# Inhalation therapy for multidrug-resistant Gram-negative bacteria to treat HAP/VAP

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# Intravenous administration for pneumonia

- Insufficient parenchymal lung tissue penetration
- Bronchial secretions :insufficient drug concentration at the target site

→ Aerosolized therapy to bypass the alveolar-capillary barrier

# Is Inhaled Antibiotics Therapy Effective To Treat HAP/VAP Patients with resistant pathogens?

**P**: Patients with HAP/VAP due to resistant pathogens

**I**: Systemic therapy

**C**: Inhaled therapy or systemic plus inhaled combination therapy

**O**: Clinical outcomes (mortality, treatment failure, resolution, hospital LOS), adverse drug effects (systemic toxicity as nephrotoxicity)

# Drug for inhalation therapy

- **Aminoglycosides**
  - **Amikacin**
  - **Tobramycin**
  - **Gentamycin**

- **Colistin**

# Method

1) **Adjunctive therapy**

: Nebulized colistin or aminoglycoside administered to patients already receiving IV colistin or aminoglycosides

2) **Substitution therapy**

: Nebulized colistin or aminoglycoside administered to patients already not receiving IV colistin or aminoglycosides, but only standard first-line IV antibiotics

# Aminoglycosides

# Endotracheal Gentamicin in Bronchial Infections in Patients with Tracheostomy*

*Jean Klastersky, M.D.; Christiane Geuning, M.D.;** Emile Mouawad, M.D.;** and Didier Daneau*

**Table 3—*Relationship between the Outcome and the Levels of Gentamicin in the Blood and in the Sputum.***

| | Microorganism | Cure: Bacteriologic | Cure: Clinical | Colonization of the Respiratory Tract | Levels of Gentamicin (μg/ml): Serum | Levels of Gentamicin (μg/ml): Sputum |
|---|---|---|---|---|---|---|
| Intramuscular Gentamicin | | | | | | |
| 1 | *Pseudomonas* | No | No | | 12 | <0.5 |
| 2 | *Klebsiella* | No | No | *Proteus mirabilis* | 4 | <0.5 |
| 3 | *Klebsiella* | No | No | | 4 | <0.5 |
| 4 | *Proteus mirabilis* | No | No | *Pseudomonas* | 8.5 | <0.5 |
| 5 | *Klebsiella* | Yes | Yes | | 11 | <0.5 |
| 6 | *Pseudomonas* | Yes | Yes | | 3 | <0.5 |
| 7 | *Klebsiella* | No | No | | 3 | <0.5 |
| 8 | *E. coli* | No | No | Yeasts, *Pseudomonas* | 5 | <0.5 |
| Intratracheal Gentamicin | | | | | | |
| 1 | *Proteus mirabilis* | Yes | Yes | | 1.7 | >20 |
| 2 | *E coli* | Yes | Yes | *Klebsiella* | 2.0 | >20 |
| 3 | *Pseudomonas* | No | Yes | | 1.9 | >20 |
| 4 | *Proteus mirabilis* | No | Yes | | 1.3 | >20 |
| 5 | *Klebsiella* | Yes | Yes | | 3.0 | 8 |
| 6 | *Pseudomonas* | Yes | Yes | | 6.8 | 7.5 |
| 7 | *Pseudomonas* | No | Yes | | 1.9 | >20 |

Chest (1972) 62 (2) 117-120

# Double-Blind Study of Endotracheal Tobramycin in the Treatment of Gram-Negative Bacterial Pneumonia

RICHARD B. BROWN,[1,2]* JAMES A. KRUSE,[3] GEORGE W. COUNTS,[4] JAMES A. RUSSELL,[5] NICHOLAS V. CHRISTOU,[6] MICHAEL L. SANDS,[1,2] AND THE ENDOTRACHEAL TOBRAMYCIN STUDY GROUP†

TABLE 2. Information on assessable patients

| Treatment or response | No. (%) of patients who received: ETT ($n$ = 25) | Placebo ($n$ = 16) |
|---|---|---|
| Antibiotic | | |
| Cefazolin | 7 (28) | 3 (19) |
| Piperacillin | 18 (72) | 13 (81) |
| Clinical response | | |
| Improvement | 20 (80) | 13 (81) |
| Relapse or failure | 5 (20) | 3 (19) |
| Bacteriologic response | | |
| Pathogen eliminated[a] | 17 (68) | 5 (31) |
| Recurrence | | |
| Same susceptibility | 3 (12) | 2 (13) |
| Resistance | 1 (4) | 0 |
| New pathogen | 1 (4) | 2 (13) |
| Failure | 3 (12) | 7 (44) |

[a] $P < 0.005$ between treatment groups.

Antimicrob agents and chemo (1990) 269-272

# Aerosolized Tobramycin in the Treatment of Ventilator-Associated Pneumonia: A Pilot Study*

ALI HALLAL,[1] STEPHEN M. COHN,[2] NICHOLAS NAMIAS,[1] FAHIM HABIB,[1]
GIO BARACCO,[1] RONALD J. MANNING,[1] BRUCE CROOKES,[3] and CARL I. SCHULMAN[1]

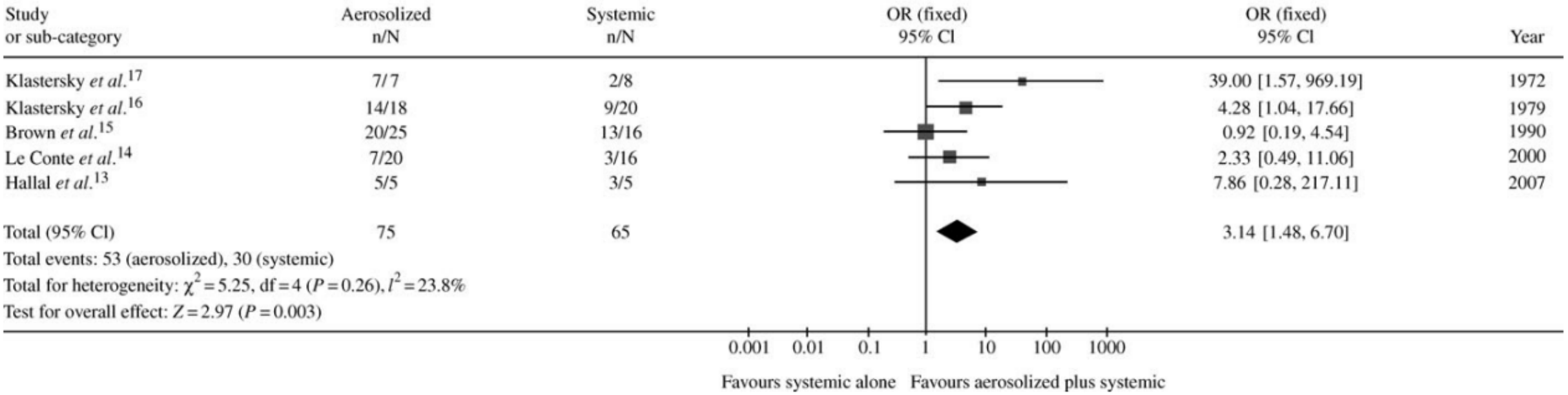
Positive culture for P.aeruginosa or A. baumannii spp. (5/5)

***Results*: All TOBI patients had clinical resolution of VAP. Two TOBRA patients were considered failures. One had deterioration in MODS, and the other had doubling of his serum creatinine concentration. The patients treated with TOBI may have had more ventilator-free days than those receiving TOBRA, but the difference was not statistically significant owing to the small sample size (24 ± 3 vs. 14 ± 13 days; p = 0.12).**

***Conclusion*: Aerosolized tobramycin for the treatment of VAP appeared safe and effective in this pilot study. A larger study is warranted to determine if aerosolized tobramycin will lead to better outcomes than intravenous tobramycin when used for the treatment of VAP.**

Surgical infections (2007) 8:1:73-81

# Treatment success




Favor systemic alone

Favor aerosolized + systemic

*Journal of Antimicrobial Chemotherapy* (2007) **60**, 1216–1226

# Colistin

- High molecular weight
- Hydrophobicity
- Cationic nature of decapeptide

→ **Low tissue penetration during IV administration**

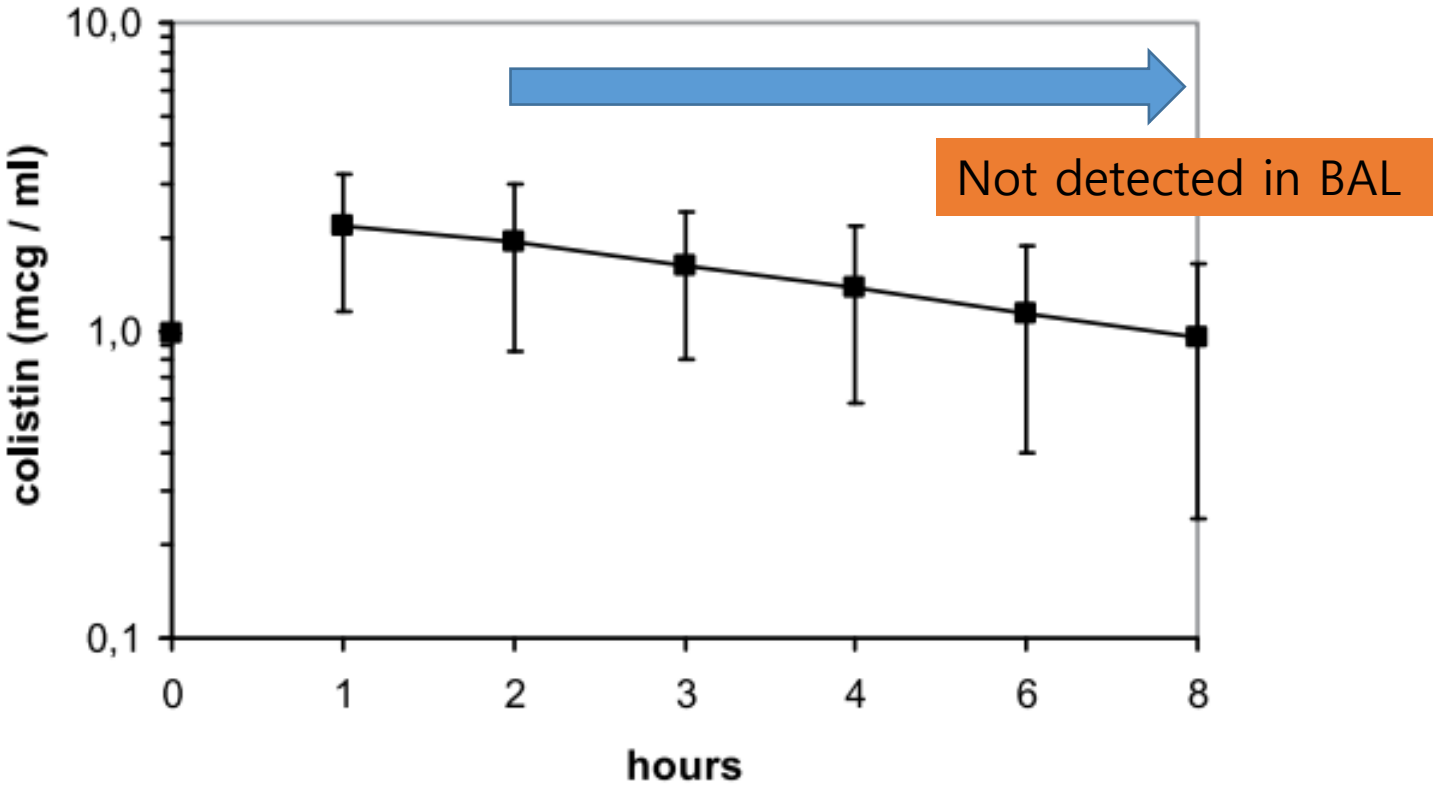



FIGURE 1. Plasma concentration of colistin at steady state. Two million International Units (174 mg) of colistin methanesulfonate (CMS) were administered IV in 30 min at time 0. Colistin in plasma was measured at the indicated time points. Data are presented as mean ± SD.

