patients receiving at least one aerosol treatment were on ventilators with bias flow settings during invasive ventilation. The most commonly utilized aerosol generator was the pneumatic jet nebulizer, which was used in 67.2% (84/125) of the patients, followed by a vibrating mesh nebulizer (15.2%), a metered-dose inhaler (MDI) (12.8%), and an ultrasonic nebulizer (4.8%). For the pneumatic jet nebulizers, 63.1% (53/84) of the individuals were driven by the ventilator to generate aerosol synchronized with inspiration (breath-synchronized nebulizer) (Table 3), and 64.2% (34/53) were placed close to the Y piece on the inspiratory limb. The remaining 31 individuals on the jet nebulizers were powered by an external compressed gas source operated continuously (continuous nebulizer), with 71% (22/31) of them placed close to the Y piece in the inspiratory limb, and 12.9% (4/31) being placed 20–30 cm away from the Y piece in the inspiratory limb. The vibrating mesh nebulizer and ultrasonic nebulizer were both placed close to the Y piece in the inspiratory limb (Figure 2) for patients receiving aerosol with MDI. Among patients who used an MDI ( $n=18$ ), only 1 (5.6%) patient used a spacer chamber.

No ventilator modes were changed during aerosol therapy. Ventilator parameters were changed in 8 (6.4%) invasively ventilated patients, with decreasing inspiratory flow ( $n=3$ , 2.4%) and increasing inspiratory trigger

**Table 3** Aerosol generator and its placement in the ventilator circuit during mechanical ventilation

Aerosol generator	Placement of the aerosol device in the ventilator circuit	Invasive ventilation (n=125)	Noninvasive ventilation (n=35)
Pneumatic (jet) nebulizer		84 (67.2%)	27 (77.1%)
Ventilator integrated (dual limb ventilator)		53 (63.1%)	5 (18.5%)
	Between artificial airway/mask and the Y piece	17 (32.1%)	1 (20%)
	Inspiratory limb just before the Y piece	34 (64.2%)	4 (80%)
Not ventilator integrated	Inspiratory limb 20–30 cm from the Y piece	2 (3.8%)	NA
		31 (36.9%)	22 (81.5%)
	Between artificial airway and Y piece	5 (16.1%)	NA
	Inspiratory limb just before the Y piece	22 (71%)	NA
	Inspiratory limb 20–30 cm from the Y piece	4 (12.9%)	NA
	Between mask and exhalation port (single limb ventilator)	NA	17 (77.3%)
Vibrating mesh nebulizer	Between exhalation port and inspiratory limb (single limb ventilator)	NA	5 (22.7%)
		19 (15.2%)	4 (11.4%)
	Inspiratory limb just before the Y piece	19 (100%)	NA
pMDI	Between exhalation port and inspiratory limb (single limb ventilator)	NA	4 (100%)
		16 (12.8%)	NA
	Without spacer	15 (93.8%)	NA
With spacer	Inspiratory limb just before the Y piece	15 (100%)	NA
		1 (6.3%)	NA
Ultrasonic nebulizer	Inspiratory limb just before the Y piece	1 (100%)	NA
		6 (4.8%)	4 (11.4%)
	Between mask and exhalation port (single limb ventilator)	NA	4 (100%)

pMDI, pressurized metered dose inhaler.

sensitivity (n=2, 1.6%) being the main adjustments, while 75% (6/8) used breath-synchronized nebulizer.

