What is the Role of Inhaled Polymyxins for Treatment of Respiratory Tract Infections?
CONCLUSIONS: Patients with *Pseudomonas* and *Acinetobacter* VAP may experience favorable survival (p=0.001) when treated with adjunctive aerosolized antibiotics, i.e. colistin or tobramycin, despite greater severity of illness and a greater incidence of multidrug-resistant infection.

Large randomized trials are needed to further explore this therapy.
Concerns regarding the low lung tissue concentration of colistin via IV administration and high mortality rates of ventilator-associated pneumonia due to multi-drug resistant Gram-negatives was the cause to search for alternative treatment modalities such as the Inhalation Route.
Dosage Schedules of Inhaled Colistin

- The recommended dose of colistin when given by inhalation is 500,000 IU every 12 h for patients with a body weight <40 kg and 1,000,000 IU every 12 h for patients who weigh >40 kg.

- For severe pulmonary infections, the dose can be doubled to 2,000,000 IU administered every 8 h.

- Nevertheless, the exact optimal dosing remains unclear, as the precise pharmacokinetics and pharmacodynamics of the drug have not yet been clarified.

- Colistin is not approved by the FDA (Food and Drug Administration) to be inhaled via a nebulizer.
The Kinetics of Inhaled Colistin

Donatello's pulpit on the façade of the Cathedral-Prato
Prospective, open-label study in 13 adult patients with VAP

CMS IV 2 MU q8h for at least 2 days

BAL was performed at 2h after at least 2 days of treatment with CMS

Colistin was measured by a selective, sensitive HPLC

Colistin was undetectable in BAL
Median colistin concentrations in epithelial lining fluid (ELF) after mini-BAL in 20 patients with VAT:

- At 1h: 6.7 (4.8-10.1) μg/ml
- At 4h: 3.9 (2.5-6.0) μg/ml
- At 8h: 2.0 (1.0-3.8) μg/ml

The obtained levels were fivefold higher than those achieved in serum (mean serum levels: 1.2, 0.75, 0.31 μg/ml)

A dose of 1 MU of inhaled CMS every 8 h may not be adequate for the treatment of lower respiratory tract infections due to multi-drug resistant GNB (Colistin susceptibility breakpoint: 2-4 μg/ml)

*Aeroneb-nebulizer
Post 1 MU of Nebulized Colistin

* Breakpoint of Enterobacteriaceae
MIC = 4* μg/ml

* Breakpoints of *Pseudomonas aeruginosa*
Clinical Efficacy of Nebulized Colistin in HAP and VAP
21 patients were treated with nebulized polymyxin E (colistin) 1 MU twice a day\(^a\) for 14 d (2-36 d)

None received parenteral colistin or other antibiotics active against the MDR Gram-negatives

Overall clinical and microbiological response rates were 85.7% and 61.1%, respectively

Attributable mortality: 14.3% (3pts)

1 patient expressed bronchospasm

No renal toxicity

Nebulized colistin may be reasonably efficacious and safe for treating MDR pneumonia

\(^a\) Type of nebulizer not defined
Salvage treatment of pneumonia and initial treatment of tracheobronchitis caused by multidrug-resistant Gram-negative bacilli with inhaled polymyxin B

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Brazil 2007

• 141 ICU patients with VAP caused by MDR Gram-negatives were treated with inhaled colistin x 14 d.

• Colistin was given at the dose of 500 000 IU twice a day plus IV colistin

• Cure occurred in 53%, improvement in 42% and failure in 1 pts
Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: A prospective study

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Aerosolized Colistin as Adjunctive Therapy of VAP

- 60 critically ill patients with a mean APACHE II score 16.7, received aerosolized* colistin for the treatment of VAP due to MDR pathogens
- Half of the isolated pathogens were susceptible only to colistin.
- Mean daily dosage of aerosolized colistin was 2.2 (± 0.7) MU for a mean of 16.4 d.
- Fifty-seven patients received concomitant intravenous treatment with colistin
- Bacteriological and clinical response of VAP was observed in 50/60 (83.3%) patients
- The obtained clinical outcomes were better compared with historical controls with comparable severity of disease

*Siemens Servo Ventilator 300
Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study (1)

- Retrospective cohort study of patients with microbiologically documented VAP
- 78 patients with VAP received IV plus inhaled colistin, whereas 43 patients received IV colistin alone
- The mean SD daily dosage of IV colistin was 7.0 ± 2.4 and 6.4 ± 2.3 MIU, respectively (p = 0.13)
- The average daily dosage of inhaled colistin* was 2.1 ± 0.9 MU

*Siemens Servo Ventilator 300
Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study (2)

<table>
<thead>
<tr>
<th></th>
<th>Cure</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>IV Colistin</td>
<td>60.5%</td>
<td>44.2%</td>
</tr>
<tr>
<td>IV plus inhaled colistin</td>
<td>79.5%</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

