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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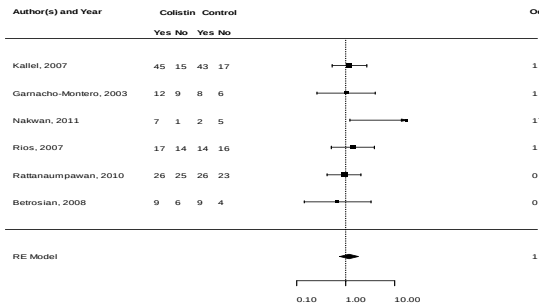
Background

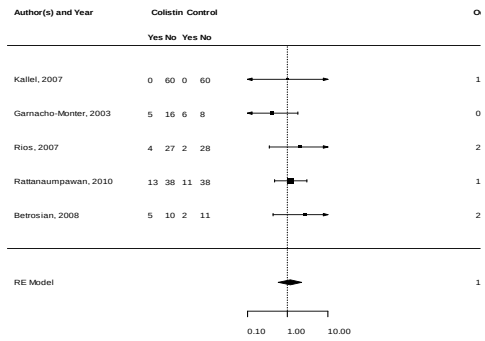
- The effectiveness of intravenous colistin for treatment of ventilator-associated pneumonia (VAP) has been debated because of its poor penetration into the pulmonary parenchyma.
- Aerosolized colistin might be an alternative option for treatment of patients with VAP since the drug achieves high concentration in the respiratory tract while avoiding systemic effects.
- Experience with intravenous and aerosolized form of colistin for the treatment of VAP in non-cystic fibrosis patients is limited.
- We aimed to assess the safety and efficacy of colistin for the treatment of VAP.

Methods

- We searched MEDLINE and Cochrane Database of Systematic Reviews for studies comparing colistin vs. other antibiotics for treatment of VAP in non-cystic fibrosis patients.
  - Studies were considered eligible if they reported the safety and efficacy of intravenous and/or aerosolized colistin for the treatment of VAP.
  - QUOROM guidelines were followed.
  - I^2 method was used for heterogeneity, and random-effects model for odds ratio (OR) estimates.
- Definitions
  - Nephrotoxicity in patients with normal renal function was defined as an increase in serum creatinine value >2mg/dl or a 50% reduction in the calculated creatinine clearance compared with baseline value, or need for renal replacement therapy.
  - Nephrotoxicity in patients with pre-existing renal impairment was defined as 50% increase in the baseline creatinine level or 50% reduction in the calculated creatinine clearance compared with the baseline or need for renal replacement therapy.
  - Pneumonia was considered VAP if the onset occurred ≥48h after intubation and provided that the same infection was not present before 48h.
  - Pneumonia was diagnosed based on new or progressive pulmonary infiltrates and at least 2 of the following: fever >38C or hypothermia <35.5C, leukocytosis >12,000cells/ml or leukopenia <4,000cells/ml, purulent bronchial secretions; if bronchoalveolar lavage was performed ≥10^4CFU/ml were isolated in the culture.
  - Clinical response was defined as clinical cure and clinical improvement (complete and respectively partial resolution of signs and symptoms of the infection by the end of therapy).
  - Microbiological response was defined as no growth of the causative pathogen at the end of therapy, regardless of the clinical outcome.
- Because there is no standard formulation of colistimethate sodium used worldwide, we standardized the doses used to colistin base activity:
  - ~12,500IU colistimethate sodium was equivalent to 1mg of colistimethate sodium
  - ~2.67mg of colistimethate sodium was equivalent to 1mg of colistin base
  - 1mg of colistin base was equivalent to 2.4mg of colistimethate sodium and 30,000IU of colistimethate sodium



Clinical response with colistin compared with control antibiotics



Risk of nephrotoxicity with colistin compared with control antibiotics

Results

Six two-arm studies (359 patients) met the inclusion criteria.

