RESEARCH ARTICLE

Practice pattern of aerosol therapy among patients undergoing mechanical ventilation in mainland China: A web-based survey involving 447 hospitals

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Abstract

Background and objective
Aerosol therapies are widely used for mechanically ventilated patients. However, the practice pattern of aerosol therapy in mainland China remains unknown. This study aimed to determine the current practice of aerosol therapy in mainland China.

Methods
A web-based survey was conducted by the China Union of Respiratory Care (CURC) from August 2018 to January 2019. The survey was disseminated via Email or WeChat to members of CURC. A questionnaire comprising 16 questions related to hospital information and 12 questions related to the practice of aerosol therapy. Latent class analysis was employed to identify the distinct classes of aerosol therapy practice.

Main results
A total of 693 valid questionnaires were returned by respiratory care practitioners from 447 hospitals. Most of the practitioners used aerosol therapy for both invasive mechanical ventilation (90.8%) and non-invasive mechanical ventilation (91.3%). Practitioners from tertiary care centers were more likely to use aerosol therapy compared with those from non-tertiary care centers (91.9% vs. 85.4%, respectively; p = 0.035). The most commonly used drugs for aerosol therapy were bronchodilators (64.8%) followed by mucolytic agents (44.2%), topical corticosteroids (43.4%) and antibiotics (16.5%). The ultrasonic nebulizer (48.3%) was the most
commonly used followed by the jet nebulizer (39.2%), the metered dose inhaler (15.4%) and the vibrating mesh nebulizer (14.6%). Six latent classes were identified via latent class analysis. Class 1 was characterized by the aggressive use of aerosol therapy without a standard protocol, while class 3 was characterized by the absence of aerosol therapy.

Conclusions
Substantial heterogeneity among institutions with regard to the use of aerosol therapy was noted. The implementation of aerosol therapy during mechanical ventilation was inconsistent in light of recent practice guidelines. Additional efforts by the CURC to improve the implementation of aerosol therapy in mainland China are warranted.

Introduction
Aerosol therapy, widely used for patients undergoing mechanical ventilation (MV), has the ability to confer positive effects via multiple mechanisms [1]. Nebulized drugs can be directly delivered to the airways and the lung parenchyma, thereby increasing the concentrations of these drugs locally and lowering the potential for systemic toxicities [2]. Increased local concentrations of nebulized antibiotics and rapid bacterial killing were noted in the lungs following the administration of these drugs during MV [3,4]. Nevertheless, there is limited evidence regarding the use of nebulized antibiotics in ventilated patients [5]. Although the effectiveness of aerosol therapy with regard to patient-centered outcomes is controversial [6–8], an international survey showed that most physicians (99%) support the use of this therapy during both invasive MV (IMV) and non-invasive MV (NIMV) [9]. A major obstacle for drug delivery via nebulization is the low delivery efficiency of the nebulizers [10]; the majority of the aerosol is generally deposited into the ventilator circuit and the endotracheal tube. The jet nebulizers, in particular, are limited by their high residual volume. A variety of technologies and techniques have been developed to address this problem. For example, the vibrating mesh and ultrasonic nebulizers were shown to increase the delivered dose to the patient when compared with the jet nebulizer [11,12]. Furthermore, ventilator settings, respiratory parameters and nebulizer position can influence drug delivery [13,14].

The majority of the previous studies were conducted in vitro and in animal models; in vivo studies using radiolabeling are limited. Thus, there is a lack of randomized controlled trials to determine the most appropriate technique or ventilator setting in terms of the clinical outcomes measured [15]. The practice patterns of aerosol therapy have evolved over time and varied substantially in different institutions. The jet, ultrasonic and vibrating mesh nebulizers were used in 55%, 44% and 14% respondents in previous surveys [9]. China is a large country with substantial variances in the practice of aerosol therapy during MV [16]. However, sufficient information about the use of aerosol therapy by respiratory care practitioners and intensivists in China is lacking. Thus, the present study aimed to determine the current practices involved in aerosol therapy across mainland China using latent class analysis to categorize institutions into a number of classes with distinct practice patterns. We believe that this information will aid in developing better policies and educational programs.