Chest (2010) 138:1333-1339

# High concentration in lung tissue or epithelial lining fluid on aerosolized colistin therapy

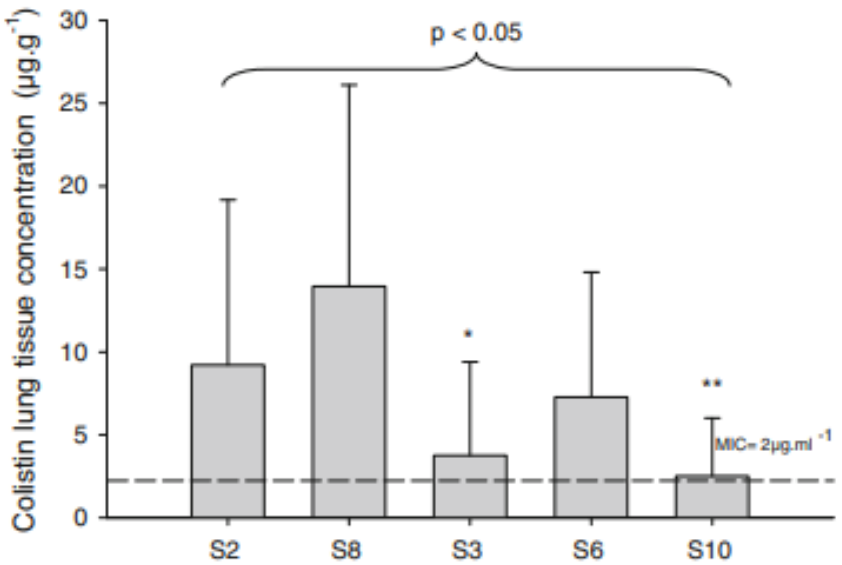



**Fig. 1** Regional distribution of colistin peak lung tissue concentrations measured 1 h after the third aerosol of colistin on lung specimens obtained in different lung segments (*S*) representative of each lobe: upper lobe (*S2*), middle lobe (*S3*), and lower lobe (*S6*, *S8*, and *S10*). *MIC* Minimal inhibitory concentration. $p < 0.05$ at the top of the figure indicates statistically significant difference existing between lung segments compared using one-way analysis of variance for repeated measures. Comparisons between two lung segments were performed using post hoc Fisher LSD test: *S3 versus S8, $p < 0.05$, **S10 versus S8, $p < 0.05$

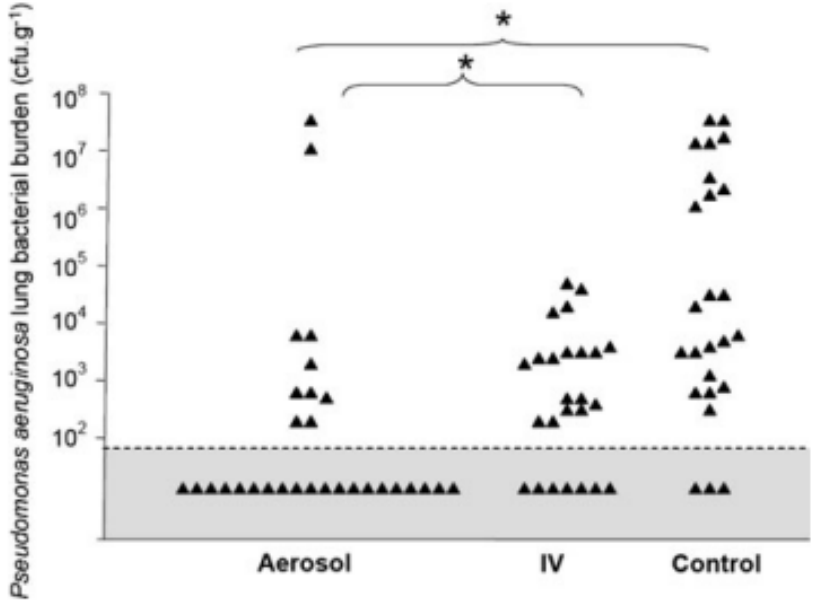



**Fig. 3** Lung bacterial burden of *Pseudomonas aeruginosa* after 24 h of colistin administration. Lung segments (*triangles*) were sampled 1 h after the third aerosol in the aerosol group and after the fourth infusion in the intravenous group (*IV*) and 49 h after the bacterial inoculation in the untreated control group. The *grey area* indicates the lower limit of quantification for bacterial counts. *Asterisk* at the top of the figure indicates statistically significant difference existing between the percentage of lung segments characterized by bacterial counts ranging between 0 and $10^2$ cfu $g^{-1}$ in aerosol and intravenous groups and in aerosol and control groups

Intensive Care Med (2020) 36:1147-1155

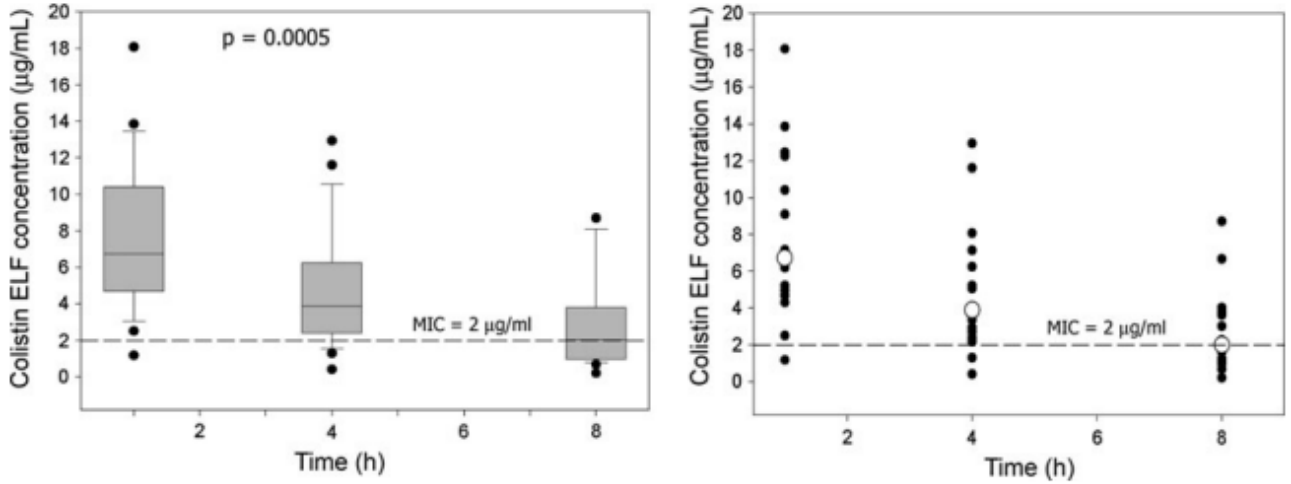



**Fig. 1** Colistin concentrations in ELF at 1, 4 and 8 h after administration of 80 mg of nebulized CMS. *Left panel* shows medians and 25–75 % IQRs; *right panel* shows individual values. *Dashed lines* represent MIC of colistin for *A. baumannii* and *K. pneumoniae* according to EUCAST susceptibility breakpoints. Variation among median concentrations at the different time points was significant ($P = 0.0005$); the median colistin concentration at 1 h was significantly higher than the concentration at 8 h ($P < 0.001$, Dunn's multiple comparisons post hoc test)

1, 4, 8hr (BAL)

0.16, 0.5, 1, 2, 4, 8hr (Serum)

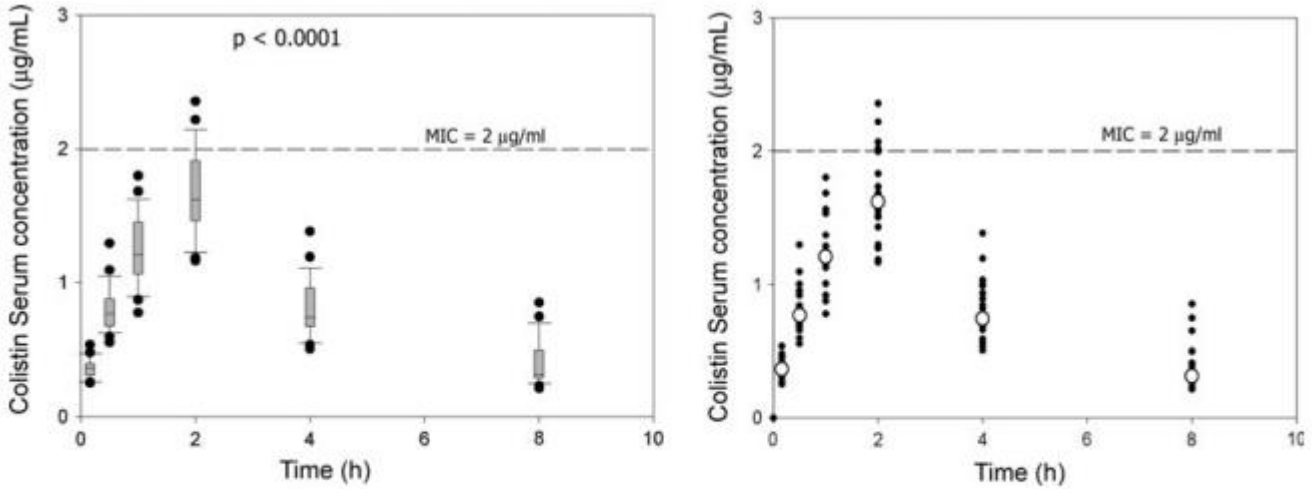



**Fig. 2** Colistin concentrations in serum at 0.16, 0.5, 1, 2, 4 and 8 h after administration of 80 mg of nebulized CMS. *Left panel* shows medians and 25–75 % IQRs; *right panel* shows individual values. *Dashed lines* represent MIC of colistin for *A. baumannii* and *K. pneumoniae* according to EUCAST susceptibility breakpoints. Variation among median concentrations at the different time points was significant ($P < 0.0001$); the median concentration at 2 h was significantly higher than the concentrations at other time points ($P < 0.001$, Dunn's multiple comparisons post hoc test)

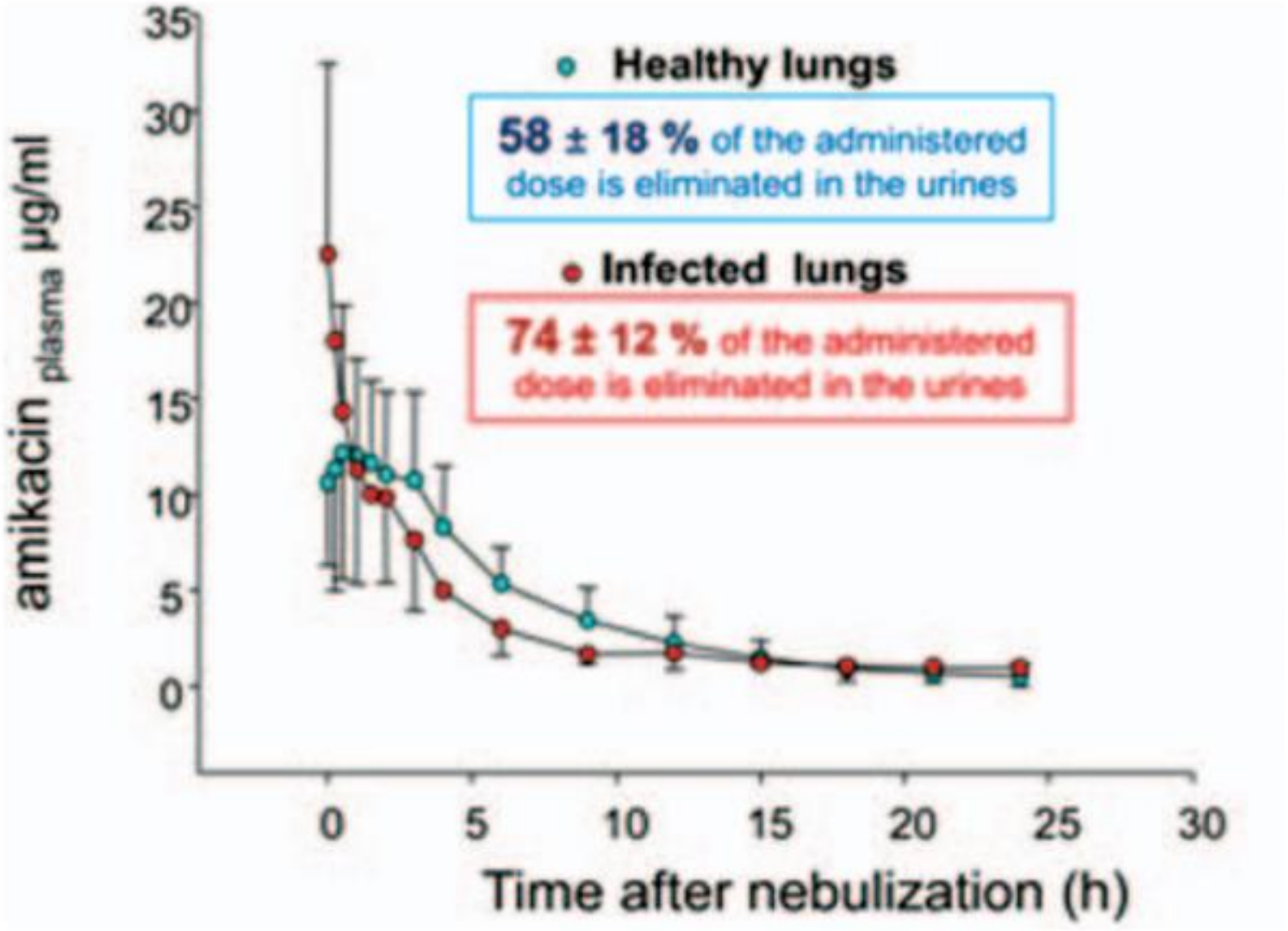
Intensive Care Med (2012) 38:1779-1786

**Table 2** Pharmacokinetic and pharmacokinetic/pharmacodynamic ELF and serum parameters for inhaled colistin. Values are medians (25–75 % interquartile ranges)

| Parameter | ELF | Serum |
|---|---|---|
| $AUC_{0-8h}$ (μg/mL × h) | 29.8 (21.9–54.5) | 6.8 (6.2–8.2) |
| AUC/MIC | 40.0 (26.8–60.1) | 9.7 (6.0–13.7) |
| Maximum observed concentration (μg/mL) | 6.7 (4.8–10.1) | 1.6 (1.5–1.9) |
| Maximum observed concentration/MIC | 9.7 (5.2–21.8) | 2.4 (1.4–3.3) |
| Minimum observed concentration (μg/mL) | 2.0 (1.0–3.8) | 0.3 (0.3–0.5) |
| Half-life (h) | – | 2.7 (2.5–3.1) |
| Volume of distribution/fraction of dose absorbed (l) | – | 25.0 (21.7–29.4) |
| Clearance/fraction of dose absorbed (l/h) | – | 6.4 (4.8–6.8) |
| Time colistin concentration above MIC (h)[a] | 4.1 (2.0–6.0) | – |
| Serum/ELF ratio | | |
| At 1 h | 0.17 (0.13–0.26) | |
| At 4 h | 0.19 (0.15–0.25) | |
| At 8 h | 0.19 (0.11–0.29) | |