- The overall clinical response did not differ significantly between colistin and control groups OR 1.14 (95% CI, 0.74-1.77, p=0.56), I^2=0%,Q=4.98, p=0.42.
- The effect of colistin was independent of study design:
  - Prospective OR 0.89 (95%CI 0.48-1.66, p=0.71, I^2=0%),
  - Retrospective OR 1.45 (95%CI 0.79-2.68, p=0.23, I^2=0%),
  - Randomized trials OR 0.86 (95%CI, 0.43-1.74, p=0.68,I^2=0%).
- There was no change in clinical response after controlling for concomitant antibiotic treatment (intercept 0.121, slope 0.0315,p=0.95).
- Toxicity (colistin vs. control):
  - No impact on nephrotoxicity (5 studies, 344 patients) OR1.14 (95%CI 0.59-2.20, p=0.69), I^2=0%,Q=3.14, p=0.53;
  - No impact on neurotoxicity (3 studies, 183patients) OR1.39 (95%CI 0.17-11.61, p =0.76),I^2=0%,Q=0.41, p=0.82.
- Length of stay did not differ significantly between colistin and control groups:
  - ICU stay (4 studies, 244 patients) 2.63 days (95% CI, -5.46, 10.73, p=0.52),I^2=67%, Q=9.0922, P=0.028;
  - Hospital stay (2 studies, 96 patients) 7.48 days (95%CI-12.66,27.61, p=0.47), I^2=55.79%, Q=2.2622, p=0.1326.
- Mortality between colistin and control group - no significant difference :
  - Hospital mortality (5 studies, 331patients) OR 0.92 (95%CI 0.50-1.67, p=0.78),I^2=34.59%, Q=6.12, p=0.19;
  - ICU mortality (2 studies, 155 patients) OR1.27 (95%CI 0.66-2.43, p=0.47),I^2=0%, Q=0.057, p=0.81;
  - VAP-related death (2 studies, 135patients) OR1.11 (95%CI 0.55-2.24, p=0.77), I^2= 0%, Q=0.00, p=0.997;
  - 28-day mortality (2 studies, 148patients) OR1.62 (95%CI 0.795-3.32, p=0.18), I^2= 0%, Q=0.0011, p=0.97.

Conclusions

- Colistin may be as safe and as efficacious as other antibiotics for the treatment of VAP caused by multidrug-resistant Gram negative organisms.
- Once the susceptibility is available, colistin appears a safe and efficacious alternative.
- Clinical response and mortality were similar to other antibiotics used for VAP.

Author, year of publication	Type of study	Sample size Colistin/Control	Country	Colistin manufacturer	Route of administration	Organisms isolated	Susceptibility testing for colistin	Susceptibility testing for other antibiotics	Concomitant antibiotics administered
Kallel et al, 2007	Retrospective 2-arms	60/60	Tunisia	Bellon; Rhone-Poulenc, France	IV	*A.baumanii* *P. aeruginosa*	Disk diffusion	Disk diffusion	No
Garnacho-Montero et al, 2003	Prospective 2-arms	21/14	Spain	Bellon; Rhone-Poulenc, France	IV	*A. baumanii*	Microdilution method	Microdilution method	No
Nakwan et al, 2011	Retrospective 2-arms	8/7	Thailand	Atlantic Pharmaceutical Co Ltd., Thailand	nebulized	*A.baumanii*	Disk diffusion	Disk diffusion	Yes
Rios et al, 2007	Retrospective 2-arms	31/30	Argentina	N/A	IV	*A.baumanii* *P.aeruginosa*	Disk diffusion	Disk diffusion	No
Rattanaumpawan et al, 2010	Prospective 2-arms	51/49	Thailand	Atlantic Pharmaceutical Co Ltd., Thailand	nebulized	*A.baumanii* *P.aeruginosa* *K. pneumoniae* *E coli*	Disk diffusion E-test	Disk diffusion E-test	Yes
Betrosian et al, 2008	Prospective 2-arms	15/13	Greece	Norma, Athens, Greece	IV	*A.baumanii*	Disk diffusion	Kirby-Bauer disk-diffusion Microdilution method	No