Methods
Survey questionnaire
This study was approved by the institutional review board of the Sir Run Run Shaw hospital (Hangzhou, China) (20151201–17). Informed consent was obtained from all the participants.
A web-based survey was conducted from August 2018 to January 2019. The survey was disseminated via Email or WeChat to 2000 members via the platform of the China Union of Respiratory Care (CURC). Deidentified dataset is available as supporting information (S1 Dataset). The aim of the CURC, which comprises respiratory care practitioners from mainland China, is to improve the quality of the respiratory care and conduct clinical researches. Members of CURC included respiratory care practitioners from mainland China. Only one member was invited from one department (e.g. one hospital may have several departments such as medical and surgical ICUs in which aerosol therapy is used. They could have different practice patterns of aerosol therapy). The questionnaire was explained in a detailed manner by the organizer of the meeting. The questions on aerosol therapy included the following topics: type of drug delivered during IMV or NIMV, type of nebulizer used, type of jet nebulizer used, position of the nebulizer in the case of small-volume nebulizers, position and use of a spacer chamber with a metered-dose inhaler (MDI), frequency of changing the filters in a ventilator circuit, ventilator setting during aerosol therapy, positive end-expiratory pressure (PEEP) level during nebulization, ventilator mode during nebulization, use of a nebulization protocol, and assessment of the effectiveness of the nebulization. The full questionnaire can be accessed at the following web link: http://client.rup-china.com/icu/wx/?from=singlemessage&isappinstalled=0#/time=1549868372. A translated version of this questionnaire is enclosed as a supporting file (S1 Questionnaire).

Tertiary care refers to the specialized consultative healthcare provided to inpatients and patients referred from primary and secondary healthcare centers for advanced medical investigation and treatment. The respondents in this study were categorized into two groups, those from tertiary care hospitals and those from non-tertiary care hospitals.

**Statistical analysis**

Categorical variables were expressed as numbers and percentages. Differences between tertiary and non-tertiary care centers were compared using the Chi-square or Fisher’s exact test as appropriate. Continuous data were expressed as median and interquartile range and were compared using non-parametric tests between groups [17]. Statistical descriptions and bivariate inferences were performed using the CBCgrps package [18]. All statistical analyses were performed using RStudio (Version 1.1.463).

Latent class analysis (LCA) was performed to identify the classes of hospitals with distinct practice patterns of aerosol therapy [19]. The rationale for using LCA was that this technique allows for the modeling of distinct practice patterns of aerosol therapy using individual questions in the form of a questionnaire. The identification of distinct practice patterns may help formulate specific training programs and policies for different hospitals. LCA models with one to seven classes were fitted using response variables, which included all of the 12 questions related to aerosol therapy. Some questions with more than two response items were dummyfied resulting in k-1 variables (k, number of response items). The fitness of each model was then compared (how well each model described the underlying data). Entropy describes the dispersion (or concentration) in a probability mass function and is expressed as a value ranging from 0 to 1. An entropy value approaching 0 indicates that the observations were well categorized into the latent classes, whereas a value approaching 1 indicates a model that categorizes the observations poorly. Thus, among all the fitted models, we intended to choose the one with the lowest entropy value. Other statistics such as Bayesian information criterion (BIC), corrected Akaike information criterion (cAIC), and adjusted BIC (aBIC) were also reported. Lower BIC and AIC values indicate a better-fitted model [20–22].
Results

General description of the practice of aerosol therapy

A total number of 693 completed questionnaires (returning rate 693/2000 = 34.7%) were returned by the respiratory care practitioners from 447 hospitals. The samples were distributed across all the provinces of mainland China. Fifty-seven respondents (9.2%) reported never using aerosol therapy during MV, 15.4% exclusively used jet nebulizers, 26.3% exclusively used ultrasonic nebulizers, and 2.0% exclusively used metered dose inhalers (MDIs). Practitioners from tertiary care centers were more likely to use aerosol therapy when compared to those from non-tertiary care centers (91.9% vs. 85.4%, respectively; p = 0.035).

