Intensive Care Med (2016) 42:192–201
DOI 10.1007/s00134-015-4114-5

ORIGINAL

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Aerosol therapy in intensive and intermediate care units: prospective observation of 2808 critically ill patients

Received: 7 August 2015
Accepted: 18 October 2015
Published online: 24 November 2015

Take-home message: Aerosol therapy concerns every fourth critically ill patient and every fifth ventilated patient. Implementation modalities appeared heterogeneous and suboptimal in a significant number of cases calling for action on the educational level to improve knowledge translation from research to clinical practice.

The investigators/contributors of the centers participating in the AT@ICU study group are listed in the Acknowledgments.

Electronic supplementary material The online version of this article (doi:10.1007/s00134-015-4114-5) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* Unlike in the outpatient setting, delivery of aerosols to critically ill patients may be considered complex, particularly in ventilated patients, and benefits remain to be proven. Many factors influence aerosol delivery and recommendations exist, but little is known about knowledge translation into clinical practice. *Methods:* Two-week cross-sectional study to assess the prevalence of aerosol therapy in 81 intensive and intermediate care units in 22 countries. All aerosols delivered to patients breathing spontaneously, ventilated invasively or noninvasively (NIV) were recorded, and drugs, devices, ventilator settings, circuit set-up, humidification and side effects were noted. *Results:* A total of 9714 aerosols were administered to 678 of the 2808 admitted patients (24 %, CI_{95} 22–26 %), whereas only 271 patients (10 %) were taking inhaled medication before admission. There were large variations among centers, from 0 to 57 %. Among intubated patients 22 % ($n = 262$) received aerosols, and 50 % ($n = 149$) of patients undergoing NIV, predominantly (75 %) inbetween NIV sessions. Bronchodilators ($n = 7960$) and corticosteroids ($n = 1233$) were the most frequently delivered drugs (88 % overall), predominantly but not exclusively (49 %) administered to patients with chronic airway disease. An anti-infectious drug was aerosolized 509 times (5 % of all aerosols) for nosocomial infections. Jet-nebulizers were the most frequently used device (56 %), followed by metered dose inhalers (23 %). Only 106 (<1 %) mild side effects were observed, despite frequent suboptimal set-ups such as an external gas supply of jet nebulizers for intubated patients.
Conclusions: Aerosol therapy concerns every fourth critically ill patient and one-fifth of ventilated patients.

Keywords Administration, inhalation [MeSH] · Metered dose inhalers [MeSH] · Nebulizers and vaporizers [MeSH] · Bronchodilator agents [MeSH] · Anti-bacterial agents [MeSH] · Respiration, artificial [MeSH]

Introduction

Aerosol therapy, i.e., the delivery of medication particles carried by inhaled gases, constitutes the cornerstone of chronic broncho-dilatory and anti-inflammatory therapy for patients suffering from asthma and chronic obstructive pulmonary disease. It is associated with improved long-term patient-centered outcomes [1–3]. Similarly, antibiotic aerosol therapy has proven effective to treat lung infection in patients suffering from cystic fibrosis [4].

In the acute setting, particularly in the critically ill patients, evaluation of patient-centered outcomes is lacking. Nevertheless, a large body of work has evaluated optimal implementation of aerosol therapy in patients undergoing artificial ventilation in terms of practicability and safety, and has shown significant physiologic efficacy of several inhaled drugs in this setting [5–11]. Significant reductions in respiratory system resistance of ventilated patients have been demonstrated after delivery of bronchodilator using various nebulizer and metered dose inhaler (MDI) set-ups [6, 12, 13]. In ventilator-associated pneumonia, optimized nebulization set-ups such as a low inspiratory peak flow, increased inspiratory time, interrupted humidification and nebulizer placement upstream in the inspiratory limb seem to deliver inhaled antibiotics effectively to treat lung infections [14–17]. Large-scale international studies on ventilatory support have not recorded data about aerosol therapy [18, 19]. In a previous study using an e-mail self-administered survey, we obtained responses from 854 physicians who declared being confident in aerosol therapy efficacy and using it frequently in critically ill patients [20]. In this previous study, knowledge appeared very heterogeneous [20]. A Scandinavian observational study reported the use of aerosol therapy in 50 % of 186 ventilated patients (mainly beta-2-adrenergic receptor agonists), without providing data about implementation modalities [21]. This lack of large-scale prospective data hampers optimal knowledge translation towards the clinical setting and optimal research and educational resources allocation. The aim of the present work was to assess the frequency, modalities and short-term safety of aerosol therapy in critically ill patients either breathing spontaneously or undergoing invasive or noninvasive (NIV) artificial ventilation.