[a] Estimated from single-dose data

Intensive Care Med (2012) 38:1779-1786




Anesthesiology 117:1364-1380

**Lung dose** *reaching bronchioles and alveoli*

**Bronchioles**

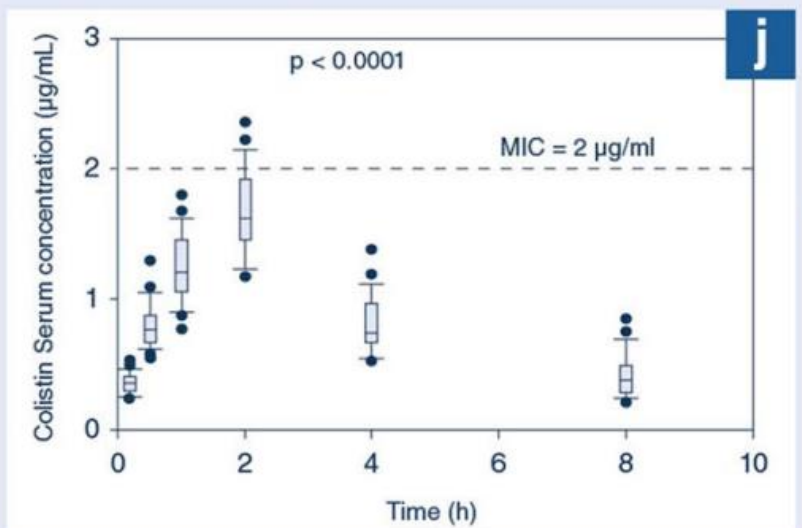
**Alveoli**

**Exhaled dose**
*tracheal suctioning*

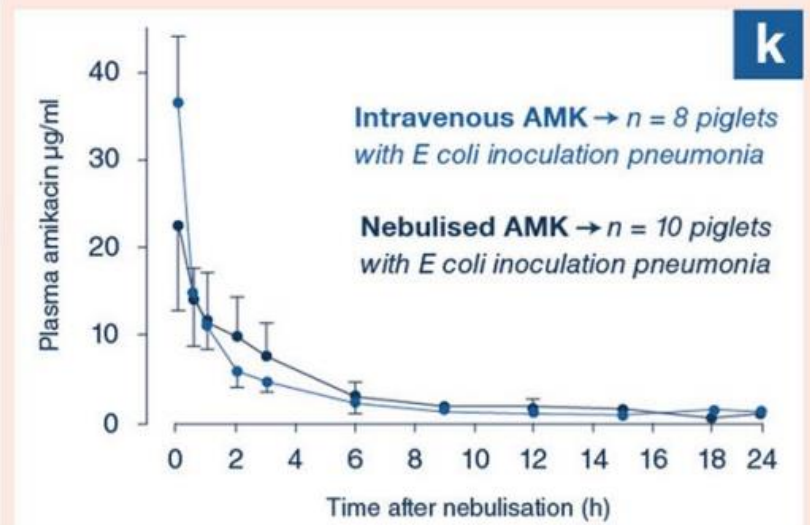
**Systemic absorption**

Routine dosage of trough plasma levels to detect systemic toxicity

**Colistin**
*in presence of lung infection, low sistemic diffusion*




**Amikacin**
*in presence of lung infection, high sistemic diffusion*




**Urinary excretion**

Intensive Care Med (2020) 766-770
Anesthesiology 117:1364-1380

RESEARCH ARTICLE Open Access

# A retrospective observational study on the efficacy of colistin by parenteral administrat nosocomial pneumon multidrug-resistant *Ps*

Reinout Naesens[1*], Erika Vlieghe[2], Walter Verbrug

**Abstract**

**Background:** Colistin is used as last treatment option for pneumonia associated with multidrug-resistant (MDR) *Pseudomonas* spp.. Literature about the best administration mode (inhalation versus parenteral treatment) is lacking.

**Methods:** A retrospective study of 20 intensive care patients with a pneumonia associated with MDR *P. aeruginosa* receiving colistin sulphomethate sodium (Colistineb®) between 2007 and 2009 was performed. A strain was considered multidrug-resistant if it was resistant to at least 6 of the following antibiotics: piperacillin-tazobactam, ceftazidime, cefepime, meropenem, aztreonam, ciprofloxacin, and amikacin. The administration mode, predicted mortality based on the SAPS3 score, SOFA score at onset of the colistin treatment, clinical and microbiological response, and mortality during the episode of the infection were analysed. The non parametric Kruskal-Wallis and Fisher's Exact test were used for statistical analysis of respectively the predicted mortality/SOFA score and mortality rate.

**Results:** Six patients received colistin by inhalation only, 5 were treated only parenterally, and 9 by a combination of both administration modes. All patients received concomitant beta-lactam therapy. The mean predicted mortalities were respectively 72%, 68%, and 69% (p = 0.91). SOFA scores at the onset of the treatment were also comparable (p = 0.87). Clinical response was favorable in all patients receiving colistin by inhalation (6/6) and in

**Clinical response : inhalation / parenteral/combination**
**100%(6/6) vs 40%(2/5) (p=0.06) vs 78% (7/9) (p=0.27)**
**Mortality:**
**0/6 (inhalation) vs 5/5 (parenteral) 3/9 (combination)**

BMC Infectious Disease (2011) 11:317

Original Article

# Aerosolized Colistin for the Treatment of Multidrug-resistant *Acinetobacter baumannii* Pneumonia: Experience in a Tertiary Care Hospital in Northern Taiwan

| | |
|---|---|
| Microbiology outcome | |
| Eradication | 17 (37.8) |
| Persistence of colistin susceptible-only *Acinetobacter baumannii* | 8 (17.8) |
| Indeterminate | 20 (44.4) |
| Clinical outcome | |
| Cure or improvement | 26 (57.8) |
| Failure | 14 (31.1) |
| Indeterminate | 5 (11.1) |
| Discharge from hospital | 26 (57.8) |
| Death | 19 (42.2) |

J Microbiol Immunol Infect 2010;43(4):323–331

*J Antimicrob Chemother* 2010; **65**: 2645–2649
doi:10.1093/jac/dkq360 Advance Access publication 28 September 2010

Journal of Antimicrobial Chemotherapy

# Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

**Results:** The baseline characteristics of the patients and conventional therapy of VAP in both groups were comparable. Most of the cases of VAP were caused by MDR *A. baumannii* and/or *P. aeruginosa*. All isolates of Gram-negative bacteria were susceptible to colistin. Favourable clinical outcome was 51.0% in the CMS group and 53.1% in the control group ($P=0.84$). Patients in the CMS group had significantly more favourable microbiological outcome when compared with patients in the control group (60.9% versus 38.2%, $P=0.03$). Bronchospasm was observed in 7.8% of patients in the CMS group and in 2.0% of patients in the control group ($P=0.36$). Renal impairment was observed in 25.5% of patients in the CMS group and in 22.4% of patients in the NSS group ($P=0.82$).

**Conclusions:** Nebulized CMS as adjunctive therapy of Gram-negative VAP seems to be safe. However, a beneficial effect on clinical outcomes of adjunctive nebulized CMS for therapy of Gram-negative VAP was not ascertained.

**Adjunctive therapy**

**Gram-negative VAP**

**RCT, 100 adults**

J Antimicrob Chemother (2010) 65:2645-2649

# Studies for Inhalation therapy for VAP by resistant pathogens

- RCT
  - Palmer (2008) (mixed susceptibility) : aerosolized amikacin, gentamycin or vancomycin
  - Palmer and Smaldone (2014) (mixed susceptibility, high risk of MDRO) : same as above
  - Niederman (2012) (resistant pathogens) : aerosolized amikacin **(Adjunctive)**
  - Hallal (2007) (not mentioned susceptibility): aerosolized tobramycin **(Substitution)**
  - Rattanaumpawan (2010) (not mentioned susceptibility): aerosolized colistin **(Adjunctive)**
- Non-RCT
  - Ghannam (2009)(resistant pathogens): aerosolized aminoglycosides or colistin**(Substitution)**
  - Kofteridis (2010)(resistant pathogens): aerosolized colistin **(Adjunctive)**
  - Doshi (2013)(resistant pathogens): aerosolized colistin **(Adjunctive)**
  - Tumbarello (2013)(resistant pathogens): aerosolized colistin **(Adjunctive)**

# Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults

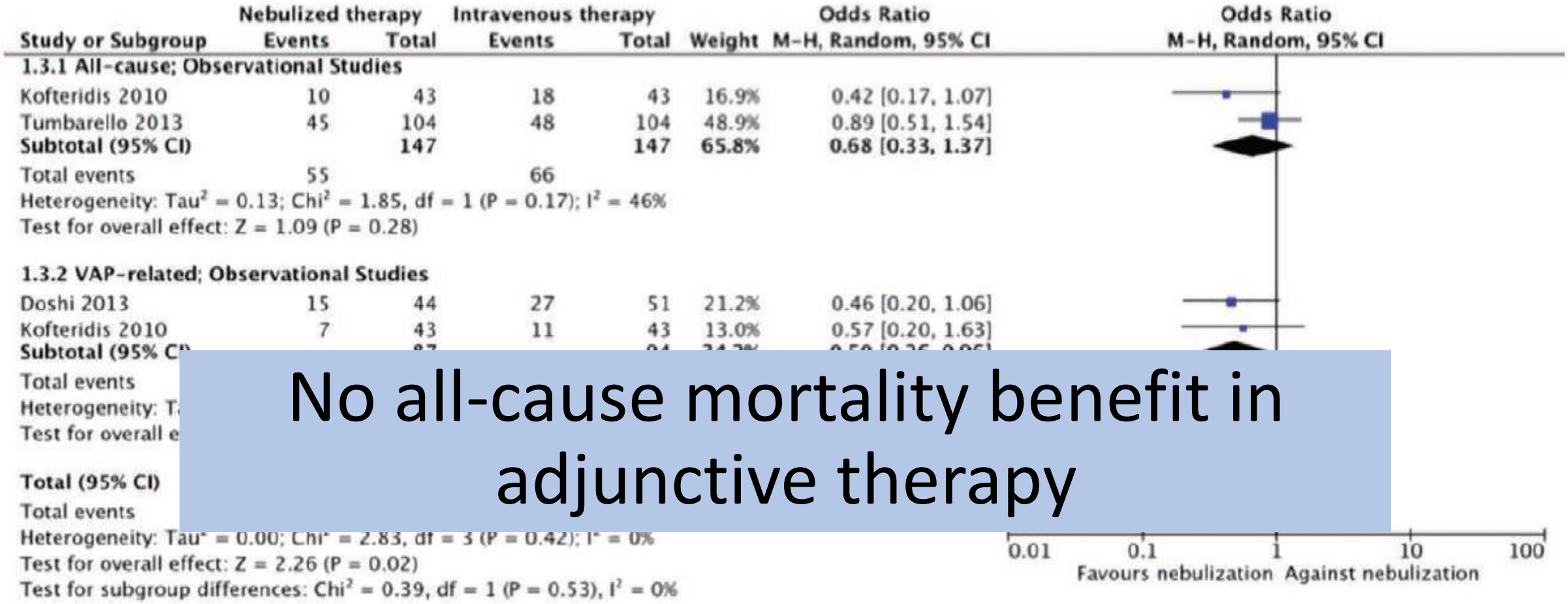
## *A Systematic Review and Meta-analysis*

Candela Solé-Lleonart, M.D., Jean-Jacques Rouby, M.D., Ph.D., Stijn Blot, R.N., Ph.D., Garyfallia Poulakou, M.D., Jean Chastre, M.D., Lucy B. Palmer, M.D., Matteo Bassetti, M.D., Ph.D., Charles-Edouard Luyt, M.D., Ph.D., Jose M. Pereira, M.D., Jordi Riera, M.D., Ph.D., Tim Felton, M.D., Jayesh Dhanani, F.C.I.C.M., M.D., Tobias Welte, M.D., Jose M. Garcia-Alamino, B.Sc., Jason A. Roberts, Ph.D., Jordi Rello, M.D., Ph.D.