The most commonly used drugs for aerosol therapy were bronchodilators (64.8%) followed by mucolytic agents (44.2%), topical corticosteroids (43.4%) and antibiotics (16.5%). Interestingly, practitioners from tertiary care centers were more likely to use mucolytic agents (p = 0.03) and topical corticosteroids (p = 0.01) when compared to those from the non-tertiary centers. Ultrasonic nebulizers (48.3%) were most commonly used followed by jet nebulizers (39.2%), metered-dose inhalers (15.4%), and vibrating mesh nebulizers (14.6%). Jet nebulizers were used with an external gas source by 27.1% of the practitioners, while 20.2% used other external nebulizer pumps; about 28.6% reported the use of ventilator-integrated systems. Metered-dose inhalers were used via an inhalation chamber (344 respondents; 49.6%) placed within the circuit or directly into the tracheal tube after disconnecting the patient (111 respondents; 16%); 11.4% of the practitioners never think about this problem. The most common position of nebulizer for small-volume nebulizer was placed at the inspiratory limb near the Y-piece (39.8%). In terms of changing the ventilator settings, 40.8% of the respondents reported not changing the setting during aerosol therapy, whereas 11.3% and 17% of the respondents reported increasing the tidal volume and the inspiratory time, respectively.

Most practitioners assessed the effectiveness of the aerosol therapy by observing the waveform (45.6%), relying on the auscultation of the pulmonary sound (33.8%), and observing the breathing by physical examination (31.2%). Only 9.4% responders reported not assessing the effectiveness of the therapy (Table 1).

Latent class analysis

Table 2 illustrates the statistics for choosing the most appropriate number of classes. The 6-class model showed the lowest entropy (0.92) and the lowest values in BIC (30125.84). aBIC demonstrated a continuous decrease from the 6-class to the 7-class model, albeit marginal. Furthermore, the increase in cAIC values from the 6-class model to the 7-class model was markedly greater than that from the 5-class model to the 6-class model (163.4 vs. 2.6, respectively). Thus, the 6-class model was considered as the best fit model. Class 1 was characterized by heterogeneous practice in each item (e.g. aggressive use of aerosol therapy without standard). For example, all answers to the question “how to assess the effectiveness of nebulization” were marked as yes (Fig 1). All drugs were used during ventilation. Class 3 was characterized by not using aerosol therapy; thus, most questions related to aerosol therapy were left unanswered. Class 5 was characterized by the uniform practice of aerosol therapy that each question had one choice, for example, most respondents in class 5 assess the effectiveness of nebulization by examining the waveform; and most of them used an ultrasonic nebulizer. This could be explained by the use of a standard protocol in these centers.

While class 4 and 5 were characterized by high proportion of tertiary care centers, class 1 and 3 were more likely from non-tertiary care centers (Table 3). Class 4 was characterized by...
Table 1. Comparing Aerosol therapies between tertiary and non-tertiary care hospitals.