Methods

This prospective cross-sectional point prevalence study was carried out over 14 days in 81 intensive care units in 22 countries (see the list of centers and investigators in the Appendix). Centers were recruited on a voluntary basis among participants of the aforementioned e-mail survey by purposive sampling through e-mail contact of members of the European Society of Intensive Care Medicine, French and Spanish intensive care societies (Société de Réanimation de Langue Française, Revista Electrónica de Medicina Intensiva) and members of the REVA network (Réseau Européen de recherche en Ventilation Artificielle) [20]. The study was approved by the ethics commission of the French intensive care society and additional ethical approval gained at each participating institution if legally required. Given the non-interventional study design, the need for written informed consent was waived by those independent commissions. All patients or their next of kin were informed about the study with the possibility to decline participation. The 2-week participation periods for each unit were staggered over March and April 2013.

All patients present in the unit during the study period and not declining participation were included. Each day, patients' ventilator statuses were prospectively recorded: (1) "invasive artificial ventilation": patient breathing or ventilated through a tracheal tube or tracheostomy; (2) "NIV": patient who underwent at least one NIV session (including continuous positive airway pressure) but no "invasive artificial ventilation"; and (3) "spontaneous breathing" otherwise. Each time a patient received inhaled medication during the study period (aerosol therapy, but also instillation of drugs in the tracheal tube, except 0.9 % sodium chloride instillation for tracheal suctioning), extensive data were recorded (see electronic supplement Tables 1, 2 and 3 for an extensive list of recorded variables). Investigators were invited to report any significant adverse event without specific a priori definition.

Data were entered into a web-based database (Clin-Info, Lyon, France) and analyses performed using R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). Quantitative variables were expressed as mean ± standard deviation and compared with Student's *t* test, except in cases of non-Gaussian distribution [median (25th, 75th percentile)]. Qualitative variables were expressed as counts (%) and compared between groups using the Chi-square test. The 95 % confidence interval (CI_{95}) of proportions was calculated for the main variables of aerosol therapy (no missing value, no data imputation). A p value lower than 0.05 was considered significant.

Results

A total of 2808 patients were included (Table 1), predominantly in intensive care units [10,689 (81 %) vs. 2514 (19 %) patient-days in intermediate care], and 9714 inhaled drug administrations were recorded. Follow-up was complete; participating countries and centers are detailed in the electronic supplement (Table 4).

Frequency of aerosol therapy

A total of 678 patients (24 % CI_{95} 22–26 %) received at least one inhaled medication over the 2-week period [median number of 7 (2, 18) per patient], while only 271 patients (10 %) were taking inhaled medications chronically at home. Frequency of aerosol therapy was heterogeneous between centers (range 0–57 % of patients; see electronic supplement Table 4). Aerosol-generating devices and patients' ventilation status during aerosol therapy are detailed in Table 2. Overall, aerosols were mainly delivered either to patients breathing spontaneously ($n = 4832$ aerosols, 50 %) or into the ventilator circuit of intubated patients ($n = 4532$, 47 %), representing two distinct clinical and therapeutic situations. Aerosols under NIV represented only 3 % of all aerosols.

Spontaneously breathing patients

Among 4832 aerosols performed in patients breathing spontaneously, jet nebulizers were used predominantly ($n = 3388$, 70 %), followed by MDIs ($n = 790$, 16 %).

NIV

Among 305 patients who underwent one or several days of NIV, 149 (49 % CI_{95} 40–57 %) received at least one aerosol on such days. Aerosols were predominantly delivered when patients were breathing spontaneously inbetween NIV sessions ($n = 1057$ aerosols, i.e. 75 % of aerosols in patients undergoing NIV) and infrequently directly into the ventilatory circuit ($n = 350$ aerosols, i.e. 25 % of aerosols in patients undergoing NIV). Among

