Weill Cornell Medicine

Inhaled Colistin: What Have We Learned During The Last Decade?

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Desirable Aerosol Antibiotic Characteristics

Table 3. Desirable Characteristics for an Aerosol Antibiotic

Soluble and able to be effectively delivered as an aerosol
Concentration-dependent pharmacokinetics
Does not degrade with nebulization and retains activity at the airway surface
Activity persists in the airway for hours after nebulization
Penetrates well into and through sputum
Associated with serious adverse effects when given systemically
Minimal systemic absorption
Minimal adverse effects at the airway surface (eg, inflammation, bronchospasm)

Rubin BK. Resp Care 2011; 56:1411

Inhaled Colistin: Polymyxin E

- Colistimethate sodium (CMS) is a prodrug that is hydrolyzed to the active drug. CMS better tolerated at the airway level than Colistin sulfate (CS).
- 80 mg CMS = 1 Million units
- Bactericidal, in a concentration-dependent manner, acting on the cell membrane, narrow spectrum vs. gram negatives , low risk of emergence of resistance.
- Polycationic with hydrophilic and hydrophobic properties
- Peak concentration at 1-1.5 hours post inhalation. Half life of 4.5 h, mean residence time after inhalation of 7 hours
- NOT as prophylactic therapy; ? Adjunctive with systemic therapy to salvage MDR pathogen pneumonia vs. routine adjunctive therapy vs. monotherapy

Patient Variables Affecting Nebulizer Therapy

- Degree of airway disease
- Degree of parenchymal disease/pneumonia
  - Consolidated vs bronchopneumonia
- Depth/rate of breathing
- Spontaneous breathing vs Mechanical Ventilation
  - Mode of mechanical ventilation

Delivery of Aerosolized Antibiotics

- To get maximal benefit need to optimize aerosol delivery
  – NOT your father’s nebulizer anymore!

Nebulizer and Drug Variables

- Nebulizer type: ultrasonic, jet, vibrating mesh plate, dry powder inhaler
  - No data to favor one over another for antibiotic delivery. Falagas M, et al. Int J Animicrob Agents 2010; 35:101
- Particle size
- Drug viscosity
- Particle composition: degradation
  - Novel particles and nanoparticles
- Coordination with inhalation
- Antibiotic: liquid vs. dry powder
- If on ventilator: position in circuit , inspiratory flow rates, tidal volume, sedation , coordination with inspiration, circuit humidification (dry is better)

Engineered Aerosol Particles

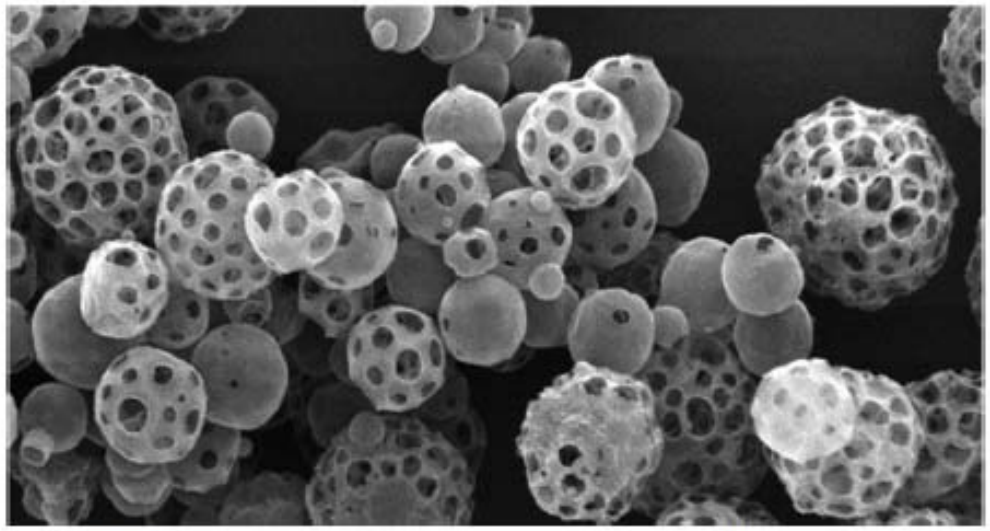


Fig. 7. PulmoSpheres are large, engineered, hollow, and porous particles with low surface energy and a mass median aerodynamic diameter similar to smaller and denser particles. These can be delivered using a very simple dry-powder inhaler. (Courtesy of