| Variables | Overall (n = 693) | Non-tertiary care (n = 123) | Tertiary care center (n = 570) | p  |
|-----------|------------------|-----------------------------|-------------------------------|----|
| Nebulization for IMV, n (%) | 629 (90.8) | 105 (85.4) | 524 (91.9) | 0.035 |
| Nebulization for NIMV, n (%) | 633 (91.3) | 108 (87.8) | 525 (92.1) | 0.173 |
| Drugs for IMV nebulization | | | | |
| Bronchodilators, n (%) | 449 (64.8) | 78 (63.4) | 371 (65.1) | 0.804 |
| Antibiotics, n (%) | 114 (16.5) | 18 (14.6) | 96 (16.8) | 0.642 |
| Mucolytic agent, n (%) | 306 (44.2) | 43 (35.0) | 263 (46.1) | 0.030 |
| Topical corticosteroids, n (%) | 301 (43.4) | 40 (32.5) | 261 (45.8) | 0.010 |
| Systemic corticosteroids, n (%) | 59 (8.5) | 9 (7.3) | 50 (8.8) | 0.729 |
| Others, n (%) | 14 (2.0) | 1 (0.8) | 13 (2.3) | 0.486 |
| No. of drug types used in aerosol therapy in a department (median [IQR]) | 3.00 [2.00, 4.00] | 2.00 [1.00, 4.00] | 3.00 [2.00, 4.00] | 0.019 |
| Nebulizer type | | | | |
| Ultrasonic nebulizer (%) | 335 (48.3) | 60 (48.8) | 275 (48.2) | 0.993 |
| Jet nebulizer, n (%) | 272 (39.2) | 40 (32.5) | 232 (40.7) | 0.113 |
| Vibrating-mesh nebulizer, n (%) | 101 (14.6) | 12 (9.8) | 89 (15.6) | 0.126 |
| Metered dose inhaler, n (%) | 107 (15.4) | 21 (17.1) | 86 (15.1) | 0.678 |
| Others, n (%) | 24 (3.5) | 2 (1.6) | 22 (3.9) | 0.339 |
| No. of nebulizer type used in a department (median [IQR]) | 2.00 [2.00, 3.00] | 2.00 [1.00, 3.00] | 2.00 [2.00, 3.00] | 0.146 |
| Jet nebulizer implementation | | | | |
| External gas source, n (%) | 188 (27.1) | 39 (31.7) | 149 (26.1) | 0.251 |
| External nebulizer pump, n (%) | 140 (20.2) | 25 (20.3) | 115 (20.2) | 1.000 |
| Nebulizer within ventilator, n (%) | 198 (28.6) | 23 (18.7) | 175 (30.7) | 0.010 |
| Others, n (%) | 9 (1.3) | 0 (0.0) | 9 (1.6) | 0.335 |
| No. of jet nebulizer implementations used in a department (median [IQR]) | 2.00 [2.00, 2.00] | 2.00 [1.00, 2.00] | 2.00 [2.00, 2.00] | 0.060 |
| Position of nebulizer for small-volume nebulizer* | | | | |
| Inspiratory limb near Y-piece, n (%) | 276 (39.8) | 47 (38.2) | 229 (40.2) | 0.763 |
| Humidifier proximal to ventilator, n (%) | 126 (18.2) | 22 (17.9) | 104 (18.2) | 1.000 |
| Humidifier proximal to patient, n (%) | 125 (18.0) | 17 (13.8) | 108 (18.9) | 0.226 |
| Position of nebulizer for metered dose nebulization* | | | | |
| Inspiratory limb near Y-piece, n (%) | 298 (43.0) | 49 (39.8) | 249 (43.7) | 0.496 |
| Humidifier proximal to ventilator, n (%) | 115 (16.6) | 18 (14.6) | 97 (17.0) | 0.610 |
| Humidifier proximal to patient, n (%) | 104 (15.0) | 16 (13.0) | 88 (15.4) | 0.586 |
| Use of holding chambers / spacers for metered dose nebulization | | | | |
| Yes, n (%) | 344 (49.6) | 58 (47.2) | 286 (50.2) | 0.611 |
| No, n (%) | 111 (16.0) | 21 (17.1) | 90 (15.8) | 0.829 |
| Never use, n (%) | 79 (11.4) | 8 (6.5) | 71 (12.5) | 0.084 |
| How often did your institution change the filter at expiratory circuit | | | | |
| Every time after nebulization, n (%) | 196 (28.3) | 39 (31.7) | 157 (27.5) | 0.413 |
| Once daily, n (%) | 141 (20.3) | 19 (15.4) | 122 (21.4) | 0.172 |
| Twice a week, n (%) | 74 (10.7) | 13 (10.6) | 61 (10.7) | 1.000 |
| Once a week, n (%) | 100 (14.4) | 13 (10.6) | 87 (15.3) | 0.229 |
| More than once a week, n (%) | 24 (3.5) | 3 (2.4) | 21 (3.7) | 0.680 |
| Change ventilator parameters during nebulization | | | | |
| Never change, n (%) | 283 (40.8) | 47 (38.2) | 236 (41.4) | 0.581 |
| Increase PEEP, n (%) | 121 (17.5) | 21 (17.1) | 100 (17.5) | 1.000 |
| Decrease inspiratory flow, n (%) | 90 (13.0) | 12 (9.8) | 78 (13.7) | 0.304 |
| Use constant inspiratory flow, n (%) | 101 (14.6) | 16 (13.0) | 85 (14.9) | 0.688 |
| Increase inspiratory time, n (%) | 118 (17.0) | 16 (13.0) | 102 (17.9) | 0.240 |