Table 1 Characteristics of patients receiving or not aerosol therapy

	All patients $n = 2808$	Patients who received aerosols $n = 678$	Other patients $n = 2130$
Age (years)	59 ± 21	61 ± 19	58 ± 21
Male/female	1713 (61 %)/1095 (39 %)	429 (63 %)/249 (37 %)	1284 (60 %)/846 (40 %)
Simplified acute physiology score II	38 ± 19	40 ± 16	37 ± 20
Type of admission[a]			
Medical	1918 (73 %)	531 (78 %)	1385 (65 %)
Scheduled surgery	381 (14 %)	48 (7 %)	333 (16 %)
Emergency surgery	335 (13 %)	61 (9 %)	274 (13 %)
History of cardiovascular disease	939 (33 %)	244 (36 %)	695 (33 %)
History of respiratory disease	673 (24 %)	371 (55 %)	302 (14 %)
Chronic obstructive pulmonary disease	486 (17 %)	287 (42 %)	199 (9 %)
Chronic restrictive pulmonary disease	135 (5 %)	66 (10 %)	69 (3 %)
Pulmonary arterial hypertension	68 (2 %)	29 (4 %)	39 (2 %)
Asthma	95 (3 %)	58 (8 %)	37 (2 %)
Chronic use of inhaled medication	271 (10 %)	176 (26 %)	95 (4 %)
Main admission diagnosis			
Shock	404 (14 %)	87 (13 %)	317 (15 %)
Severe sepsis	120 (4 %)	26 (4 %)	94 (4 %)
Acute respiratory failure	675 (24 %)	333 (49 %)	342 (16 %)
De novo	378 (56 %)	132 (40 %)	246 (72 %)
Exacerbation of chronic respiratory failure	297 (44 %)	201 (60 %)	96 (28 %)
Coma/seizure	268 (9 %)	42 (6 %)	226 (11 %)
Cardiac arrest	106 (4 %)	17 (3 %)	89 (4 %)
Monitoring	690 (25 %)	85 (13 %)	605 (28 %)
Post-operative	542 (78 %)	71 (84 %)	471 (78 %)
Medical monitoring	148 (21 %)	14 (16 %)	134 (22 %)
Other	665 (24 %)	114 (17 %)	551 (26 %)

[a] Defined according to the simplified acute physiology score II [22]. Data are presented as mean ± standard deviation and count (%). All comparisons between patients who received at least one aerosol and patients never receiving aerosols were statistically significant except for gender and history of cardiovascular disease

Table 2 Characteristics of aerosols

	$n = 9714$
Aerosol generation devices	
Jet nebulizer	5436 (56 %)
Ultrasonic nebulizer	940 (10 %)
Vibrating mesh nebulizer	999 (10 %)
Hand held devices[a]	2216 (23 %)
Instillation[b]	123 (1 %)
Ventilation during aerosol delivery	
Spontaneous breathing	4832 (50 %)
NIV[c]	350 (4 %)
Invasive ventilation	4532 (47 %)
Number of molecules within one aerosol[d]	
1	5583 (57%)
2	3657 (38 %)
≥3	474 (5 %)

Data are presented as count (%)

MDI metered dose inhaler

[a] Metered dose inhalers only in ventilated patients, metered dose inhalers and dry powder inhalers in spontaneous breathing

[b] Only instillations other than 0.9 % sodium chloride used for tracheal suctioning were recorded

[c] Aerosol delivered within the non-invasive ventilation (NIV) circuit

[d] 0.9 % sodium chloride was not considered as an additional drug when being used as a solvent for another molecule

1057 aerosols delivered inbetween NIV sessions, only 171 aerosols (16 %) specifically triggered NIV interruption in order to deliver the inhaled therapy.

Intubated patients

Among 1215 patients who underwent invasive artificial ventilation, 262 (22 % CI_{95} 20–24 %) received at least one aerosol while intubated. Aerosols delivered during artificial ventilation were mostly delivered in patients intubated and ventilated with a two-limb ventilatory circuit ($n = 4499$, 92 %) (Fig. 1; Table 3). Bronchodilators and corticosteroids were mainly delivered using nebulizers ($n = 2264$ bronchodilator aerosols, 63 %; $n = 355$ corticosteroid aerosols, 69 %). In intubated patients, antibiotics were delivered using jet, ultrasonic and vibrating mesh nebulizers in 221 (62 %), 105 (29 %) and 31 (9 %) cases, respectively. Ventilator settings were changed for administration of 107 anti-infectious aerosols (30 %) as compared to only 74 (2 %) of bronchodilator aerosols ($p < 0.01$). Similarly, when using a heated humidifier, the device was turned off for 119 (59 %) anti-infectious aerosols as compared to 249 (15 %) of bronchodilator aerosols ($p < 0.01$). Placement of the nebulizer upstream in the inspiratory limb at a distance from the Y piece remained infrequent even for administration of anti-infectious aerosols ($n = 33$, 9 % of anti-infectious aerosols) (Fig. 1). Among 1867 aerosols delivered using a jet nebulizer, a ventilator integrated breath-actuated jet nebulization system was available in 1115 cases (60 %); when available, it was used for nearly all cases ($n = 1109$, 99 %). Placement of a filter on the expiratory limb to protect the ventilator was done for 2997 (66 %) aerosol administrations; this filter was infrequently changed in relation to nebulization (Fig. 1).

