Original Article

Treatment of ventilator-associated pneumonia with high-dose colistin under continuous veno-venous hemofiltration

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ABSTRACT

Background and Objectives: High-dose colistin (COL) ensures adequate treatment of pneumonia caused by multidrug resistant gram-negative bacteria (MDR-GNB) but must be weighed against a higher risk of nephrotoxicity. Continuous veno-venous hemofiltration (CVVH) clears COL by filtering and membrane adsorption that permits to avoid dose accumulation and excessively high peak concentrations. We evaluated clinical/microbiological efficacy of the high-dose COL treatment under CVVH in patients with newly diagnosed MDR-GNB ventilator-associated pneumonia (VAP). **Methods**: Observational cohort study in critically ill adult patients with MDR-GNB VAP. Colistimethate sodium (CMS) was administered as a 9 million international units (MIU) of loading dose followed by 3 × 4.5 MIU daily. CVVH was performed over a highly adsorptive membrane. Clinical and microbiological efficacies were assessed at the end of therapy. In survivors, serum creatinine level was evaluated before and at the end of therapy. **Results**: Fourteen patients (8 male patients, aged 57 ± 14 years) were consecutively included. Isolated pathogens were *Pseudomonas aeruginosa* in 7, *Klebsiella pneumoniae* in 5, and other *Enterobacteriaceae* in 2 patients. A favorable clinical response was observed in 9 patients (64%). Full and presumed microbiological eradication was observed in 12 patients (86%). Two patients were diagnosed with Stage 1 acute kidney injury. **Conclusions**: In patients with MDR-GNB VAP, CVVH may represent an interesting option to enable effective high-dose COL treatment.

Key words: colistin, ventilator-associated pneumonia, continuous veno-venous hemofiltration, acute kidney injury, nephrotoxicity

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INTRODUCTION

Ventilator-associated pneumonia (VAP) remains a challenging disease in mechanically ventilated critically ill patients. Akin to VAP is prolonged ventilation time, longer duration of intensive care unit (ICU) and hospital stay, and increased mortality.[1] Prognosis is even poorer in patients with VAP caused by multidrug-resistant gram-negative bacteria (MDR-GNB), with mortality rates that are 3- to 6-fold higher as compared to non-MDR-infected VAP patients.[2,3] Colistin (COL) is an old antibiotic that was abandoned from clinical use in the 1970s because of significant renal and neurological toxicity.[4] At present, COL is increasingly put forward as salvage or first-line treatment for severe MDR-GNB infections, particularly in the ICU.[5] COL is administered intravenously as the inactive prodrug colistimethate sodium (CMS) that is hydrolyzed to COL. From a pharmacodynamic/pharmacokinetic (PK/PD) viewpoint, COL possesses rapid concentration-dependent bacterial killing against susceptible strains, but the ratio of the area under the concentration time curve of the unbound fraction to the minimal inhibitory concentration (MIC) of the pathogen is the PK/PD parameter that correlates best with its antibacterial effect.[6]

The efficacy of COL to treat pneumonia has been questioned. Usually recommended doses of COL (2 million international units (MIU) q8h) result in suboptimal plasma concentrations and undetectable intrapulmonary levels.[7] The PK/PD rationale favors a higher COL dose but this must be weighed against a higher risk of nephrotoxicity.[8]

COL is effectively cleared by continuous renal replacement therapy (CRRT), in particular when a convective method such as continuous veno-venous hemofiltration (CVVH) is used.[9] Thus, CVVH might act as an elegant "prophylactic" method to reconcile efficacy and safety when high doses of COL are used for an extended period of time. We tested the feasibility of this concept by examining clinical/microbiological efficacy and safety of high-dose COL treatment under CVVH in a cohort of patients with newly diagnosed MDR-GNB VAP.

MATERIAL AND METHODS

This is a retrospective, observational cohort study conducted in adult ICU patients with MDR-GNB VAP only susceptible to COL. The study was approved by the Institutional Review Board of the University Hospital Brussels (BUN 143201732239) and performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The need for informed consent was waived. All patients received CMS (Colistineb™) either in monotherapy or in combination with other antibiotics. Patients did not receive nebulized COL. CMS was administered as a 9-MIU loading dose followed by a maintenance dose of 4.5 MIU q8h. CVVH was performed under regional citrate anticoagulation at a dose of 35 mL/kg/h using a highly adsorptive acrylonitrile 69 surface-treated (AN69 ST) membrane with a 1.5-m² surface area. CVVH was initiated in all patients as a deresuscitation measure to correct treatment-related fluid overload.