- The use of inhaled colistin was independently associated with cure of VAP in a multivariable analysis
Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of VAP caused by Gram-negative bacteria

- A randomized controlled study in 100 adults with Gram-negative VAP
- Nebulized* CMS equivalent to 75 mg of colistin base (CBA) every 12 h
- Favorable 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 favorable microbiological outcome (60.9% versus 38.2%, P=0.03)
- 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

* Jet or ultrasonic nebulizer
** Several active parenteral antibiotics in both groups
Aerosolized plus Intravenous Colistin versus Intravenous Colistin Alone for the Treatment of Ventilator-Associated Pneumonia: A Matched Case-Control Study (1)

Retrospective matched case-control study at the ICU of the University Hospital of Heraklion, Greece (January 2005 through December 2008)

- 43 patients with VAP due to gram-negative MDR pathogens received Aerosolized plus IV colistin and were matched on the basis of age and APACHE II score
- 43 served as control patients and received IV colistin alone
- Dosage: 1 MU every 12 h aerosolized* colistin
  3 MU IV colistin every 8 h

* Type of nebulizer not defined

Kofteridis D, et al. CID 2010; 51: 1238
Demographic characteristics, clinical status, and gram-negative isolated pathogens were similar between the 2 treatment groups.

*Acinetobacter baumannii* (66 cases [77%]) was the most common pathogen, followed by *Klebsiella pneumoniae* (12 cases [14%]) and *Pseudomonas aeruginosa* (8 cases [9.3%]).

No colistin-resistant strains were isolated during treatment from patients in either group.

No significant differences between the 2 groups were observed regarding eradication of pathogens (P=.679), clinical cure (P=.10), and mortality (P=.289).

8 patients (19%) in each treatment group developed reversible renal dysfunction.

**Addition of Aerosolized colistin to IV colistin did not provide additional therapeutic benefit to patients with VAP due to MDR gram-negative bacteria**
Figure 1. All-cause mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.
Figure 2. Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV, intravenous.
## What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

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### Subgroup Analysis of Clinical Response With Colistin for Treatment of Ventilator-Associated Pneumonia in Single-Arm Studies

<table>
<thead>
<tr>
<th>By route of administration</th>
<th>Studies, No (Patients, No)</th>
<th>Efficacy of colistin, % (95% CI)</th>
<th>Heterogeneity of studies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>9 (178)</td>
<td>66 (.58-.74)</td>
<td>Q=11.50; p=.18</td>
</tr>
<tr>
<td>Aerosolized</td>
<td>3 (121)</td>
<td>80 (.60-.999)</td>
<td>Q=22.9; p&lt;.0001</td>
</tr>
<tr>
<td>Intravenous+aerosolized</td>
<td>3 (130)</td>
<td>78 (.71-.85)</td>
<td>Q=0.19; p=.91</td>
</tr>
</tbody>
</table>

Florescu DF, et al. CID 2012; 54: 670

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The important points which could potentially confound the results of the reported studies should be clarified:

1. The timing of initiation of colistin therapy
2. Concurrent use of other antibiotics
3. Variability in dosage schedules
4. Methods of aerosolized delivery of Colistin
• Colistimethate was prepared for nebulization by dilution of one million IU of colistin in 4mL of sterile normal saline 0.9%

Take care of the Appropriate Nebulizer!
30-40% of the administered dose is delivered to the lung.

Only 15% of the nebulized drug is delivered to the lung.
A vibrating mesh or plate with multiple apertures to produce aerosolized particles is used. The drug output is 2-3 times higher than that with jet nebulizers.

The main advantage of these nebulizers is that the temperature of the antibiotic solution does not change during operation, thereby preventing evaporative losses of the drug.

The produced particles are of 1 μm.

Drug delivery to the lung reaches 60%.
Efficacy of High-dose Nebulized Colistin in Ventilator-associated Pneumonia Caused by Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Qin Lu, M.D., Ph.D.,* Rubin Luo M.D.,† Liliane Bodin, M.D.,* Jianxin Yang, M.D.,† Noël Zahr, Pharm.D.,‡ Alexandra Aubry, M.D., Ph.D.,§ Jean-Louis Golmard, M.D., Ph.D.,‖ Jean-Jacques Rouby, M.D., Ph.D.#; and the Nebulized Antibiotics Study Group**

*Anesthesiology* 2012; 117: 1335
Patients with VAP caused by *P. aeruginosa* or *A. baumannii* (n = 222)

- Patients with VAP susceptible to β-lactams (n = 153)
  - Excluded patients (n = 31):
    - Bacteremia (n = 18)
    - Urinary tract infection (n = 4)
    - Catheter infection (n = 1)
    - Concomitant use of nebulized or IV colistin (n = 8)

  - Sensitive strain group (n = 122)
    - Treatment of VAP by IV β-lactam combined with a 3-day IV aminoglycoside (n = 122)

- Patients with VAP resistant to β-lactams (n = 69)
  - Excluded patients (n = 26):
    - Bacteremia (n = 6)
    - Catheter infection (n = 1)
    - Peritonitis (n = 1)
    - Lung abscess (n = 1)
    - Concomitant use of IV antibiotics (n = 17)

  - Multidrug resistant strain group (n = 43)
    - Treatment of VAP by nebulized colistin (n = 43)
      - Treatment of VAP by nebulized colistin combined with a 3-day IV aminoglycoside (n = 15)

  - Treatment of VAP by nebulized colistin monotherapy (n = 28)
Patients received an aerosol* of 5 MU CMS every 8 h for 7–19 days

Aerosolized colistimethate dose was calculated according to a 40% extrapulmonary deposition.