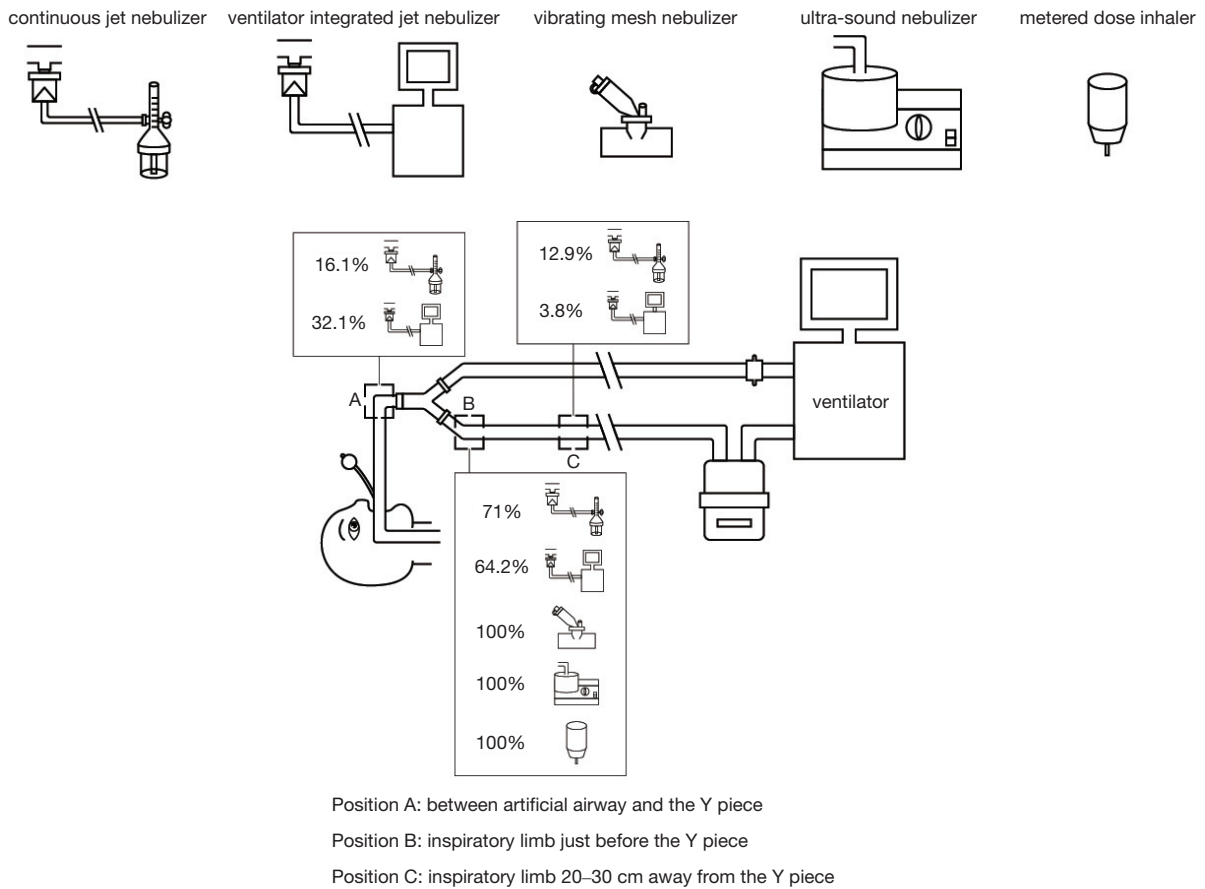
During aerosol therapy, 110 of 125 (88%) of the patients used active humidifiers, with 9 (8.2%) turned off humidifiers. Fifteen patients used heat moisture exchangers (HME), with only 26.7% of the patients (4/15) having HME removed during aerosol therapy. During invasive ventilation, 54.4% (68/125) of the patients did not have a filter placed on the expiratory port.

