2019台灣胸腔暨重症加護醫學會

2019 Taiwan Society of Pulmonary and Critical Care Medicine

修改稀釋技術以減少Colistin在噴射霧化治療時結晶的形成
Modified Dilution Technique to Reduce Colistin Crystallization at the End of Jet-Nebulized Aerosol Therapy

Yung-Fang Lin (林永芳)[1]* ,Shiau-Ling Chou (周小鈴) [1], Shin-Yi Liang(梁心怡) [2], Ho-Sheng Lee(李和昇)[1]

[1]Division of Respiratory Medicine, Department of Internal Medicine, E-DA Hospital, Kaohsiung city, Taiwan (義大醫療財團法人義大醫院 呼吸胸腔內科)

[2]Department of Pharmacy, E-Da Hospital, Kaohsiung city, Taiwan(義大醫療財團法人義大醫院 藥劑部)

This study was supported by the grant from E-DA Hospital (EDAHP104104)

Aerosol history

The Mudge inhaler, invented by Dr John Mudge in 1778,

The Sales-Girons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science

First pMDI – Riker Labs 1956

Aerosol antibiotics Have a long history

Potter BP Aerosol antibiotic therapy in suppurative diseases of the lung and bronchi. *Dis Chest (now CHEST)* 1949;15;436-448

Aerosol Antibiotic Therapy in Suppurative Diseases of the Lung and Bronchi*

B. P. POTTER, M.D., F.C.C.P.**

Jersey City, New Jersey

Inhalation therapy has become very popular both with physicians and the laity. While the use of antibiotics by nebulization is rather recent, the utilization of germicidal mists and therapeutic gases dates back many years. Those interested in a complete review of the historical background for aerosol therapy should read Segal's excellent article on the subject.[1]

Bryson, V., Lansome E. and Laskin, S.: "Aerosolization of Penicillin Solution," *Science*, 100:33,1944.

See reference (2)

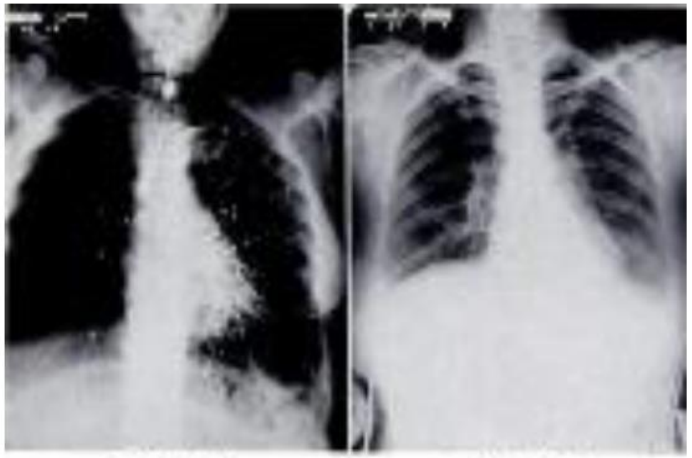


FIGURE 15 FIGURE 16

Figure 15. [illegible] Figure 16. [illegible]

1) The results in 46 cases of bronchopulmonary suppuration treated by aerosolized antibiotics are reported.

Antibiotics by aerosol

Advantages:

High concentration in airway

Minimal systemic effect/toxicity

User friendly (compared to IV)

Disadvantages:

Does not penetrate to most involved deep lung

Potential development of antimicrobial resistance

Can produce cough, irritation, bronchospasm

Intravenous

Inhaled

Adjunctive nebulized antibiotic therapy as a treatment of last resort is also recommended

Host
- Immunodepression
- Chronic lung disease

Host-pathogen interactions with high risk of therapy failure

Pathogen
- Virulence
- Resistance

Tracheobronchitis

Pneumonia

Resistance emergence prevention

Minimal Inhibitory Concentration

Less resistance

Higher efficacy

Pulmonary PK

Limited diffusion of hydrophilic antibiotics

Intravenous antibiotic infusion

Systemic effects

Extrapulmonary deposition

Resistance emergence prevention

Minimal Inhibitory Concentration

Serum PK

Extrapulmonary deposition

Filter to protect expiratory block

Inhaled antibiotics

Nebulizer type

$\searrow \dot{V}_i$
$\searrow RR$
$\nearrow T_i$

Ventilator

15-40 cm

residual volume

Jet >> Ultrasonic >> Mesh

Tracheal tube decontamination

Particle size:
- 3-5 µm : proximal deposition
- 1-3 µm : alveolar deposition

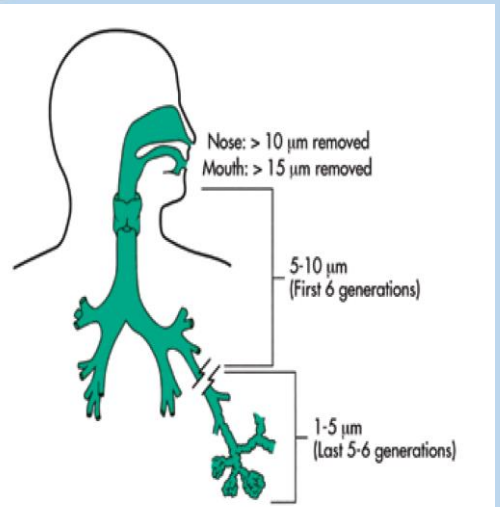


Figure 1. A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways
(From Reference 6, with permission)

Original Article

Comparison of Microbiological Eradication and Mortality in Patients Receiving Single Therapy of Aerosolized Colistin and Combination Therapy of Aerosolized Colistin and Intravenous Antibiotics

Shin-Yi Liang[1], *Chien-Tung Chiu*[2], *Jiun-Ling Wang*[3], *Yi-Ping Hsiang*[1], *Yu-Shuang Liu*[4], *Jiun-Nong Lin*[2,5,6]

Objective: Aerosolized colistin has been used for multidrug-resistant gram-negative bacilli pneumonia. The aim of this study was to compare the clinical response and microbiological eradication of single therapy with aerosolized colistin and combination therapy of aerosolized colistin and intravenous antibiotics.

Methods: Patients older than 18 years with pneumonia caused by gram-negative bacilli and receiving colistin therapy during January 1, 2013 to June 30, 2014 were retrospectively included in this study. Demographic data, clinical information, outcome, and microbiological eradication were compared between the single therapy and combination therapy groups.

Results: During the study period, 84 patients were included. Among these, 53 (63.1%) were male and the mean age was 69.3 years. The most prevalent comorbidity was hypertension (56%), followed by chronic kidney disease (35.7%). Nineteen (22.6%) patients received aerosolized colistin alone and 65 (77.4%) used combination therapy of aerosolized colistin and intravenous antibiotics. The overall eradication rate of microorganism was 66.7%. *Pseudomonas aeruginosa* was more difficult to be eradicated than *Acinetobacter baumannii* (adjusted odds ratio [OR], 5.43; 95% confidence interval [CI], 1.44 – 20.44; $p = 0.012$). Single therapy of aerosolized colistin was significantly associated with eradication failure (adjusted OR, 4.42; 95% CI, 1.07 – 18.23; $p = 0.040$). Chronic obstructive pulmonary disease (adjusted OR, 11.49; 95% CI, 2.61 – 50.49; $p = 0.001$) and failure of microbiological eradication (adjusted OR, 7.11; 95% CI, 1.55 – 32.63; $p = 0.012$) were independent risk factors of mortality in patients who received aerosolized colistin treatment.

Conclusions: Combination therapy of intravenous antibiotics and aerosolized colistin is suggested in patients with multidrug-resistant gram-negative bacilli pneumonia.

