ESGCIP
ESCMID STUDY GROUP FOR CRITICALLY ILL PATIENTS
European Society of Clinical Microbiology and Infectious Diseases

Educational Workshop
Learning from ESCMID clinical practice guidelines: practical aspects of antibiotic nebulization in patients with respiratory infections

PRACTICAL ASPECTS REGARDING ANTIBIOTICS TO BE NEBULIZED

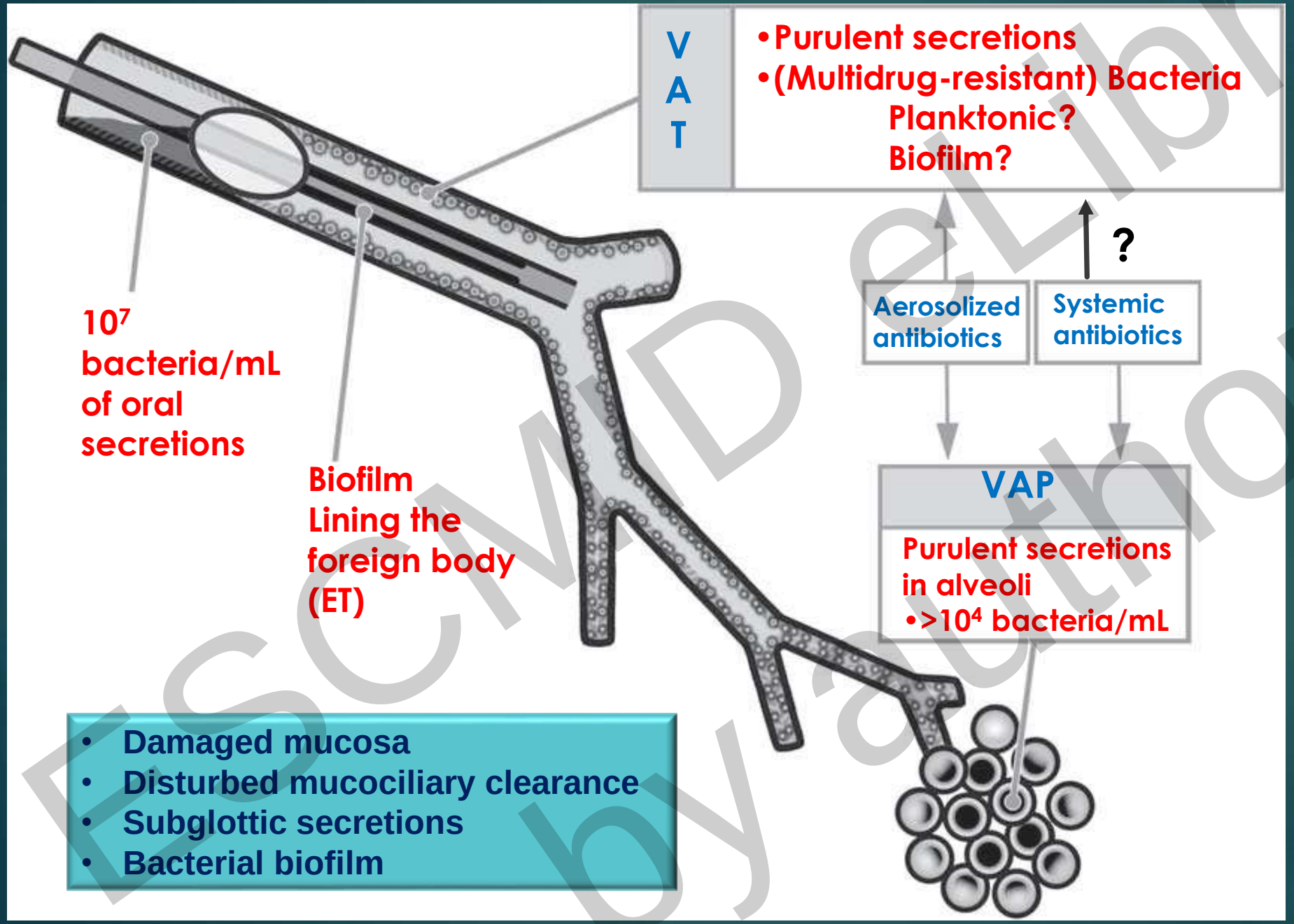
Garyphallia Poulakou
4th Dept of Internal Medicine,
Attikon University Hospital of Athens,

Conflicts of Interest

Speaker and Advisory Honoraria/Research Grants

Pfizer, Astellas, Merck, Bayer

Why do we need nebulized antibiotics for mechanically ventilated patients with Ventilator-Associated-Pneumonia (VAP) and Ventilator-Associated-Tracheobronchitis (VAT)?



Pathway of microbial transfer and particular conditions explaining difficulty of treatment in VAP and VAT

Adapted from
Palmer LB
Curr Opin Pulm Med
2015, 21:239–249

Clinical and microbiological outcomes are not always desirable in VAP and VAT WHY?

- Concentrations in the airway may be lower than in the bloodstream
- Parenteral antibiotics often achieve suboptimal perfusion into consolidated areas of the lungs
- The presence of biofilm may decrease the efficacy of systemic antibiotics
  - The bacteria in this environment may require 10–25 times the minimum inhibitory concentration for bacterical activity