VAP was defined as pneumonia occurring at least 48–72 h after endotracheal intubation, characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, increased white blood cell count), purulent sputum, and detection of a causative microorganism.[10]

The following data were collected at admission in all patients: age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, comorbidities, concomitant antibiotic therapy, body mass index, and type/MIC of the causative pathogen. Occurrence of acute kidney injury (AKI) was assessed based on serum creatinine values recorded before the start of CVVH, 2 days after withdrawing CVVH, and at hospital discharge in survivors. Values were stratified according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria and duration of COL therapy.[11]

Clinical and microbiological efficacies were assessed at the end of therapy. Clinical efficacy was defined as favorable (resolution of systemic signs and symptoms of infection, radiological improvement) or failure (persistent or progressive infection). Microbiological response was defined as eradication (i.e., no evidence of any MDR-GNB pathogen in a deep respiratory sample [bronchoalveolar fluid] or at least two consecutive negative tracheal aspirations or oral sputum samples during the next 14 days), presumed eradication (clinical efficacy but no microbiological data), or failure (recurrence of a single representative respiratory sample with signs of inflammation [semi-quantitative presence of a moderate to high white blood cell count] and a single positive respiratory sample culture (same pathogen) after at least 5 days of antibiotic treatment). The MIC was determined by broth microdilution method (Sensitest™). The SOFA score was recorded daily during the course of COL therapy. Mortality was defined as all-cause ICU mortality. The results were expressed as means ± SD or medians (range).

RESULTS

Fourteen patients were enrolled in this study. Patient characteristics and outcome were depicted in Table 1. All patients were endotracheally intubated, ventilated in pressure-controlled mode and initiated on CVVH at the start of COL therapy. The mean age was 57 ± 14 years. APACHE II score at ICU admission was 26 ± 11, which corresponds to a predicted mortality of approximately 55%. The most frequent comorbidities were congestive heart failure/ischemic cardiomyopathy (*n* = 5) and type 2 diabetes mellitus (*n* = 3). One patient had chronic kidney disease. All except one patient received combination antibiotherapy. Aztreonam, meropenem, and amikacin were most frequently prescribed. The patients received COL for 12 ± 5 days. CVVH was provided for 13 (6–27) days. The patients stayed in the ICU for 52 ± 31 days.

Isolated pathogens were *Pseudomonas aeruginosa* in 7 patients (50%), *Klebsiella pneumoniae* in 5 patients (36%), and other Enterobacteriaceae in 2 patients (14%). The MIC values ranged from 0.03 to 3 mg/L with mean values of 0.52, 0.68, and 0.25 mg/L, respectively, for *P. aeruginosa*, *K. pneumoniae*, and other Enterobacteriaceae. A favorable clinical response was observed in 9 patients (64%). The remaining 5 patients were considered as clinical failure. Microbiological eradication was observed in 9 patients (64%), 3 patients (22%) had presumed microbiological eradication, and 2 patients (14%) were considered to be microbiological failures. The mean SOFA scores before

Table 1: Patient characteristics and outcome

Age (years)	57 ± 14
Gender *n* (%)	
• Male	8 (57)
Body mass index (kg/m²)	27,1
Concomitant antibiotic therapy *n* (%)	
• Aztreonam	5 (36)
• Meropenem	5 (36)
•• Tigecycline	1 (7)
• Trimethoprim-sulfamethoxazole	2 (14)
• Amikacin	5 (36)
• None	1 (7)
Colistin treatment duration (days)	12 ± 5
APACHE II score	26 ± 11
Pathogen *n* (%)	
• *Pseudomonas aeruginosa*	7 (50)
• *Klebsiella pneumoniae*	5 (36)
• Other *Enterobacteriaceae*	2 (14)
ICU length of stay (days)	52 ± 31
Clinical response *n* (%)	
• Favorable	9 (64)
• Failure	5 (36)
Microbiological response *n* (%)	
•• Eradication	9 (64)
• Presumed eradication	3 (22)
• Failure	2 (14)
ICU mortality *n* (%)	
• Survivor	6 (43)
• Non-survivor	8 (57)
AKI during colistin treatment *n* (%)	
• yes	2 (14)
• no	12 (86)

Values are means ± standard deviation unless indicated otherwise.

