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Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia

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Summary *Objective:* To compare the safety and efficacy of ampicillin/sulbactam (Amp/Sulb) and colistin (COL) in the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP).
Methods: A prospective cohort study in adult critically ill patients with VAP. Patients were randomly assigned to receive Amp/Sulb (9 g every 8 h) or COL (3 MIU every 8 h) intravenously. Dosage was adjusted according to creatinine clearance.
Results: A total of 28 patients were enrolled (15 COL, 13 Amp/Sulb). Resolution of symptoms and signs occurred in 60% (9/15) of the COL group and 61.5% (9/13) of the Amp/Sulb group, improvement in 13.3% (2/15) vs. 15.3% (1/13) and failure in 26.6% (4/15) vs. 23% (3/13), respectively. The difference was not statistically significant. Bacteriologic success was achieved in 66.6% (10/15) vs. 61.5% (8/13) in the COL and Amp/Sulb groups, respectively ($p < 0.2$). Mortality rates (14 days and 28 days) were 15.3% and 30% for the Amp/Sulb and 20% and 33% for the COL group, respectively. Adverse events were 39.6% (including 33% nephrotoxicity) for the COL group and 30.7% (15.3% nephrotoxicity) for the Amp/Sulb group (p = NS).
Conclusion: Colistin and high-dose ampicillin/sulbactam were comparably safe and effective treatments for critically ill patients with MDR *A. baumannii* VAP.

Introduction

Ventilator-associated pneumonia due to *Acinetobacter baumannii* carries significant morbidity and mortality in

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the intensive care unit (ICU) setting.[1] It commonly occurs more than 5–7 days of mechanical ventilation (late-onset VAP) and is associated with antibiotic prescribing practices in the initial ICU stay.[2] *A. baumannii*, a nonfermenting gram-negative pathogen, is characterized by the rapid development of resistance to all the major antibiotic classes, including the antipseudomonal penicillins, monobactams, carbapenems, quinolones, and aminoglycosides.[3] The emerging therapeutic gap has been partially counterbalanced by the revival of older drugs such as polymyxin E (colistin) and sulbactam, although ongoing studies for newer drugs like glycylcyclines yields promising results.[4–6]

Polymyxins are the only antibiotic drug class with relatively unharmed in vitro activity against infection from multidrug resistant (MDR) *A. baumannii* strains.[7] Sulbactam is a β-lactamase inhibitor that has antimicrobial activity against *A. baumannii* strains.[5] In a previous report, we showed that high-dose regimen of this compound (provided in the form of ampicillin/sulbactam, Amp/Sulb) may be an alternative treatment option for late-onset VAP from MDR *A. baumannii* strains.[8] In this study we aimed to compare the clinical efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of *Acinetobacter* VAP.

Methods

This study was performed at a 7-bed and a 12-bed polyvalent intensive care units of the Hippokration General Hospital (Athens, Greece) and the Evgenidion University Hospital (Athens, Greece). The study was approved by the ethical committee and conducted in accordance to its guidelines. Informed consent was requested by the patients' next of kin. Patients were enrolled during a one-year period.

Study design

All mechanical ventilated patients for >72 h who developed VAP were enrolled in the study. When *A. baumannii* was isolated and quantitative culture of bronchoscopic bronchoalveolar lavage (BAL) was achieved the case was considered to be aetiologicaly confirmed. Cases of VAP with mixed isolated microorganisms were excluded from the study. Other exclusion criteria were combination antibiotic therapy, allergy to β-lactamase or penicillin or previous enrolment to similar studies.[8]

Patients were randomly assigned to receive intravenous colistin (COL group) 3 MIU every 8 h or ampicillin/sulbactam (Amp/Sulb group) 9 g (at a rate 2:1) every 8 h. The latest was administered as follows: three vials (20 ml each) containing 3.0 g of ampicillin/sulbactam were diluted in 200 ml of 5% dextrose provided within 1 h duration infusion.

Following the enrolment list, randomization was performed by the alternative and consecutive allocation of patients to each of the groups. Treatment duration was 8–10 days for both groups; however, the dosing period was extended as needed. Dosage was adjusted according to measured creatinine clearance (CL_{CR}) as follows: patients in colistin group and CL_{CR} 20–50 ml/min had a dose reduction of 25%, administered twice daily (bid); when $CL_{CR} < 20$ ml/min the dose reduction was 75% administered once daily. Patients in Amp/Sulb group and mild renal failure ($CL_{CR,}$ 31–60 ml/min) had a dose reduction by 25% without changes in dosing intervals. In severe renal failure ($CL_{CR,}$ 7–30 ml/min) the dose was reduced by 50% and administered twice daily. Follow-up BAL was performed on the 5th day after treatment initiation.