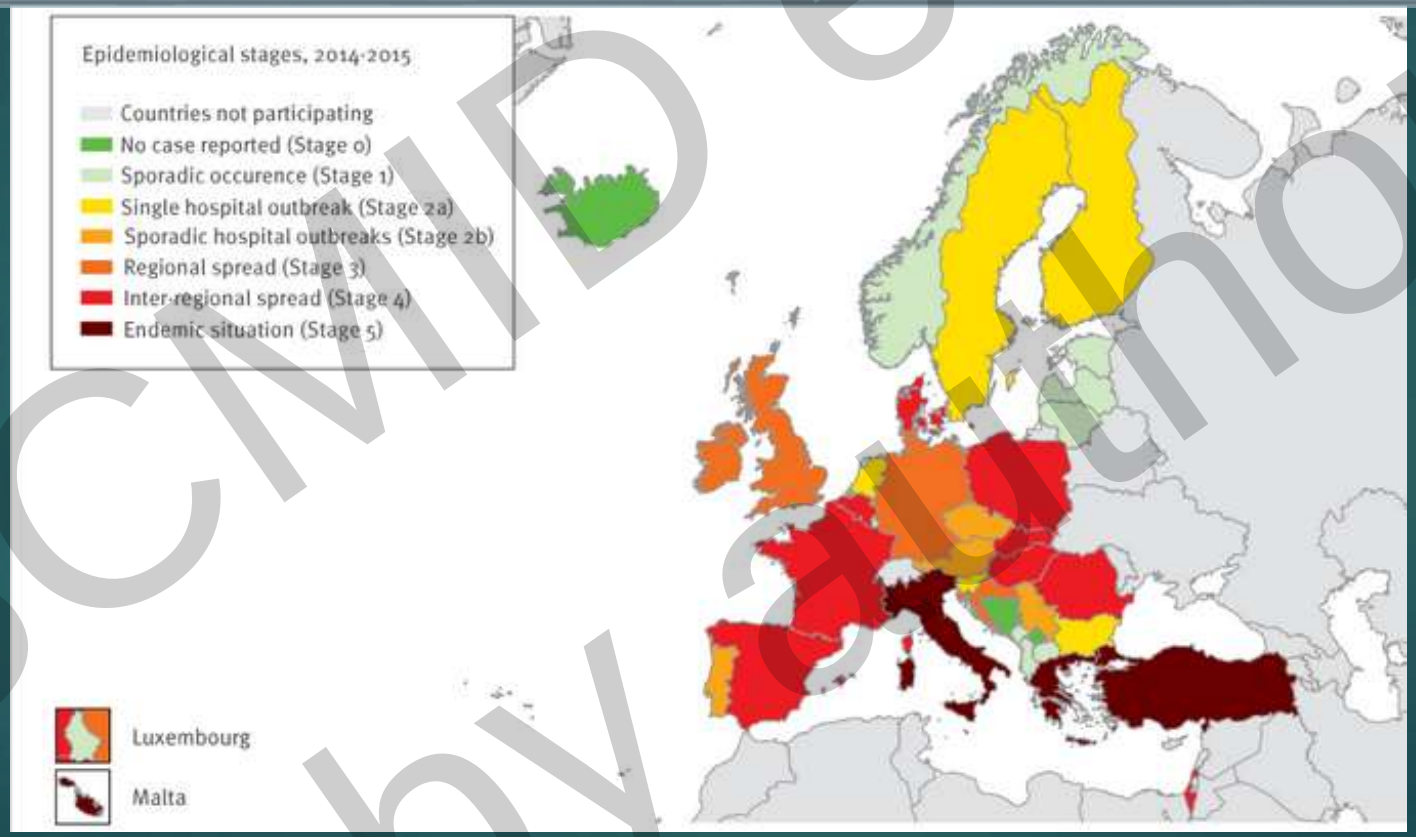
Gil-Perotin S,. Crit Care 2012; 16:R93 *Mendelman PM, Am Rev Respir Dis 1985; 132:761–765.*

Potential benefits of using the inhaled than the intravenous route

1. Increase the clinical and bactericidal efficacy by increasing lung tissue concentrations
2. Reach directly the infected lung parenchyma without crossing cell membranes
3. Decrease systemic toxicity
4. Prevent emergence of resistance

Difficult to treat bacteria further complicate VAP and VAT treatment

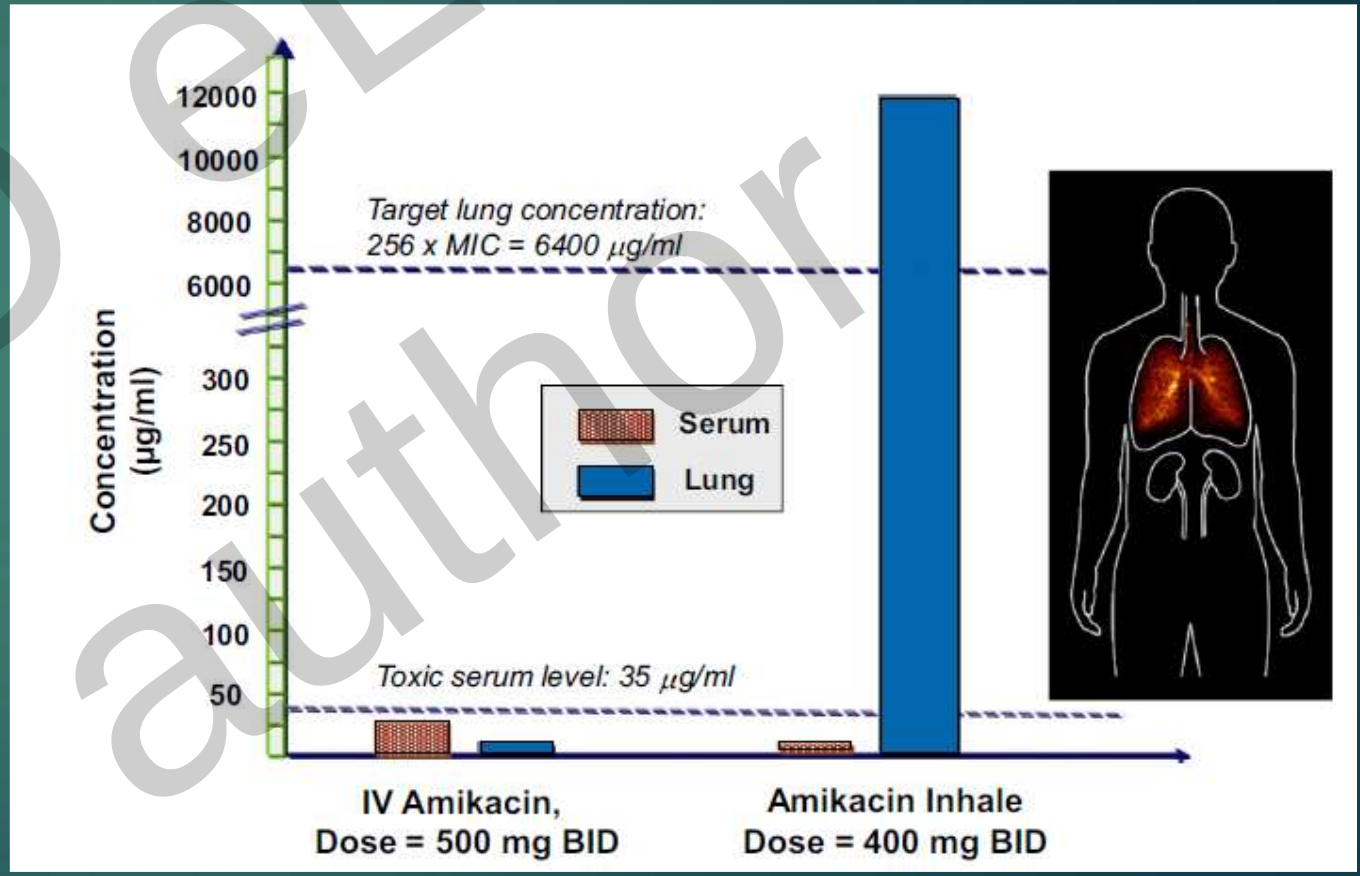
Spread of Carbapenemase –producers in Europe, as of May 2015