***Nebulized colistin or aminoglycoside***
***Patients with VAP, VAT***
***Adjunctive, Substitution***

Anesthesiology (2017) 126:890-908

# Mortality for VAP by resistant pathogens (adjunctive therapy)



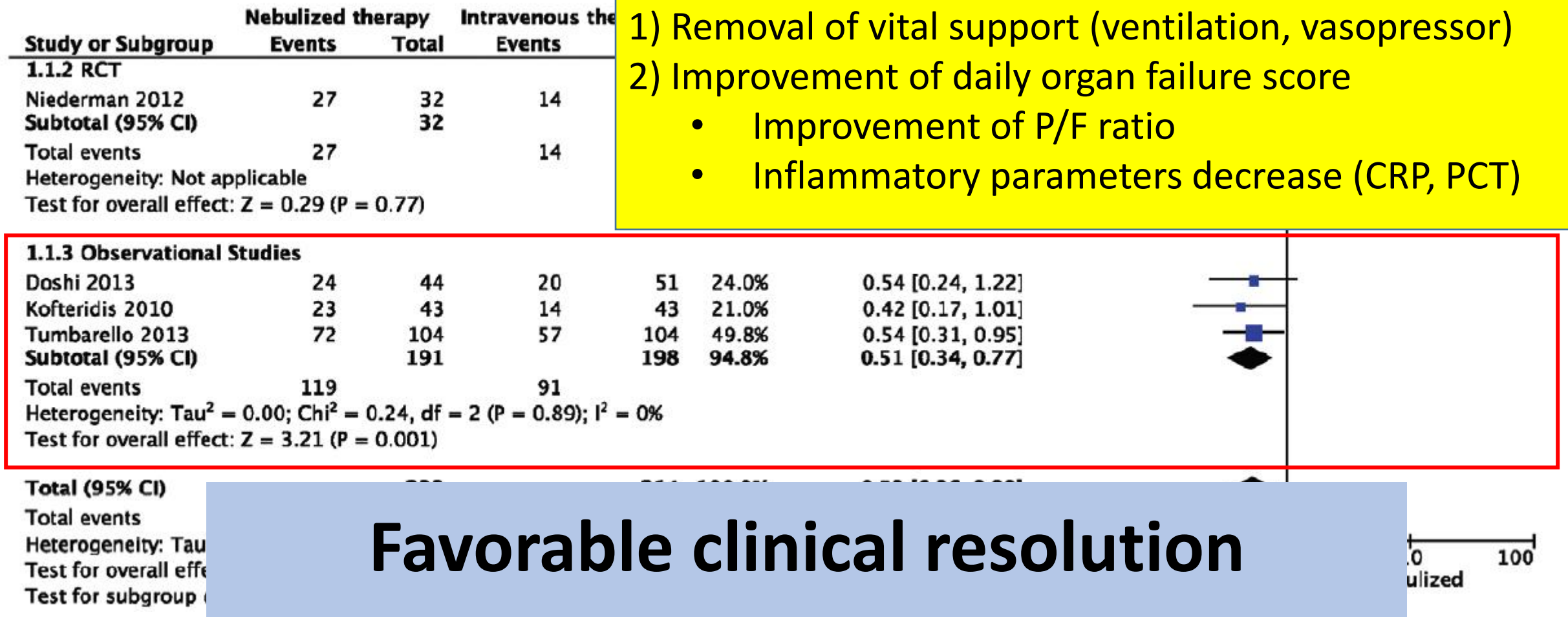

No all-cause mortality benefit in adjunctive therapy

Anesthesiology (2017) 126:890-908

# Clinical resolution for VAT by resistant pathogens (adjunctive therapy

**Clinical resolution** (after 8 days)

1) Removal of vital support (ventilation, vasopressor)
2) Improvement of daily organ failure score
   - Improvement of P/F ratio
   - Inflammatory parameters decrease (CRP, PCT)

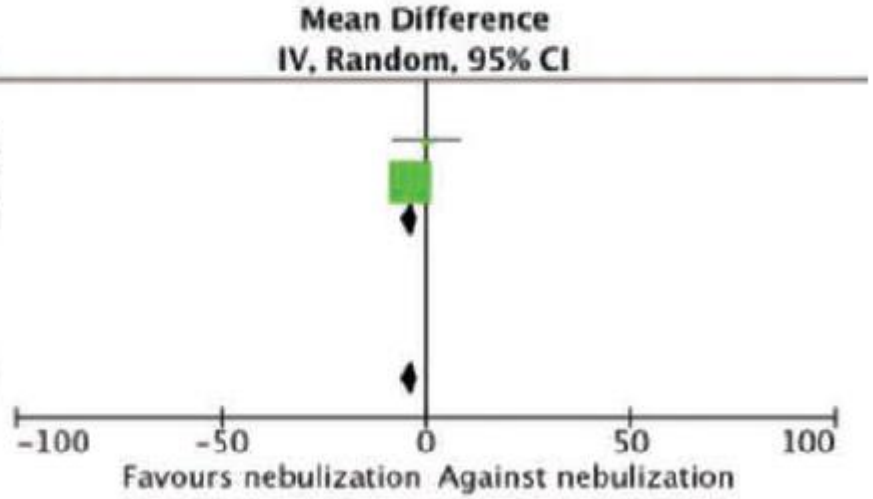



**Favorable clinical resolution**

Anesthesiology (2017) 126:890-908

# MV duration for VAP by resistant pathogens (adjunctive therapy)

| Study or Subgroup | Nebulized therapy Mean | SD | Total | Intravenous therapy Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.2.2 Observational Studies** | | | | | | | | |
| Doshi 2013 | 21.65 | 17.22 | 44 | 21.51 | 23.8 | 51 | 6.6% | 0.14 [-8.14, 8.42] |
| Tumbarello 2013 | 8 | 6.29 | 104 | 12 | 9.62 | 104 | 93.4% | -4.00 [-6.21, -1.79] |
| **Subtotal (95% CI)** | | | **148** | | | **155** | **100.0%** | **-3.72 [-5.86, -1.59]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 3.42 (P = 0.0006) | | | | | | | | |
| **Total (95% CI)** | | | **148** | | | **155** | **100.0%** | **-3.72 [-5.86, -1.59]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: Z = 3.42 (P = 0.0006) | | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | | |

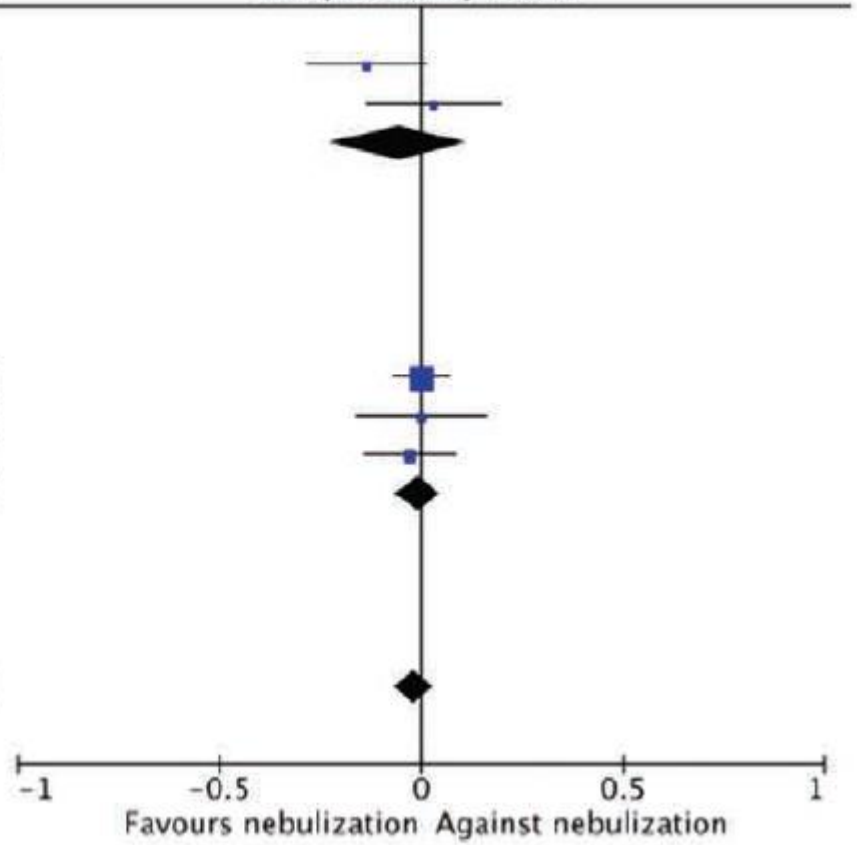



Anesthesiology (2017) 126:890-908

# Nephrotoxicity for VAP (Adjunctive administration)

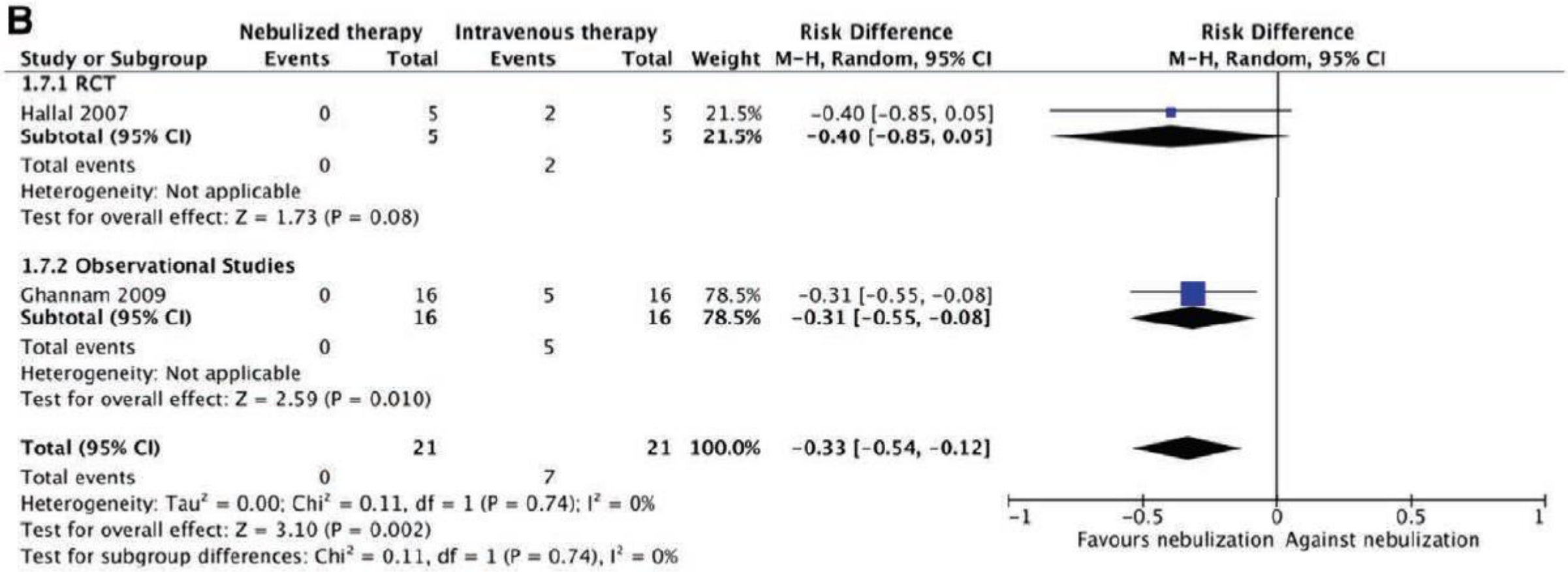
**A**

| Study or Subgroup | Nebulized therapy Events | Total | Intravenous therapy Events | Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 RCT** | | | | | | |
| Niederman 2012 | 0 | 45 | 3 | 22 | 11.4% | -0.14 [-0.29, 0.01] |
| Rattanaumpawan 2010 | 13 | 51 | 11 | 49 | 9.1% | 0.03 [-0.14, 0.20] |
| **Subtotal (95% CI)** | | **96** | | **71** | **20.5%** | **-0.06 [-0.23, 0.12]** |
| Total events | 13 | | 14 | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.41$, df = 1 (P = 0.12); $I^2 = 58\%$ | | | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | | | |
| **1.6.2 Observational Studies** | | | | | | |
| Arnold 2012 | 0 | 19 | 0 | 74 | 50.8% | 0.00 [-0.07, 0.07] |
| Kofteridis 2010 | 8 | 43 | 8 | 43 | 9.4% | 0.00 [-0.16, 0.16] |
| Tumbarello 2013 | 23 | 104 | 26 | 104 | 19.2% | -0.03 [-0.14, 0.09] |
| **Subtotal (95% CI)** | | **166** | | **221** | **79.5%** | **-0.01 [-0.06, 0.05]** |
| Total events | 31 | | 34 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.30$, df = 2 (P = 0.86); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | | | |
| **Total (95% CI)** | | **262** | | **292** | **100.0%** | **-0.02 [-0.07, 0.03]** |
| Total events | 44 | | 48 | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.06$, df = 4 (P = 0.55); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.28$, df = 1 (P = 0.59), $I^2 = 0\%$ | | | | | | |




Anesthesiology (2017) 126:890-908

# Nephrotoxicity for VAP (Substitution administration)



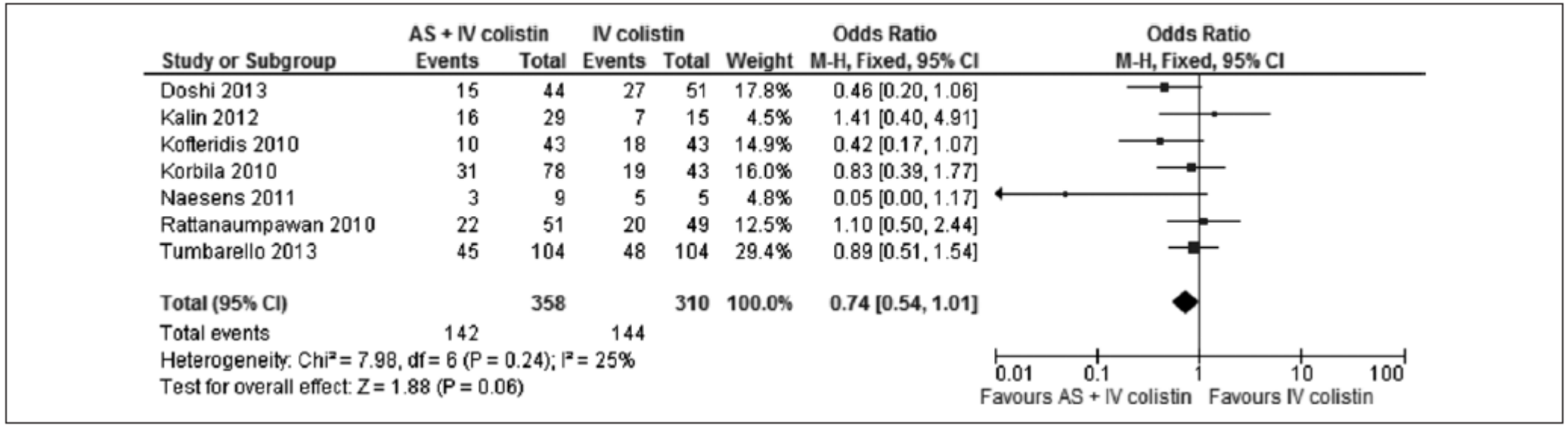

Anesthesiology (2017) 126:890-908

# The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

**IV colistin VS IV colistin + Aerosolized colistin**

Antonis Valachis, MD, PhD[1]; George Samonis, MD, PhD[2]; Diamantis P. Kofteridis, MD, PhD[2]