Drugs delivered

Drugs were frequently delivered as a combination ($n = 4131$ aerosols, 42 %; Table 2). This mainly concerned association of a short acting beta-2-adrenergic agonist and an anticholinergic drug ($n = 2317$, 56 % of combined aerosols). Bronchodilators ($n = 7960$ aerosols) represented 82 % of administrations and concerned 89 % of patients receiving aerosols (Table 4). Corticosteroids were the second most frequent inhaled drugs ($n = 1233$, i.e. 13 % of aerosols and 26 % of patients receiving aerosols). Together, bronchodilators and corticosteroids represented 88 % of aerosols. These drugs were delivered far beyond the patients suffering chronic obstructive pulmonary diseases or asthma, who accounted for 312 patients among the 626 receiving bronchodilators and/or corticosteroids (50 %). Indeed, in a majority of cases, bronchodilator and corticosteroid aerosols were delivered to treat exacerbation of COPD, acute asthma or acute bronchospasm of another origin ($n = 2204$, 51 % of aerosols with only one molecule), but various other heterogeneous indications were observed such as infection ($n = 579$, 13 %) or wheezing of undetermined origin ($n = 293$, 7 %) (see Table 5 of the electronic supplement).

A total of 509 anti-infectious aerosols were recorded, predominantly colistin ($n = 400$, 79 % of anti-infectious aerosols) and amikacin ($n = 49$, 10 %). Anti-infectious aerosols were primarily indicated to treat nosocomial pneumonia ($n = 342$, 67 %) and to a lesser extent tracheobronchitis/bronchial colonization ($n = 94$, 19 %). Prophylactic anti-infectious aerosols accounted for a smaller proportion ($n = 31$, 6 %). Overall, anti-infectious

Table 3 Aerosol therapy in intubated patients

	Observed practice $n = 4532$	Recommendations for optimal efficacy/safety
Aerosol generating devices		
Jet nebulizer	1867 (42 %)	
Use of ventilator integrated breath-actuated system if available	1109 (99 %)	To be preferred if use of a jet-nebulizer
No integrated breath-actuated system available	752 (40 %)	
Ultrasonic nebulizer	790 (17 %)	
Vibrating mesh nebulizer	495 (11 %)	
MDI	1331 (29 %)	Metered dose inhaler to be preferred if drug available
Use of a ventilator circuit access port/circuit disconnection	1283 (96 %)/48 (4 %)	Avoid circuit disconnection
Use of an inhalation chamber	359 (27 %)	Prefer use of a chamber
Position		
Close to the Y piece	3639 (80 %)	May induce expiratory loss of drug
Immediately downstream/immediately upstream	1850 (51 %)/1789 (49 %)	
At distance of the Y piece	748 (16 %)	Upstream position improves delivery
Upstream in the inspiratory limb, using an extra connection tubing	707 (94 %)	
At the ventilator output	41 (5 %)	
Other	145 (3 %)	
Heated humidifier interrupted (if used)	373 (18 %)	Interruption may improve aerosol delivery
Use of a protective filter on the expiratory limb	2997 (66 %)	Filter to be used to avoid expiratory block dysfunction, to be changed to avoid filter obstruction
Filter changed several times during nebulization	72 (2 %)	
Filter changed at the end of nebulization	287 (10 %)	
Filter not changed in relation with nebulization	2638 (88 %)	
Connection tubing between Y piece and tracheal tube removed/left in place (if used)	140 (4 %)/3750 (96 %)	Connection tubing may reduce aerosol delivery

Some percentages may sum up to less than 100 % due to some minor other practices not reported in the table. Data are presented as count (%)