Keywords: Colistin, aerosolized therapy, multidrug resistance, gram-negative bacilli, pneumonia

From the [1]Department of Pharmacy, E-Da Hospital, Kaohsiung, [2]Department of Critical Care Medicine, E-Da Hospital, Kaohsiung, [3]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, [4]Department of Nursing, E-Da Cancer Hospital, Kaohsiung, [5]Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital, Kaohsiung, and [6]School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan

Received: Feb 1, 2019 Accepted: June 5 , 2019

Address reprint request and correspondence to: Jiun-Nong Lin, Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan. Tel:+886-7-615-0011 ext. 251469, E-mail: ed103623@edah.org.tw

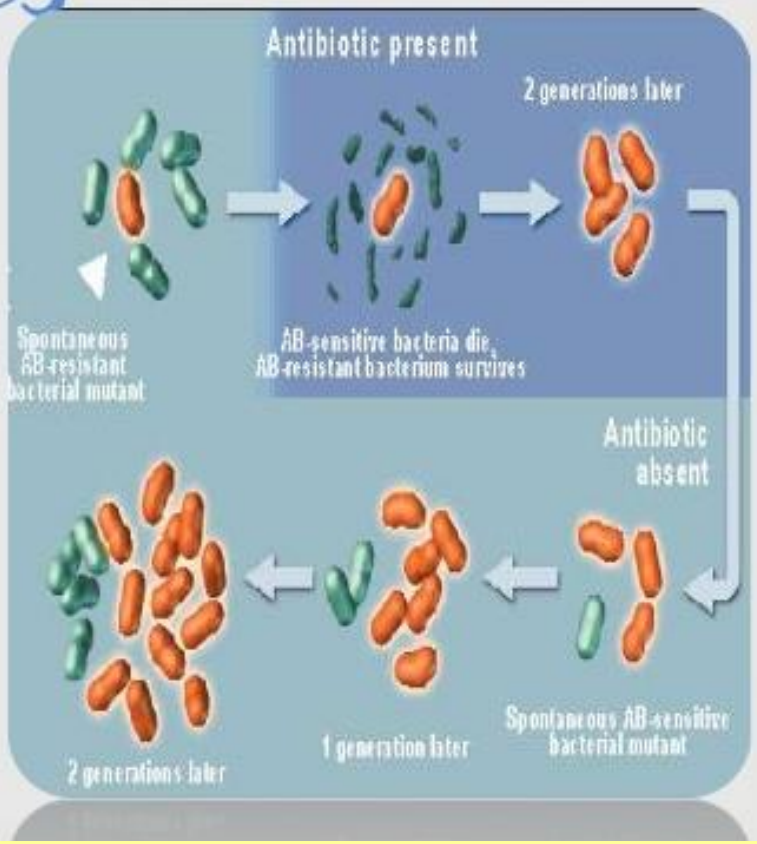
Looking forward

Looking back past 50 years

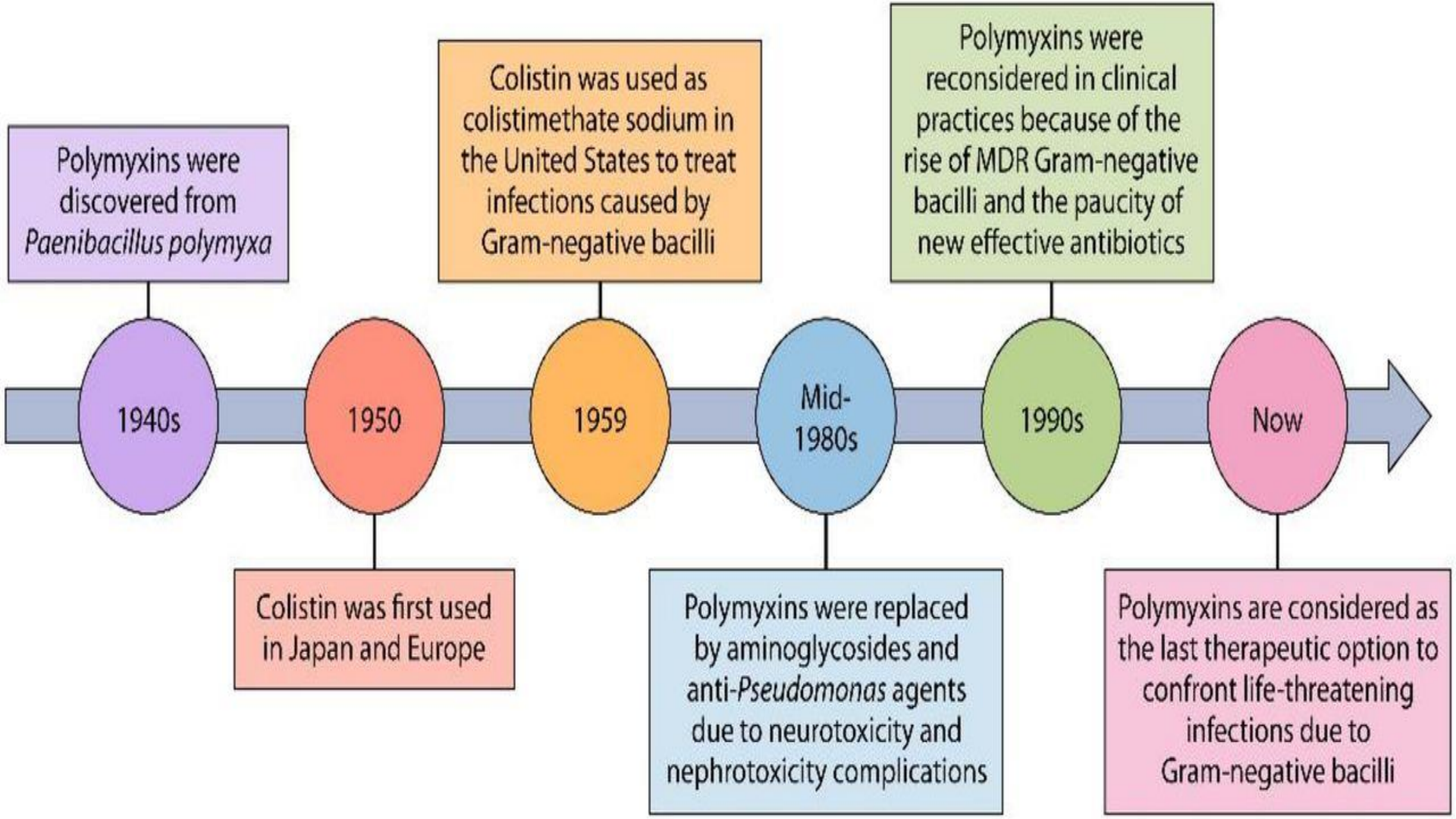
Colistin:

Re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections.

- Increasing multidrug resistance in Gram-negative bacteria, in particular Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae, presents a critical problem. Limited therapeutic options have forced infectious disease clinicians and microbiologists to reappraise the clinical application of colistin, a polymyxin antibiotic discovered more than 50 years ago



Colistin也可以稱它為polymyxin E，機轉作用在葛蘭氏陰性桿菌之細胞膜上，破壞其細胞膜屏障而達到殺菌的效果；曾經因其不良反應而封塵一陣子，因多重抗藥菌的肆虐而重出江湖。



April 2019 Volume 57 Issue 4 e01390-18 Journal of Clinical Microbiology

Superbugs kill over 35K a year, CDC says

Ken Alltucker
USA TODAY

Drug-resistant "superbugs" infect 2.8 million people and cause more than 35,000 deaths each year, underscoring the public health threat of germs in what one official describes as a "post-antibiotic era," according to a new Centers for Disease Control and Prevention report.

The report, which analyzes electronic health records and other data, shows an infection every 11 seconds and a death every 15 minutes on average from bugs that resist treatment from antibiotics. The CDC said there are nearly twice as many deaths from antibiotic-resistant infections when compared with the agency's 2013 report, which likely underestimated the numbers.

In a letter accompanying the report, CDC Director Robert Redfield urged the public to "stop referring to a coming post-antibiotic era – it's already here," with drug-resistant bugs in every U.S. state and around the globe.

"You and I are living in a time when some miracle drugs no longer perform miracles and families are being ripped apart by a microscopic enemy," Redfield wrote.

The report establishes a new baseline of infections and deaths from antibiotic-resistant germs and categorizes emerging threats as urgent, serious or concerning. It is part of a broad public health effort to prevent infections in health-care facilities, promote responsible use of antibiotics in humans and animals and halt the spread of new, dangerous germs.

'Superbugs'

The report identified five bugs described as "urgent threats":

Two emerging bugs:

- **Candida auris**, a drug-resistant fungus.
- **Carbapenem-resistant acinetobacter**, which can cause pneumonia in hospital intensive care units.