**Overall mortality** (odds ratio, 0.74; 95% CI, 0.54-1.01; p = 0.06; $I^2$ = 25%)



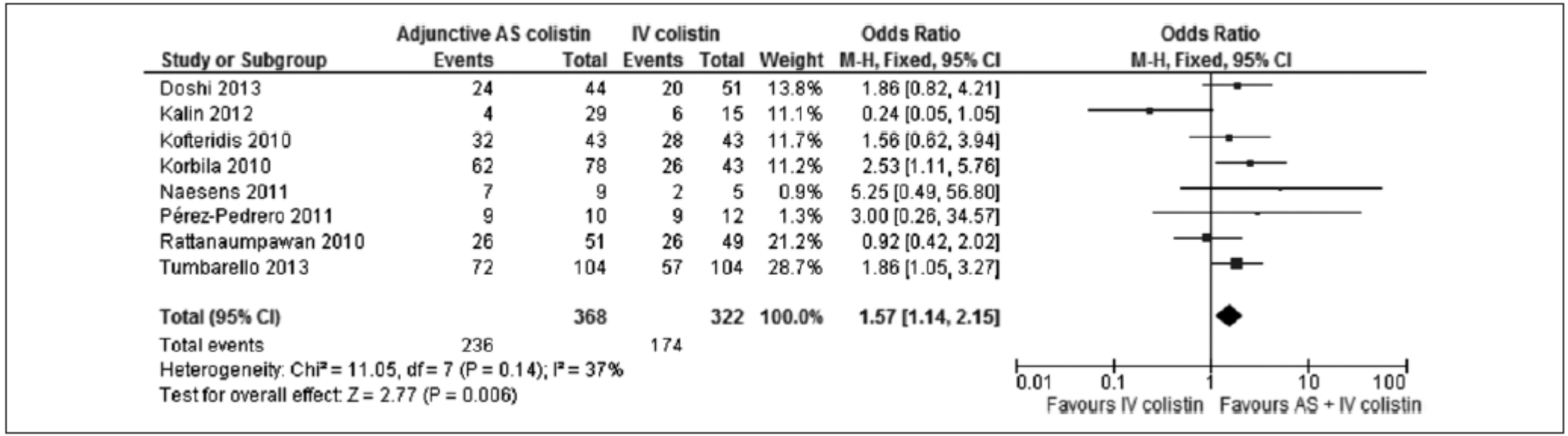
| Study or Subgroup | AS + IV colistin Events | Total | IV colistin Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Doshi 2013 | 15 | 44 | 27 | 51 | 17.8% | 0.46 [0.20, 1.06] |
| Kalin 2012 | 16 | 29 | 7 | 15 | 4.5% | 1.41 [0.40, 4.91] |
| Kofteridis 2010 | 10 | 43 | 18 | 43 | 14.9% | 0.42 [0.17, 1.07] |
| Korbila 2010 | 31 | 78 | 19 | 43 | 16.0% | 0.83 [0.39, 1.77] |
| Naesens 2011 | 3 | 9 | 5 | 5 | 4.8% | 0.05 [0.00, 1.17] |
| Rattanaumpawan 2010 | 22 | 51 | 20 | 49 | 12.5% | 1.10 [0.50, 2.44] |
| Tumbarello 2013 | 45 | 104 | 48 | 104 | 29.4% | 0.89 [0.51, 1.54] |
| **Total (95% CI)** | | **358** | | **310** | **100.0%** | **0.74 [0.54, 1.01]** |
| Total events | 142 | | 144 | | | |

Heterogeneity: Chi² = 7.98, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 1.88 (P = 0.06)



Crit Care Med (2015) 43:527-533

# **Clinical response** (odds ratio, 1.57; 95% CI, 1.14-2.15; p = 0.006)



| Study or Subgroup | Adjunctive AS colistin Events | Total | IV colistin Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Doshi 2013 | 24 | 44 | 20 | 51 | 13.8% | 1.86 [0.82, 4.21] |
| Kalin 2012 | 4 | 29 | 6 | 15 | 11.1% | 0.24 [0.05, 1.05] |
| Kofteridis 2010 | 32 | 43 | 28 | 43 | 11.7% | 1.56 [0.62, 3.94] |
| Korbila 2010 | 62 | 78 | 26 | 43 | 11.2% | 2.53 [1.11, 5.76] |
| Naesens 2011 | 7 | 9 | 2 | 5 | 0.9% | 5.25 [0.49, 56.80] |
| Pérez-Pedrero 2011 | 9 | 10 | 9 | 12 | 1.3% | 3.00 [0.26, 34.57] |
| Rattanaumpawan 2010 | 26 | 51 | 26 | 49 | 21.2% | 0.92 [0.42, 2.02] |
| Tumbarello 2013 | 72 | 104 | 57 | 104 | 28.7% | 1.86 [1.05, 3.27] |
| **Total (95% CI)** | | **368** | | **322** | **100.0%** | **1.57 [1.14, 2.15]** |
| Total events | 236 | | 174 | | | |

Heterogeneity: Chi² = 11.05, df = 7 (P = 0.14); I² = 37%
Test for overall effect: Z = 2.77 (P = 0.006)



**Microbiological eradication** (odds ratio, 1.61; 95% CI, 1.11-2.35; p = 0.01; $I^2$ = 0%)
**Infection-related mortality** (odds ratio, 0.58; 95% CI, 0.34-0.96; p = 0.04; $I^2$ = 46%)
**Nephrotoxicity** (odds ratio, 1.18; 95% CI, 0.76-1.83; p = 0.45; $I^2$ = 0%).

Crit Care Med (2015) 43:527-533

# **ATS/IDSA guideline** (2016)

**Should Patients With VAP Due to Gram-Negative Bacilli Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?**

- For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest **both inhaled and systemic antibiotics**, rather than systemic antibiotics alone (weak recommendation, very low-quality evidence).
- **Values and Preferences**: This recommendation places a high value on achieving clinical cure and survival; it places a lower value on burden and cost.
- **Remarks**: It is reasonable to consider adjunctive inhaled antibiotic therapy as a treatment of last resort for patients who are not responding to intravenous antibiotics alone, whether the infecting organism is or is not multidrug resistant.

# **French guideline for HAP** (2018)

We **suggest** administering **nebulised colimycin** (sodium colistimethate) and/or **aminoglycosides** in documented **HAP due multidrug-resistant Gram-negative bacilli documented pneumonia** established as sensitive to colimycin and/or aminoglycoside, when no other antibiotics can be used (based on the results of susceptibility testing).

**(Grade 2+, Strong agreement)**

Table 2. Aerosolized Antimicrobials and Their Clinical Uses*

| Antimicrobial | Clinical Uses | Formulation | Administration | Adverse Effects |
|---|---|---|---|---|
| Aminoglycosides | | | | |
| Gentamicin | CF, NCFB, VAP | Inhalation | Nebulizer | Bronchospasm |
| Amikacin | CF, NCFB, VAP, NTMB | Liposomal formulation<br>Nonliposomal formulation<br>Inhalation | Nebulizer | Hearing loss, nephrotoxicity, vertigo, dysphonia |
| Tobramycin | CF, NCFB, VAP, COPD, post-lung transplant infections | | Nebulization<br>Dry powder inhaler | Bronchospasm, hearing loss, tinnitus, voice alteration |
| Polymyxins | | | | |
| Colistin | CF, NCFB, VAP, post-lung transplant infections | Inhalation | Nebulizer<br>Dry powder inhaler | Bronchospasm, throat irritation |
| Colistimethate sodium | CF, NCFB, VAP | Inhalation | Nebulizer<br>Dry powder inhaler | Cough, bronchospasm |
| Glycopeptides | | | | |
| Vancomycin[11] | Nosocomial pneumonia | 100 mg 4 times daily | Jet nebulizer | Myocardial infarction, Gram-negative septic shock,† nephrotoxicity, bronchospasm |
| Monobactams | | | | |
| Aztreonam | CF | Inhalation | Nebulizer | Wheezing, bronchospasm |
| β-lactams | | | | |
| Ceftazidime | CF, VAP | Inhalation | Nebulizer | Wheezing, cough |
| Fluoroquinolones | | | | |
| Ciprofloxacin | CF | Liposomal solution for inhalation<br>Dry powder | Nebulizer<br>Dry powder inhaler | Bronchospasm |
| Levofloxacin | CF, NCFB, VAP | Inhalation | Nebulizer | None reported |
| Antifungals | | | | |
| Amphotericin | Pulmonary aspergillosis in AIDS, post-lung transplant | Deoxycholate<br>Liposomal formulation | Nebulizer | Bronchospasm, shortness of breath, cough, taste disturbances, chest tightness, nausea, vomiting |
| Pentamidine | PJP prophylaxis | 300 mg every 4 wk | Nebulizer | Cough, throat irritation, bronchospasm, fatigue, dizziness |

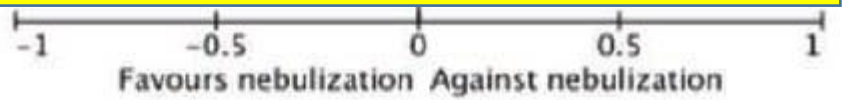
Resp Care (2021)

# Respiratory complications due to nebulized antibiotics

| Study or Subgroup | Nebulized therapy Events | Total | Intravenous therapy Events | Total |
|---|---|---|---|---|
| **1.9.1 RCT** | | | | |
| Hallal 2007 | 0 | 5 | 0 | 5 |
| Lu 2011 | 6 | 20 | 0 | 20 |
| Niederman 2012 | 2 | 45 | 0 | 22 |
| Rattanaumpawan 2010 | 4 | 51 | 1 | 49 |
| **Subtotal (95% CI)** | | **121** | | **96** |
| Total events | 12 | | 1 | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.25$, df = 3 (P = 0.10); $I^2 = 52\%$ | | | | |
| Test for overall effect: Z = 1.72 (P = 0.09) | | | | |
| **1.9.2 Observational Studies** | | | | |
| Arnold 2012 | 0 | 19 | 0 | 74 |
| Kofteridis 2010 | 0 | 43 | 0 | 43 |
| **Subtotal (95% CI)** | | **62** | | **117** |
| Total events | 0 | | 0 | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$ | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | |
| **Total (95% CI)** | | **183** | | **213** |
| Total events | 12 | | 1 | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.42$, df = 5 (P = 0.01); $I^2 = 65\%$ | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | |
| Test for subgroup differences: $Chi^2 = 2.58$, df = 1 (P = 0.11), $I^2 = 61.2\%$ | | | | |

**Cardiorespiratory complication**

1) Hypoxemia
2) Cough
3) Bronchoconstriction
4) Lung injury or ARDS
5) Problem with nebulization system (obstruction of the expiratory filter)
6) Arrhythmias
7) Cardiopulmonary arrest



# **ESCMID position paper for VAP** (2017)

## VAP d/t resistant pathogens

We **suggest avoiding** the use of nebulized antibiotics such as colistin or aminoglycosides, **added to conventional IV antibiotic therapy** already including IV colistin or aminoglycosides for the treatment of **VAP caused by resistant pathogens** as standard clinical practice.

**(Weak recommendation, very low quality of evidence)**

We **suggest avoiding** the use of nebulized antibiotics such as colistin or aminoglycosides **instead of their IV administration** for the treatment of **VAP caused by resistant pathogens** as standard clinical practice.