Recommendations for optimal efficacy mainly apply to aerosol delivery of anti-infectious molecules, as bronchodilator efficacy is good even in the absence of optimization measures. Recommendations are based on in vitro and in vivo studies, literature reviews and guidelines on aerosol therapy and are only to be considered as a general indicative framework for understanding safety and efficacy issues (see electronic supplement Table 6 for detailed recommendations). Best practice has to be tailored to each patient

MDI metered dose inhaler

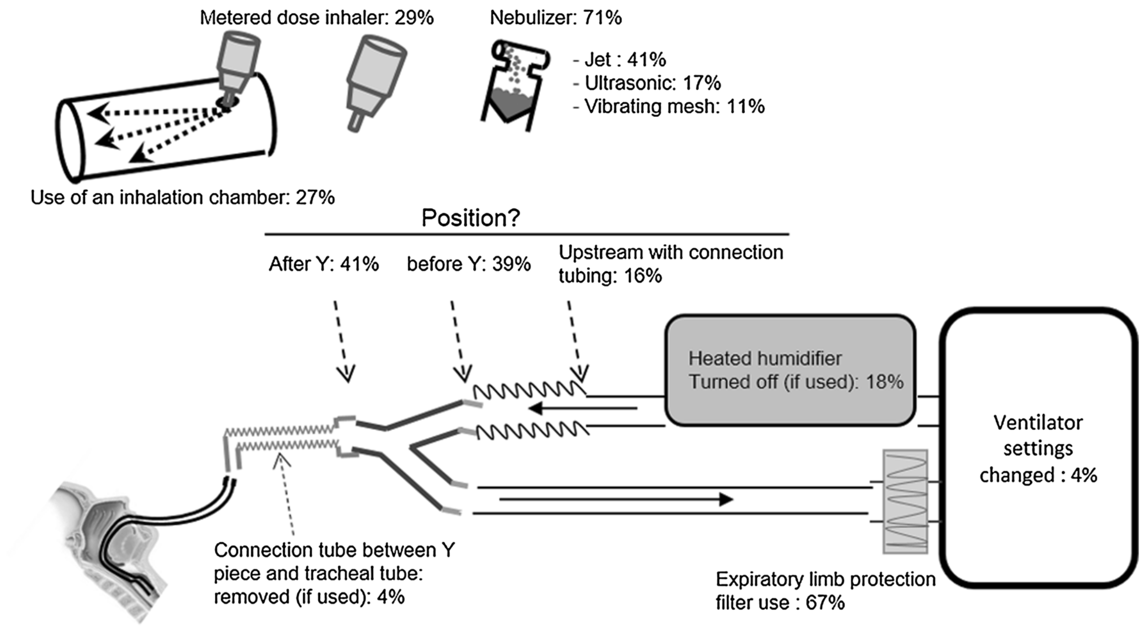

Fig. 1 Main determinants of aerosol set-ups used in intubated patients. In intubated patients, aerosol therapy was predominantly performed using jet nebulizers placed close to the Y piece while ventilator settings were left unchanged

aerosols concerned 31 patients (1 %) in 14 centers (17 %).

Side effects

A total of 106 administrations (<1 %) prompted notification of a side effect, mainly tachycardia and arterial hypertension ($n = 39$), arterial hypotension ($n = 16$), hypoxemia ($n = 20$) and cough ($n = 23$). Bronchospasm was reported three times (colistin nebulization in all cases).

Discussion

The main results of this large-scale prospective international cross-sectional prevalence study is that aerosol therapy is used in one-fourth of critically ill patients and in every fifth intubated patient, confirming smaller-scale observations and declarative data [20, 21]. Aerosol therapy appeared even more frequent in patients undergoing NIV, as half of those patients received aerosols, mainly inbetween ventilation sessions. Bronchodilators and corticosteroids were the overwhelmingly predominant drugs delivered as aerosols (88 %); anti-infectious aerosols, even though representing a smaller proportion of aerosols (5 %), were frequently recorded over the 14-day study period and almost exclusively delivered to treat nosocomial infections; only 3 % of aerosols were mucus-modulating drugs. Albeit only a limited number of side effects were recorded in the present study, the high prevalence of aerosol therapy observed raises questions about the optimization of technical implementation and long-term safety in the critical care setting.

Spontaneous breathing

The predominant use of nebulizers to deliver aerosols in critically ill patients is in accordance with guidelines addressing aerosol therapy for severe asthma and chronic obstructive pulmonary disease exacerbation in the emergency department as proper use of MDIs may be difficult for those patients [11].