#### *Aerosol therapy practice during noninvasive ventilation*

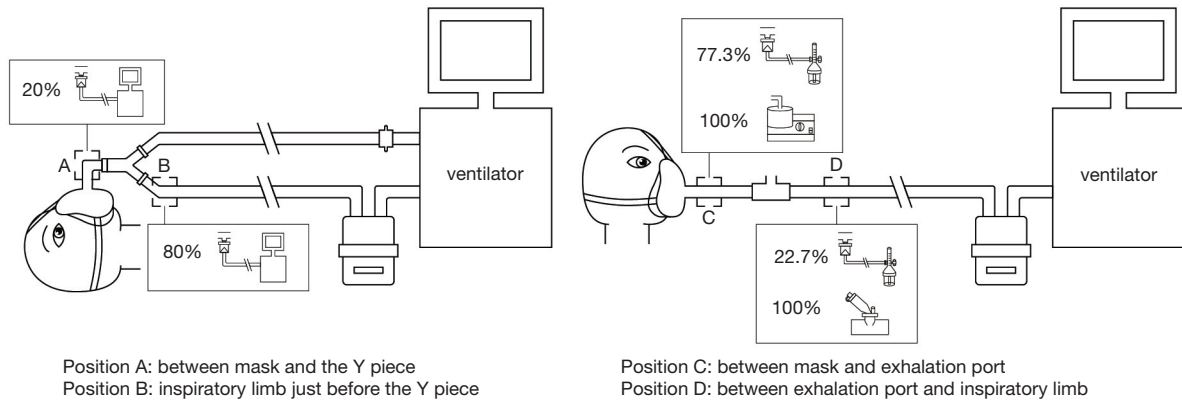
Among the 81 patients on noninvasive ventilation, 35

patients (43.2%) received aerosol therapy. Among the 35 patients, jet nebulizer (n=27, 77.1%) was the most common, while a vibrating mesh nebulizer and an ultrasonic nebulizer were used in 11.4% (4/35) and 11.4% (4/35) of the patients, respectively. Dual limb ventilators were used in 14.3% (5/35) of the patients, and all of them used ventilator-integrated jet nebulizers, with 80% (4/5) of them placed close to the Y piece in the inspiratory limb. Continuous jet nebulizers were used by 73.3% (22/30) of the remaining 30 patients who used single limb ventilators, with 77.3% (17/22) placed between the mask and exhalation port. Vibrating mesh nebulizers were used by 13.3% (4/30) of patients, and all of the nebulizers were placed between





**Figure 2** The portions of aerosol generator placements during invasive ventilation.



**Figure 3** The portions of aerosol generator placements during noninvasive ventilation using dual limb and single limb ventilators.

the exhalation port and inspiratory limb (Figure 3). The ventilation mode was not changed for aerosol therapy. Only 14.3% (5/35) of the patients had increased trigger sensitivity.

**Short term safety of aerosol therapy**

No adverse effect of aerosol therapy was observed in 92% (115/125) of the invasively ventilated patients and 85.7%

(30/35) of the noninvasively ventilated patients. Among the patients who suffered adverse effects, a cough was the most common complication and was developed by 2.4% (3/125) and 5.7% (2/35) of patients who received invasive ventilation and noninvasive ventilation, respectively. However, hypoxemia was found in one invasively ventilated patient and one noninvasively ventilated patient, and tachycardia was found in two invasively ventilated patients.

#### *Patients who received optimal aerosol delivery*

Using the guide from *Tables 1* and *2*, only 36.3% (58/160) (95% CI: 28.7–43.8%) of patients received aerosol therapy under optimal practice, and the proportions of invasively and noninvasively ventilated patients were 29.6% (37/125) (95% CI: 21.5–37.7%) and 60.0% (21/35) (95% CI: 42.9–77.1%), respectively.

## Discussion

### *Nebulizer placement in the ventilator circuits*

Traditional pneumatic jet nebulizers generate aerosol continuously, resulting in a waste of aerosol during the exhalation phase (13), which is usually 2–3 times longer than the inhalation phase. Additionally, when the continuous jet nebulizer is connected to the ventilator system, the extra compressed gas used to power the jet nebulizer affects the ventilator function (29), which may cause patient-ventilator asynchrony, air-trapping or even ventilator-associated lung injury (30). As such, some ventilator manufacturers integrate gas delivery ports to power jet nebulizers during inspiration to avoid or minimize the impact on the ventilator's function (17). Breath synchronization improves inhaled dosage compared to a continuous jet nebulizer, but only when the nebulizer is placed close to the Y-piece in the inspiratory limb of a dual limb ventilator during invasive ventilation (13).