Albiger B, Euro Surveill. 2015 Nov 12;20(45)

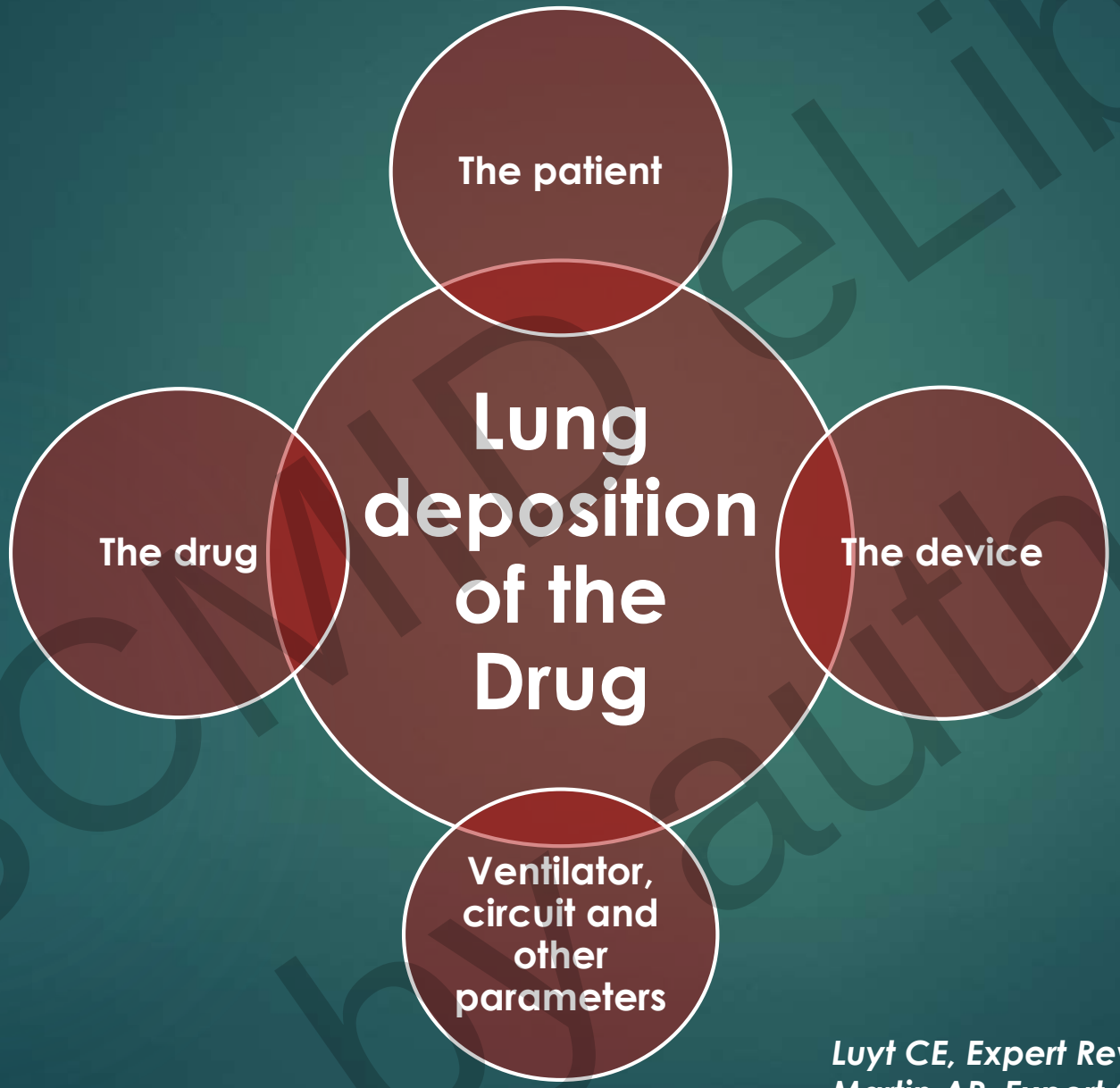
Significant improvements in lung targeting following aerosol administration with corresponding low systemic concentrations

Comparison of mean serum and bronchial secretion concentrations of amikacin following intravenous administration of a 500 mg dose twice daily and inhalation administration of a 400mg dose of Amikacin Inhale twice daily to pneumonia patients



