

Intratracheal Administration of Antimicrobial Agents in Mechanically Ventilated Adults: An International Survey on Delivery Practices and Safety

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BACKGROUND: Intratracheal antibiotic administration is increasingly used for treating respiratory infections. Limited information is available on delivery devices, techniques, and safety. **METHODS:** An online survey on intratracheal administration of anti-infective agents in mechanically ventilated adults was answered by health-care workers from 192 ICUs to assess the most commonly used devices, current delivery practices, and safety issues. We investigated whether ICU usage experience (≥ 3 y) impacted its performance. **RESULTS:** Intratracheal antibiotic administration was a current practice in 87 ICUs (45.3%), with 40 (46%) having experience with the technique (≥ 3 y). Sixty-six (78.6%) of 84 health-care workers reported avoiding intratracheal antibiotic administration due to an absence of evidence-based guidelines (78.6%). Jet nebulizers were the most commonly used devices for delivery, in 24 less experienced ICUs (27.6%) and in 18 (20.7%) experienced ICUs. Direct tracheal instillation (6; 6.9%) was still considered for drug prescription in 12 ICUs (6.9%). More experience resulted in neither greater adherence to measures improving the drug's delivery efficiency (93 measures in the experienced group; 27.9%) nor a greater adoption of measures to increase safety. Indeed, the expiratory filter was changed after each nebulization in only 2 experienced ICUs (6.9%), whereas 15 (51.7%) changed it daily instead. **CONCLUSIONS:** Intratracheal antibiotic administration is a common therapeutic modality in ICUs, but inadequate practices were widely encountered, independent of the level of experience with the technique. This suggests a need to develop standardization to reduce variability and improve safety and efficacy. *Key words:* delivery device; nebulizer; antibiotics; aerosol therapy. [Respir Care 2016;61(8):1008–1014. © 2016 Daedalus Enterprises]

Introduction

Nosocomial respiratory infections are the leading cause of life-threatening infections in the ICU.¹ Ventilator-associated

respiratory infections are associated with increased morbidity,^{2,3} being even more challenging when caused by multidrug-

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resistant pathogens, such as *Pseudomonas aeruginosa*.⁴⁻⁶ Forty years ago, studies were published suggesting that aerosolized polymyxins administered to critically ill subjects could decrease the rate of nosocomial bronchopneumonia.^{7,8} The technique, however, was abandoned due to the development of antibiotic resistance and questionable efficacy and/or frequent adverse events.

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Since the 2000s, intratracheal antibiotic administration as a possible treatment for ventilator-associated respiratory infections has been revived for 3 main reasons. (1) There is now a better understanding of conditions required to reach the deep lung during mechanical ventilation.^{9,10} (2) Studies in experimental models of inoculation pneumonia have defined the rationale for comparing intravenous and inhaled dose and have shown much higher lung tissue antibiotic concentrations and higher bactericidal activity for antibiotics administered by nebulization.¹¹ (3) Technology has evolved for new generation devices, which have shown their ability to generate mass median aerodynamic diameter of $<5 \mu\text{m}$, a condition required to reach the infected lung parenchyma.¹²⁻¹⁵ Meanwhile, health-care workers all around the globe are increasingly challenged by the controversial

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QUICK LOOK

Current knowledge

Since the 2000s, intratracheal administration of antibiotics as a possible treatment of ventilator-associated respiratory infections has been revived. New-generation devices such as ultrasonic and vibrating mesh nebulizers have shown their ability to generate mass median aerodynamic diameter $<5 \mu\text{m}$, a condition required to reach the infected lung parenchyma. Meanwhile, multiple drug-resistant organisms are emerging and health-care workers are increasingly challenged by controversial issues related to prescription of nebulized antibiotics for respiratory infections in mechanical ventilated patients.