'Nightmare bacteria':

- **Carbapenem-resistant enterobacteriaceae** (CRE)
- **Antibiotic-resistant gonorrhea**
- **Clostridioides difficile** (C. diff)

The report identified 18 bacteria and fungi public health officials must monitor, including five bugs described as "urgent threats."

The tally of annual infections and deaths becomes even more dramatic when C. diff is included. The infection is rarely resistant to antibiotics but can cause deadly diarrhea and is often diagnosed in people who are taking antibiotics. About 12,800 people died and more than 223,000 people were infected with this germ in 2017, the report said.

The number of C. diff infections in hospitals and nursing homes declined in recent years amid more careful efforts to use antibiotics, control infections and improve cleaning and disinfection. Still, the number of cases outside health-care facilities increased.

Aerosol therapy

But in clinical finding…Crystallization at end of the End of Jet-Nebulized Aerosol Therapy

Neonate ventilator circuit(expiratory valve) without filter protect

A challenge for respiratory therapist from technology to clinical care

Nebulized antibiotics in mechanically ventilated and Non-ventilator support patients

Therefore, we want to find easy and reproducible dilution techniques with nebulization to reduce crystallization.

If Jet Nebulizer must be used multiple dose of colistin may compensate for poor delivery performance..?

With a high concentration consisting of 2 vials.

Nebulizer design

Table 1 Advantages and disadvantages of three types of nebulizers

	Jet nebulizer		Ultrasonic nebulizer		Vibrating mesh nebulizer
Mechanism of aerosol generation	Compressed gas and Venturi effect		High-frequency drug solution agitation by a piezoelectric crystal		High-frequency mesh vibrations pumping the drug solution trough tapered holes
Residual volume	Large	>	Medium	>	Small
Medication restriction	None		Degradation of heat-sensitive drugs		Highly concentrated or viscous solutions may cause damage to the nebulizer
Ergonomics	Not portable, need of compressed gas Loud Disposable Potential interference with the ventilator		Bulky Silent Need for decontamination No interference with the ventilator		Portable, small size Silent Disposable No interference with the ventilator

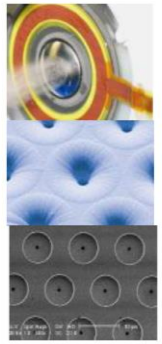
The particle sizes generated depend on each individual nebulizer model rather than the nebulizer type, and they are substantially impacted by the measurement conditions (e.g., temperature and humidity). For example, some specific jet nebulizers may deliver large particles (>5 μm for proximal targeting), whereas others deliver nanoparticles. All nebulizers available for clinical use produce sufficient droplets in the 1–5 μm size range of for pulmonary delivery during mechanical ventilation

Table 1 displays advantages and drawbacks of available nebulizers. Jet nebulizers appear to be less efficient than ultrasonic and vibrating mesh nebulizers for antibiotic delivery

And insulin by vibrating mesh micropump nebulizer (Aerogen)

New delivery systems

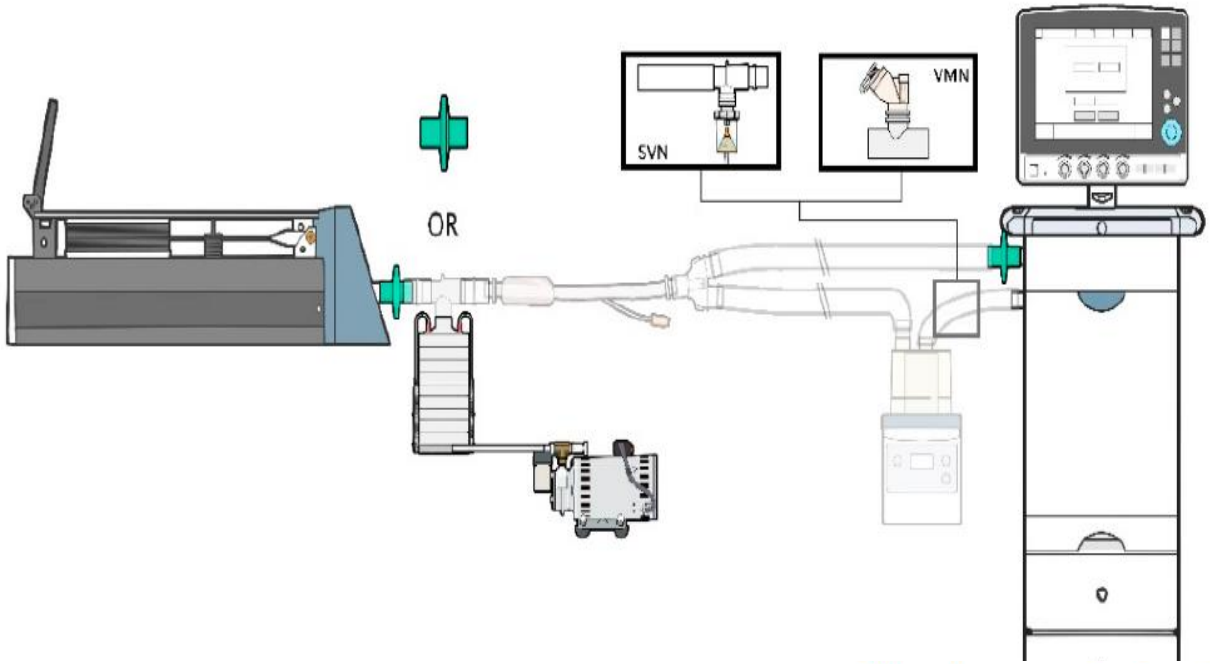
- Respimat soft mist inhaler
- Vibrating mesh nebulizers
  - eFlow
  - AeroNeb Go
  - Omron NE-U022
- "Smart" nebulizers
  - AerX
  - Halolite/ProDose
- Breath-Control nebulizers
  - iNeb
  - Akita



Vibrating mesh devices

Piezo-element vibrates a mesh or horn in contact with drug to create aerosol

- Small
- Portable
- Battery or AC-powered
- Silent operation
- Faster than jet neb
- High doses possible



"Open" mesh devices

Match aerosol characteristics of jet nebulizers
Faster delivery times
Generally more expensive

Aeroneb Go

Omron MicroAir

eFlow Rapid

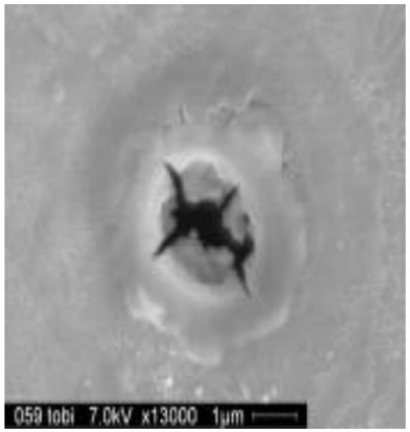
Vibrating mesh devices: Challenges

Viscous drugs

May disrupt drug-carrier complexes (eg, liposomes)

Clogging of pores
- Suspensions
- Drug or soap residues

Cleaning process
- Many parts
- Handling of mesh



1. 依照AARC Aerotherapy guideline僅有4-5ml吸入稀釋劑量，並無提及抗生素乾粉吸入

Pulmonary Disease Aerosol Delivery Devices

A Guide for Physicians, Nurses, Pharmacists, and Other Health Care Professionals3rd Edition. Copyright ©2017 by the American Association for Respiratory Care

2.2018台灣肺炎診治指引

第三章：院內型肺炎

“每次劑量以5ML稀釋”

病原菌	建議之抗生素
綠膿桿菌	
血行動力學狀況穩定	依據藥物敏感試驗選擇抗生素
血行動力學狀況不穩定	單一抗生素治療 兩種抗生素合併治療
鮑氏不動桿菌	
血行動力學狀況穩定且非多重抗藥	Ampicillin/sulbactam 3g IV q6h Imipenem/cilastatin[a] sodium 500mg IV q6h Meropenem[a] 1g IV q8h
血行動力學狀況不穩定或是只對多粘菌素類抗生素有效	Colistin 5mg/Kg IV給予1劑後，2.5mg×(1.5×CrCl+30) IV 分為q12h給予 +/- Imipenem/cilastatin sodiuma 500mg IV q6h 或 Meropenem 1g IV q8h 或 Ampicillin/sulbactam 3g IV q6h + 合併吸入(adjunctive inhaled) colistin[b]每日劑量1.25-15MIU[1]分為q8-12h，每次劑量以5mL無菌生理食鹽水稀釋