J.Weers / Advanced Drug Delivery Reviews 85 (2015) 24–43

Efficiency of antibiotic nebulization



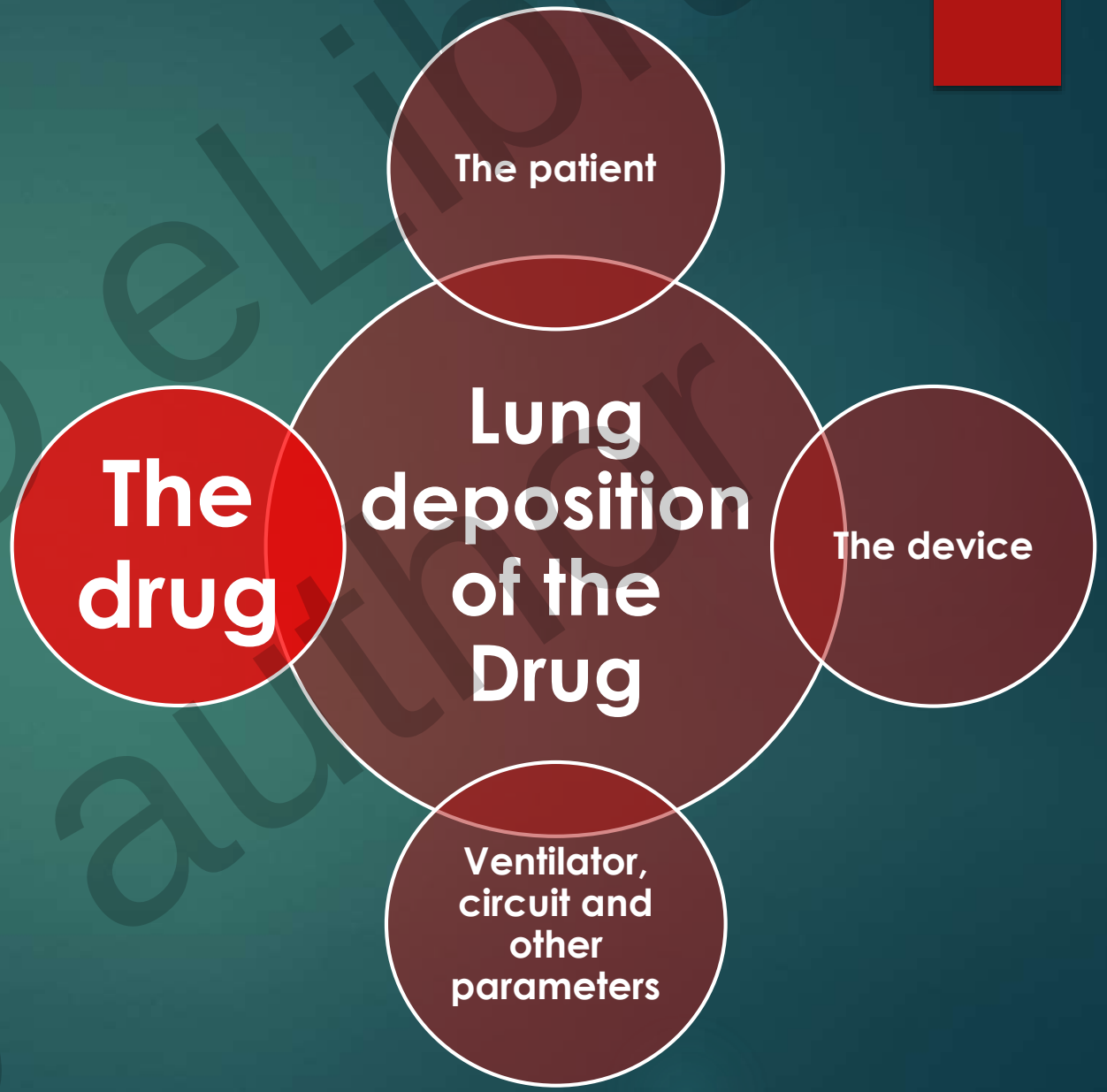
Luyt CE, Expert Rev Anti Infect Ther. 2013; 11:511-521.
Martin AR, Expert Opin Drug Deliv. 2014; 23:1-12.

Efficiency of antibiotic nebulization

Antibiotic characteristics

- charge,
- chemical formula,
- viscosity,
- surface tension,
- dose
- volume of dilution
- bronchial concentration
- toxicity parameters