Therefore, the resulting fraction of colistimethate reaching the respiratory tract was 60% of the initial dose placed in the nebulizer chamber, representing a daily dose equivalent to 3 MU delivered to the respiratory tract every 8 h.

* Aeroneb-nebulizer

Nebulized colistin with “Aeroneb” at a dose of 5 mil IU q8h is effective to treat VAP caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*. The clinical cure rate is noninferior to that obtained in VAP caused by susceptible *P. aeruginosa* and *A. baumannii* (66% vs 67%). The risk of developing colistin resistance after nebulization is low. Nebulized colistin does not increase the risk of kidney failure (12% vs 8% in the control), although repeated nebulization induces systemic accumulation.
Colistin peak and trough plasma concentrations measured at day 2 and day 3 of treatment with nebulized colistin either as monotherapy (n = 9) or combined with a 3-day intravenous administration of aminoglycoside (n = 7) in patients of the multidrug-resistant strains group.
Evolution of serum creatinine during the treatment period at baseline, day 3, day 7, and day 14 in patients of the sensitive strain group treated with intravenous β-lactams combined with a 3-day intravenous administration of aminoglycoside or quinolone (red squares) and those of the multidrug-resistant strain group treated with nebulized colistin either in monotherapy (n = 28) or combined with a 3-day intravenous administration of aminoglycoside (n = 15) (blue circles).
Inhalational +/- Intravenous Administration of Polymyxins for Treatment of VAP

Summary of Literature Review

Until 2012:

- 3 Studies non comparable of inhaled + IV colistin: favor the combination (versus literature results without inhalation)

- 3 Studies of inhalation + IV colistin versus IV:
  - 1 favorable
  - 2 indifferent

- 3 studies only inhaled colistin: 2 favorable, 1 indifferent
Aerosolization drawbacks

A. **Adverse effects of antibiotic inhalation**: disagreeable taste, bronchospasm

B. **Parenchymal lung penetration**: Most studies evaluating aerosolized antibiotics in patients with VAP found high antibiotic levels only in the tracheal aspirates

C. **Antibiotic inactivation by inhibitors in sputum**

D. **Emergence of resistant strains**: Aerosolization must be managed prudently, particularly concerning treatment duration, which should be kept as short as possible

E. **Cost**: Most of the devices, especially those of newest generation (vibrating-mesh nebulizer), are expensive. Most companies have developed antibiotic formulations to be administered via a specific device, thereby, further increasing the cost of delivery by nebulization.

F. **Legal concerns**: In the United States, to date, the FDA has not approved the use of inhaled colistin and tobramycin to treat VAP.
Safety of Inhaled Colistin

- Seldom inhaled colistin can cause bronchospasm particularly in patients with history of bronchial asthma.

- However, treatment with inhaled $\beta_2$-agonists before the initiation of aerosolized colistin could prevent the development of such adverse effects from the respiratory system.

- It should be emphasized that aerosolized colistin should be administered immediately after its preparation because of the molecule instability.
The importance of protecting the mechanical ventilator during colistin methanesulfonate nebulization

- Clinicians must be aware that aerosol administration of CMS, as also of other drugs, can lead to sudden and potentially dangerous malfunction of mechanical ventilators.

- Automatic monitoring and alarming of expiratory resistance are important safety features of ventilators, but personnel should also be trained in detecting and correcting ventilator malfunctions.

Conclusions

Key Recommendations

- Difficulty to reach statistical significance for the potentially therapeutically additive effect of nebulized colistin to the intravenously administered colistin. Thus it remains unresolved and is debated whether to administer nebulized colistin as adjunctive to the intravenous formulation.

- It is very possible that discrepancies in the results should be also attributed to the variety of nebulizers applied.

- Inhalation therapy with colistin without the parenteral drug is still questionable. However, high doses of Colistin seem to be more effective, even without the parenteral formulation.
Conclusions
Key Recommendations

- It is obvious that well organized, randomized, prospective, multicenter studies with a big number of patients are required, in which three randomized groups of patients with VAP will be included:
  1. IV Colistin (control)
  2. Inhaled high dose Colistin (monotherapy!)
  3. Inhaled high dose plus IV Colistin

The Appropriate nebulizer should be used by all patients included!