In 2010, Ari *et al.* compared the placement of continuous jet nebulizers and vibrating mesh nebulizers during invasive ventilation with bias flow. They found that the inhaled dose with the nebulizer placed at the inlet of the humidifier was higher than that with the nebulizer placed close to the patient, regardless of the nebulizer type (7). Three years later, Berlinski *et al.* further confirmed this finding in their pediatric models, regardless of ventilator settings (5). Both researchers explained that the improvement was due to the reservoir effects of the humidifier chamber and inspiratory limb. Since then, continuous nebulizers have

been recommended to be placed at the inlet or outlet of the humidifier while breath-synchronized jet nebulizers should be placed close to the Y piece in the inspiratory limb during invasive ventilation (22).

However, this rule does not apply for noninvasive ventilation. The inhaled dose was shown to be higher when both continuous jet and mesh nebulizers were placed between the mask and the Y piece than that with nebulizers placed at the inlet of the humidifier in a recent *vitro* study using a dual limb ventilator for pediatric manikin (31). No studies have investigated the placement of ventilator-integrated jet nebulizer during noninvasive ventilation. Thus, its optimal placement in the dual limb ventilator is still unknown. When using a single limb circuit with a fixed leak for NIV with a turbine-type ventilator, *in vitro* studies in adult and pediatric models have confirmed that a continuous jet nebulizer, vibrating mesh nebulizer, and pMDI should be placed between the fixed leak exhalation port and the patient (8,32–34).

The most common error in our observation was the placement of continuous nebulizers (including jet, mesh, and ultrasonic nebulizers) during invasive ventilation with a biased flow setting. None of the participants placed the continuous nebulizers at correct locations in the inspiratory limb of the circuit. This is problematic because the aerosol generated in the exhalation phase could be collected in the humidifier or inspiratory limb, which serves as a reservoir, increasing the inhaled dose available to the patient.

During NIV, the optimal position for the stabilizing nebulizer is an upright operating position, which can present challenges. For example, the placement of the jet or mesh nebulizer between the fixed exhalation port and patient mask in the single limb ventilator. Modifications on some noninvasive ventilation masks that allow for the nebulizer to be directly placed on the mask might help to resolve this dilemma (31,34,35). However, this type of mask has not been broadly utilized yet, and follow-up studies are warranted to determine its clinical efficacy.

### *The utilization of a spacer when using MDI in-line with ventilator circuits*

More than two decades ago, Rau *et al.* found that using a spacer with an MDI to deliver albuterol was more efficient than using a T-adaptor to place MDI in-line during invasive ventilation directly (14). This finding has since been widely confirmed (15,16,36). However, in our study, only 1 of 16 patients were treated with an MDI and a spacer;

this finding was consistent with our previous national survey (37), which was implemented 8 years ago. A spacer chamber for pMDI delivery with an MDI for in-line aerosol delivery for ventilated patients in Chinese markets was not widely available, and this shortage might still exist today.

### *The need to turn off humidifiers during aerosol therapy*

Previous studies have reported that humidification during invasive ventilation reduced aerosol delivery to the airways (4,11-13,36), with some researchers suggesting that the humidifier should be turned off during aerosol delivery. However, two recent randomized control trials demonstrated that there were no significant differences in lung deposition and clinical outcomes (38,39). Moreover, dry gas might cause airway irritation, mucus plug, and airway membrane injury. Therefore, turning off the humidifier should be avoided (40). However, 8.2% of patients in our study still received aerosol treatments with dry gas, even though it was clearly stated in the clinical consensus created by the Respiratory Care Committee of the Chinese Thoracic Society (26). Additionally, AARC recommended removing HME during aerosol treatment to avoid HME to filter the aerosol (41); however, in our study, less than one-third of participants did so. More education and quality improvement projects are called for.

### *Limitations*

Nevertheless, in contrast with Ehrmann *et al.*'s study (28), wherein data were collected through individual treatments, our data were collected for each patient. Our method was intended to avoid a potential bias with patients receiving a large number of repeated aerosol treatments rather than clinical practice trends with the individual patient. However, our approach meant that we could not reflect the changes in aerosol devices, medications, or delivery techniques during the study. However, none of the devices or delivery techniques in our study changed for the same patient, and only 3.75% (6/160) of patients changed medications during study, which should not significantly impact the results.