- Nano drug delivery to encapsulate antibiotic to prevent degradation and enhance absorption, enhance cellular uptake
  - Generally liposomal preparations or nanoparticles given by DPI or nebulizer

TIP: tobramcyin inhaled powder
Rubin BK. Resp Care 2011; 56:1411

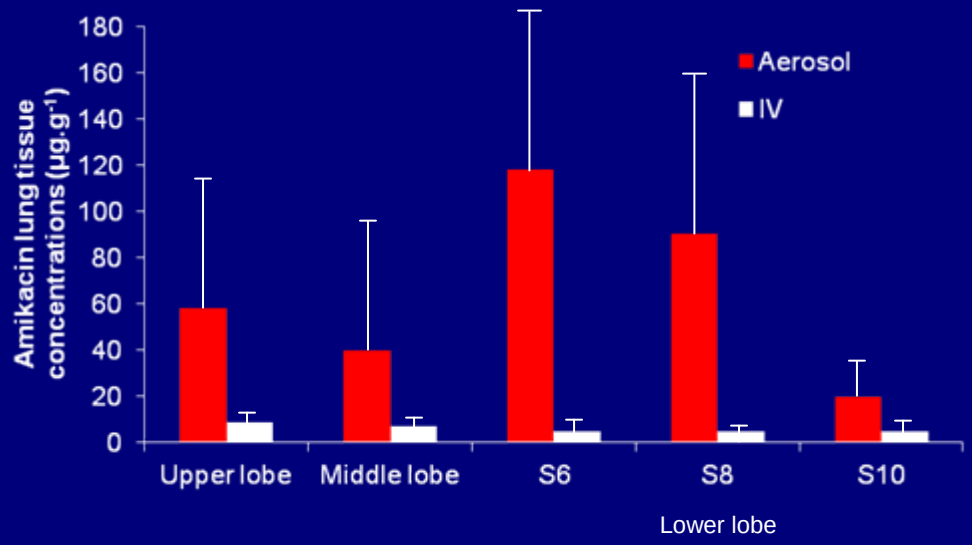
- Andrade F, et al. Advanced Drug Deliv Rev 2013; 65:1816

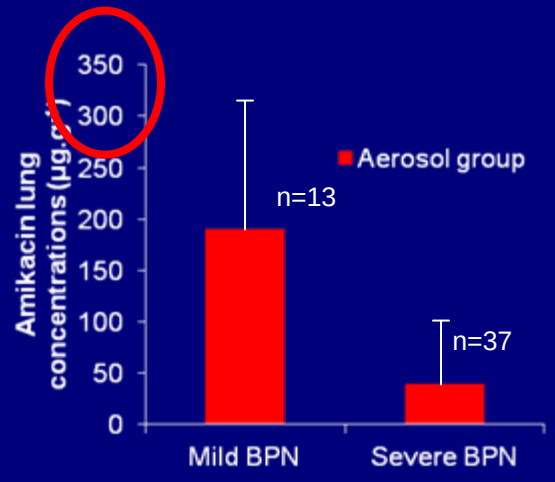
Issues Surrounding Aerosol Therapy Delivery for HAP and VAP

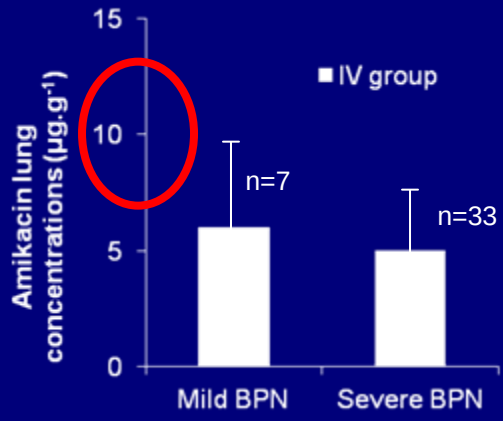
- Which delivery device best deposits drug in the LRT?
  - What percent is retained in the lung?
  - Does enhanced deposition reduce risk of resistance?
- How can delivery be coordinated with the ventilator, and how is it achieved in non-ventilated patients?
  - Where should the delivery device be in the ventilator circuit?
- Does pneumonic inflammation promote enhanced systemic absorption of an inhaled drug?
  - Can inhaled drugs penetrate pneumonic lung?