Definitions

The diagnosis of ventilator-associated pneumonia was established when the BAL quantitative culture grew the microorganism at a concentration of at least 10^4 colony-forming units (CFU)/mL.

The clinical indicators for VAP included abnormal temperature (>38 °C or <36 °C), leukocytosis (white blood cell count > 10,000) or leukopenia (white blood cell count < 4000), macroscopically purulent sputum, and new or changing infiltrate on chest radiograph.[9]

The primary outcome measure was the clinical cure of VAP; secondary end points were microbiological cure, the 14-day mortality (attributable) and the all-cause (28 days) mortality. The attributable or VAP-related mortality was defined as death that occurred during the treatment period due to septic shock related to *A. baumannii* VAP.

MDR *A. baumannii* strains were defined as resistant to all antibiotic agents routinely tested, including penicillins, aminoglycosides, ampicillin/sulbactam, cephalosporins, aztreonam, carbapenems, fluoroquinolones, tetracyclines, excluding polymyxin E (colistin).

Antimicrobial susceptibility testing was performed for all antimicrobials by using both the Kirby–Bauer disk-diffusion method and the VITEK II system method. Additionally, susceptibility to Amp/Sulb was tested by the *E*-test method (AB Biodisk, Solna, Sweden) according to the recommendations of the manufacturer.

Interpretation of the susceptibility results was according to the current CLSI/NCCLS guidelines[10] as follows: Kirby–Bauer: ampicillin/sulbactam (mm) *R* (resistant): 11, I (intermediate): 12–14, and *S* (sensitive): 15; VITEK II (breakpoints) and *E*-test: ampicillin/sulbactam (μg/ml) *S*: ≤8, I: 16, and *R*: ≥32. Equivalent minimal inhibitory concentration (MIC) breakpoints (μg/mL) for ampicillin/sulbactam were according to the CLSI/NCCLS criteria: $R > 32/16$ and $S < 8/4$. Susceptibility to colistin was tested by the disk-diffusion method with the use of 10 μg of colistin sulfate disk and the VITEK II system method.

Efficacy evaluation

Evaluation of efficacy was based on both clinical (success, improvement or failure) and bacteriologic (success or failure) responses to therapy. The clinical response was rated as (i) success, if symptoms and signs of VAP resolved at the end of therapy, (ii) failure, if symptoms and signs persisted for >3 days, which required an additional antibiotic treatment, and (iii) improvement, if resolution of some, but not all, signs and symptoms of infection at the end of treatment.

Bacteriologic success was defined by the eradication of *A. baumannii* isolates as noted on the follow-up BAL; suppression of *A. baumannii* isolates was defined as a 2-log reduction or greater in the colony counts on the follow-up BAL. Suppression response was considered a success when in addition to the presence of criteria for clinical success.

Bacteriologic failure was defined by persistence of *A. baumannii* isolates ($>10^4$ CFU/ml) on the follow-up culture of BAL. In such cases, a rifampicin/imipenem or meropenem combination therapy was provided.

Safety evaluation

Physical evaluation, vital signs and laboratory values were performed daily until the end of treatment to evaluate the safety and tolerability of study treatment. Adverse events were analyzed with specifications on the date of onset, the duration, the severity and the possible relation with the study treatment. Patients were monitored daily for neurotoxic reactions like seizures, encephalopathy, neuromuscular blockade and apnea. In patients with normal renal function, nephrotoxicity was defined as a serum creatinine value >2 mg/dl, as a reduction in the calculated creatinine clearance of 50% compared to therapy initiation or as a decline in renal function that prompted renal replacement therapy. In patients with pre-existing renal dysfunction nephrotoxicity was defined as an increase of $>50\%$ of the baseline creatinine level, as a reduction in the calculated creatinine clearance of 50% relative to the value at therapy initiation.

Statistical analysis

All data were analyzed by using SPSS Version 11.0. Data are presented as mean $\pm$ SD. Clinical and bacteriological success or failure of the two groups was compared by using the Fisher Exact test. A p-value of <0.05 was considered significant.

Results

During the study period 30 critically ill patients with MDR *A. baumannii* VAP were identified. Two patients were excluded from the study because combined antibiotic treatment was provided. Two patients received combination antibiotic therapy and were excluded. Data on the remaining 28 patients are presented in Table 1. The mean ($\pm$SD) duration of therapy was 9.2 ± 1.5 days and 9.9 ± 2.6 days for the 2 groups, respectively. The mean ($\pm$SD) duration of mechanical ventilation prior to VAP was 10 ± 4 in the COL group and 11 ± 5 days in the Amp/Sulb group, respectively. A dosage reduction by 25% due to pre-existing renal failure was provided in four patients in the COL group and five patients in the Amp/Sulb group, while one patient from the first group had 75% reduction in the daily scheduled dosage. The mean daily antibiotic dosage was 5.83 ± 2.3 MIU for the COL group and 23.5 ± 4.55 g for the Amp/Sulb group. The MIC of *A. baumannii* for colistin was <0.5 mg/L (μg/ml) and for Amp/Sulb $>32/16$ mg/L (μg/ml).