3. 儘管霧化本身會產生某種形式的加溼，霧化時要小心持續超過1小時，以免損壞纖毛上皮和氣管內管阻塞“若分2次吸藥，會造成吸藥時間超過1小時，且人員負擔增加，病人可能不耐煩而自行取下。

4. 吸入性藥物會受到黏稠度(viscosity)、表面張力(surface tension)及均質性(homogeneity)的影響

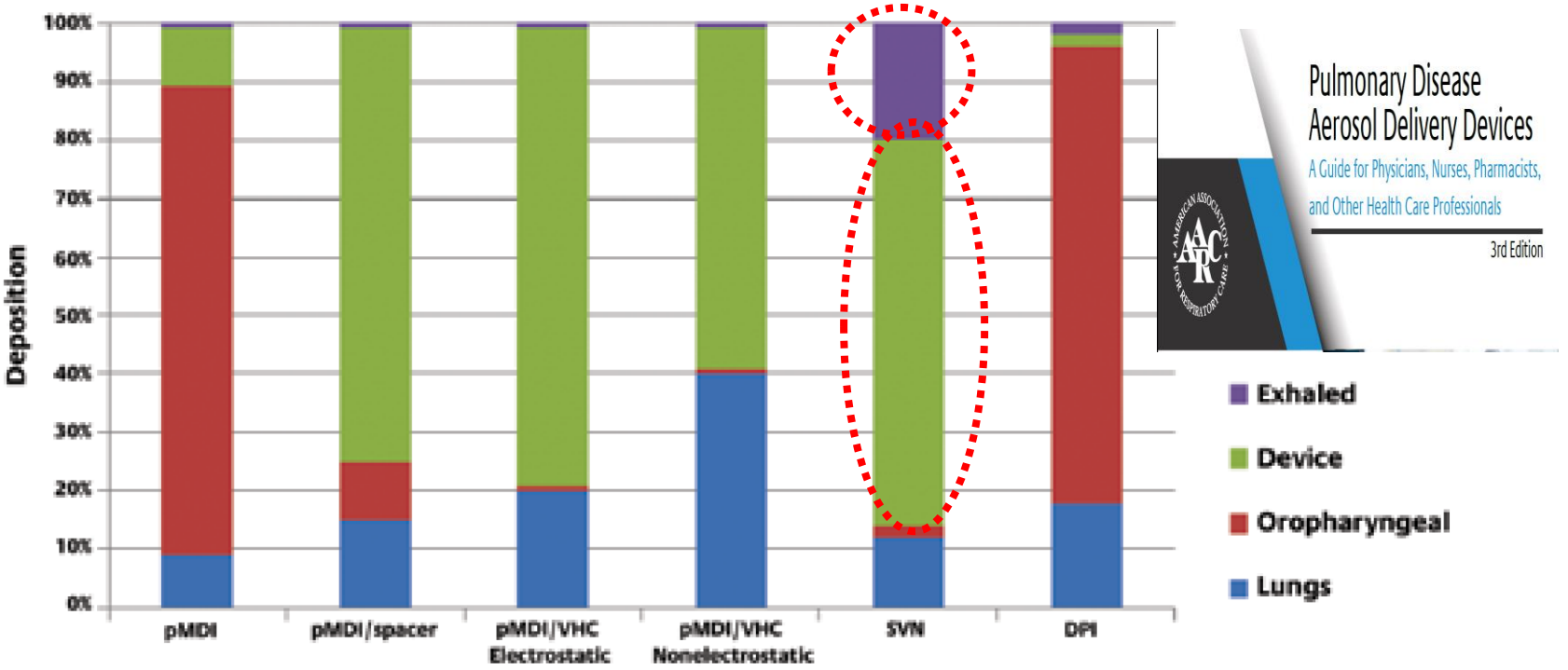


Figure 2. Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath.

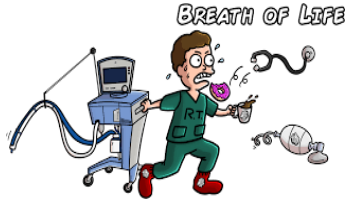
pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber;
SVN = small-volume nebulizer; DPI = dry-powder inhaler
(Modified, with permission, from References 9 and 12)

SVN

Device:60-70% >Exhaled 20%>lungs 10%-15%

Motivation

1. When high doses of colistin are prescribed, clinicians may reduce the dilution volume, and air is mixed with high concentrated colistin solution in a nebulizer to shorten the treatment time.



2. Colistin is likely to foam during the dilution procedure and produce large quantities of crystal in a ventilator circuit and nebulizer kit.

3. However, the increase of drug concentration and the quantity of the drug remaining in the nebulizer at the end of aerosol therapy have patients exposed to higher concentrations of inhaled colistin, which may cause more toxicity.

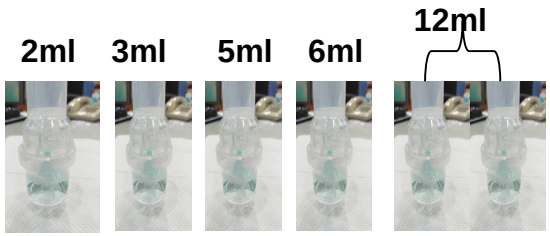
Materials and Methods

Q1： Foaming effect related crystallization at the end of aerosol therapy?

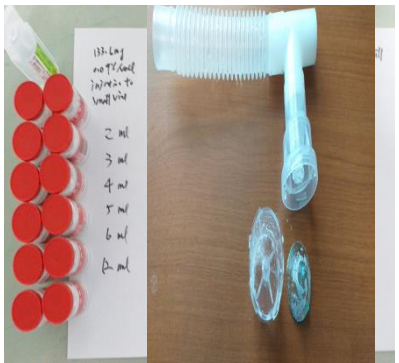
high concentrated colistin

Foaming effect ?

(Experimental)



4 million units (133.6 mg, two vials) of colistin powder were dissolved in 2, 3, 5, 6, and 12 mL of 0.9% sodium chloride



400 MIU

Colomycin (Toyo, Taiwan) enables 0.9% sodium chloride to be added to or withdrawn from a vial with the use of a needle.

Assembly with mouthpiece and delivery time of more than 60 min, powered by oxygen at 8 L/min. (pneumomatic jet nebulizer;SVN) Gas-powered jet nebulizers (Control)

4 million units (133.6 mg, two vials) of colistin powder were dissolved in 4 mL of 0.9% sodium chloride (recommended),