What this paper contributes to our knowledge

Our findings suggest that intratracheal antibiotic administration for the treatment of respiratory infections in the critically ill invasively mechanically ventilated adult has emerged as a common therapy, with broad diversity and frequently associated with inadequate practices. This was independent of the experience of the health-care workers with the technique. Standardization of the procedure is required to increase efficacy and minimize the risk of potential adverse events.

issues related to prescription of nebulized antibiotics for severe respiratory infections.¹⁶

Very limited outcome data comparing various delivery techniques are available,¹⁷ including differences between nebulization in subjects who are spontaneously breathing and those who undergo noninvasive mechanical ventilation.¹⁸ Safety considerations are important, particularly regarding humidification.¹⁹ In this scenario, a questionnaire was created to broadly assess the current clinical practice of health-care workers regarding intratracheal antibiotic administration in mechanically ventilated patients. Our primary objective was to assess the delivery process particularities and potential barriers to implementation. A secondary objective was to assess safety issues, because health-care workers performing antibiotic nebulization should be aware of the particularities of the procedure. Our hypothesis was that extended ICU experience (≥ 3 y) with this procedure would significantly influence the appropriate delivery and safety practices.

Methods

Study Population

The survey was performed from October 18, 2014, to January 31, 2015, using an electronic platform (SurveyMonkey),

being distributed through members of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections In Critically Ill Patients (ESGCIIP). The survey link was also posted on the website of the ESCMID, which endorsed the project. It was an online and anonymous questionnaire. Therefore, no specific data about patients were demanded, no informed consent was required, and no ethical committee approval was needed.

To obtain a more accurate vision of real practice and due to geographical variability of roles, we encouraged all health-care workers devoted to the care of critically ill patients to participate, regardless of their background: physicians, nurses, pharmacists, and respiratory therapists were asked to answer the questionnaire. It was requested that only one professional per unit complete the questionnaire to avoid data multiplication. Children and neonatal ICUs were excluded.

Questionnaire

The survey included 18 questions (simple answer and multiple-choice questions), regarding 3 different aspects: (1) 8 questions on the background of the health-care workers, (2) 6 questions on their experience on practical aspects of the nebulization, and (3) 4 questions on the occurrence of adverse events. The formulated questions are available in Appendix 1 of the supplementary material available at <http://www.rcjournal.com>. A global search strategy was systematically performed in 3 different databases: MEDLINE through the PubMed search Engine, EMBASE, and the Cochrane Library Database. We identified 898, 327, and 210 studies, respectively. The search was conducted in June 2014 (by CS) and limited to articles written in English, French, or Spanish. Non-related, cystic fibrosis, and children were the main causes of exclusion. After manual adjustment for duplication, 77 studies were excluded. Selected questions were based on 190 studies assessed. Final questions were chosen by agreement among the panel of investigators (with a final decision made by J Roberts and J Rello). Information regarding specific data on antimicrobial agents and/or dosage was beyond the scope of this paper.

Some of these questions were specifically aimed at assessing the adherence of health-care workers to practices recognized to be efficient in increasing the delivery of drug to the lungs, by adapting the ventilator settings while performing a nebulization and avoiding asynchronies with the ventilator. The accepted standards for adequate practices evaluated were: using a constant inspiratory flow, decreasing the inspiratory flow, increasing the inspiratory time, inserting an end-inspiratory pause, increasing the tidal volume, active humidification withdrawal, placing a filter on the expiratory limb, and using short-action seda-

tion if necessary to avoid asynchronies, based on expert opinion reports.^{10,11,20}

Health-care workers were requested to report the experience in their ICU. Our hypothesis was that having ICU experience with this practice (estimated by the use of intratracheal nebulization of drugs in their ICUs for ≥ 3 y) would significantly influence the appropriate delivery and safety practices. This break point was used based on medians. Based on this assumption, ICUs were divided into less experienced (< 3 y of nebulization practice) and more experienced.

Statistical Analysis

Responses were analyzed by using descriptive statistics, reporting proportions (percentages). A chi-square test was performed to evaluate a potential association between the experience with nebulization and the appropriate delivery practices and prevention measures of severe adverse events. $P < .05$ was considered statistically significant.