(Continued)
| Variables                                      | Overall (n = 693) | Non-tertiary care (n = 123) | Tertiary care center (n = 570) | p   |
|-----------------------------------------------|-------------------|------------------------------|-------------------------------|-----|
| Use inspiratory pause, n (%)                  | 58 (8.4)          | 11 (8.9)                     | 47 (8.2)                      | 0.941 |
| Increase tidal volume, n (%)                  | 78 (11.3)         | 8 (6.5)                      | 70 (12.3)                     | 0.093 |
| Stop heated humidifier, n (%)                 | 64 (9.2)          | 7 (5.7)                      | 57 (10.0)                     | 0.185 |
| Place filter on expiratory circuit, n (%)     | 76 (11.0)         | 6 (4.9)                      | 70 (12.3)                     | 0.026 |
| Sedation to avoid dysynchrony, n (%)          | 40 (5.8)          | 7 (5.7)                      | 33 (5.8)                      | 1.000 |
| Use base flow rate, n (%)                     | 24 (3.5)          | 3 (2.4)                      | 21 (3.7)                      | 0.680 |
| Others, n (%)                                 | 7 (1.0)           | 0 (0.0)                      | 7 (1.2)                       | 0.460 |
| No. of MV parameter changes (median [IQR])    | 2.00 [2.00, 4.00]  | 2.00 [1.00, 4.00]            | 2.00 [2.00, 4.00]             | 0.032 |
| PEEP level during nebulization (cmH2O)        |                   |                              |                               |      |
| 0, n (%)                                      | 61 (8.8)          | 10 (8.1)                     | 51 (8.9)                      | 0.909 |
| 1–5, n (%)                                    | 242 (34.9)        | 45 (36.6)                    | 197 (34.6)                    | 0.747 |
| 6–10, n (%)                                   | 106 (15.3)        | 19 (15.4)                    | 87 (15.3)                     | 1.000 |
| >10, n (%)                                    | 11 (1.6)          | 0 (0.0)                      | 11 (1.9)                      | 0.248 |
| PEEP not changed, n (%)                       | 52 (7.5)          | 6 (4.9)                      | 46 (8.1)                      | 0.303 |
| Mode during nebulization                      |                   |                              |                               |      |
| Pressure control, n (%)                       | 231 (33.3)        | 39 (31.7)                    | 192 (33.7)                    | 0.752 |
| Pressure support, n (%)                       | 191 (27.6)        | 31 (25.2)                    | 160 (28.1)                    | 0.593 |
| Volume control, n (%)                         | 169 (24.4)        | 28 (22.8)                    | 141 (24.7)                    | 0.729 |
| SIMV, n (%)                                   | 149 (21.5)        | 24 (19.5)                    | 125 (21.9)                    | 0.638 |
| High-frequency ventilation, n (%)             | 40 (5.8)          | 3 (2.4)                      | 37 (6.5)                      | 0.125 |
| Others, n (%)                                 | 19 (2.7)          | 2 (1.6)                      | 17 (3.0)                      | 0.595 |
| No. of ventilation mode (median [IQR])        | 2.00 [1.00, 2.00]  | 2.00 [1.00, 2.00]            | 2.00 [1.00, 3.00]             | 0.291 |
| Nebulization protocol, n (%)                  | 290 (41.8)        | 56 (45.5)                    | 234 (41.1)                    | 0.417 |
| How to assess the effectiveness of nebulization|                   |                              |                               |      |
| Waveform, n (%)                               | 316 (45.6)        | 53 (43.1)                    | 263 (46.1)                    | 0.606 |
| Breathing sound, n (%)                        | 234 (33.8)        | 35 (28.5)                    | 199 (34.9)                    | 0.205 |
| Inspection of breathing appearance, n (%)     | 216 (31.2)        | 38 (30.9)                    | 178 (31.2)                    | 1.000 |
| Not assess routinely, n (%)                   | 65 (9.4)          | 11 (8.9)                     | 54 (9.5)                      | 0.990 |
| Others, n (%)                                 | 19 (2.7)          | 3 (2.4)                      | 16 (2.8)                      | 1.000 |
| No. of method to assess nebulization effectiveness (median [IQR]) | 2.00 [1.00, 3.00]  | 2.00 [1.00, 3.00]            | 2.00 [1.00, 3.00]             | 0.319 |
| Bed No. (median [IQR])                        | 1500 [1000, 2227]  | 876 [500, 1890]              | 1600 [1000, 2447]             | <0.001 |
| Overall evaluation of nebulization, n (%)     | 2 (0.3)           | 2 (1.6)                      | 0 (0.0)                       | 0.024 |
| No response                                   |                   |                              |                               |      |
| Very good                                     | 459 (66.2)        | 78 (63.4)                    | 381 (66.8)                    |       |
| Neutral                                       | 217 (31.3)        | 42 (34.1)                    | 175 (30.7)                    |       |
| Unsatisfactory                                | 12 (1.7)          | 1 (0.8)                      | 11 (1.9)                      |       |
| Poor                                          | 3 (0.4)           | 0 (0.0)                      | 3 (0.5)                       |       |
| Previous survey experience of this type, n (%)|                   |                              |                               | 0.010 |
| No response                                   | 2 (0.3)           | 2 (1.6)                      | 0 (0.0)                       |       |
| Yes                                           | 228 (32.9)        | 40 (32.5)                    | 188 (33.0)                    |       |
| No                                            | 463 (66.8)        | 81 (65.9)                    | 382 (67.0)                    |       |

Note
* these percentages did not sum to 100 within a column because there were some non-respondents.