Lung Deposition of Nebulized Amikacin in Ventilated Piglets with *E. coli* Pneumonia

- Piglets with bronchopneumonia from intrabronchial inoculation of E. coli
- AMK 24 hours later via ultrasonic neb (45 mg/kg) in inspiratory limb, 40 cm proximal to the Y-piece, or IV (15 mg/kg)
- 38% of nebulized dose retained in bronchial tree
- Neb led to lung tissue concentrations 3-30X greater than IV.
  - Higher concentrations after aerosol in less severe lung lesions
  - Higher levels in severe BPN lung after aerosol vs. IV







Goldstein I, et al. Am J Respir Crit Care Med 2002;166:1375

How To Optimize Aerosol Delivery of Antibiotics in Ventilated Patients

- Ultrasonic or vibrating plate nebulizers preferred to jet nebulizers. BUT ultrasonic nebs may heat the antibiotic.
  - Vibrating plates can synchronize with inspiration and up to 60% of reservoir dose deposits in lung. Particle size < 5 microns
  - Place vibrating plate in inspiratory limb before the Y connector and ETT tip
- Nebulized dose= systemic IV dose + extrapulmonary deposition (tubing, expiratory filter)
- Limit inspiratory flow turbulence
  - Controlled mode ventilation (NOT assist, and may need sedation), VT of 7-9 ml/kg, constant inspiratory flow, MV < 6L/min, R=12, I/E ratio of 1:1, end inspir pause of 20% of the duty cycle
- Remove HME filter , add humidification if delivery time > 30 min

Rouby JJ, et al. Anesthesiology 2012; 117:1364-1380

Summary of Clinical Experience with Inhaled Colistin in VAP

Table 2. Nebulized colistin and disease outcomes in adult hospital/ventilator-acquired pneumonia (HAP/VAP) patients.

Authors	Number of patients	Daily dose	Bacterial strains	Monotherapy/ combined regimen	APACHE score	Duration of therapy	Therapeutic response rate
Michalopoulos *et al.* 2005 [1]	8	1.5 - 6 mil IU	*Acinetobacter baumannii* *Pseudomonas aeruginosa*	Nebulized colistin-intravenous colistin (n = 7)	14.6	10.5	87.5%
Falagas *et al.* 2009 [2]	5	0.5 - 4 times daily 1 mil IU three times daily	*A. baumannii* *P. aeruginosa* *Klebsiella pneumoniae*	Nebulized colistin piperacillin/tazobactam, meropenem, ceftriaxone, ciprofloxacin	11-27	6-11	80
Michalopoulos *et al.* 2008 [3]	n = 78 with nebulized colistin n = 43 without nebulized colistin	2.1 mil IU	*A. baumannii* *P. aeruginosa* *K. pneumoniae*	Nebulized colistin/ piperacillin/tazobactam, meropenem, gentamicin	11-24	6-11	80%
Lin *et al.* 2010 [4]	n = 45	4.29 million IU	*A. baumannii* *P. aeruginosa*		22.5	34	37.8% microbiological response 57.8% clinical response

Antoniou SA, et al. Expert Opin Drug Delivery 2012; 9:333-42

Aerosolized colistin as adjunctive therapy for ventilated patients

- Retrospective evaluation of ICU patients given adjunctive aerosolized colistin for MDR pathogen pneumonia
- Identified 8 patients (6 mechanically ventilated)
  - 7 with *Acinetobacter* spp.; 1 with *P. aeruginosa*
  - 80 mg =1 million units
  - Aerosolized colistin 0.5–1.5 million IU q6–8h (1 mg = 12,500 IU); delivery device not specified
  - Duration: 6–19 days (mean 10.5 days)
  - All patients received systemic antibiotics, including colistin in 6
  - 7/8 with cure or improvement
  - 4/5 with culture data, had organism eradication
  - No selection of resistance or superinfection
  - No bronchospasm; 1 patient had worsened renal function

Michalopoulos A et al. *Crit Care* 2005;9:R53–R59

Lack of Benefit of Adjunctive Colistin Inhaled in an RCT: ? Wrong Aerosol Delivery System