Table 1 Clinical characteristics of patients with *Acinetobacter baumannii* ventilator-associated pneumonia

Characteristics	COL group ($n = 15$)	Amp/Sulb group ($n = 13$)
Age (mean $\pm$ SD)	67 ± 9	72 ± 5
Sex (male/female)	7/8	7/6
APACHE II score[a] (mean $\pm$ SD)	14 ± 2	14 ± 5
Primary diagnosis		
Postoperative respiratory failure	4 (26.6%)	3 (23%)
COPD $-$ acute respiratory failure	7 (46.6%)	6 (46.1%)
Acute pancreatitis $-$ ARDS	1 (6.6%)	2 (15.3%)
Subarachnoid hemorrhage	2 (13.3%)	2 (15.3%)
Guillain–Barre syndrome	1 (6.6%)	0 (0%)
Mechanical ventilation prior VAP (mean $\pm$ SD)	10 ± 4	11 ± 5
Mean duration of ICU stay (mean $\pm$ SD)	24 ± 13	31 ± 14

[a] APACHE II, Acute Physiology and Chronic Health Evaluation, score obtained on the admission day to the ICU.

The clinical and bacteriologic outcomes for patients treated with colistin vs. Amp/Sulb are summarized in Table 2. Resolution of symptoms and signs occurred in 60% (9/15) of COL group and 61.5% (9/13) of Amp/Sulb group, improvement in 13.3% (2/15) vs. 15.3% (1/13) and failure in 26.6% (4/15) vs. 23% (3/13), respectively. The difference was not statistically significant. Bacteriologic success was achieved in 66.6% (10/15) vs. 61.5% (8/13) in the COL and Amp/Sulb groups, respectively ($p < 0.2$). Eradication of *A. baumannii* from the follow-up BAL was achieved in 7/15 (46.6%) patients in the COL vs. 6/13 (46.1%) in the Amp/Sulb group, while suppression of the microorganism with favorable clinical success was observed in 3/15 (20%) vs. 2/13 (15.3%), respectively. Four patients from the COL group and two from the Amp/Sulb group had positive blood cultures from the causative microorganism. Among patients with bacteriologic failure treated with rifampicin–carbapenem combination, two patients from the COL group and three from the Amp/Sulb group were considered therapeutic failures and died after 9 days of therapy. All *A. baumannii* strains were resistant to rifampicin.

The mortality rates for the two groups and the adverse reactions are listed in Table 2. Both the attributable and the all-cause 28-day mortality did not differ significantly between the two groups. Adverse reactions to antibiotic treatment with regard to nephrotoxicity were observed in five (33.3%) patients in the COL group vs. two (15%) in the Amp/Sulb group; all the patients with nephrotoxicity had pre-existing renal failure except one in the COL group with normal renal function on enrolment. However, none of the treatment regimens were discontinued because of this adverse effect. Temporary skin rash and diarrhea were observed in two patients from the Amp/Sulb group. Neurotoxic side effects were not observed in any patients from both study groups.

Table 2 Clinical and bacteriologic outcome, mortality rates and adverse events in both study groups

	COL group, $n = 15$ (%)	Amp/Sulb group, $n = 13$ (%)	p-Value
Clinical			
Success	9 (60)	9 (61.5)	
Improvement	2 (13.3)	1 (7.6)	NS
Failure	4 (26.6)	3 (23)	
Bacteriological			
Success	10 (66.6)	8 (61.5)	
a: Eradication	7 (46.6)	6 (46.1)	
b: Suppression	3 (20)	2 (15.3)	NS
Failure	5 (33.3)	5 (38.4)	
Mortality			
14 Days	3 (20)	2 (15.3)	NS
28 Days	5 (33.3)	3 (30.0)	NS
Adverse effects			
Nephrotoxicity	5 (33)	2 (15.3)	NS
Other	1 (6.6)	2 (15.3)	NS

Discussion

The main finding of this study is that high-dose regimen of ampicillin/sulbactam therapy is at least as effective as conventional colistin monotherapy in the treatment for VAP due to MDR *A. baumannii* strains. Ampicillin/sulbactam in a dose of 9 g intravenously every 8 h was found to induce a clinical success rate equivalent to that of colistin. Additionally, no significant differences in the mortality rates and in the adverse effects were noted.