Abbreviations: MV: mechanical ventilation; SIMV: simultaneous intermittent mechanical ventilation; PEEP: positive end expiratory pressure; IQR: interquartile range; NIMV: non-invasive mechanical ventilation.

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larger number of hospital bed than class 3. Class 1 and 3 were from high-income regions, whereas class 5 was more likely to be in low income provinces.

**Discussion**

The present study demonstrates that the practice patterns of aerosol therapy varied substantially in mainland China. While some respondents believed that patients supported by

| log-likelihood | BIC       | aBIC      | cAIC      | likelihood-ratio | Entropy | No. of classes |
|----------------|-----------|-----------|-----------|------------------|---------|----------------|
| -15521.13      | 31859.89  | 31463.00  | 31984.89  | 23285.36         | 1.00    | 2              |
| -14930.47      | 31090.66  | 30493.73  | 31278.66  | 22104.04         | 0.93    | 3              |
| -14489.70      | 30621.20  | 29824.23  | 30872.20  | 21222.49         | 0.96    | 4              |
| -14066.13      | 30186.14  | 29189.14  | 30500.14  | 20375.35         | 0.98    | 5              |
| -13829.94      | 30125.84  | 28928.80  | 30502.84  | 19902.96         | 0.92    | 6              |
| -13674.09      | 30226.23  | 28829.16  | 30666.23  | 19591.27         | 0.95    | 7              |

Abbreviations: BIC: Bayesian information criterion; cAIC: corrected Akaike information criterion; aBIC: adjusted Bayesian information criterion.

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Fig 1. Characteristics of the latent classes. All questions related to the aerosol therapy are labeled on the horizontal axis. Each question was followed by an answer annotated by uppercase letters such as A, B, C, D and E. Annotations: how to assess the effectiveness of aerosol therapy (AssessEffectHow): A: Waveform B: Breathing sound C: Inspection of breathing appearance D: Not assess routinely E: others Filter exchange frequency (FilterExchange.freq) A: Every time after nebulization B: Once daily C: Twice a week D: Once a week E: More than once a week Nebulizer position for Metered dose nebulization (FixedDose.connector) A: Inspiratory limb near Y-piece B: Humidifier proximal to ventilator C: Humidifier proximal to patient D: others Use of holding chambers / spacers for metered dose nebulization (FixedDose.Container) A: yes B: no C: never use Use of aerosol therapy for invasive mechanical ventilation (IMV.nebulization.flag) A: Yes Type of jet nebulizer (JetNebulizer.type) A: external gas source B: external nebulizer pump C: nebulizer within ventilator D: others Nebulizer position for small-volume nebulizer (LowDose.connector) A: Inspiratory limb near Y-piece B: Humidifier proximal to ventilator C: Humidifier proximal to patient D: others Change of MV setting during nebulization (MVparameter.onNebu) A: Never change B: Increase PEEP C: Decrease inspiratory flow D: Use constant inspiratory flow E: Increase inspiratory time F: Use inspiratory pause G: Increase tidal volume H: Stop heated humidifier I: Place filter on expiratory circuit J: Sedation to avoid dyssynchrony K: Use base flow rate L: Others Type of nebulization drug (Nebu.Drug) A: bronchodilators B: antibiotics C: mucolytic agent D: topical steroids E: systemic steroids F: others Type of nebulizer (Nebulizer.type) A: ultrasonic nebulizer B: jet nebulizer C: vibrating mesh nebulizer D: metered dose E: others Use of protocol for aerosol therapy (NebuProtocol.flag) A: yes Use of nebulization during noninvasive mechanical ventilation (NIMV.nebulization.flag) A: yes PEEP level during aerosol therapy (PEEP.onNebu) A: 0 B: 1–5 C: 6–10 D: >10 E: PEEP not changed Model of ventilator setting during aerosol therapy (SpecialNebu) A: Pressure control B: Pressure support C: volume control D: SIMV E: High-frequency ventilation F: others.