**(Weak recommendation, very low quality of evidence)**

# Recommended direction for further study : substitution therapy than adjunctive

# Studies for Inhalation therapy for VAP by resistant pathogens

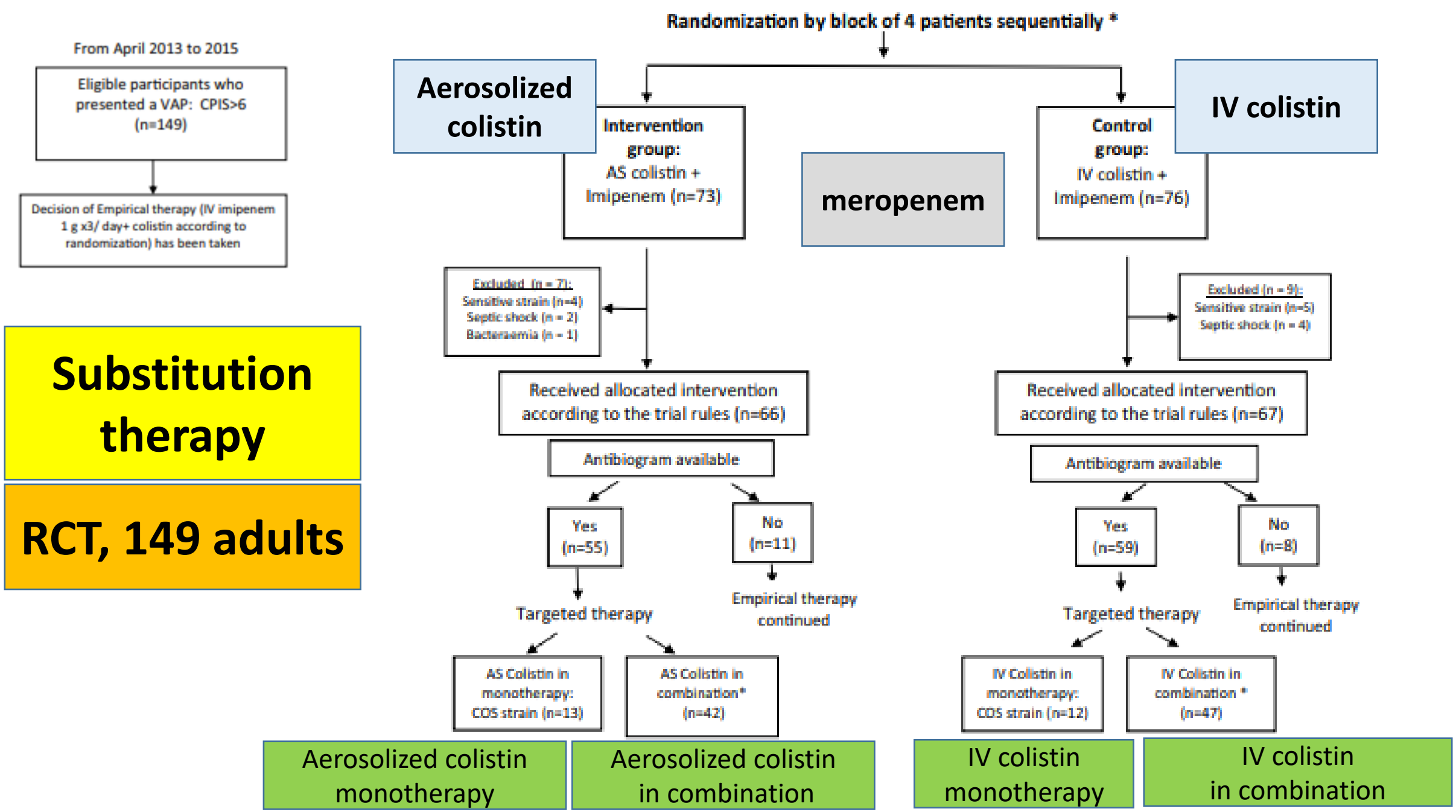
- RCT
  - Niederman (2012) (resistant pathogens) : aerosolized amikacin **(Adjunctive)**
  - Palmer (2008) (mixed susceptibility) : aerosolized amikacin, gentamycin or vancomycin
  - Palmer and Smaldone (2014) (mixed susceptibility, high risk of MDRO) : same as above
  - Hallal (2007) (not mentioned susceptibility): aerosolized tobramycin (Substitution)
  - Rattanaumpawan (2010) (not mentioned susceptibility): aerosolized colistin **(Adjunctive)**
  - **Abdellatif (2016)**(mixed susceptibility): aerosolized colistin **(Substitution)**
  - **Kollef (2017)** (mixed): aerosolized amikacin fosfomycin inhalation system **(Adjunctive)**
  - **Niederman (2020)** (mixed): aerosolized amikacin **(Adjunctive)**
- Non-RCT
  - Ghannam (2009)(resistant pathogens): aerosolized aminoglycosides or colistin(Substitution)
  - Kofteridis (2010)(resistant pathogens): aerosolized colistin (Adjunctive)
  - Doshi (2013)(resistant pathogens): aerosolized colistin (Adjunctive)
  - Tumbarello (2013)(resistant pathogens): aerosolized colistin (Adjunctive)

RESEARCH Open Access

# Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

Sami Abdellatif, Ahlem Trifi*, Foued Daly, Khaoula Mahjoub, Rochdi Nasri and Salah Ben Lakhal

Annals of Intensive Care (2016) 6:26




**Substitution therapy**

**RCT, 149 adults**

Annals of Intensive Care (2016) 6:26

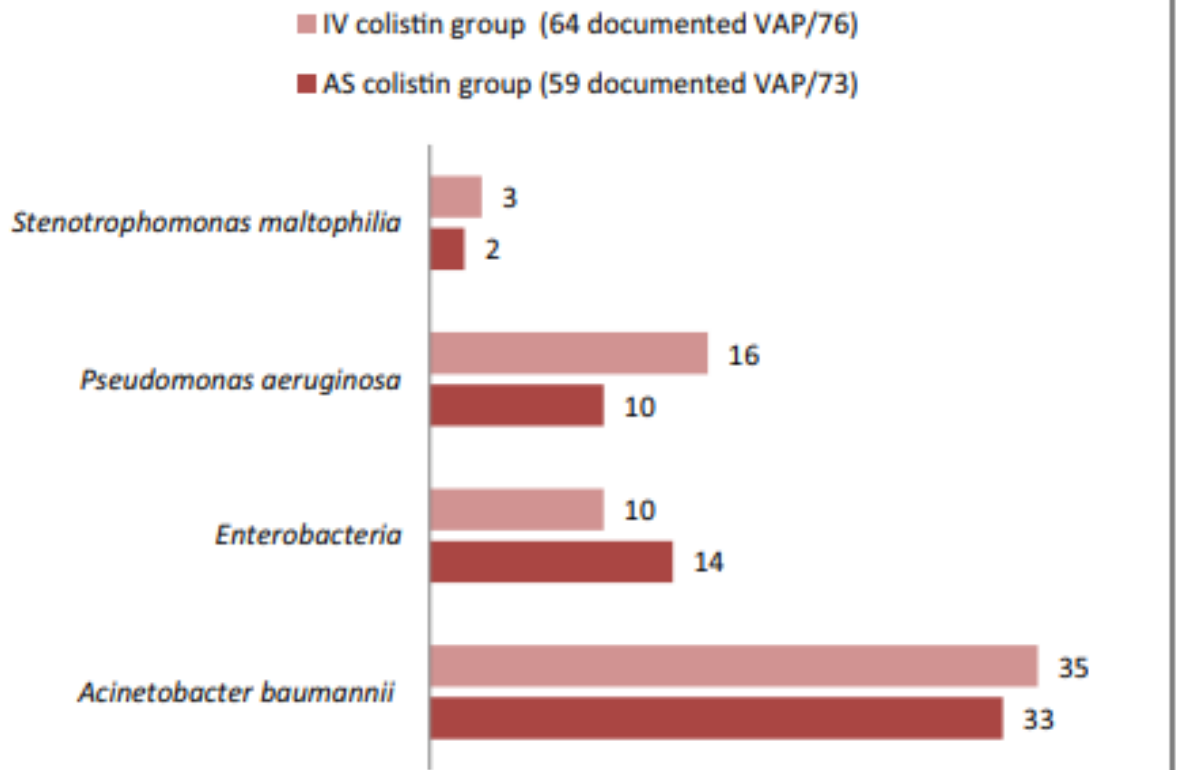



**Fig. 2** Microorganism's distribution in study groups

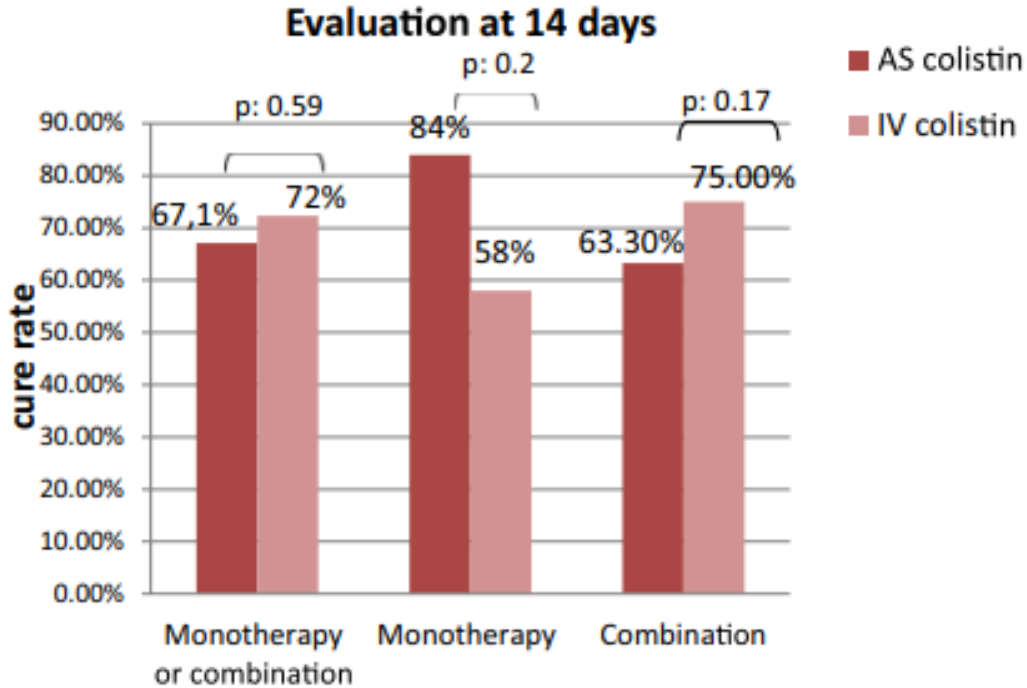
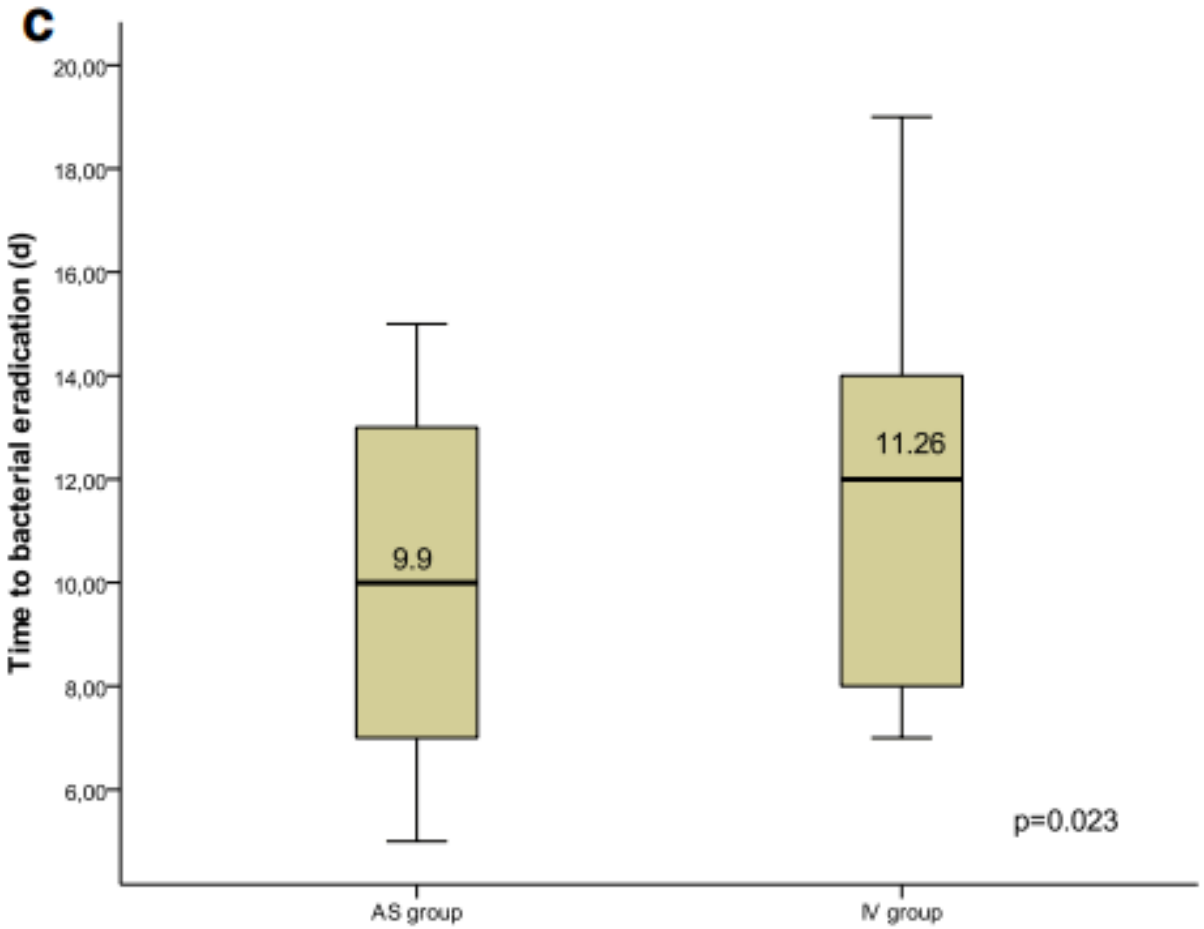
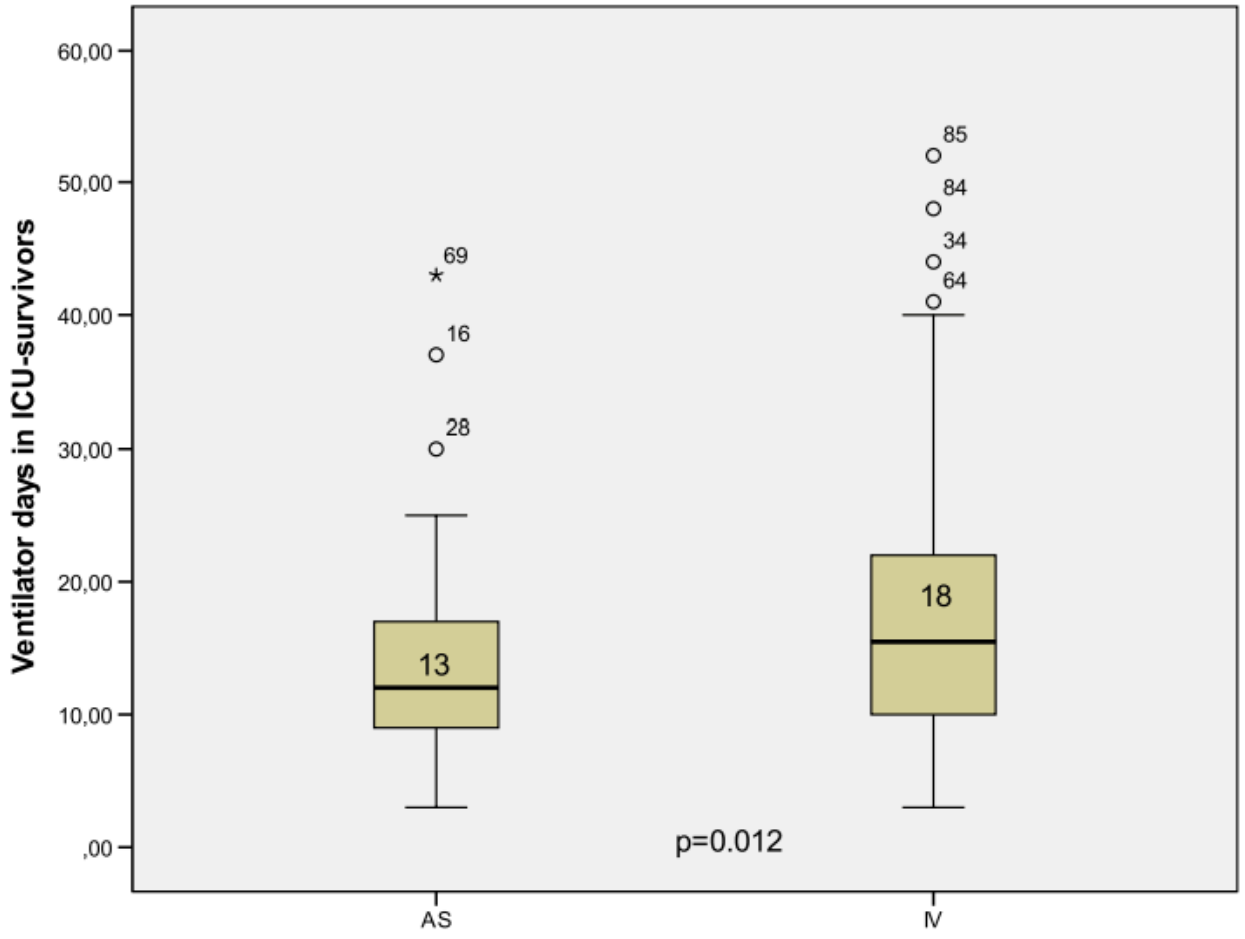