NIV

Interestingly, about a quarter of aerosols delivered to patients breathing spontaneously concerned patients otherwise undergoing NIV. This may suggest poor knowledge translation given existing data on the efficacy of inhaled bronchodilators delivered within NIV circuits [23–26]. Conversely, one may hypothesize that clinicians and nursing staff consider aerosol delivery into ventilator circuits too cumbersome, thus calling for progress in equipment simplification.

Intubated patients

Safety and efficacy issues may be discussed based on the current literature (briefly summarized in the electronic

Table 4 Drugs delivered as aerosols

	Aerosols ($n = 9714$)	Patients ($n = 678$)
Bronchodilators	7960 (82 %)	600 (89 %)
Short acting beta-2-adrenergic agonists	6780 (95 %)	463 (86 %)
Long acting beta-2-adrenergic agonists	88 (1 %)	24 (4 %)
Anticholinergic drugs	4958 (70 %)	198 (37 %)
Corticosteroids	1233 (13 %)	173 (26 %)
Beclomethasone dipropionate	269 (22 %)	31 (18 %)
Budesonide	897 (74 %)	130 (77 %)
Fluticasone	60 (5 %)	11 (6 %)
Other	5 (<1 %)	1 (<1 %)
Anti-infectious drugs	509 (5 %)	31 (5 %)
Amikacin	31 (6 %)	9 (30 %)
Amphotericin B	33 (6 %)	4 (13 %)
Colistin	400 (79 %)	19 (63 %)
Gentamicin	21 (4 %)	2 (7 %)
Ceftazidime	6 (1 %)	3 (10 %)
Tobramycin	14 (4%)	2 (<1 %)
Mucus modulating drugs	241 (3 %)	39 (6 %)
Acetylcysteine	136 (61 %)	22 (65 %)
Recombinant human deoxyribonuclease	12 (5 %)	7 (21 %)
2-Mercapto ethane sodium sulfonate (Mesna)	93 (42 %)	11 (32 %)
Electrolyte solutions	503 (5 %)	71 (9 %)
0.9 % sodium chloride[a]	440 (87 %)	65 (91 %)
Hypertonic sodium chloride	16 (3 %)	2 (3 %)
Sodium bicarbonate	47 (9 %)	4 (6 %)
Other	14 (<1 %)	5 (<1 %)

Data are presented as count (%)

Due to potential association of several molecules within one aerosol, percentages may sum up exceeding 100 %. For each therapeutic class, the number of aerosol administrations including at least one drug of the considered class is indicated; the corresponding percentage represents the proportion within all administrations. Similarly at the molecule level, the number of administrations including this molecule is indicated; the corresponding percentage represents the proportion within the therapeutic class. Numbers of patients refer to patients having received at least one aerosol of the considered class or molecule; percentages were calculated relative to all patients and within each therapeutic class

[a] 0.9 % sodium chloride was not considered when being used as a solvent for another molecule

supplement Table 6) [5–17]. Regarding safety, the predominant use of nebulizers to deliver bronchodilators and corticosteroids in ventilated patients seems intriguing, as they are available as MDIs. In fact, as aerosols were predominantly delivered using jet nebulizers, with breath-actuated ventilator integrated systems frequently unavailable, about every fourth aerosol administration exposed intubated patients to uncontrolled tidal volumes (the jet nebulizer being supplied by an external gas source) [27]. The use of MDIs, when available, might be preferred. Actually, only about 9 % of bronchodilator and/or corticosteroids aerosols in intubated patients were delivered with a MDI connected to an inhalation chamber, whereas this simple technique is the one with the most extensively evaluated efficacy [5–13]. The second important safety issue relates to particles cleared through the expiratory limb, which may interfere with the proper function of the ventilator expiratory block, particularly when nebulizing antibiotics or performing continuous nebulization [10]. One-third of aerosols ($n = 1502$) were administered in intubated patients with no filter protecting the expiratory block. No dysfunction was documented over the 2-week study period, in part due to the predominant delivery of bronchodilators and corticosteroids; nevertheless, given the very severe complications reported, including pneumothorax and cardiac arrest, additional educational efforts are warranted in order to promote better practice [10, 14, 28–30].