Like Ehrmann *et al.*'s study, this study lasted for 2 weeks and was implemented in summer, when there tend to be fewer respiratory patients than in winter (42,43). The numbers of patients admitted to ICU due to community-acquired pneumonia or asthma have been reported to peak in winter (43,44), thus our study may underestimate the use of aerosol therapy in those patient populations. This study

was performed in mainland China, and the results may not extrapolate to other countries or regions.

In this study, we not only reported on the current practice of aerosol therapy but also found that there is a gap between the clinical practice and current optimal evidence in 28 Chinese ICUs. The clinical practice of aerosol therapy varied across the different ICUs, and only 36.3% of the patients received aerosol treatments under conditions consistent with the evidence of optimal aerosol delivery efficiency.

### **Conclusions**

Aerosol therapy varies in different ICUs in mainland China, and only one-third of patients in our study received aerosol treatments under optimal aerosol delivery efficiency from the available published evidence. More education and quality improvement projects are warranted. Nebulization protocols with evidence-based guidelines and recommendations are highly recommended for individual ICUs with the availability of equipment, including aerosol devices and types of ventilators. Aerosol auxiliary devices, such as spacers, for mechanical ventilation are needed in the Chinese market.

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### **Footnote**

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. It was registered on ClinicalTrials.gov (NCT03597334) and was conducted by the Respiratory Care Committee of the Chinese Thoracic Society. Recruitment advertisement was posted on the official social media (WeChat App, Tencent, Hangzhou, China) of the Respiratory Care Committee of the Chinese Thoracic Society and centers were enrolled voluntarily. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the leading hospital (Peking University People's Hospital, IRB approval No. 2018PHB058-01). Additional ethical approvals were gained at each participating institution if required by the participating hospital. Written informed consent was obtained from patients or legal surrogates in all participating ICUs.

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## Appendix 1 The investigators and centers in this study

Investigator	Centers
Shan Lyu	Department of Critical Care Medicine, Peking University People's Hospital
Guoqiang Jing	Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital
Qionglan Dong	Department of Critical Care Medicine, The Third People's Hospital of Mianyang
Mengmeng Wu	Department of Critical Care Medicine, Binzhou People's Hospital
Guanghan Wu	Department of Critical Care Medicine, People's Hospital of Jianghua Yao Autonomous County, Hunan Province
Weiwei Shu	Department of Critical Care Medicine, Yongchuan Hospital of Chongqing Medical University
Lihua Chen	Department of Critical Care Medicine, Gansu Second Provincial People's Hospital
Ping Liu	Department of Critical Care Medicine, the Seventh Affiliated Hospital, Sun Yat-sen University
Zhenyan Wang	Department of Critical Care Medicine, Peking University International Hospital
Limin Yang	Department of Respiratory Care, Zhejiang University School of Medical Sir Run Run Shaw Hospital
Xiaoliang Du	Department of Neurosurgical, Tongji Medical College of Huazhong University of Science & Technology Tongji Hospital
Chunjuan Ye	Department of Surgical Intensive Care Unit, the First Affiliated Hospital of Xi'an Jiaotong University
Wei Tan	Department of Respiratory and Critical Care Medicine, the First Hospital of China Medical University
Hao Qin	Department of Respiratory and Critical Care Medicine, Shanghai Changhai Hospital
Jun Duan	Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University
Liucun Li	Department of Respiratory and Critical Care Medicine, the Second Xiangya Hospital of Central South University
Binhai Pan	Department of Respiratory and Critical Care Medicine, Jinling Hospital
Xiaoyi Liu	Department of Critical Care Medicine, Dazhou Central Hospital
Xu Tan	Department of Respiratory and Critical Care Medicine, Union Hospital Affiliated with Tongji Medical College of Huazhong University of Science and technology
Dehua He	Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine
Haiyan Wang	Department of Emergency Critical Care Medicine, West China Hospital Sichuan University-Ziyang Hospital
Zhong Ni	Department of Respiratory and Critical Care Medicine, West China Medical Center, Sichuan University
Libo Chuan	Intensive Care Unit, the First People's Hospital of Yunnan Province
Tinggan Fu	Department of Surgical Intensive Care Unit, the First Affiliated Hospital, Sun Yat-sen University
Yajuan Zong	Department of Critical Care Medicine, Yixing No. 2 People's Hospital
Guilan Zeng	Department of Critical Care Medicine, Zhangzhou Hospital Traditional Chinese Medicine
Ping He	Department of Cardiac Surgery, Southwest Hospital, the First Hospital Affiliated to Army Medical University
Fang Ni	Department of Respiratory and Critical Care Medicine, the Central Hospital of Wuhan