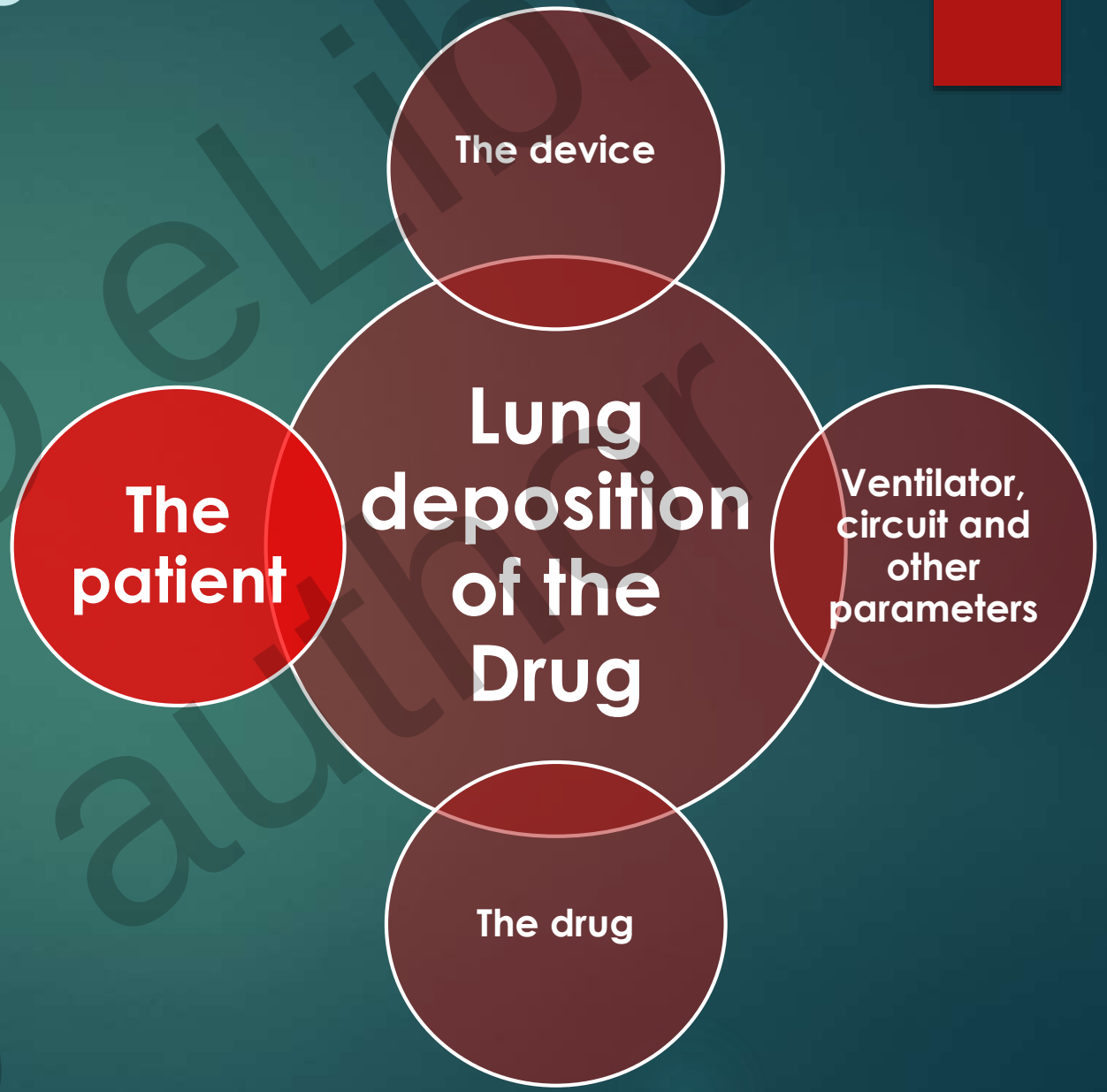
Particle size: 1-5 microns



Efficiency of antibiotic nebulisation

Hyperdynamic hyperinflation
- ARDS
- COPD
- Asthmatic

Production of high volumes of secretions



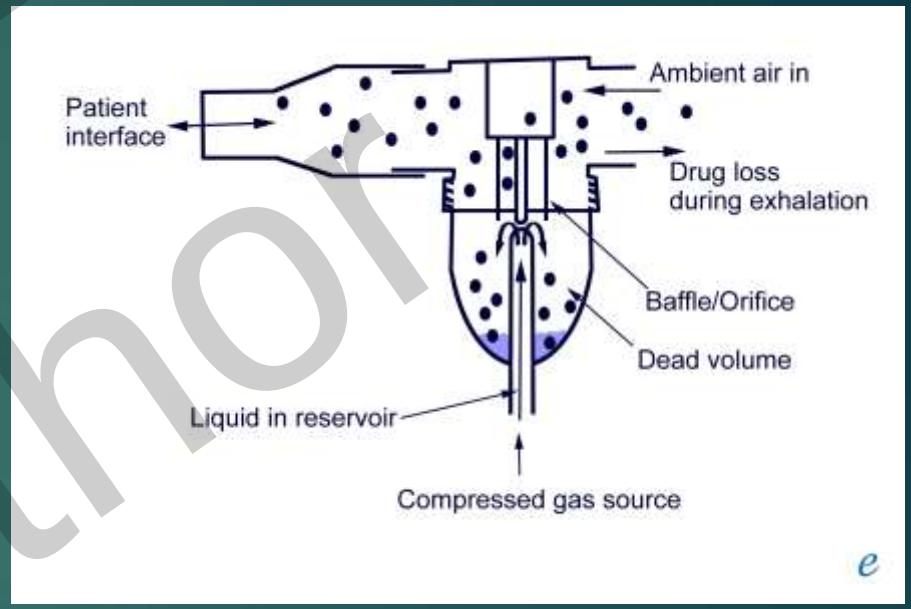
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Online Lecture Library

Slide withheld at request of author

Jet nebulizers

- The most common devices used for antibiotic nebulization in MV patients
- Generation of aerosol particles of antibiotic by exposing it to a highly-pressurized gas flow (high-pressure air or oxygen) which is delivered into the circuit by a connection to the inspiratory limb [continuously, through a direct connection to a wall system (external gas source), or intermittently, when the nebulizer is connected to the ventilator (ventilator-integrated system)]



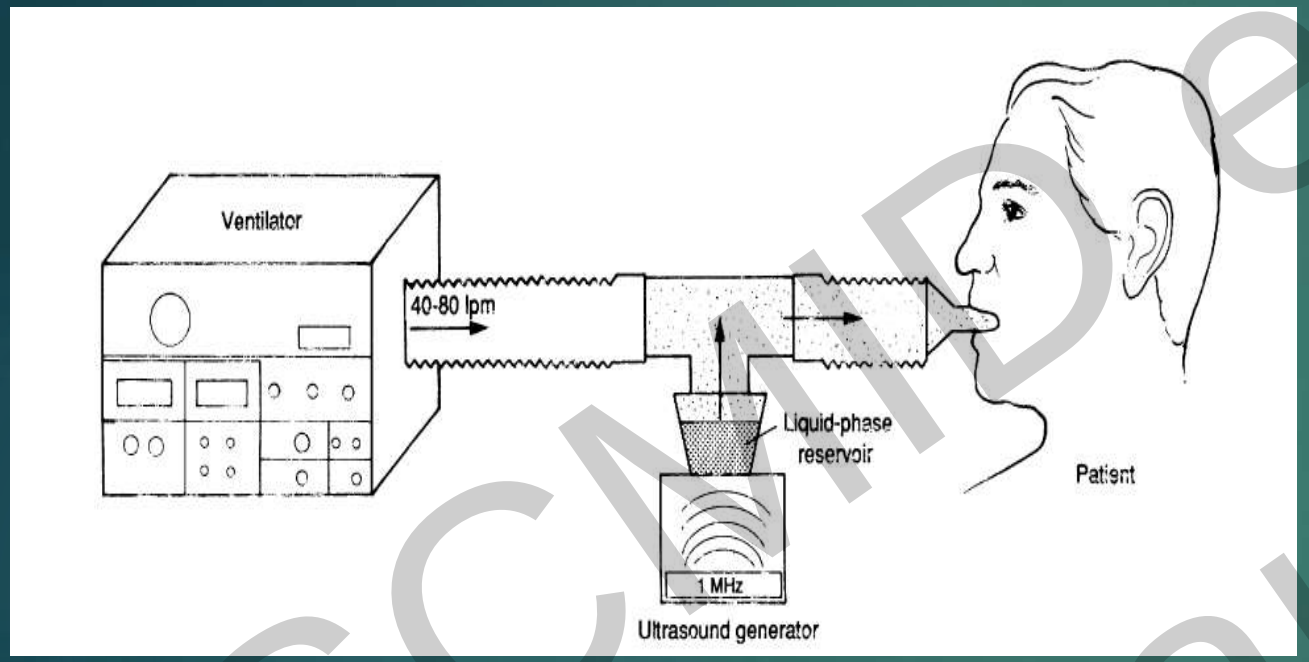
Rouby JJ, Anesthesiology 2012; 117(6):1364-1380.
Figure source http://ekgmachines.org/article/85171733/jet-nebulizer