**Fig. 3** Cure rates between the study groups. The cure rates were shown when colistin was prescribed in monotherapy, in combination or both

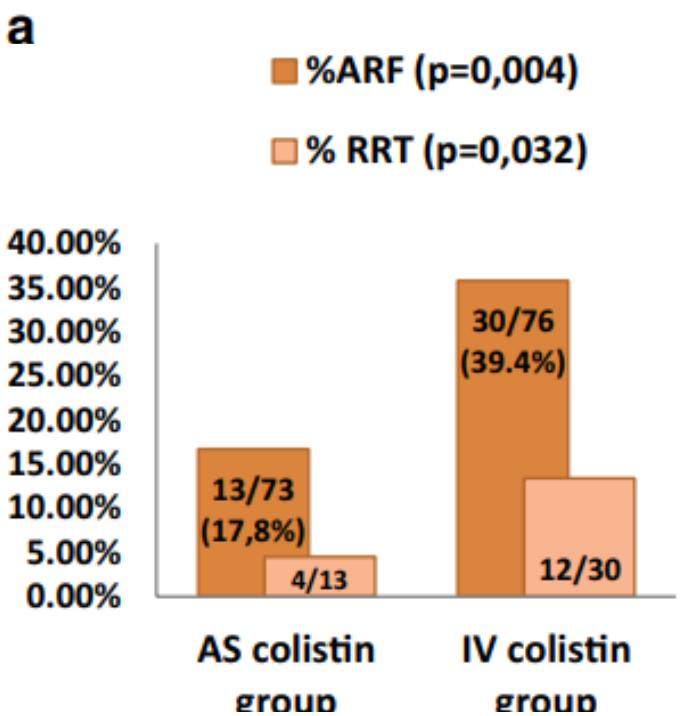
## Time to bacterial eradication




## Ventilator days in ICU survivors



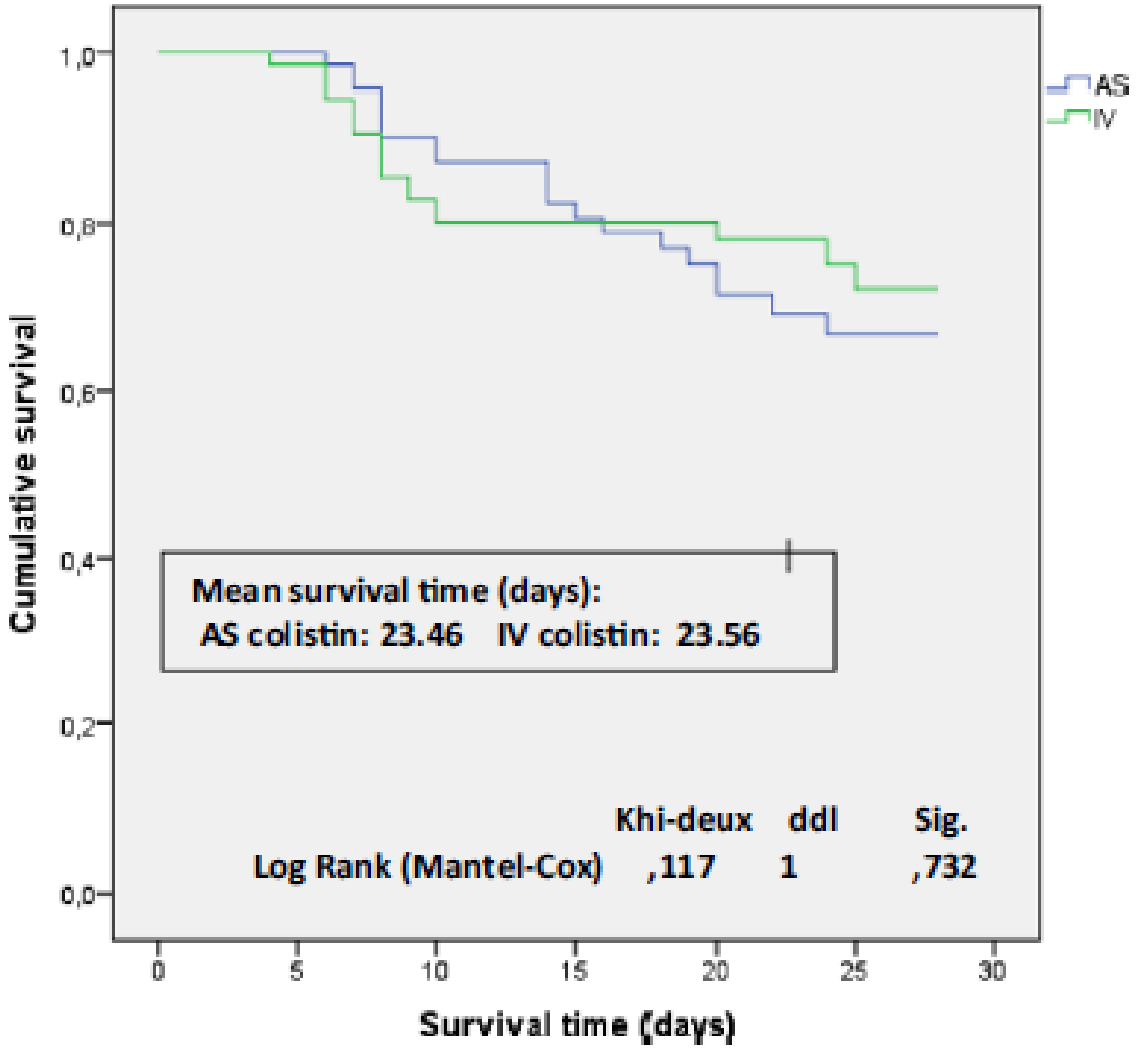

Annals of Intensive Care (2016) 6:26




## Conclusion

We conclude that the use of inhaled colistin seems to be beneficial in therapy of MDR bacilli VAP. Therapeutic effectiveness of such regimen was as effective as parenteral colistin. Further, it provided several benefits: a renal safety, a better improvement of *P*/*F* ratio, a shortened bacterial eradication time and an earlier weaning from ventilator in ICU survivors.

We suggest the regimen of aerosolised colistin as the first-line therapy in VAP due to MDR bacilli outside a septic shock and/or bacteraemia.



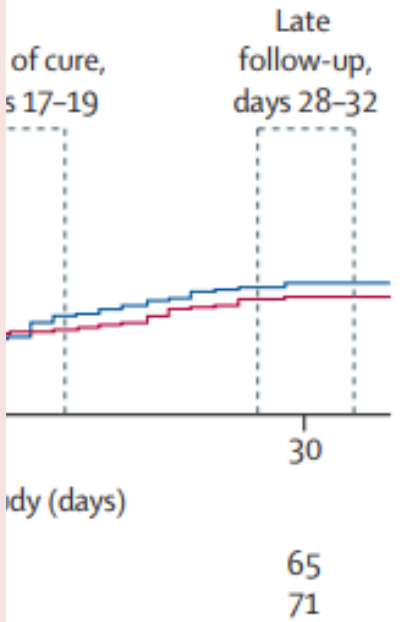

Annals of Intensive Care (2016) 6:26

# Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gra… ran…trial

## Implications of all the available evidence

Taken together, the findings from INHALE and IASIS suggest there is no survival benefit associated with the use of aerosolised amikacin adjunctive to intravenous antibiotics in patients with drug-resistant, ventilator-associated, Gram-negative pneumonia. Current pneumonia treatment guidelines recommend the adjunctive use of inhaled antibiotics as rescue therapy and in patients with drug-resistant infections susceptible only to aminoglycosides and polymyxins. Prospective controlled trials might be warranted to determine whether inhaled antibiotics have demonstrable benefit in these circumstances.

| | | |
|---|---|---|
| **Primary endpoint*** | | |
| Survival at days 28–32 (n=255 *vs* n=25… | | |
| Treatment successful | | |
| Treatment unsuccessful | | |
| **Secondary endpoints** | | |
| Mortalities (n=255 *vs* n=253) | | |
| Pneumonia-related deaths | | |
| Pneumonia-unrelated deaths | | |
| Early clinical response (n=255 *vs* n=25… | | |
| Achieved early response | | |
| Did not achieve early response | | |
| Duration of mechanical ventilation, da… | | |
| Mean (SD) | | |
| Median (IQR) | | |
| Duration of intensive care unit stay, da… | | |
| Mean (SD) | 21·3 (8·2) | 21·9 (8·0) |
| Median (IQR) | 28·0 (13·0–28·0) | 28·0 (14·0–28·0) |




Lancet Resp Medicine (2020) 20:330-340

# Aerosolized antibiotics for ventilator-associated pneumonia: a pairwise and Bayesian network meta-analysis

Feng Xu[1], Lu-Lu He[1], Luan-Qing Che[1], Wen Li[1], Song-Min Ying[1], Zhi-Hua Chen[1] and Hua-Hao Shen[1,2*]