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; AKI: acute kidney injury.

starting and at the end of COL therapy were 8 ± 4 and 7 ± 5, respectively. The SOFA score decreased in all but one patient with a favorable clinical response. The median serum creatinine level was 2.1 (0.4–5.0) mg/dL before the start of CVVH and 2.3 (0.6–2.7) mg/dL on Day 2 after withdrawing CVVH. Two patients developed KDIGO stage 1 AKI with a 1.7- and 1.8-time increase in serum creatinine level from baseline, respectively. Both fully recovered renal function upon hospital discharge. The serum creatinine levels remained stable or decreased in the other patients. All-cause ICU mortality rate for the whole population was 57% (8/14). No patient died while receiving COL/CVVH treatment. Two patients, both infected with *P. aeruginosa*, who initially had a favorable clinical and microbiological response, died after 67 and 101 days in the ICU. All surviving patients had normal or recovered baseline renal function at hospital discharge.

DISCUSSION

The highest achievable steady-state plasma COL concentration should be pursued in MDR-GNB VAP. As the MIC usually is unknown at the initiation of treatment, a steady-state plasma COL concentration of 2 mg/L seems to be a reasonable target.[12] For years, 9 MIU COL daily was prescribed for the treatment of systemic MDR-GNB infections in adult patients. However, the first relevant PK/PD evaluation of this dose in critically ill patients with moderate-to-good renal function demonstrated that COL concentrations during the first 48 h of treatment were largely below the MIC of the causative pathogens.[13] As such, the use of a high loading dose and an extended interval high maintenance dose was suggested.[14] To remain within safety limits, it was emphasized that the loading dose should not exceed 10 MIU and that the first maintenance dose was administered after 24 h. Moreover, large interpatient PK/PD variabilities were observed, particularly in critically ill patients who frequently present altered distribution volume, organ failure, and hypoalbuminemia. These results in COL plasma concentrations that may either be too low to ascertain an antibacterial effect or that overlap those causing nephrotoxicity. Reaching an optimal PK/PD goal with high-dose COL must also be weighed against a higher risk for nephrotoxicity. AKI often develops during therapy and was observed to strongly correlate with advanced age, average plasma COL steady-state concentrations exceeding 2 mg/mL, hypoalbuminemia, high body mass index, concomitant nephrotoxic medication, long treatment duration, and disease severity.[15-17] Moreover, CMS and COL accumulate in AKI making dose adjustments necessary.

The current study demonstrates the feasibility of CRRT-shielded administration of high-dose COL. CRRT is progressively replacing intermittent dialysis in critically ill patients because it is better hemodynamically tolerated, offers rapid correction of metabolic alterations, and may lower the incidence of post-ICU need for chronic dialysis.[18] Moreover, CRRT is increasingly positioned as a "deresuscitative" strategy to control practice-dependent fluid overload. Rapid achievement of a negative fluid balance is associated with improved outcome, even in patients with normal kidney function.[19] CMS/COL handling is dramatically altered when convective CRRT modes such as CVVH are used. Tubular reabsorption, which is extensive in patients with normal renal function,

is virtually absent in this condition. Instead, CMS is continuously eliminated by convection, whereas COL is mainly eliminated by adsorption.[20] Moreover, a highly bulk adsorptive filter such as the AN69 ST membrane permits an even higher clearance.[21] Continuous loss by filtration prevents dose accumulation of COL, whereas bulk membrane adsorption avoids huge or persisting peak concentrations. In a cohort of patients with mainly blood-borne MDR-GNB infections, Karaiskos *et al.* found that application of a 9-MIU CMS loading dose resulted in COL plasma concentrations exceeding 1.5 mg/L. However, the subsequent 9-MIU CMS maintenance dose, apt to reach therapeutic COL concentrations in patients with normal renal function, produced a steady-state level of only 1.72 mg/L.[22] This strengthens the idea to use higher maintenance doses to obtain an acceptable antibacterial effect.