Data concerning the comparative effectiveness and toxicity of colistin monotherapy vs. ampicillin/sulbactam therapy in patients with MDR *A. baumannii* VAP are lacking. Colistin, a relatively old polymyxin antibiotic, has gained new attention due to its excellent in vitro activity against the carbapenem-resistant *A. baumannii* strains.[11] However, in vitro studies did not correlate with clinical studies in which clinical response rates for VAP treated with intravenous colistin ranged from 25% to 62%.[12] This discrepancy between in vitro and in vivo studies may be due to the inadequate penetration of the drug into the lung parenchyma.[13] In one study utilizing an immunocompetent mice experimental pneumonia model, Montero et al. have shown that colistin had the weakest antibacterial effect among a number of antimicrobials including sulbactam.[14] However, most recent literature on this topic supports the use of colistin (intravenous or inhaled) treatment for MDR *A. baumannii* VAP.[11,15]

Sulbactam has been successfully used as a single agent and in combination with ampicillin for the treatment of severe *Acinetobacter* infections including bacteremia and VAP.[5,8,16] Its mechanism of antimicrobial activity against *A. baumannii* strains is related to its intrinsic affinity for essential penicillin-binding proteins (PBPs) of these organisms and to alter the permeability of the outer membrane of gram-negative bacilli resulting in the leakage of β-lactamases and thus better penetration by other antibacterial agents.[17] Sulbactam has a good penetration in the lower respiratory tract during bacterial pneumonia and reaches therapeutically active concentrations in the alveolar lining fluid similar to that in serum.[18] The use of high doses of the drug was based on our previous experience[8] and the knowledge that, since sulbactam has time dependent activity, a high dose could achieve a higher $t > \text{MIC}$, which is an important parameter of the in vivo efficacy of β-lactamase−β-lactam combination.[19] Although the study lacks pharmacokinetic analysis, experimental data support our view.[20] In a mouse model of bacteremia from *Escherichia coli* strains of various ranges of susceptibility to ampicillin/sulbactam, Lister et al. comparing two-dose (1.5—and 3.0 g) regimens, showed a dose depended reduction of bacterial count with the highly resistant strain (MIC > 128/64 μg/ml), as opposed to susceptible and intermediate strains (MIC < 8/4, and 16/8—32/16 μg/ml, respectively) were both regimens showed equivalent results in lowering the bacterial load.[20]

The results of the study show that, in terms of clinical response, the clinical cure of VAP was similar in both study arms. Also, the outcome (secondary end point) for patients treated with Amp/Sulb did not differ from that of COL-treated patients. Both VAP-related mortality (14 days mortality) and the all-cause mortality rates (28 days) did not differ between the two groups. The mortality rates in our series were in agreement with those reported in the literature. Garnacho-Montero et al. reported 38% mortality rates in MDR *A. baumanni* VAP treated with colistin, while Choi et al. reported 33% (7 day mortality) in patients treated with cefoperazone/sulbactam.[21,22]

Data evaluating the safety of high dose or nontraditional dosage of ampicillin/sulbactam are limited.[23,24] Patients safely received 10—12 g/day sulbactam for the treatment of MDR *A. baumannii* strains and vancomycin-resistant *Enterococcus faecium* bacteremia. Documented toxicity of sulbactam at dosages greater than 240 mg/kg/day has been reported in animal studies.[5] Regarding neurotoxicity of ampicillin, epileptogenicity has been reported to occur when peak serum concentration exceeds 1 g/L, which can be achieved after 160 mg/kg dose in experimental studies.[20]

With regard to adverse effects, nephrotoxicity, as expected, was higher, in the COL group. Renal dysfunction after colistin use in ICU patients is reported to be 14—37%, and is more severe in those with prior compromised renal function.[25] When correct adjustment of the dose is provided, colistin might not be as nephrotoxic as previously reported. To our knowledge, there are no reports on nephrotoxicity with the use of sulbactam.

This study has limitations and strengths. Limitations include the small sample size and therefore interpretation of the results should be done with caution. Indeed, with this number of patients in each group, the study would have power of 6% to yield a statistical significant difference. Perhaps this is an explanation for not establishing a statistical significant difference in efficacy rate, mortality or adverse effects between the two treatments. However, few patients with VAP caused by multidrug resistant *A. baumanii* are available, so the small trial group size could be accepted and our results

should not be underestimated. The strengths include the prospective design, the accurate definition of VAP by using quantitative cultures from BAL and the follow-up BAL.

In conclusion, the present study revealed that colistin and high-dose ampicillin/sulbactam were comparably safe and effective treatments for critically ill patients with MDR *A. baumannii* VAP. We do not suggest that ampicillin/sulbactam is superior for MDR *A. baumannii* infections or that it should be administered routinely in such an aggressive manner, but this dosing strategy was successful in this cohort of patients.

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