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CRITICAL CARE

Effect of Aerosolized Colistin as Adjunctive Treatment on the Outcomes of Microbiologically Documented Ventilator-Associated Pneumonia Caused by Colistin-Only Susceptible Gram-Negative Bacteria

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Background: **The increasing frequency of ventilator-associated pneumonia (VAP) caused by colistin-only susceptible (COS) gram-negative bacteria (GNB) is of great concern. Adjunctive aerosolized (AS) colistin can reportedly increase alveolar levels of the drug without increasing systemic toxicity. Good clinical results have been obtained in patients with cystic fibrosis, but conflicting data have been reported in patients with VAP.**

Methods: **We conducted a retrospective, 1:1 matched case-control study to evaluate the efficacy and safety of AS plus IV colistin vs IV colistin alone in 208 patients in the ICU with VAP caused by COS *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or *Klebsiella pneumoniae*.**

Results: **Compared with the IV colistin cohort, the AS-IV colistin cohort had a higher clinical cure rate (69.2% vs 54.8%, *P* = .03) and required fewer days of mechanical ventilation after VAP onset (8 days vs 12 days, *P* = .001). In the 166 patients with posttreatment cultures, eradication of the causative organism was also more common in the AS-IV colistin group (63.4% vs 50%, *P* = .08). No between-cohort differences were observed in all-cause ICU mortality, length of ICU stay after VAP onset, or rates of acute kidney injury (AKI) during colistin therapy. Independent predictors of clinical cure were trauma-related ICU admission (*P* = .01) and combined AS-IV colistin therapy (*P* = .009). Higher mean Simplified Acute Physiology Score II (*P* = .002) and Sequential Organ Failure Assessment (*P* = .05) scores, septic shock (*P* < .001), and AKI onset during colistin treatment (*P* = .04) were independently associated with clinical failure.**

Conclusions: **Our results suggest that AS colistin might be a beneficial adjunct to IV colistin in the management of VAP caused by COS GNB.** ***CHEST 2013; 144(6):1768–1775***

Abbreviations: AKI = acute kidney injury; AS = aerosolized; COS = colistin-only susceptible; GNB = gram-negative bacteria; ICU-LOS = length of ICU stay; MDR = multidrug-resistant; MIC = minimum inhibitory concentration; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia

Despite active preventive efforts,[1,2] ventilator-associated pneumonia (VAP) remains the most frequent infectious complication of intensive care, affecting 10% to 20% of patients receiving mechanical ventilation (MV).[3] Reported mortality rates vary from 10% to > 70%, depending on the underlying conditions and the pathogenicity of the infecting organisms.[4-11] Recent years have witnessed a steady increase in the proportion of VAP cases caused by multidrug-resistant (MDR) gram-negative bacteria (GNB)—*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* in particular. The polymyxins are one of the few drug classes that are still active against these organisms.[12,13] Widely abandoned in the 1980s because of toxicity issues, they have been recalled into active service as a last-resort

treatment of MDR GNB infections.[12,14] The best-known polymyxin, colistin (colistimethate sodium), displays good activity against carbapenem-resistant strains of *A baumannii*, *P aeruginosa*, and *K pneumoniae*,[15] but its polycationic/hydrophilic structure limits its penetration of lung tissue, and its efficacy in VAP remains controversial.[16,17]

Nebulization has been proposed to achieve bactericidal concentrations of antimicrobials (especially colistin and aminoglycosides) at the alveolar level in patients with MDR GNB VAP.[18] Inhaled antimicrobial aerosols produce high drug levels in the lungs without increasing the risks of systemic toxicity and the emergence of MDR gut microflora.[19] The efficacy of this approach has been demonstrated in cystic fibrosis,[20] but its value in the treatment of GNB VAP is less certain. The studies that have explored the possibility are generally quite small, and they have produced conflicting results.[21-28] We analyzed a large homogeneous cohort of patients with VAP caused by colistin-only susceptible (COS) *A baumannii*, *P aeruginosa*, or *K pneumoniae* to assess the efficacy and safety of aerosolized (AS) and IV colistin therapy compared with IV colistin alone.