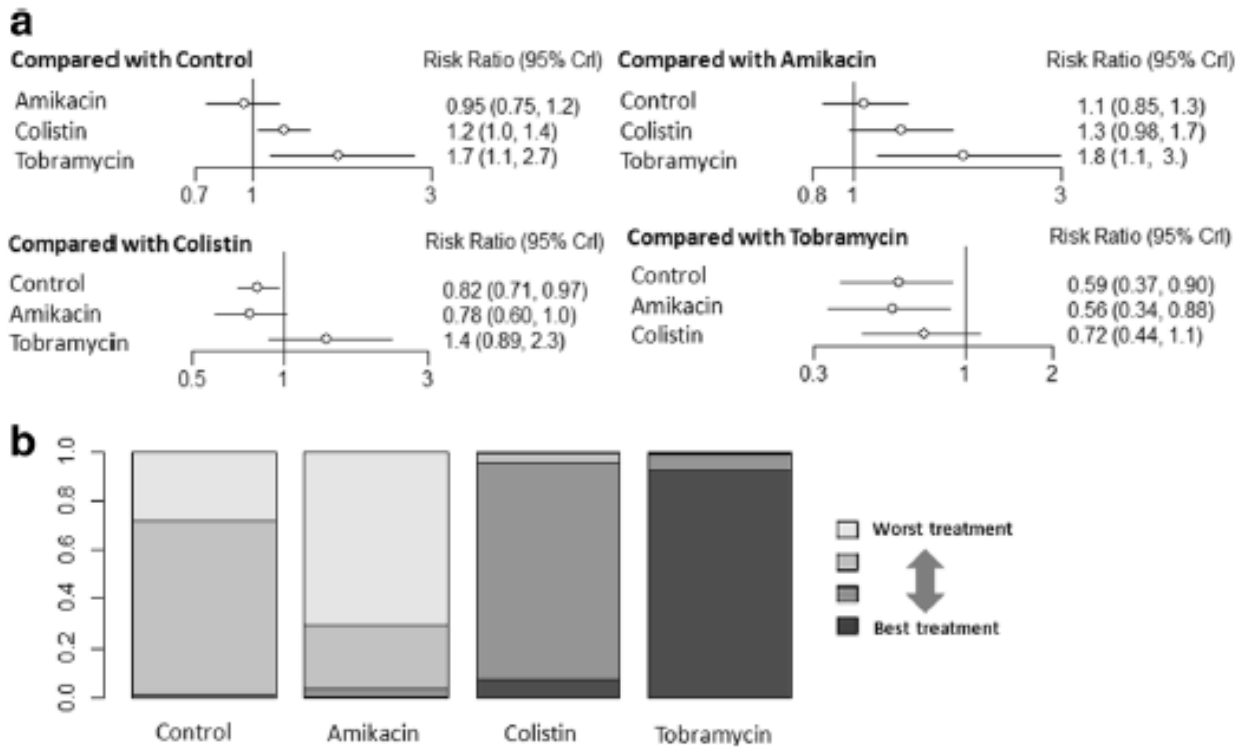



**Fig. 2 a** Network estimates among aerosolized antibiotics for clinical recovery. **b** Rank probabilities among aerosolized antibiotics for clinical recovery based on the network meta-analysis. The number of patients in each antibiotic arm: control, 476; amikacin, 135; colistin, 372; and tobramycin, 48. CI confidence interval

Crit Care (2018) 22:301

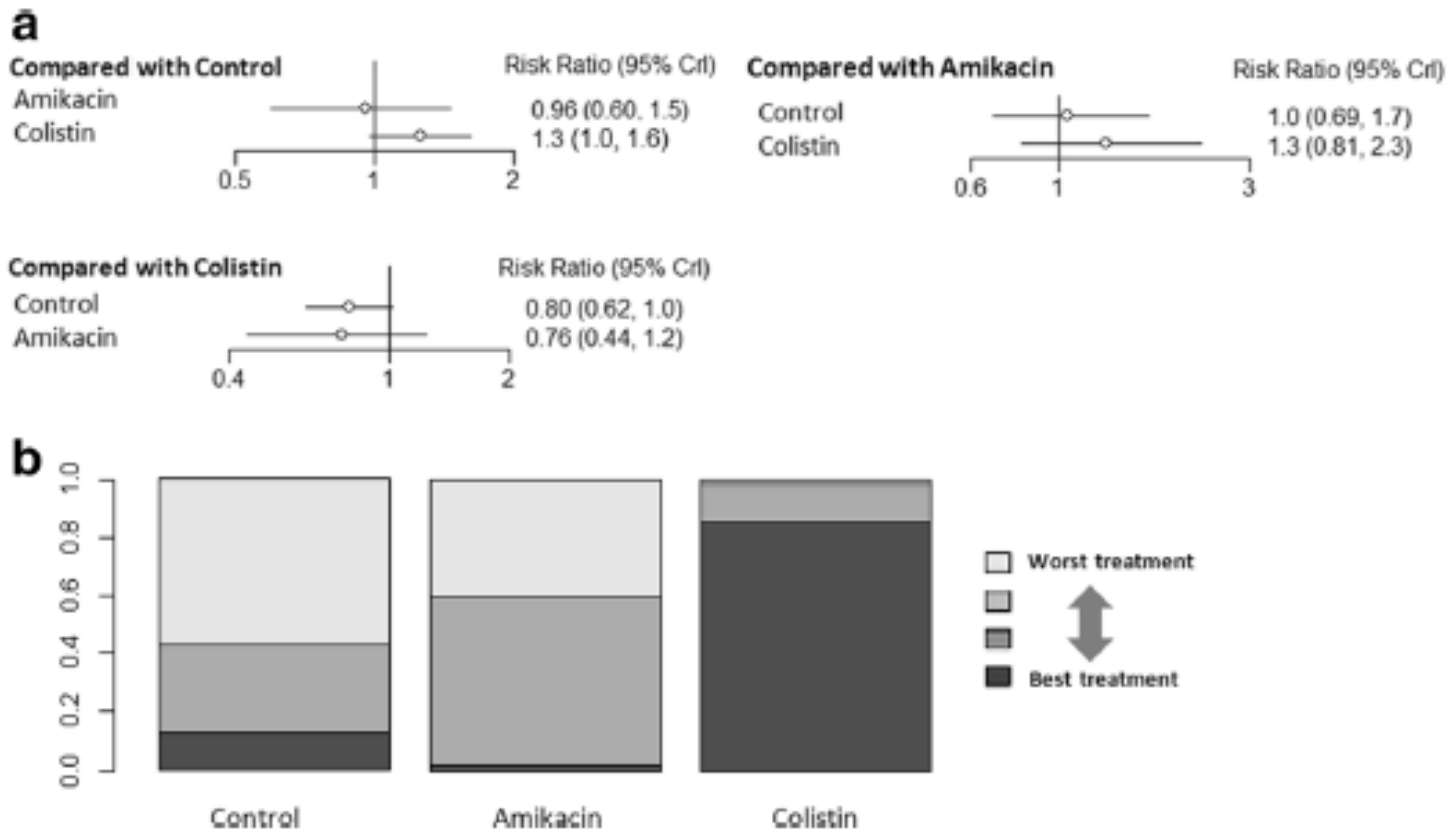



**Fig. 3 a** Network estimates among aerosolized antibiotics for microbiological eradication. **b** Rank probabilities among aerosolized antibiotics for microbiological eradication based on the network meta-analysis. The number of patients in each antibiotic arm: control, 271; amikacin, 74; and colistin, 241. CI confidence interval

**Initial dose** inserted into the nebuliser's chamber

Mesh nebuliser chamber retention

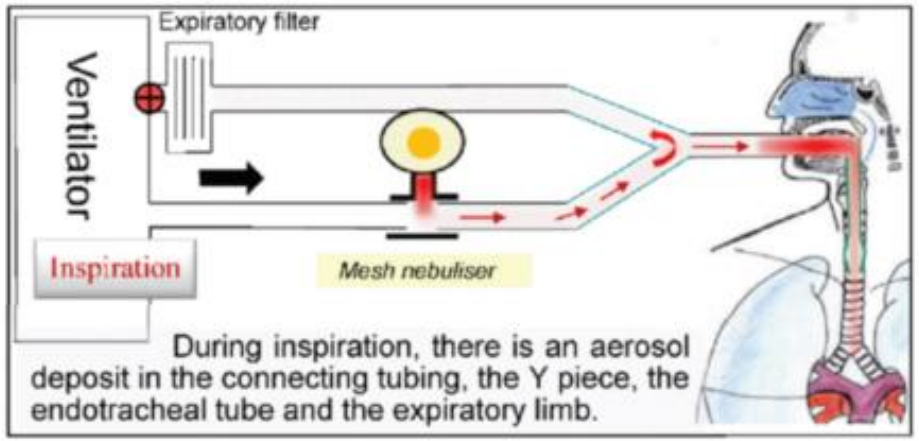
< 5 %

With mesh nebulisers, chamber retention (blue colour) is low = **0.1 ml/12 ml.** With jet nebulisers chamber retention can be as high as 50 %

In vitro studies show that if during nebulisation, the conventional humidifyer is not interrupted, the particles size markedly increases, inducing a rainout effect in the circuits and a reduction in lung deposition.

≈ 15 %

**Nebulised dose**

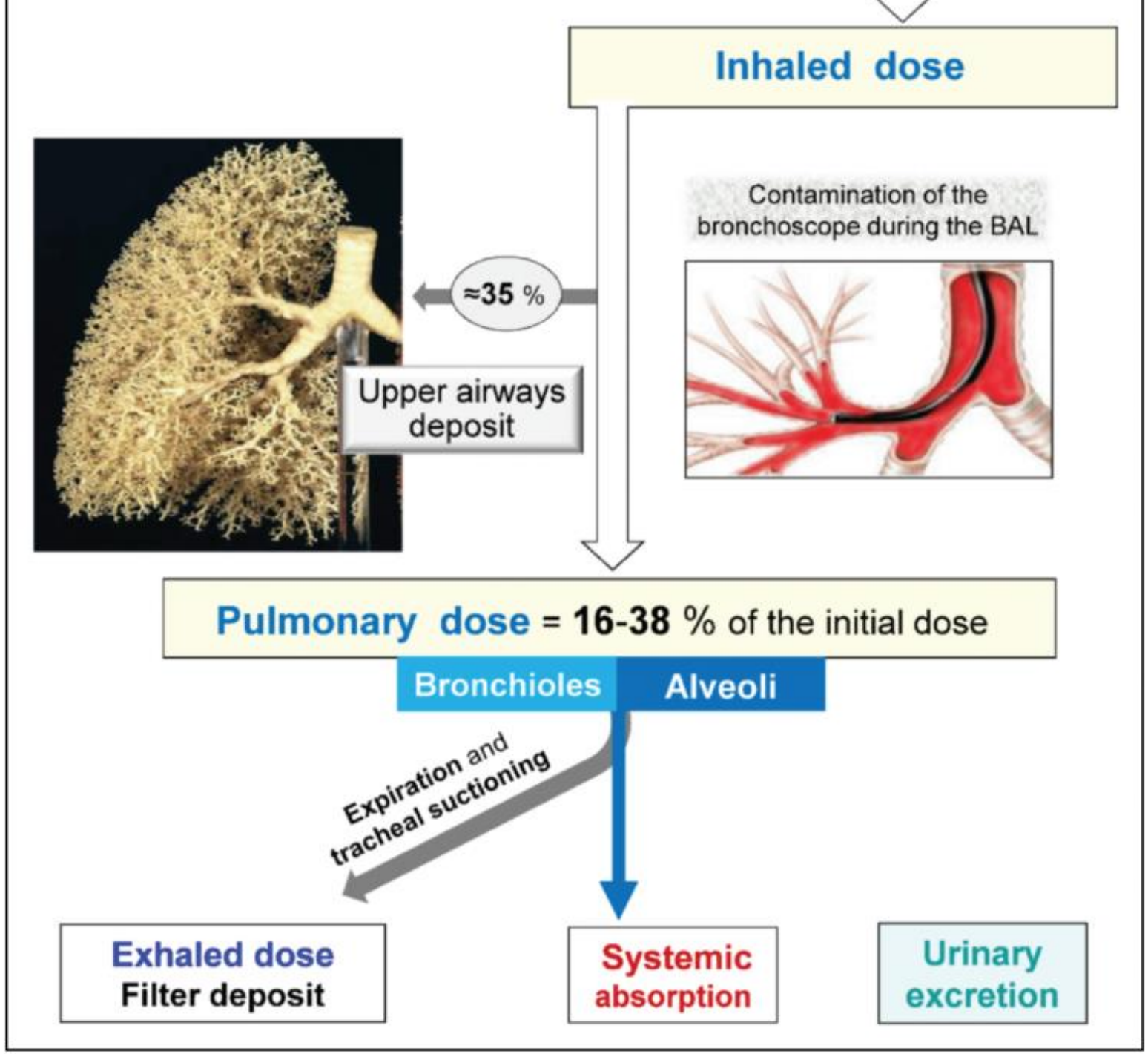



During inspiration, there is an aerosol deposit in the connecting tubing, the Y piece, the endotracheal tube and the expiratory limb.

Circuits deposit

≈ 30 %

**Curr Opin Infect Dis** 2021, 34:156–168




**Curr Opin Infect Dis** 2021, 34:156–168

# Optimisation of nebulization to maximized antibiotic lung deposition

- Limiting inspiratory flow velocity

  : Reducing inertial impaction in the airways and optimizing lung deposition
- Volume-controlled mode than pressure-support mode
- Mesh-nebulizer (10-15cm before the Y piece on the inspiratory limb)

  : than zet nebulizer (smaller) for antibiotic delivery
- Removal of heat and moisture exchanger/heated humidifier

  : Avoiding hygroscopic growth of the aerosolized particles and a rainout effect in the circuit

JJ Rouby et al. Intensive Care Med (2020) 46:766-770

# Summary

- **Adjunctive (aerosolized + IV) therapy  vs IV therapy alone**
  - No mortality benefit
  - Higher clinical resolution (MDR pathogens)
  - No difference in safety (nephrotoxicity)

- **Aerosolized therapy**
  - Efficacy : not inferior to IV therapy
  - Safety : lower systemic toxicity (nephrotoxicity)

# Conclusion (Recommendation)

In patients with MDR HAP/VAP patients (MDR GNB), we suggest administering inhalation therapy (aerosolized colistin and/or aminoglycosides) if susceptible for colistin or aminoglycosides, when no other antibiotics can be used.

# Thank you for your attentions