**Table S1** Studies compared aerosol delivery via continuous jet and vibrating mesh nebulizer in invasive ventilated patients with humidification and bias flow

Author, year	Study type	Population	Ventilator setting	Inhaled dose of continuous jet nebulizer			Inhaled dose of vibrating mesh nebulizer		
				Before Y-piece	Inlet to humidifier	P	Before Y-piece	Inlet to humidifier	P
Ari, 2010 (7)	<i>In vitro</i>	Adult	Vt 500 mL, PEEP 5, f 20	4.0%±0.1%	4.7%±0.4%		9.7%±0.6%	21.4%±0.4%	0.001
Ari, 2010 (7)	<i>In vitro</i>	Pediatric	Vt 100 mL, PEEP 5, f 20	3.8%±0.3%	4.1%±0.4%		8.4%±0.2%	10.6%±0.3%	0.01
Berlinski, 2015 (45)				102±7 µg	218±41 µg	<0.02	184±29 µg	238±128 µg	0.36
Berlinski, 2013 (5)			Vt 200 mL, PEEP 5, f 20	2.0%±0.1%	5.4%±0.6%	<0.01	8.7%±2.5%	28.5%±8.6%	<0.01
Berlinski, 2015 (45)				90±17 µg	230±38 µg	<0.02	123±17 µg	326±96 µg	<0.03

**Table S2** Studies compared aerosol delivery via continuous jet and vibrating mesh nebulizer in noninvasive ventilated patients with single limb ventilator

Author, year	Study type	Population	Ventilator setting	Inhaled dose of continuous jet nebulizer			Inhaled dose of vibrating mesh nebulizer		
				Placed between exhalation port and mask	Placed between exhalation port and ventilator	P	Placed between exhalation port and mask	Placed between exhalation port and ventilator	P
Michotte, 2016 (18)	<i>In vitro</i>	Adult	IPAP 15, EPAP 5				115±1 mg	31±1 mg	<0.001
Chatmongkolchart, 2002 (8)			IPAP 20, EPAP 5	24.5%±1.3%	5.2%±0.4%	<0.001			
Calvert, 2006 (46)				544±85 µg	647±67 µg	>0.05			
Abdelrahim, 2010 (32)				1207.2±161.3 µg	341±69.5 µg	<0.001	2572.5±150.9 µg	935.5±273.3 µg	<0.001
Michotte, 2014 (33)				61.2±3.6 mg	46.2±5.3 mg	<0.05	221.1±5.1 mg	70.1±6.3 mg	<0.001
Berlinski, 2019 (34)		Pediatric		5.9%	0.9%	<0.001	14.9%	4.3%	<0.001
Dai, 2014 (47)	<i>In vitro</i>	Adult	IPAP 25, EPAP 5	24.18%±1.08%	22.23%±0.79%	<0.05			
Peng, 2018 (48)				17.66%±0.83%	16.16%±1.90%				

**Table S3** Studies compared aerosol delivery via continuous jet and vibrating mesh nebulizer in noninvasive ventilated patients with dual limb ventilator

Author, year	Study type	Population	Ventilator setting	Inhaled dose of continuous jet nebulizer				Inhaled dose of vibrating mesh nebulizer			
				Placed between Y-piece and mask	Placed before Y-piece	Inlet to humidifier	P	Placed between Y-piece and mask	Placed before Y-piece	Inlet to humidifier	P
Velasco, 2018 (31)	<i>In vitro</i>	Pediatric	IPAP 20, EPAP 5		3.8%	3.5%			17.6%	13.3%	0.01
Bodet-Contentin, 2019 (49)	<i>In vitro</i>	Adult	IPAP 15, EPAP 5					729±61 µg	555±44 µg		



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