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ventilators cannot be treated with aerosol therapy, most respiratory care practitioners preferred to use this therapy for both IMV and NIMV. The most commonly used devices included jet, ultrasonic, and vibrating mesh nebulizers. There was a disparity between the tertiary and non-tertiary care centers with regard to the use of aerosol drugs. The practice pattern in this study was categorized into six latent classes. While class 1 was characterized by the aggressive use of aerosol therapy without a standard protocol, class 3 included respondents who did not use aerosol therapy. The clinical implication of the latent classes was to target hospitals that could benefit from the establishment of a practice protocol to standardize the implementation of the aerosol therapy. Different training programs can be implemented according to the distinct practice patterns of aerosol therapy. In the class 1 model, the practitioners were familiar with all the components of aerosol therapy, but they lacked knowledge about the effectiveness of each type of component; thus, the training program can focus on the indications of each component. Conversely, for institutions in the class 3 model, the training program should focus more on the technical details of each aspect of aerosol therapy.

Most of the results in the current study are consistent with that of an international survey conducted by the REVA (« Re´seau Europe´en » de recherche en Ventilation Artificielle) research network [9]. For example, both studies reported that bronchodilators and steroids were the most commonly used drugs for nebulization during MV. However, there are some distinctive characteristics with regard to the practice of aerosol therapy. The proportion of respondents who never changed the ventilator setting during nebulization was 77% in the international survey and 40% in the current study. This discrepancy may be attributed to the fact that jet nebulizers are not as widely used as ultrasonic and vibrating mesh nebulizers in Europe. The ultrasonic and vibrating mesh nebulizers do not add flow to the circuit and do not require changes in ventilator settings during therapy; on the other hand, ventilator settings need to be changed for the jet nebulizer. The current study was conducted six years after the REVA study, and there is emerging evidence of the importance of ventilator settings during aerosol therapy[23,24]. Furthermore, some clinical practice guidelines have been issued over the past few years [25]. Nebulization of antimicrobial agents was frequently performed, and ventilator-associated tracheobronchitis was one of the most common indications for this procedure [26]. Consistent with our study, inadequate practices were widely encountered, independent of the level of experience with the technique (e.g. direct tracheal instillation was considered for drug prescription in the majority of the ICUs) [27]. The jet nebulizer was most commonly used for antimicrobial agents as reported in a recent global survey [28]. However, the present study focused on all nebulization agents and found that the ultrasonic nebulizer was the most commonly used, followed by the jet nebulizer.

In the international survey, 65% respondents reported the integration of jet nebulization in the ventilator systems when compared to 28.6% in the current study. Almost 47.3% of the

| Table 3. Characteristics of hospitals by latent classes. |
|--------------------------------------------------------|
| Class 1 (n = 99) | Class 2 (n = 181) | Class 3 (n = 158) | Class 4 (n = 66) | Class 5 (n = 22) | Class 6 (n = 167) | p     |
|------------------|------------------|------------------|-----------------|-----------------|------------------|-------|
| Tertiary care, n (%) | 78 (78.8) | 144 (79.6) | 122 (77.2) | 61 (92.4) | 20 (90.9) | 145 (86.8) | 0.027 |
| Bed No. (median [IQR]) | 1584 [1000, 2458] | 1400 [996, 2000] | 1200 [800, 2000] | 2000 [1068, 2993] | 1288 [1000, 2430] | 1500 [861, 2474] | 0.001 |
| Provinces categorized by GDP (%) | <0.001 |
| High | 65 (65.7) | 111 (61.3) | 104 (65.8) | 21 (31.8) | 12 (54.5) | 86 (51.5) |
| Moderate | 15 (15.2) | 38 (21.0) | 26 (16.5) | 30 (45.5) | 2 (9.1) | 50 (29.9) |
| Low | 19 (19.2) | 32 (17.7) | 28 (17.7) | 15 (22.7) | 8 (36.4) | 31 (18.6) |

Abbreviations: GDP: gross domestic product; IQR: interquartile range.