Expert opinion suggests organ-related target steady-state COL concentrations and MIC breakpoints. Inferior efficacy of CMS and COL was reported in a murine lung infection model.[23] Imberti et al. found undetectable COL levels in bronchoalveolar lavage fluid of critically ill patients after intravenous (IV) administration of 6-MIU CMS for at least 2 days.[7] Adding aerosolized COL to IV COL might exhibit better clinical cure but studies are inconclusive because of marked heterogeneity in prescribed COL dose, nebulization techniques, and ventilator manipulation.[24] Aerosolized plus IV COL also did not lower mortality in patients with MDR-GNB pneumonia.[25] Combining COL with other antibiotics did not provide better outcomes compared with COL monotherapy.[26, 27]

Clinical response was favorable in two-thirds of our patients and 86% had a complete or presumed microbiological eradication. This indirectly supports the PK/PD-based idea of using high-dose COL under a prophylactic CVVH "shield." Observed mortality was in line with predicted mortality but higher as compared with a recent meta-analysis of patients with VAP treated with COL, which showed an ICU and in-hospital mortality of 29% and 34%, respectively.[28] It has been repeatedly demonstrated that infection cure or microbiological eradication obtained with high-dose COL regimens are not correlated with improvements in mortality. [29-31] Therefore, consensus is gaining ground that mortality may not be a relevant clinical end point to evaluate efficacy of an antimicrobial treatment in critically ill patients because it also depends on severity of disease, presence of comorbidities, occurrence of secondary infections, and therapy- or procedure-related complications incurred during an ICU stay.

AKI occurred in 2 (14%) patients. Both patients received concomitant nephrotoxic drugs. AKI was not severe

and fully reversible. Determining the true incidence of COL-related nephrotoxicity is cumbersome because of differences in AKI definition, product formulation, posology standardization, and duration of treatment and whether or not a loading dose is used.[32] Two meta-analyses including 796[28] and 1167 patients[26] with MDR-GNB VAP found no significant difference in nephrotoxicity between COL and other antibiotic treatments. These meta-analyses reported an incidence of nephrotoxicity ranging between 5.7% and 7%. Our study observed an incidence of 14%, which is acceptable when accounting for the much larger COL dose than the one used in the studies included in the meta-analyses. As the total cumulative rather than the daily CMS or COL dose is associated with nephrotoxicity,[33,34] renal side effects could be further minimized by shortening treatment duration and by carefully considering the use of concomitant nephrotoxic drugs. No other COL-related toxicity was observed.

Leuppi-Taegtmeyer *et al.* recently reported that a CMS loading dose of 9 MIU followed by a 3 MIU q8h maintenance dose achieved steady-state COL concentrations largely exceeding 2.0 mg/L in patients mainly undergoing continuous veno-venous hemodialysis with an AN69-ST membrane. CRRT clearance in this study accounted for, on an average, 28% of total COL clearance.[35] This clearance is more than half lower than reported by Karaiskos et al. during continuous veno-venous hemodiafiltration[22] and explains the remarkable differences in mean steady-state COL concentrations between both studies (4.67 ± 1.48 mg/dL *vs.* 1.59 ± 0.73 mg/dL). The reason for this important divergence in clearance remains unclear but may be imputed on differences in distribution volume, membrane adsorption capacity, acute-phase COL-binding protein levels, epuration technique (convection vs. diffusion), and total effluent (i.e., filtration + dialysate fluid rate) dose. [36,37]

Our study has major limitations. The patient sample was small, which precludes valid assessment of patient-centered outcomes such as length of ICU stay, duration of mechanical ventilation, and mortality. COL was mostly combined with other antibiotics, which impedes to ascribe the observed clinical cure only to the use of high-dose COL. Therapeutic COL monitoring was not performed, yet it is conceivable that COL levels in our patients are in the same range as those reported by Karaiskos *et al.* because both studies used a similar epuration technique, effluent dose, and dialysis membrane.

CONCLUSION

Infusing a high-dose COL under CVVH "control" is a feasible and safe option for the treatment of MDR-

GNB VAP only susceptible to COL. In an ideal situation, patients should receive an individual dosing regimen based on the type and MIC of the pathogen, plasma protein concentration, residual diuresis, type of adsorptive dialysis membrane, and CRRT mode.

Conflict of Interest

There is no competing interest related to the article.

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