- Randomized trial of 100 patients with Gram negative VAP (PA and AB) in Thailand
- Systemic therapy + Placebo or nebulized (75 mg q 12 h, 2.25 MIU) colistin for duration of IV therapy
- Given by ultrasonic or jet nebulizer for 10 minutes. Levels not measured
- NO benefit in clinical outcome, but 1-2 days shorter duration of IV therapy with adjunctive inhaled colistin, and better microbiologic outcome

Table 2. Clinical and microbiological outcomes of the study patients

	CMS group (n=51)	NSS group (n=49)	% Risk difference (95% CI)	Risk ratio (95% CI)	P value
28 day clinical outcome					
favourable outcome	51.0%	53.1%	−2.1% (−22%–18%)	0.96 (0.66–1.40)	0.84
death due to VAP	39.2%	36.7%	2.5% (−17%–22%)	1.07 (0.65–1.76)	0.80
overall mortality	43.1%	40.8%	2.3% (−17%–22%)	1.06 (0.67–1.68)	0.81
Favourable microbiological outcome	60.9%	38.2%	22% (3%–41%)	1.57 (1.03–2.37)	0.03
Incidence of complication	31.4%	24.5%	7% (−11%–24%)	1.28 (0.68–2.42)	0.44
bronchospasm	7.8%	2.0%	6% (−3%–14%)	3.84 (0.45–33.19)	0.36
renal impairment	25.5%	22.4%	3% (−14%–20%)	1.13 (0.56–2.29)	0.82

Rattanaumpawan P, et al. JAC 2010; 65:2465-9

Can Adjunctive Aerosol Therapy Improve The Outcome in MDR VAP?

- Retrospective , matched case-control study of 43 patients with VAP due to MDR GNB rx with aerosol (2 million units/d) +IV colistin (9 million units/d) vs. IV colistin alone (43 controls)
  - Few details about nebulization methods
- 77% with *Acinetobacter baumannii*. No colistin resistance
- Trend to more clinical cure with aerosol in logistic regression model (p=0.08)
- Kofteridis DP, et al. Clin Infect Dis 2010; 51:1238-44

Outcome	No. (%) of patients		P
	IV colistin group (*n* = 43)	AS-IV colistin group (*n* = 43)	
Clinical outcome			
Clinical cure	14 (32.5)	23 (54)	.05
Clinical improvement	12 (28)	9 (21)	.451
Clinical failure	14 (32.5)	7 (16)	.126
Recurrence	3 (7)	4 (9)	>.99
Bacteriological outcome[a]			
Eradication	17 (50)	19 (45)	.679
Persistent	12 (35)	10 (24)	.272
Recurrence	2 (6)	5 (12)	.450
Colonization	3 (9)	8 (19)	.208
Mortality			
All-cause	18 (42)	10 (23)	.066
VAP-related	11 (26)	7 (16)	.289
Adverse events			
Nephrotoxicity	8 (19)	8 (19)	>.99
Neurotoxicity	0	0	

No difference in eradication , clinical success, mortality or renal dysfunction (in 19% in each group)

Retrospective Cohort Study of Adjunctive Inhaled Colistin

- 78 with VAP given IV + inhaled colistin vs. 43 matched controls. IV and aerosol for at least 3 days
  - 95% *Acinetobacte*r baumannii or *P. aeruginosa*
- Mean daily colistin inhaled dose of 2.1 MU. No nebulization information.
- Adjunctive aerosol with: more clinical cure (79.5% vs 60.5%, p=0.025)
- Inhaled colistin the only independent variable assoc with cure of VAP in multivariate model (OR=2.5)
- No mortality difference
- Adjunctive rx. group got significantly longer duration systemic rx than controls (16.9 d vs 13.7 d, p=0.013). ? Impact on findings
  - Korbila IP , et al. CMI 2010; 16:1230-1236

Adjunctive Aerosolized Colistin in MDR GNB VAP

- 5% MV patients with colistin-only sensitive VAP (*Acintobacter, P. aeruginosa Klebsiella*)
- Retrospective matched cohort of IV colistin vs. IV colistin +aerosol (1 MU tid, via jet or ultrasonic neb). 104 each group
- Started after identified resistant pathogen
- Aerosol: higher cure rate (69.2% vs 54.8%, p=0.03),fewer days MV after onset VAP (8 vs 12, p=0.001), more bacti eradication (p=0.08). No mortality impact
- Predictor of cure (OR=2.58) in multivariate model
- Tumbarello M, et al. Chest 2013; 144:1768-75