Results

Characteristics of ICUs

A total of 192 health-care workers completed the survey. Most reports came from Asia (76; 39.6%) and Europe (65; 33.9%), followed by North America (25; 13%), Australasia (14; 7.3%), Latin America (10; 5.2%), and Africa (2; 1%). Eighty-seven ICUs (45.3%) reported intratracheal administration of antibiotics in mechanically ventilated patients as a current practice: 37 in Asia (48.6%), 32 in Europe (49.2%), 15 in North America and Australasia (38.4%), and 3 in Latin America (30%). One hundred sixty-six physicians (86.4%), 17 pharmacists (8.8%), and 9 respiratory therapists/nurses (4.7%) completed the survey.

104 ICUs (54.2%) were small or medium-sized, with < 20 beds. The rest of the ICUs (88; 45.8%) were bigger units with ≥ 20 beds; of those, 17 units (19.3%) had > 41 beds. Ninety-four ICUs (48.9%) had acute medical, post-surgical, and trauma patients but also had chronically ventilated patients with tracheostomy for ≥ 1 month. Eighty-seven ICUs (45.3%) were dedicated to medical patients, 71 ICUs (36.9%) reported dedication to post-surgical patients, 44 (22.9%) to trauma patients, and 23 (11.9%) to patients with chronic conditions. One hundred twenty-seven units reported ≥ 2 different types of patients under their care. Seventy-eight ICUs (40.6%) reported having transplant patients under their care.

One hundred eight health-care workers (56.2%) reported delivery of intratracheal antibiotics in mechanically ventilated patients. Among the 84 health-care workers (43.7%) avoiding intratracheal prescription of antibiotics, their main concern was the lack of evidence-based guidelines (66;

Table 1. Concerns Regarding Nebulization Among 84 Health-Care Workers Avoiding Use of Nebulization

Concern	<i>n</i>	%	% of Cases
Lack of evidence-based guidelines	66	36.5	78.6
Lack of personal experience	41	22.6	48.8
Lack of appropriate materials/resources	28	15.5	33.3
Potential increase in resistance pattern	26	14.4	30.9
Potential risk of adverse events	20	11	23.8
Total	181*	100	215.4

* Multiple answers delivered by some health-care workers.

Table 2. Type of Devices Used According to the Experience of the ICUs

	<3 y of Experience (<i>n</i> = 47)		≥3 y of experience (<i>n</i> = 40)	
	Answers	%	Answers	%
Devices				
Jet nebulizer	24	48.9	18	38.2
Ultrasonic nebulizer	17	34.6	17	36.1
Vibrating mesh nebulizer	2	4.0	6	12.7
Tracheal instillation	6	12.2	6	12.7
Total	49	100	47	100
Gas source for jet nebulizers				
External gas source	18	52.9*	7	28
Ventilator-integrated device	16	47.1	18	72
Total	34	100	25	100

* *P* < .05.

78.6%), as shown in Table 1. Lack of ICU experience with their use (41; 48.8%) and lack of appropriate materials or resources (28; 33.3%) were also reported as important reasons for avoiding their prescription. Concerns regarding a potential increase in the resistance pattern (26; 30.9%) or a potential risk of adverse events, such as bronchospasm, hypoxemia, arrhythmias, and emergence of resistances (20; 23.8%), were also reported. Overall, health-care workers reported at least 2 concerns.

Delivering Techniques and Devices

Less experience with intratracheal antibiotic administration (<3 y of practice) was reported by 47 ICUs (54%), whereas longer experience (≥3 y) was encountered in 40 (46%). Twenty-four ICUs with less experience (27.6%) reported mainly using jet nebulizers for the delivery of the drug (Table 2). Among the 40 experienced ICUs, jet nebulizers (18; 20.7%) and ultrasonic nebulizers (17; 19.5%) were used quite indistinctively. Only 2 ICUs with less experience (2.3%) versus 6 experienced units (6.9%), used

Table 3. Adherence to Efficient Practices When Performing Nebulization, According to the Experience of the ICUs

	<3 y of Experience (<i>n</i> = 47)		≥3 y of Experience (<i>n</i> = 40)	
	Answers	%	Answers	%
Adequate	100	28.5	93	27.9
Inadequate	251	71.5	240	72.1
Total	351	100	333	100

vibrating mesh nebulizers (*P* = .08). In addition, 12 ICUs (13.8%) reported the use of tracheal instillation as a means of delivery of antibiotics. Twenty ICUs (22.9%) reported using more than one type of device. No significant difference was observed in the choice of devices for delivery of antibiotics between either experience group. Use of an external gas source for jet nebulizers was more extended in less experienced units (18 [52.9%] vs 7 [28%], *P* = .035). Similar trends were reported (without statistical significance) when different breakpoints were selected.