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Online Lecture Library

Slide withheld at request of author

Ultrasonic nebulizers



- Ultrasonic nebulizers are composed by a large reservoir of the drug, and a piezoelectric quartz crystal that generates the aerosol by its vibration
- The amount of drug aerosolized is directly proportional to the amplitude of the vibration
- The size of the particle is inversely proportional to the vibration's frequency

Aerosol particles are delivered into the lung by an independent low flow together with the air flow of the ventilator, causing almost no turbulences in the circuit

Steckel H, Eur J Pharm Sci. 2003; 19: 443-455.

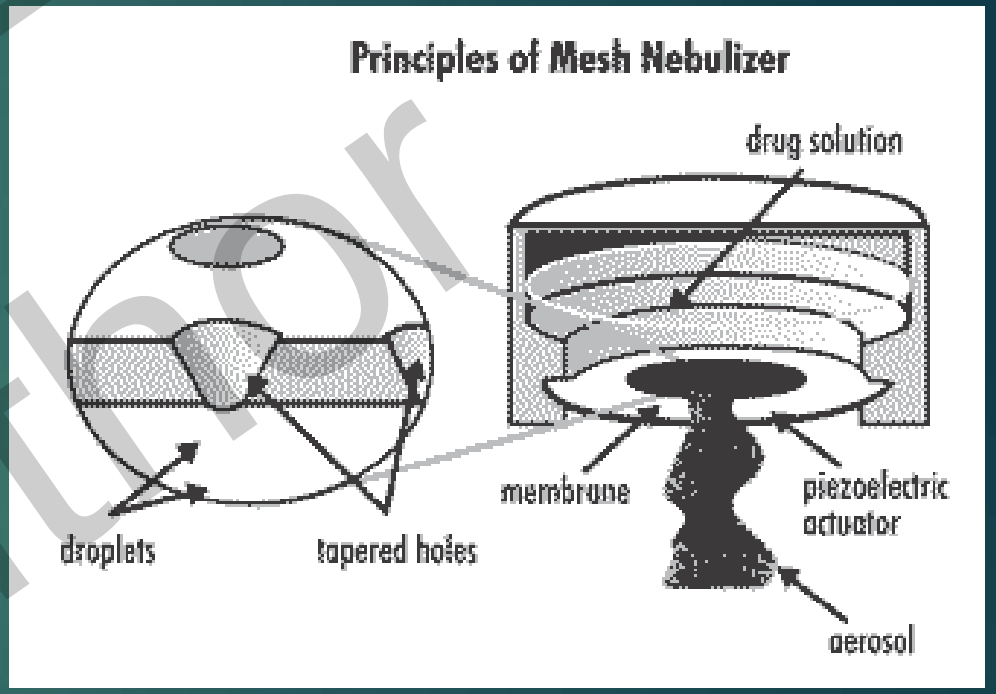
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Online Lecture Library

Slide withheld at request of author

Vibrating Mesh nebulizers

- The newest generation of nebulizers
- They consist on a drug reservoir placed above a tapered holes plate, which has a rapid upward-downward movement similar to a pump, created by a ceramic vibrational element
- The aerosol particle size depends directly on the diameter of the tapered holes of the plate, but it can vary from 1 to 5μm.
- A particular type of vibrating-mesh nebulizer is the Pulmonary Drug Delivery System (PDDS), a drug-device combination system delivering amikacin



Luyt, CE Crit Care 2009; 13: R200.
Niederman MS, Intensive Care Med. 2012; 38: 263-271.
Luyt CE, J Aerosol Med Pulm Drug Deliv. 2011; 24: 183-190.