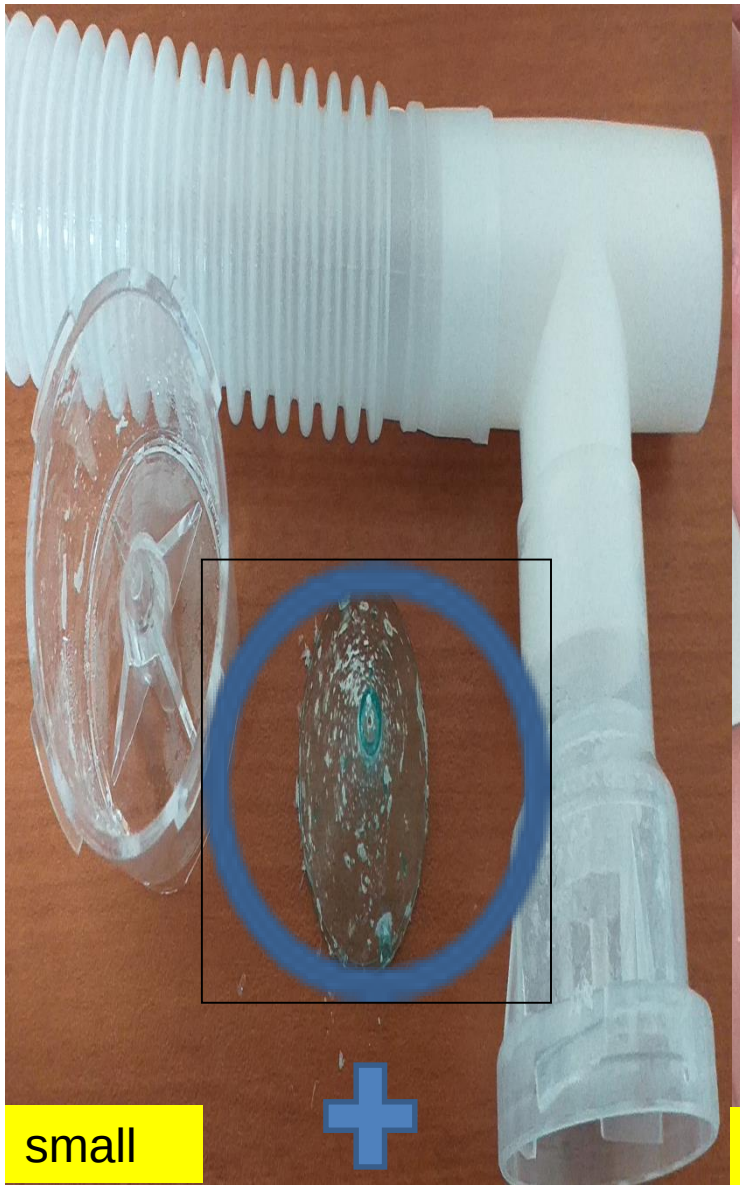
Result-1

The Colistin between the 5 and 12 mL diluent volumes without foaming effect (diluted process) reduced crystallization at the end of aerosol therapy

Injection in 2 vial (133.6mg colistin in different volume 0.9% NaCl)	Dry powder foam not disappear (crystal in SVN)	Dry powder foam disappear (crystal in SVN)
2mL	Large amount	medium
3mL	Large amount	medium
5mL	Large amount	small
6mL	Large amount	small
12mL*	Large amount	rare to small

Injection in 2 vial (133.6mg colistin in different volume 0.9% NaCl)	Dry powder foam not disappear (crystal in SVN)	Dry powder foam disappear (crystal in SVN)
4mL	Large amount	Small to Medium

Conclusion: the colistin between the 5 and 12 mL diluent volumes without foaming effect reduced crystallization at the end of aerosol therapy. It will reduce the crystallization as the 0.9% normal saline increases to 12ml.


small
+


Medium
++


Large
+++

Q2:Different dilute technique (Injection skill) affect foaming?

1

Difficulte to shaking (process and after injection)

2

Easy to mild shaking (process and after injection)

Traditional dilution technique (easy mix air and foaming)

Result-2

Different dilute technique 2 vial colistin (2,3,4,5,6 and 12ml 0.9% N.S.)	Dry powder foaming	Mix air
Modified dilution technique (rotary injection)	not easy(mild shake)	not easy(mild shake)
Traditional dilution technique	Easy	Easy

mouth-piece SVN (Ventilator with SVN)	power by extra continued oxygen flow at 8LPM	synchronized flow by ventilator provide
Treat aerosol therapy time	<1hr	>1hrs-2hrs

Conclusion: Modified dilution technique (rotary injection) can reduce foam formation.

Q3:Can improved modified dilution technique to reduce colistin crystallization at the end of jet-nebulized aerosol therapy ?

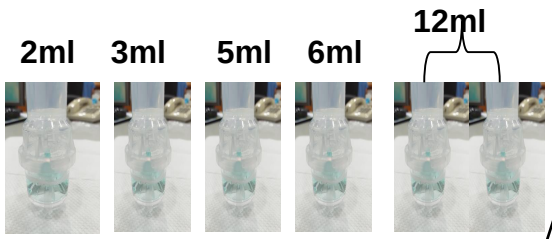
Colomycin (Toyo, Taiwan) enables 0.9% sodium chloride to be added to or withdrawn from a vial with the use of a needle.

1.vertical injection

2.Rotary injection

Assembly with mouthpiece and delivery time of more than 60 min, powered by oxygen at 8 L/min. (pneumomatic jet nebulizer;SVN) Gas-powered jet nebulizers

(Experimental)



(Control)

4 million units (133.6 mg, two vials) of colistin powder were dissolved in 2, 3, 5, 6, and 12 mL of 0.9% sodium chloride

4 million units (133.6 mg, two vials) of colistin powder were dissolved in 4 mL of 0.9% sodium chloride (recommended)

Result-3

Injection in 2 vial (133.6mg Colistin in different volume 0.9% NaCl)	Traditional dilution technique (vertical injection)	Modified dilution technique (rotary injection)	Dry powder foam disappear (crystal in SVN)
2mL	30 min dissolve	15 min dissolve	medium
3mL	18 min dissolve	10 min dissolve	medium
5mL	14 min dissolve	8 min dissolve	small
6mL	26 min dissolve	8 min dissolve	small
12mL*	28 min dissolve	5 min dissolve	rare to small

Injection in 2 vial (133.6mg colistin in different volume 0.9% NaCl)	Traditional dilution technique (vertical injection)	Modified dilution technique (rotary injection	Dry powder foam disappear (crystal in SVN)
4mL	14min dissolve	8 min dissolve	Small to Medium

Conclusion: Modified dilution technique has a lower dissolution time than traditional dilution technique. Using modified dilution technique, the dissolution time of 4ml to 6ml is about 8 minutes. It will increase the dissolution rate as the 0.9% normal saline increases to 12ml.

Discussion-1

1.Delivery of high concentrations of antibiotics to infected lung regions is the key to achieving efficient nebulized antibiotic therapy. 向感染的肺區域輸送高濃度抗生素是實現高效霧化抗生素治療關鍵。

MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med.1985;13:81–4.

2. 藥物稀釋和霧化器填充量的影響顆粒大小和藥物輸送。對於給固定的劑量，用稀釋溶液更大的填充量可以克服剩餘體積問題(ref.)

3.稀釋會增加霧化，結果是抗生素穩定性問題可能會出現。例如，可溶的（CMS）不穩定且其抗菌功效隨時間減少(ref.)相反，高濃度或粘性溶液(highly concentrated or viscous solution)會增加粒徑，可能減少肺部沉積[ref]

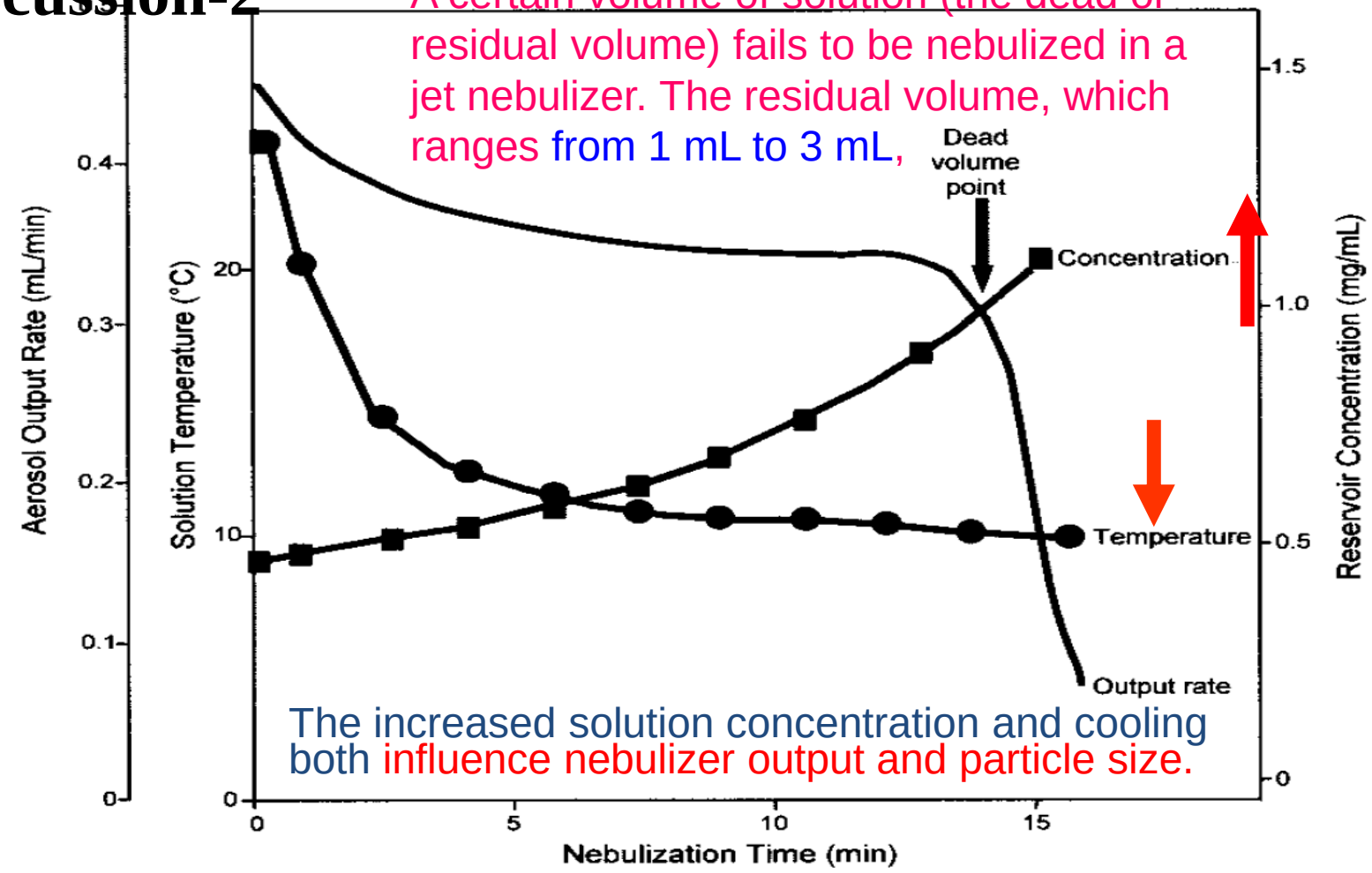
O'Doherty MJ, Thomas SH, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation. Effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis. 1992;146:383–8.