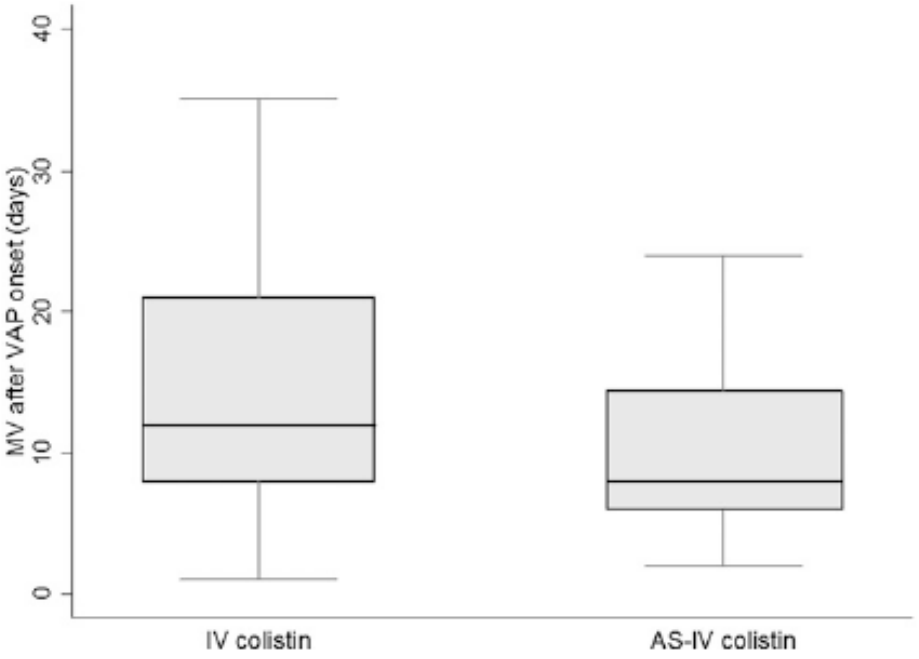
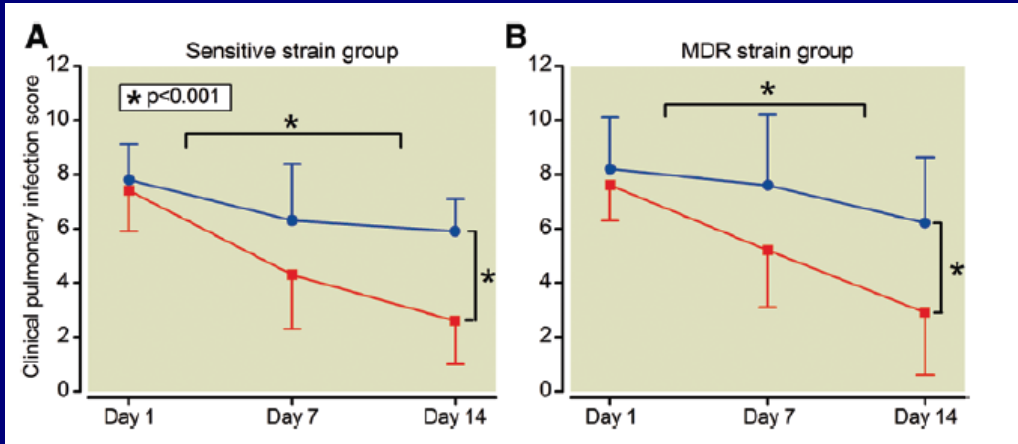


FIGURE 2. Box and whisker plots showing days of MV after onset of VAP in patients treated with IV colistin (IV cohort) and those who received IV and AS colistin (AS-IV cohort). MV duration was significantly shorter in the latter cohort ($P < .001$). Boxes repre-