Concerning the adherence to efficient practices (Table 3), 28.5% of the practices reported by health-care workers in ICUs with less experience, would be considered adequate, similar to ICUs with ≥3 y of experience (27.9%, *P* = .87).

Safety

Adherence of health-care workers to safety practices was evaluated according to the frequency of change of the expiratory filter (Table 4). Changing the filter after each nebulization was reported in <20% of cases, despite the ICUs experience. (*P* = .14). The practice of changing the filter on a daily basis increased to 33.3 in the less experienced ICUs and to 51.7% in the more experienced ICUs (*P* = .15). Administration of bronchodilators before antibiotic nebulization and a variety of measures pondered by health-care workers when facing a respiratory complication were also assessed (see Table 4). Administration of bronchodilators before antibiotic delivery was never used in 15 ICUs with less experience (44.1%) and 8 ICUs with ≥3 y of practice (21.1%) (*P* = .036). No significant differences were observed between the 2 experience groups.

Discussion

In the present study, intratracheal administration of antibiotics was found to be a widely extended practice with broad diversity, although adherence to adequate practices improving the efficacy and safety of the procedure seems to be poor, being independent of the experience with the technique. Health-care workers currently administering intratracheal antibiotic administration often follow inadequate practices that may lead to an increase in the risk of

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Table 4. Frequency of Change of the Expiratory Filter and Therapeutic Measures

	<3 y of Experience (n = 47)			≥3 y of Experience (n = 40)		
	Answers	%	% of Cases	Answers	%	% of Cases
Change of the expiratory filter						
After every nebulization	6	20	6.9	2	6.9	2.3
Daily	10	33.3	11.5	15	51.7	17.2
Once a week	9	30	10.3	10	34.5	11.5
Twice a week	5	16.7	5.7	2	6.9	2.3
Total	30	100	34.4	29	100	33.3
Administration of bronchodilators as a preemptive therapy						
Always	5	14.7	5.7	12	31.6	13.8
Sometimes	14	41.2	16.1	18	47.3	20.7
Never	15	44.1*	17.2	8	21.1	9.2
Total	34	100	39	38	100	43.7
Respiratory complication resolution possibilities						
Stop nebulization	23	65.7	26.4	18	51.4	20.7
Dilution	3	8.6	3.44	3	8.6	3.4
Reducing dose	0	0	0	1	2.9	1.1
Previous bronchodilators	6	17.1	6.9	11	31.4	12.6
Expiratory filter change	3	8.6	3.4	2	5.7	2.3
Total	35	100	40.1	35	100	40.1

* $P < .05$.

potential adverse events. Failure to change the expiratory filter after each nebulization procedure represents the most important concern. Many health-care workers were concerned about the absence of evidence-based guidelines for the technique, suggesting the need for standardization of the procedure.

In France, Ehrmann et al²¹ reported that 30% of health-care workers were regularly administering nebulized antibiotics to treat respiratory infections in mechanically ventilated patients. Our findings show that the delivery is even more widespread when considering ICUs in Asia, America, and Australasia, since 45% of participants acknowledged intratracheal antibiotic administration as a current practice in their ICUs, half of them having ≥3 y of experience.