Vibrating mesh nebulizers

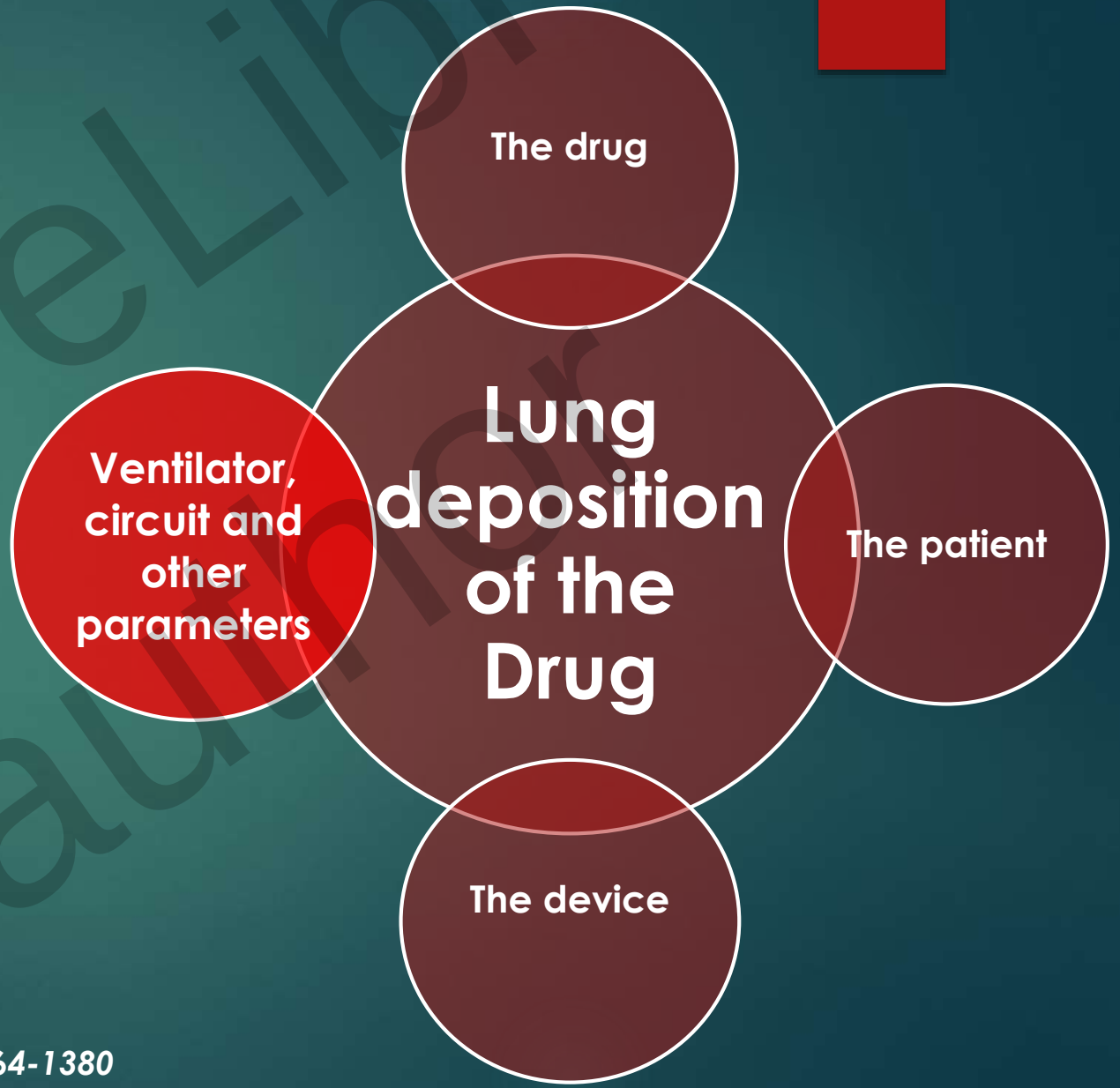
Advantages	Drawbacks
• Efficient delivery of the drug into the lungs: 40-60% of the initial dose • Homogeneous droplet's diameter • No temperature increase of the delivered drug • Good synchrony with ventilator • Low residual drug volume loss • Easy to use • Low dimension at the bedside • Single use	• High cost • Not suitable for concentrated and viscous solutions

Rouby JJ, Anesthesiology 2012; 117(6):1364-1380.
Ehrmann S, Respir Care 2014; 59: 1508-1516.

Ari A, Respir Care 2010; 55: 837-844
Dhand R. Respir Care 2007; 52: 866-884.

Efficiency of antibiotic nebulization

- Minimise turbulences
  - volume-controlled mode,
  - constant inspiratory flow,
  - tidal volume of 8ml/kg,
  - inspiratory to expiratory (I:E) ratio ≤ 50%
  - end-inspiratory pause of 20% of the duty cycle
- Avoid asynchrony with the ventilator (a temporary increase in the level of sedation may be necessary)



Rouby JJ, Anesthesiology 2012; 117(6):1364-1380
O' Doherty et al, Am Rev Respi Dis 1992 (146):383-8

Optimized use of the three types of nebulizers

	Jet nebulizer	Ultrasonic nebulizer	Vibrating mesh nebulizer
Operating mode	Continuous or intermittent[a]	Continuous	Continuous
Best position	Inspiratory limb Proximal to ventilator (15 cm from it)	Inspiratory limb Proximal to the patient (10-15cm from the Y-piece)	Inspiratory limb Proximal to the patient (10-15cm from the Y-piece)
Humidification	No	No	No

[a] depending on the gas source (external or ventilator-integrated).

Ari A, Respir Care 2010; 55: 837-844
Dhand R. Respir Care 2007; 52: 866-884.

Other parameters

Important considerations	Avoid sharp angles and rough inner surfaces in the ventilator's circuit Remove heat and moisture exchanger during the procedure Stop heat humidifiers during nebulization Change expiratory filter after each nebulization

Miller DD, Am J Respir Crit Care Med. 2003; 168: 1205-1209.
Phipps PR, Chest 1990; 97: 1327-1332.
Rao N, J Aerosol Med Pulm Drug Deliv. 2010; 23: 295-302.
Lu Q, Am J Respir Crit Care Med. 2011; 184: 106-115.

Preparation of the antibiotic solution

- The prescribed antibiotic dose should be prepared under sterile conditions, immediately before its administration, to avoid possible alterations in the stability of the drug, particularly when administering colimycin.
- The total volume of the solution should not exceed the maximum filling capacity of the device, and should be administered within a time frame of 30 to 60 minutes,
- Dosage intervals are strictly dependent on the PK/PD properties of the nebulized antibiotic
- Colimycin, which is a concentration-dependent antibiotic but has a weak post-antibiotic effect, should be administered in two or three daily doses whereas aminoglycosides once daily

Luyt, CE, Crit Care 2009; 13: R200.
Luyt CE, J Aerosol Med Pulm Drug Deliv. 2011; 24: 183-190.

Lu Q, Am J Respir Crit Care Med. 2011; 184: 106-115.
Goldstein I, Am J Respir Crit Care Med. 2002; 166: 1375-1381.
Lu Q, Intensive Care Med. 2010; 36: 1147-1155.

How to avoid toxicity related to the ventilator's circuit

- Place a filter on the expiratory limb (before the flow meter)
- Change the expiratory filter after each nebulization
- Suspend heat and humidification, EXCEPT for patients with thick secretions that tend to occlude the system and in patients with bronchial spasticity
- Minimize disconnection of the circuit, specially in patients with severe hypoxemia

ESCMID Clinical Practice Guidelines: Nebulized Antibiotic Treatment of Respiratory Infections in Critically Ill Mechanically Ventilated Patients, final draft

How to avoid toxicity related to monitoring during nebulization

- Monitor the peak airway pressure. An increase may be related to obstruction of the expiratory filter (change it immediately !) or to bronchospasm.