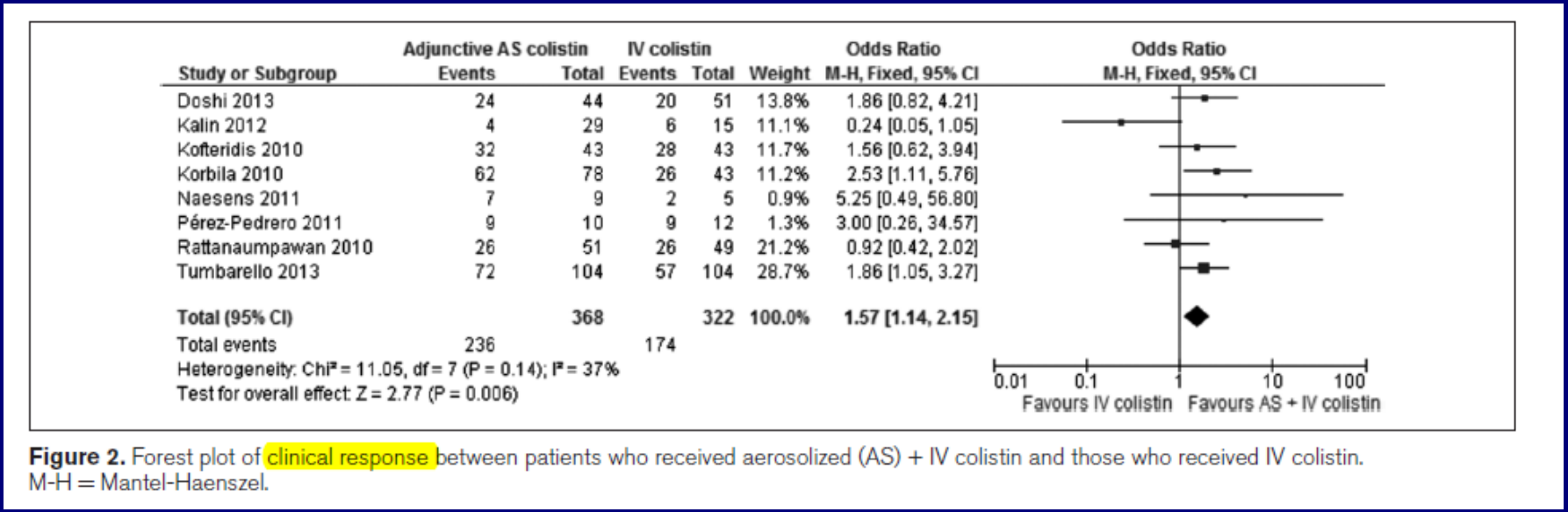
Inhaled Colistin Monotherapy For MDR VAP? Focus on Delivery Methods

- 165 with VAP due to *P. aeruginosa* or *A. baumanii*
  - 122 sensitive and given IV rx: BL + AG
  - 43 with MDR pathogens and given aerosol rx. +/- IV rx.
    - Nebulized colistin only (400 mg, 5 MU, q 8h, in 10 ml over 60 minutes) in 28/43 patients and with 3 days IV aminoglycosides in 15/43
  - Vibrating mesh plate delivery, remove humidifier, constant inspiratory flow, Vt=8 ml/kg, R=12, I/E ratio of 1:1, end inspir pause of 20% of the duty cycle. Sedate to maintain synch with ventilator.
  - Comparable cure rate (67%) for resistant pathogens as sensitive organisms (66%). Same mortality (23% vs 16%)
  - Lu et al. Anesthesiology 2012; 117; 1335-47



Meta-Analysis of Aerosolized Colistin

- 16 studies: 8 comparing aerosol vs. IV+aerosol (1 randomized trial , 2 compared aerosol monorx to systemic rx), 8 were single arm, systematic reviews.
- Higher clinical success with adjunctive aerosol (OR=1.57,p=0.006)
- Adjunctive rx with: more microbiologic eradication (p=0.01),no reduction in mortality, no increase in renal toxicity.
- Valachis A, et al. Crit Care Med 2015; 43:527-533



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)

Figure 2. Forest plot of clinical response between patients who received aerosolized (AS) + IV colistin and those who received IV colistin. M-H = Mantel-Haenszel.

Routine Use of Adjunctive Aerosolized Antibiotics for VAP?

- Data show VALUE of ADJUNCTIVE aerosolized antibiotics in VAP
  - More clinical cure
  - More microbiologic eradication
    - May even be effective ALONE for MDR VAP
  - May be more effective if we pay attention to delivery systems
  - BUT can we use aerosol alone in selected patients?
- There are benefits for GNB VAP patients. Is it now time for routine use in VAP therapy for all GNB, or reserve for failing therapy with resistant pathogens?