Regarding efficacy, unlike for bronchodilator therapy, nebulization/ventilation set-up is a key factor for success of inhaled anti-infectious therapy, in particular when aiming to treat pneumonia, which was the case for 73 % of anti-infective aerosol deliveries [31]. Indeed, delivering inhaled antibiotics to the infected, poorly aerated, distal alveolar compartment of intubated patients may be challenging [32]. In this regard, jet nebulizer, the most frequently used type of nebulizer for antibiotic administration, is well known for a high residual volume (amount of drug which remains in the nebulizer at the end of nebulization) as compared to vibrating mesh and ultrasonic nebulizers [6]. This may influence aerosol therapy efficacy. Lu et al. observed that nebulizing 400 mg of colistimethate using a mesh nebulizer enabled the treatment of nosocomial pneumonia, while the same dose placed in a jet nebulizer results in a much lower dose of drug actually deposited in the patient [14]. Similarly, Palmer et al. reported positive results nebulizing aminoglycosides and/or vancomycin using a breath-actuated jet nebulizer in patients suffering nosocomial tracheobronchitis or pneumonia [16, 17]. Again, the common practice observed in the present study, consisting in placing the nebulizer at the Y piece (Fig. 1), may be counterproductive by favoring aerosol loss in the expiratory limb and preventing the replication of favorable results in daily clinical practice [14–17, 27, 33]. Such dose/nebulizer issues may, in part, explain some discrepancies among studies evaluating the potential benefit of inhaled antibiotics to treat multidrug-resistant lung infections [34]. Furthermore, unlike in the aforementioned prospective interventional studies, ventilator settings were left unchanged and heated humidifiers kept active during, respectively, 70 and 40 % of anti-infectious aerosols recorded [14–17].

While anti-infective aerosols concerned a limited number of patients (1 %), bronchodilators and corticosteroids were extensively delivered (every fifth critically ill patient). Beyond bronchodilation, unlike in the outpatient setting, no long-term patient-centered outcomes have been evaluated in critically ill patients [2, 3, 5–13, 35]. Given potential side effects, one may question the value of their large use, far beyond the population of patients receiving it at home and with obstructive pulmonary disease, with indications such as infections which may need specific evaluation [36].

Study limits

Beyond capturing only a low incidence of side effects not defined a priori, which may be underestimated, the study design restricting observation on two consecutive weeks did not enable the capture of seasonal variations in practice. Aerosol therapy may be more frequent in the winter months due to increased respiratory infections. Albeit including a high number of centers in several countries on all continents, the international scope of the study was damped by the predominance of European centers, especially in France and Spain, and by the absence of North American centers. Thus, results cannot be extrapolated worldwide. Interestingly, some practice heterogeneity was observed (see electronic supplement Table 4) calling for additional evaluation in regions not covered by the present work. Specific case mix within each center, not captured by the present study, may in part explain the observed aerosol therapy practices. Centers participated in the study on a voluntary basis, and one cannot exclude a bias towards more experienced or expert units, physicians' knowledge being not assessed in this study. As aerosol efficacy was not evaluated in the present study, observed practice can only be put into perspective with existing knowledge and recommendations, without drawing conclusions about the efficacy of aerosol therapy in individual patients. Similarly, staff protection from potential aerosol toxicity and the types of NIV interfaces were not recorded in this study. Finally, given the non-interventional design, one cannot exclude that the study by itself induced some changes in aerosol therapy practice during the observation period.

Conclusions

Aerosol therapy is a common practice concerning a fifth to a quarter of intensive care and intermediate care patients despite the lack of proven benefit on patients centered outcome. The frequent implementation of aerosol therapy during invasive artificial ventilation seemed suboptimal in a significant number of cases and almost never performed during NIV, calling for actions on the educational level such as issuing guidelines specifically dedicated to aerosol therapy in critically ill patients.

Acknowledgments The authors acknowledge receipt of grant ANR-2010 BLAN 1119 05 from Agence Nationale de la Recherche. Beyond the investigators listed below, the authors sincerely thank all physicians, nursing and research staff who participated in the study.

List of investigators/contributors of the participating centers: all contributors actively participated in patient inclusions and data acquisition.

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Compliance with ethical standards

Conflicts of interest S.E.'s institution received research equipment and/or research funding from: Aerogen, Galway, Ireland; Axess Vision Technology, Tours, France; Fisher & Paykel, Auckland, New Zealand; La diffusion technique française, Saint-Etienne, France; Penn-Century Inc., Wyndmoor, USA; none was related to this particular study. L.B.'s laboratory received research grants from Covidien, Dräger, Vygon, Philips Respironics and GE Healthcare; none was related to this particular study. All other authors declare no conflict of interest.

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