Jet nebulizers were the most commonly used devices for antibiotic delivery. Vibrating mesh nebulizers are more efficient than jet nebulizers²² and seem to be as efficient as ultrasonic nebulizers²³ but are much easier to handle.^{4,11,24} Our findings show that vibrating mesh nebulizers are the type least used in current practice. It is remarkable that approximately 1 of 10 health-care workers also reported tracheal instillation as a way of administering antibiotics to the lungs. In ventilator-associated tracheobronchitis a survey²⁵ has reported an increased use of intratracheal antibiotic administration, with great diversity and lack of information on outcomes.

An important finding of our study is the observation that, independent of the level of experience with intratracheal antibiotic administration, only 1 of 4 health-care workers followed adequate practices when performing the delivery of the drugs. Indeed, only 1 of 5 health-care workers performing antibiotic nebulization changes the expiratory filter after each nebulization procedure. Moreover, 1 of 3 health-care workers reported that it was appropriate to change it once per week, independent of their experience with antibiotic nebulization. This is an important concern, because failure to change the expiratory filter after each nebulization procedure has been reported to be associated with obstruction of the filter and a potential risk of increase in airway pressures and cardiac arrest.^{26,27} According to these findings, it is not surprising that when health-care workers were asked about their reasons for avoiding intratracheal administration of antibiotics in mechanically ventilated patients, 1 of 3 reported the lack of evidence-based guidelines. In contrast, only 1 of 10 health-care workers fears an increase in antibiotic resistance or other adverse events. Our findings suggest that the lack of protocols and standardization of the practice of this technique could be leading to an incorrect delivery procedure, exposing patients to cardio-respiratory complications.

Pretreatment with bronchodilators is not needed for every dose in every patient. Indeed, we would argue that the risk/benefit ratio is not favorable. It should only be used in

selected patients. However, performance of this practice was used as a safety marker being a weakness of using this as an outcome due to the generalization of the practice to prevent brochospasm. Our findings suggest that a randomized controlled trial should be performed to assess its real efficacy. In addition, studies assessing the emergence of resistance (even with environmental samples after the expiratory exit) should be conducted based on respondents' concerns about the emergence of resistance.

This study has other limitations. First, like any survey, it is based on personal opinions and practice. No information on response rate was available, but the number of ICUs responding to the survey was relatively strong, with many different types of units and wide geographical distribution. Second, a small number of responses from Latin America and Africa were obtained; therefore results may not be generalized due to their heterogeneity. They cannot be generalized to children or patients breathing spontaneously or with noninvasive mechanical ventilation. Third, we used landmark reviews^{19,26,27} to consider appropriate delivery and safety practices, but the lack of evidence-based guidelines precluded standardized definitions, and analysis of predictors of appropriate practices cannot be done. Fourth, this study did not include data on drug selection and dosage. Nevertheless, a follow-up survey with this objective has been conducted.²⁸ A similar weakness is that we did not ask about drug preparation issues. Some of these are also important relative to safety/tolerability and drug delivery to the lung (eg, diluent, final volume, pH, osmolarity). Critically, the administration of colistin immediately after reconstitution should have been addressed. Finally, nebulization of other agents, such as bronchodilators, was not within the scope of this study, likewise antibiotic nebulization in noninvasively ventilated patients. However, for this same reason, the findings reported in this study are much more specific to mechanically ventilated adults. Moreover, some answers are likely to be varied based on the differences in training of the survey individuals, and they may not accurately reflect the practice of the included ICUs.

Despite these limitations, our study has important implications: a definitive guideline that is routinely updated (say every 4–5 y) and that covers administration/safety issues and treatment issues is needed. There are some very nice reviews, including the American clinical pharmacy guideline from the Society of Infectious Diseases Pharmacists (2010), but this survey shows that the lack of more definitive information is a reason why clinicians are not using aerosolized antibiotics.

Conclusions

Intratracheal antibiotic administration for the treatment of respiratory infections in critically ill mechanically ven-

tilated adults has emerged as a common therapy, but it is frequently associated with inadequate practices (lacking standardization of best practices based on the literature for drug delivery). This was independent of the experience of the health-care workers with the technique. Standardization of the technique procedure is required to increase efficacy and minimize the risk of potential adverse events. This would be a springboard for further prospective studies regarding uniform protocol implementation and efficacy of treatment.

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