Wallace SJ, Li J, Rayner CR, Coulthard K, Nation RL. Stability of colistin methanesulfonate in pharmaceutical products and solutions for administration to patients. Antimicrob Agents Chemother. 2008;52:3047–51

Boe J, Dennis JH, O'Driscoll BR, Bauer TT, Carone M, Dautzenberg B, et al. Adaptations of the European Respiratory Society guidelines by the Aerosol Therapy Group of the French Lung Society on the use of aerosol therapy through nebulization. Rev Mal spir. 2004;21:1033–8.

Discussion-2

A certain volume of solution (the dead or residual volume) fails to be nebulized in a jet nebulizer. The residual volume, which ranges from 1 mL to 3 mL,



The increased solution concentration and cooling both influence nebulizer output and particle size.

Fig. 1. Predicted nebulizer aerosol output, solution temperature, and drug concentration in the reservoir during jet nebulization. The data points are not derived from actual experiments with any particular jet nebulizer. (Adapted from Reference 65, with permission.)

Discussion-3

1.The previous study showed that 4 million units of colistin diluted in 6 mL of 0.9% sodium chloride generated MMADs of 3 μm, which is suitable for distal lung deposition.

2.There is no significant difference in plasma pharmacokinetic parameters and urinary excretion of colistin between 6 and 12 mL diluent volume, but colistin stability is superior with the 6 mL diluent volume.

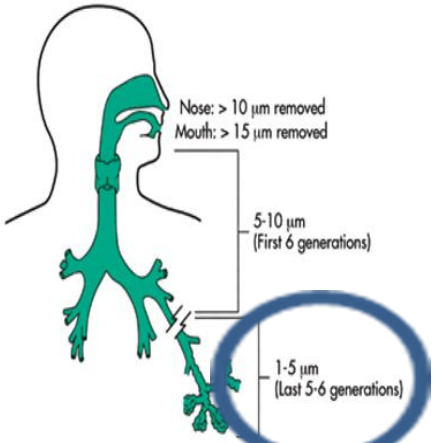
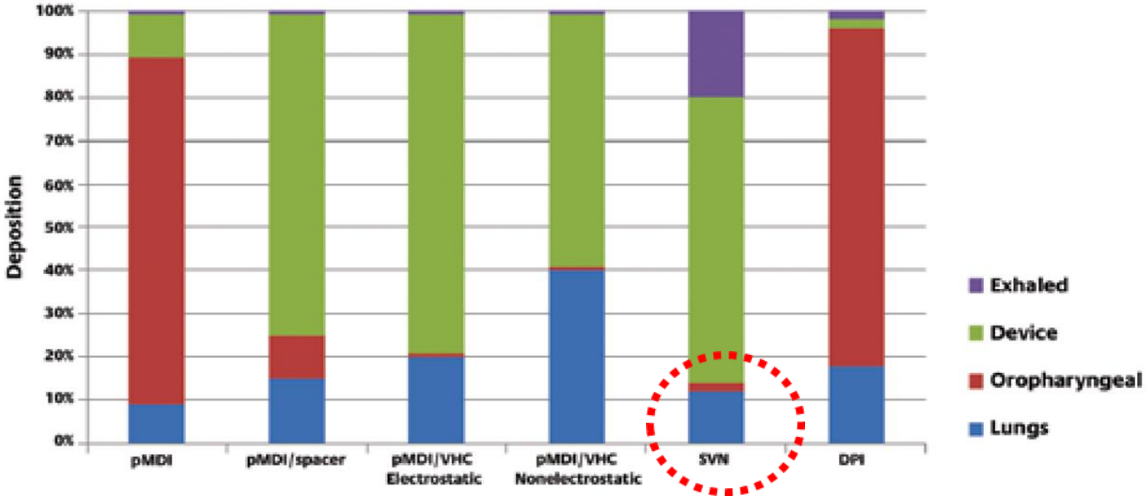


Figure 1. A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways (From Reference 6, with permission)

SVN

Device:60-70% >Exhaled 20%>lungs 10%-15%



Journal of Antimicrobial Chemotherapy, Volume 73, Issue 6, June 2018, Pages 1639–1646.

Summary

We suggest dilution of 4 million units of colistin powder in 6 mL of 0.9% sodium chloride by using a modified dilution technique including rotary injeciton and slow shaking to reduce foaming formation and increase time efficiency.

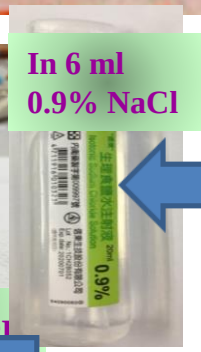
In our bedside observation, many factors influence aerosol delivery of colistin, such as nebulizer position in ventilator circuits and humidification. We need further investigations to continuously improve nebulization techniques and practices.

Key good practices for optimal antibiotic nebulization during mechanical ventilation

Injection skill (rotary and mild shaking)

Staff training

In 6 ml 0.9% NaCl

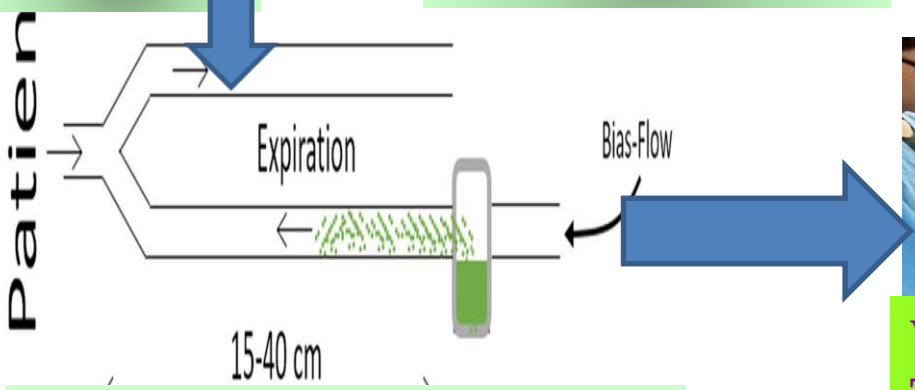


Jet nebulizer

New filter between ther expiratory limb

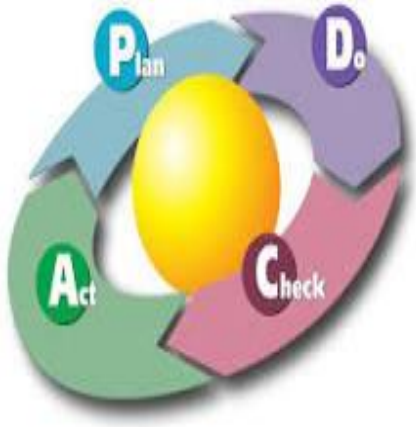
Humidification (switch it off or use dry circuit)