Materials and Methods

Setting, Study Design, and Data Sources

A retrospective matched-cohort analysis was conducted in the 18-bed general ICU of a 1,400-bed teaching hospital in Rome, Italy. The protocol was approved by the Catholic University's Ethics Committee (approval number: P/237/CE/2012). Informed patient consent was not required given the study's retrospective, observational nature. Data were collected via manual review of hospital charts and computerized interrogation of the ICU and Microbiology Laboratory databases.

Population

Eligibility criteria were as follows: (1) age ≥ 18 years; (2) ICU admission between January 1, 2005, and December 31, 2012; (3) VAP with onset after ≥ 48 h of MV and associated with a new persistent infiltrate on chest radiograph, fever > 38°C with no other identified cause, a WBC count of < 4,000 or > 12,000 cells/μL, and purulent tracheal secretions[29]; (4) quantitative BAL fluid cultures growing a single COS strain of *A baumannii*, *P aeruginosa*, or *K pneumoniae*; and (5) IV colistin therapy lasting ≥ 72 h.

Patients who also received AS colistin (AS-IV colistin group) were matched (1:1) with those treated with IV colistin alone (IV colistin group). Matching was based on age (within 10 years) and illness severity as defined by Simplified Acute Physiology Score (SAPS) II at ICU admission (within 5 points) and by Sequential Organ Failure Assessment (SOFA) scores (within 2 points) the day IV colistin was started.[30,31] When multiple control candidates met the core matching criteria, the choice was based on ICU admission dates. Investigators were blinded to case outcomes during matching.

Microbiology Studies

Respiratory specimens for culture were obtained blindly with telescopic catheters (Combicath; Prodimed) or, in 23 cases, with bronchoscopic guidance. Respiratory specimens were quantitatively cultured on blood, chocolate, and MacConkey agars. Diagnostic quantitative culture threshold was 10^4 colony forming units/mL. Blood cultures (three or more sets per patient) were inoculated into Lytic/10 Anaerobic/F and Plus Aerobic/F bottles and incubated in the Bactec 9240 system (Becton, Dickinson and Company).

Isolates were identified with the Vitek 2 system (bioMérieux, Inc) (2005-June 2009) or matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (Bruker Corporation) (July 2009-2012). Minimum inhibitory concentrations (MICs) were determined with the Vitek 2 (β-lactam inhibitor combinations, oxyiminocephalosporins, carbapenems, aztreonam, quinolones, aminoglycosides), the E-test (bioMérieux, Inc) with cation-adjusted Mueller-Hinton agar (colistin), or Sensititre broth microdilution (Thermo Fisher Scientific) (tigecycline). Colistin MICs for Enterobacteriaceae isolates were classified using European Committee on Antimicrobial Susceptibility Testing breakpoints (susceptible, MIC ≤ 2 mg/L; resistant, MIC > 2 mg/L).[32] US Food and Drug Administration breakpoints were used for tigecycline MICs (susceptible ≤ 2 mg/L; resistant, ≥ 8 mg/L).[33] Other MICs were interpreted according to Clinical and Laboratory Standards Institute breakpoints.[34] Isolates classified as COS displayed full susceptibility to colistin and nonsusceptibility to all other antimicrobials tested.

Treatment Regimens

IV colistimethate sodium was administered every 8 to 12 h at daily per-kilogram doses of approximately 100,000 International Units (a dose of 75,000 International Units in patients with creatinine clearance rates < 50 mL/min and those on continuous renal replacement therapy). When administered, AS colistin (colistimethate sodium) therapy was always started with IV colistin and discontinued when the latter was stopped. It was administered three times a day via jet or ultrasonic nebulizers (total daily dose, 3 million International Units).

Definitions and Outcomes

VAP onset coincided with the collection date of the index BAL culture. The following intervals (number of days) were recorded: time at risk (from ICU admission to pneumonia onset), length of ICU stay (ICU-LOS) (total, from ICU admission to ICU discharge or death, and post-VAP, from pneumonia onset to ICU discharge or death), and duration of MV before and after pneumonia onset. Septic shock was defined according to American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee criteria.[35] AKI was defined as a greater than twofold increase in serum creatinine or a ≥ 50% decrease in the glomerular filtration rate or oliguria (output < 0.5 mL/kg/h) for ≥ 12 h.[36]

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