If the bronchospasm is :

a) mild : withdraw nebulization and administer local bronchodilators before the following nebulization.

b) Severe and/or persistent : consider another nebulized antibiotic or change the route of administration.

- Monitor oxygenation, during nebulization process

- Monitor level of sedation. Low doses of propophol avoid asynchronies with the ventilator. Midazolam instead of propophol can be used in haemodynamically unstable patients.
- If sedation was increased to improve nebulization, it should be immediately withdrawn after its completion

How to avoid systemic toxicity following nebulization

- Monitor renal function (serum creatinine levels), specially when nebulizing aminoglycosides and colistin and particularly in patients with previous renal dysfunction
- If possible monitor serum drug levels

Lu Q, Am J Respir Crit Care Med. 2011; 184: 106-115.
Goldstein I, Am J Respir Crit Care Med. 2002; 166: 1375-1381
Burdette SD, Antimicrob Agents Chemother. 2009; 53 (10): 4568

How are inhaled antibiotics used in real life?

RESULTS FROM AN ELECTRONIC SURVEY PERFORMED BY ESGCIP

Survey of **A**ntimicrobial **NE**bulization in **ME**chanically ventilated patients (**SANEME** Study)

ESGCIP ESCMID STUDY GROUP FOR CRITICALLY ILL PATIENTS
European Society of Clinical Microbiology and Infectious Diseases

Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines

C. Solé-Lleonart[1,2], J. A. Roberts[3], J. Chastre[4], G. Poulakou[5], L. B. Palmer[6], S. Blot[7], T. Felton[8], M. Bassetti[9], C.-E. Luyt[4], J. M. Pereira[10], J. Riera[11], T. Welte[12], H. Qiu[13], J.-J. Rouby[14] and J. Rello[15], the ESGCIP Investigators

Clin Microbiol Infect 2016pii: S1198-743

- Aimed to investigate practices of nebulized antibiotics in mechanically ventilated patients among implicated physicians
- The survey was performed from October 2014 to January 2015, using an electronic platform (SurveyMonkey ®)
- A total of 192 HCW completed the survey. Between them 135 had administered nebulized antibiotics during the previous week to completing the questionnaire

Indications for use of nebulized antibiotics: results from the SANEME study

Indication reported	Total (n=87)	
	Neb + IV n (%)	Neb alone n (%)
VAP treatment	50 (58)	8 (9)
VAT treatment	38 (44)	20 (23)
Prophylaxis	18 (21)	26 (30)
MDRO treatment	58 (67)	9 (10)
MDRO colonization	24 (28)	22 (25)
Viral infection treatment	20 (23)	14 (16)
Fungal prophylaxis	24 (28)	17 (20)
Fungal treatment	28 (32)	10 (12)

Different dose-regimens depending on the indication: VAP dose>VAT dose for colistin and aminoglycosides

Neb – nebulised antibiotic therapy; IV – intravenous antibiotic therapy;
VAP – ventilator associated pneumonia; VAT – ventilator associated tracheobronchitis; MDRO – multi-drug resistant organism

Sole C, Clin Microbiol Infect 2016

The SANEME study
Indication and regimens summary

- The existence of a multidrug-resistant (MDR) pathogen was the most important factor for the initiation of nebulized antibiotics
- Treatment of VAT and VAP were the most common among various indications
- Dosing regimens varied greatly
- Colistimethate sodium, tobramycin, amikacin and colistin sulfate were the most used formulations
- At least 14 different antimicrobials were reported as nebulized in the week preceding completion of the survey!

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

Candela Solé-Lleonart MD, Jean-Jacques Rouby MD PhD, Jean Chastre MD, Garyfallia Poulakou MD PhD, Lucy B Palmer MD PhD, Stijn Blot MNSc PhD, Tim Felton MD PhD, Matteo Bassetti MD PhD, Charles-Eduard Luyt MD PhD, Joao Manuel Pereira MD, Jordi Riera MD PhD, Tobias Welte MD PhD, Jason A Roberts PhD, and Jordi Rello MD PhD

Respir Care. 2016 Mar 8. pii: respcare.04519

ESGCIP ESCMID STUDY GROUP FOR CRITICALLY ILL PATIENTS
European Society of Clinical Microbiology and Infectious Diseases

Type of Devices Used According to the Experience of the ICUs

	<3 y of Experience ($n = 47$)		≥3 y of experience ($n = 40$)	
	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

* $P < .05$.

Only 1:4 users employs adequate technique ensuring safety and efficacy of nebulized antibiotics

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

* $P < .05$.

Risk of obstruction of the filter and cardiac arrest

An RCT is needed

Solé C, Respir Care. 2016 Mar 8. pii: respcare.04519

How accustomed are physicians with the practical aspects of safety?

- Adherence to adequate practices relating to efficacy and safety is poor and independent of the experience with the technique
- Failure to change the expiratory filter after each nebulization procedure represents the most important concern.

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

Concern	*n*	%	% 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.

Solé C, Respir Care. 2016 Mar 8. pii: respcare.04519

A major practical issue:

There is a need for standardization of the use of nebulized antibiotics!

Conclusions

- Ventilator-associated respiratory infections caused by resistant Gram-negative organisms are a challenge for intensivists
- Nebulized antibiotics when delivered properly may become an important part of treating these infections
- Advanced technology devices may achieve concentrations several times above the required for treatment and development of resistance
- Careful consideration of aerosol generator, ventilator, drug and patient's parameters is important to ensure efficacious delivery of nebulized antibiotics in critically ill MV patients
- Consensus and education is needed

ESGCIP

ESCMID STUDY GROUP FOR CRITICALLY ILL PATIENTS

European Society of Clinical Microbiology and Infectious Diseases

Apply now for membership!

Business meeting:

Sunday, 10 April 2016, 12.30 h - 13.30 h (Room: E102)

Thank you for your attention

gpoulakou@gmail.com

Attikon University General Hospital of Athens