Organization



Nebulizer position 15-40 cm

Ventilator setting (long Ti and low RR)



謝謝指教

附件

J Antimicrob Chemother
doi:10.1093/jac/dky044

Journal of Antimicrobial Chemotherapy

Influence of diluent volume of colistimethate sodium on aerosol characteristics and pharmacokinetics in ventilator-associated pneumonia caused by MDR bacteria

Kevin Bihan[1], Noël Zahr[1], Marie-Hélène Becquemin[2], Xiao Lu[3,4], Jean-François Bertholon[2], Corinne Vezinet[3], Charlotte Arbelot[3], Antoine Monsel[3], Jean-Jacques Rouby[3], Olivier Langeron[3] and Qin Lu[3]*

[1]*Department of Pharmacology and CIC-1421, F-75013, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France;* [2]*Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France;* [3]*Multidisciplinary Intensive Care Unit, Department of Anesthesiology and Critical Care, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France;* [4]*Department of Emergency Medicine, Second Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, China*

*Corresponding author. Tel: (33)-1-42-17-84-38; Fax: (33)-1-42-17-73-18; E-mail: qin.lu@aphp.fr

Received 12 October 2017; returned 4 December 2017; revised 16 January 2018; accepted 23 January 2018

Objectives: Nebulized colistimethate sodium (CMS) can be used to treat ventilator-associated pneumonia caused by MDR bacteria. The influence of the diluent volume of CMS on aerosol delivery has never been studied. The main objectives of the study were to compare aerosol particle characteristics and plasma and urine pharmacokinetics between two diluent volumes in patients treated with nebulized CMS.

Methods: A crossover study was conducted in eight patients receiving nebulized CMS every 8 h. After inclusion, nebulization started with 4 million international units (MIU) of CMS diluted either in 6 mL (experimental dilution) or in 12 mL (recommended dilution) of normal saline in a random order. For each diluent volume, CMS aerosol particle sizes were measured and plasma and urine samples were collected every 2 h. Nebulization time and stability of colistin in normal saline were assessed.

Results: The mass median aerodynamic diameters were 1.4±0.2 versus 0.9±0.2 μm ($P < 0.001$) for 6 and 12 mL diluent volumes, respectively. The plasma area under the concentration–time curve from 0 to 8 h (AUC_{0-8}) of $colistin_{A+B}$ was 6.6 (4.3–17.0) versus 6.7 (3.6–14.0) μg·h/mL ($P = 0.461$) for each dilution. The total amount of colistin and CMS eliminated in the urine represented, respectively, 17% and 13% of the CMS initially placed in the nebulizer chamber for 6 and 12 mL diluent volumes ($P = 0.4$). Nebulization time was shorter [66 (58–75) versus 93 (69–136) min, $P = 0.042$] and colistin stability was better with the 6 mL diluent volume.

Conclusions: Nebulization with a higher concentration of CMS in saline (4 MIU in 6 mL) decreases nebulization time and improves colistin stability without changing plasma and urine pharmacokinetics or aerosol particle characteristics for lung deposition.

Ventilator settings

從理論上講，需要層流低的吸氣流量 促進遠端肺部氣溶膠沉積[25]。

增強霧化功效的環境包括低呼吸頻率，低吸氣流量和增加 吸氣時間

容量控制的呼吸器模式搭配持續低吸氣流量可提高療效與壓力控制通風相比（高尖峰流量，然後減速）[17，27]。

呼吸機完全同步 減少渦流並提高功效。

清醒患者的特定呼吸器設置可能很差，霧化期間的鎮靜應在case by case 。

由於以上的限制因素，限制用於大規模霧化抗生素治療臨床試驗的可行性

Circuit humidification and filter

加濕的氣體增加了氣霧顆粒的尺寸通過吸濕吸水。減少效率已證明在加熱和與乾式呼吸器迴路相比[21，22}。

加熱濕交換器是一個完整的氣霧傳遞的障礙，應在操作過程中將其清除，從而中斷了被動加濕。

使用有加熱加濕器時，請切換在霧化期間將其關閉可能是一種選擇。

儘管霧化本身會產生某種形式的加溼，霧化時要小心持續超過1小時，以免損壞纖毛上皮和氣管內管阻塞[24]。

Nebulizer position

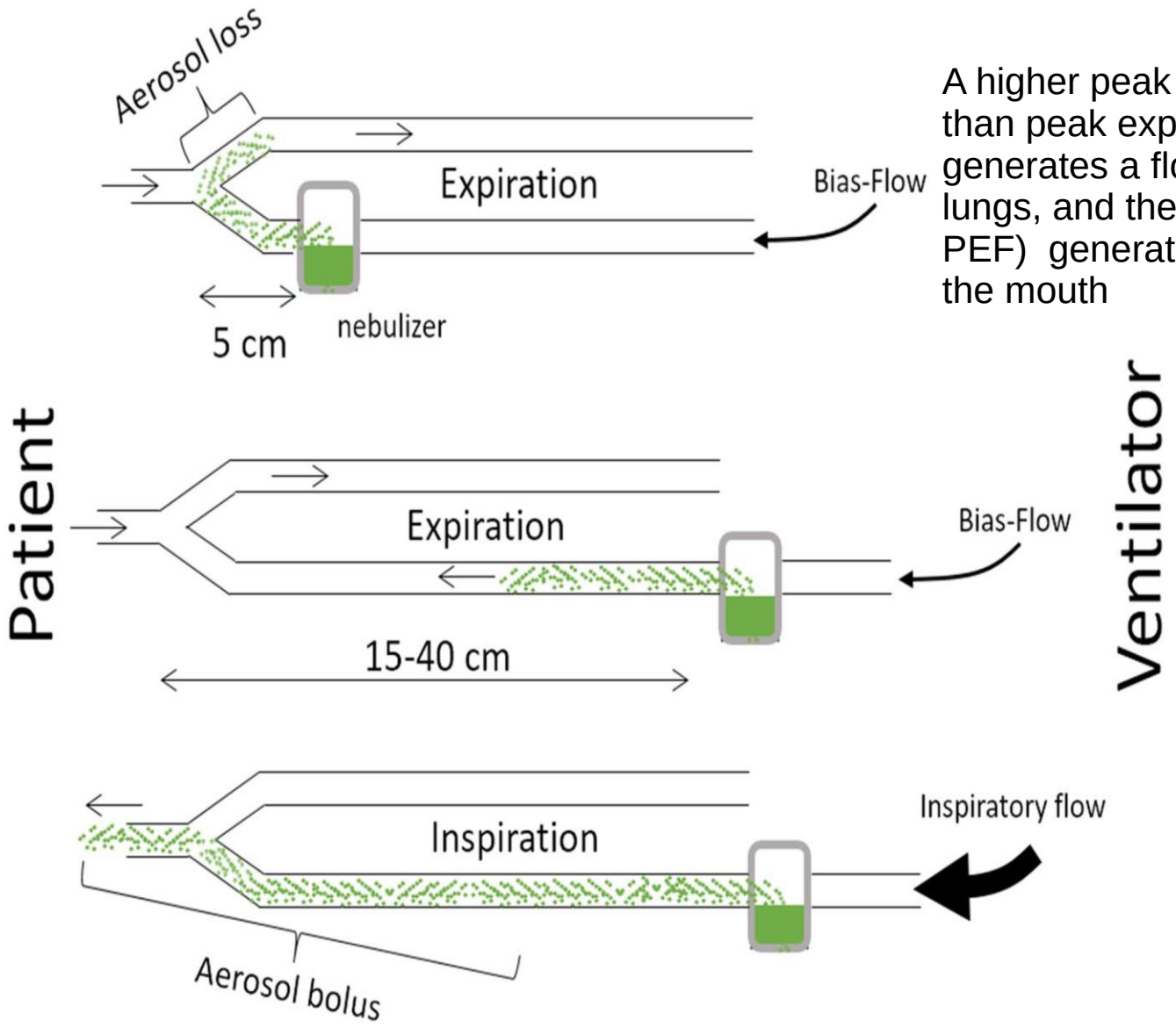
吸藥過程噴射及吐氣在均連續運行並且應在位於Y形管上15－40 cm進氣端放置噴霧器[11，17]。