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practitioners who used jet nebulizer utilized an external gas source in this study. Additional airflow affects ventilator pressure and flow, resulting in unstable ventilation. When the additional gas flow is used to operate the jet nebulizer during MV, the ventilator settings and alarms should be adjusted for patient safety [29]. In the current study, 5.8% respondents reported the need to increase sedation in order to improve ventilator-patient synchronization. Previous studies have shown that ventilation mode, breathing parameters, heat and humidity, gas density, and artificial airways influence aerosol delivery to critically ill subjects [12,14,30]. About 40.8% respondents reported never changing the ventilator settings during aerosol therapy; this included 33.9% and 20.8% of those who use the jet nebulizer and vibrating mesh nebulizer, respectively. Alternatively, 17.5% of respondents increased the PEEP, 13% decreased the inspiration flow, and 11.3% increased the tidal volume. Although a large tidal volume (VT) is associated with increased aerosol drug delivery during MV, it is essential to note that it can induce volutrauma and should not be used to improve the delivery efficiency of aerosol devices [31].

Increasing the inspiratory time leads to an increase in aerosol delivery; however, it is important to monitor the degree of intrinsic PEEP and exercise caution with this practice because it may worsen the dynamic hyperinflation in patients with airflow limitation. [23,24].

Previous in vitro studies in adult and pediatric models reported that jet nebulizer placement in the inspiratory limb farther away from the subject improved aerosol delivery during MV due to the reservoir effect of the ventilator tubing, which accumulates aerosol drugs during ventilation [12,32–34]. In the present study, 39.8% respondents chose to place the nebulizer at the inspiratory limb near the Y-piece, which is the position associated with the lowest drug delivery [35].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommended the use of specific ventilator settings during nebulization, which included the use of a volume-controlled mode using a constant inspiratory flow, a respiratory rate of 12 to 15 bpm, a tidal volume of 8 mL/kg, an inspiratory: expiratory (I:E) ratio of 50%, an inspiratory pause of 20% and a positive end-expiratory pressure of 5 to 10 cm H2O [25]. These recommendations are used specifically for aerosol antibiotics. In the current study, these recommended ventilator settings were not followed accurately; only 8.4% of the respondents used an inspiratory pause, 15.3% adjusted the PEEP to 5 to 10 cm H2O, 9.2% stopped using the heated humidifier and 14.6% used a constant inspiratory flow. Although the ESCMID recommended the use of a vibrating mesh nebulizer over the ultrasonic and jet nebulizers, only 14.6% respondents used the vibrating mesh nebulizer in the current study. Most respiratory care practitioners prefer to use ultrasonic and jet nebulizers in mainland China. Our results are consistent with another international study, wherein only a minority of the respondents used a vibrating mesh nebulizer (14%) [9]. Thus, the findings of our study indicate that more training programs are needed for respiratory care practitioners in mainland China. Furthermore, less than half of the institutions in this study employed a protocol for aerosol therapy during MV. Therefore, efforts to improve the awareness of standard aerosol therapy practice are warranted. It is the mission of the CURC to establish a practice guideline for the implementation of aerosol therapy in mainland China.

This study has several limitations. First, although the respondents were recruited from all the regions of the country, the response rate was not balanced between the regions. The majority of the respondents were from developed provinces with high GDP (Table 3). Moreover, the majority of the individual questionnaire responses were obtained from tertiary care hospitals (Table 1), indicating a potential bias. Second, the study was based on a questionnaire survey, which was subject to the recall bias. However, we have tried to minimize this bias during the training process. Members were asked to follow the detailed instructions on how to answer the questionnaire, aiming to minimize potential bias and errors. Third, this study was performed...
in mainland China, and the results may not extrapolate to other countries or regions. Finally, the survey did not link the preferred type of nebulizer with a given pharmacological agent. For example, the use of jet nebulizers for bronchodilators is appropriate as the particles do not need to be very small to reach the bronchi; alternatively, for antibiotics, tiny particles need to be generated by the nebulizers for the medication to reach the alveoli. In such cases, a vibrating mesh plate is required. Nevertheless, this survey was designed based on the idea that a single type of nebulizer is used in hospitals for all kinds of medications.

Conclusion
In conclusion, the present study examined the implementation of aerosol therapy in mainland China and found that there was substantial heterogeneity among institutions. The implementation of aerosol therapy during MV was not uniformly consistent with recent practice guidelines. Hence, additional efforts by the CURC are needed to improve the implementation of this therapy in this country.

Supporting information
S1 Dataset. Deidentified data for the current analysis.
(CSV)
S1 Questionnaire. The questionnaire used for the current study.
(DOCX)

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