該與Y型管的最佳距離取決於偏流和管路部分。確實，偏流沖洗了氣霧 在呼氣期間進入吐氣端， 氣霧損失（圖1）[11，18]。

在呼吸器給予的同步呼吸霧化時，僅在吸氣期間發生，會減少了呼氣時的氣霧損失，所以具有優勢。

此外，與驅動相比，呼吸驅動的噴射霧化器可控制潮氣; 呼吸器外部的氣體，這是一種做法 應該避免[19]。

但是，呼吸 同步以增加治療為代價 持續時間[20]，並與連續進行直接比較 在最佳條件下進行霧化需要進一步研究。



A higher peak inspiratory flow (PIF) than peak expiratory flow (PEF) generates a flow bias toward the lungs, and the inverse (ie, PIF< PEF) generates a flow bias toward the mouth

Fig. 1 Influence of the nebulizer position on aerosol losses during expiration. Nebulizer positioning upstream in the inspiratory limb enables the latter to act as a spacer/reservoir, thereby storing aerosol during expiration for an aerosol bolus delivery at the next insufflation

顆粒大小Particle size

最佳質量中值空氣動力學直徑 The optimal mass median aerodynamic diameter that allows for distal lung deposition ranges from 0.5 to 3 μm

允許遠端肺沉積範圍從0.5到3μm [10]。大於5μm的顆粒明顯 沉積在呼吸器管路和大呼吸道中。

Monitoring

- Bronchospasm and obstruction of expiratory filters are first detected as an increase in the peak airway pressure.
- These complications emphasize the need for close monitoring of the peak airway pressure and oxygenation during nebulization.
- Systemic absorption of antibiotics may be substantial in patients with renal failure, and drug monitoring is recommended when aminoglycosides are used.
- Desaturation and hypoxemia have been reported in patients receiving frequent repeated nebulization.

- Jet Nebulizers Nebulizer Output. Jet nebulizer output is affected by the fill volume, airflow and pressure operating the nebulizer continuous or intermittent nebulization placement of the nebulizer in the ventilator circuit, solution properties duration of treatment and use of a spacer.

- A certain volume of solution (the dead or residual volume) fails to be nebulized in a jet nebulizer. The residual volume, which ranges from 1 mL to 3 mL, can be reduced by using a nebulizer that has a conical shape, by improving the wetness of the plastic surfaces, and by reducing the internal surface area of the nebulizer. During operation of a jet nebulizer, the solution concentration increases and its temperature decreases secondary to evaporative losses (Fig. 1).

- The increased solution concentration and cooling both influence nebulizer output and particle size.

Feel
“Claustrophobic“
as long time :Fighting

Crystallization

Specific nebulization-related side effects need to be considered.

Table 3 Key good practices for optimal antibiotic nebulization during mechanical ventilation

Organization	Use standard operating procedures and a checklist. Ensure adequate staff training
Nebulizer	Use nebulizers with a small residual volume Do not operate jet nebulizers with gas external to the ventilator
Medication solution	Use solutions for inhalation
Nebulizer position	Position the nebulizer (continuous delivery) upstream in the inspiratory limb at 15–40 cm of the *Y*-piece
Humidification	Remove the heat and moisture exchanger during nebulization; if using a heated humidifier, consider switching it off or use of a dry circuit
Ventilator settings	Volume-controlled constant flow ventilation. Use low respiratory rate, low inspiratory flow and a long inspiratory time
Safety	Place a new filter between the expiratory limb and the ventilator for each nebulization Monitor patients closely during the nebulization, particularly in regard to airway pressure, arterial pressure and oxygen saturation Check for resumption of humidification at the end of the nebulization

一、臨床成人及小兒 ICU 及病房，常會遇到病人同時有吸入性及 IV 的 Colistin methanesulfonate(CMS) （乾粉玻璃瓶）。但給予的吸入性及ＩＶ的藥袋上過去皆註明稀釋 2ml，除了造成人員混亂外，也造成 SVN 大量的殘留。已跟藥劑部溝通過，院方已有加註注意事項：ＩＶ每瓶用 2ml 的 NS 或 diswater 溶解；INHL：1vial 用 5ml NS 及 2vial 用 6ml 溶解（與藥師討論及反應給東洋藥廠正式行文後最近更改）。

＊探討原因跟 CMS 藥物稀釋（乾粉不易溶解）及泡製有大量泡沫有關
藥袋上是 colistin 乾粉加入 2ml diswater 或 normal saline 溶解（有些 RT 或一般病房 nurse 會依此泡製）--> 操作時泡沫 --> nebulizer 易有大量白色結晶沉澱物（影響吸藥濃度及劑量）。

目前潛在問題：
1. 有時吸入性藥袋會有少藥的情形，易因ＩＶ使用拿到吸入性藥袋的藥物（同時開立情形又有留藥）
2. 發現有人員將稀釋完成的 colistin 無立即使用，抽吸存放在針筒或玻璃瓶中，再放入冰箱。

根據 FDA 發布的警訊， Colistin methanesulfonate(CMS) 經溶解後若繼續存放，將隨時間逐漸水解成為 Colistin ，吸入治療時可能產生肺部毒性；靜脈注射給藥可能增加腎毒性；因此 Colistin methanesulfonate 經溶解後應盡速使用，勿存放超過 24hr ，但有時因 Colistin 劑量為 2.5 vial 劑量，導致半瓶加入溶劑後久放，也容易與要給 IV 的混淆。宣導人員不要事前泡製 colistin 後久放。

- Practical constraints to optimizing nebulized antibiotic delivery during mechanical ventilation 在機械通氣期間優化霧化抗生素輸送的實際限制
- Delivery of high concentrations of antibiotics to infected lung regions is the key to achieving efficient nebulized antibiotic therapy. 向感染的肺區域輸送高濃度抗生素是實現高效霧化抗生素治療關鍵。
- The antibiotic dose placed in the nebulizer should take into account the significant extrapulmonary drug deposition (i.e., the residual antibiotic volume remaining in the nebulizer chamber, ventilator circuit and endotracheal tube deposition, and exhaled particles).Poor implementation may result in extrapulmonary deposition as high as 97% . 放置在霧化器中的抗生素劑量應考慮到大量的肺外藥物沉積（即霧化器，呼吸器迴路和氣管內導管沉積以及呼出的顆粒中殘留的抗生素殘留量）。實施不當可能導致高達97%的肺外沉積。
- Key practical factors need to be taken into account to optimize delivery.需要考慮關鍵的實際因素來適當運送氣霧

MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med.1985;13:81–4.

Systemic delivery by aerosol

General considerations

- Expensive medication
- Can be delivered intact to acinus and absorbed
- Safe and effective - Not inactivated at airway
- Systemic effects are desired

Patients

- Chronic use
- Administration unpleasant by other routes

Gonda I. J Aerosol Med. 2006;19:47-53

Laube BL. Respir Care. 2005;50:1161-76.

5. Conclusions

The present lung model study shows that the VMN with a low concentration of colistin yields a greater inhaled mass of colistin delivered distal to the endotracheal tube than JN with either concentration. A standard single vial nominal dose of colistin results in a higher delivered dose during mechanical ventilation with a VMN compared to a JN, with a high concentration consisting of two vials. If JN must be used, multiple doses of colistin may compensate for poor delivery performance. The dose of colistin required for the therapeutic effect and bacterial eradication rate warrants further clinical evaluation.

Box 39-5 Factors Affecting Performance of Small Volume Nebulizers

NEBULIZER DESIGN

- Baffles
- Fill volume
- Residual drug volume
- Nebulizer position
- Continuous vs. intermittent nebulization
- Reservoirs and extensions
- Vents, valves, and gas entrainment
- Tolerances in manufacturing within lots

GAS SOURCE: WALL, CYLINDER, COMPRESSOR

- Pressure
- Flow through nebulizer
- Gas density
- Humidity
- Temperature

CHARACTERISTICS OF DRUG FORMULATION

- Viscosity
- Surface tension
- Homogeneity