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Comparison of colistin monotherapy and non-colistin combinations in the treatment of multi-drug resistant *Acinetobacter spp*. bloodstream infections: A Multicenter retrospective analysis

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Abstract

Objectives: To compare the efficacy of colistin (COL) monotherapy versus non-COL based combinations in the treatment of bloodstream infections (BSIs) due to multidrug resistant *Acinetobacter spp.*(MDR-A) **. Materials and Methods:** Retrospective data of 107 MDR-A BSI cases from 27 tertiary centers in Turkey were included. **Primary End-Point:** 14-day mortality. **Secondary End-Points:** Microbial eradication and clinical improvement. **Results:** Thirty-six patients in the COL monotherapy (CM) group and 71 in the non-COL based combinations (NCC) group were included in the study. Mean age was 59.98 ± 20 years (range: 18-89) and 50.5% were male. Median duration of follow-up was 40 days (range: 9-297). The 14-day survival rates were 52.8% in CM and 47.23% in NCC group (*P* =

0.36). Microbiological eradication was achieved in 69% of CM and 83% of NCC group (P = 0.13). Treatment failure was detected in 22.9% of cases in both CM and NCC groups. Univariate analysis revealed that mean age (P = 0.001), Charlson comorbidity index (P = 0.03), duration of hospital stay before MDR-A BSI (P = 0.04), Pitt bacteremia score (P = 0.043) and Acute Physiology and Chronic Health Evaluation II score (P = 0.05) were significant in terms of 14-day mortality. Advanced age (P = 0.01) and duration of hospital stay before MDR-A BSI **(**P = 0.04) were independently associated with 14-day mortality in multivariate analysis. **Conclusion:** No significant difference was detected between CM and non-COL based combinations in the treatment of MDR-A BSIs in terms of efficacy and 14-day mortality.

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Full Text

Introduction

Bloodstream infections (BSIs) due to multidrug resistant Acinetobacter spp. (MDR-A) have high mortality rates in hospitalized patients, particularly those with severe comorbidities and followed in Intensive Care Units (ICU). [1],[2]

Acinetobacter strains exhibiting in vitro resistance to more than one antimicrobial agent in ≥3 classes of antibacterial agents are defined as "multidrug resistant". [3] Combined resistance to all available therapeutic options is increasingly being reported. [4] Carbapenem resistance, a key step for the development of MDR, has increased to 75% among nosocomial Acinetobacter strains in Turkey. [5] Despite this ominous trend, the optimal treatment of MDR Acinetobacter spp. has not been established. [6] Colistin (COL) remains to be the most efficient bactericidal agent against MDR-A strains, at least in vitro. [7]

Mortality is basically determined by the severity of the disease in Acinetobacter spp. infections. High Mc Cabe 1, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Pitt bacteremia scores (PBSs) are related with higher rates of mortality. [8],[9] The role of appropriate treatment is controversial. [6],[9] Sufficient data are not available to prove whether COL based combinations are superior to COL monotherapy (CM). Therefore, well-designed clinical trials comparing antimicrobial regimens in the treatment of MDR-A infections are necessary. In this study, we aimed to compare the efficacy of CM with non-COL based antimicrobial combinations in patients with MDR-A BSIs.

Materials and Methods

Study Design and Data Collection

This retrospective, observational, multi-center study included patients with primary or secondary bacteremia due to MDR Acinetobacter spp. registered between January 2009 and August 2012 from 27 Tertiary-Care Centers across Turkey. A total of 380 patients was registered during the study period. The whole cohort was divided into three separate study groups: 1. BSIs due to extended drug resistant (XDR) Acinetobacter spp. treated with COL combinations 2. BSIs due to MDR Acinetobacter spp. treated with COL or non-COL monotherapies 3. BSIs due to MDR (and also carbapenem resistant) Acinetobacter spp. treated with CM or non-COL based combinations. Data of this third study group comprising 107 cases with MDR-A BSI were retrieved from those pooled data. The following

demographic data were extracted from patients' charts: Age, gender, duration of hospital and ICU stay prior to development of bacteremia. Any medical interventions, such as the need for mechanical ventilation, invasive procedures such as tracheostomy and major surgery (defined as all interventions to body cavities performed under sterile conditions and general anesthesia), and the administration of parenteral nutrition, were recorded. The medical histories of the patients were also recorded. Data regarding clinical and laboratory features, and outcome measures were obtained from hospital databases on previously prepared excel files by site investigators. All the data were double-checked and transferred to Statistical Package for the Social Sciences (SPSS 17.0 Chicago, IL., USA) files for analysis by the study coordinator.

Definitions

Case

Patients with MDR-A BSIs treated with CM or non-COL based combinations for ≥72 h.

Inclusion Criteria

These were (1) bloodstream infection due to MDR Acinetobacter spp., which is isolated from ≥ 2 separate sets of hemoculture (peripheral veins and/or catheters), (2) treatment with CM or non-COL combinations for ≥ 72 h (The dosages and routes of administration being in accordance with current medical recommendations), (3) patients were supposed not to have been on any active therapy that would be effective against MDR Acinetobacter spp. already when the culture was drawn or during their treatment course, (4) only the first episode of Acinetobacter bacteremia was included in case of more than one bacteremic episodes due to the same pathogen, (5) any concomitant infection should have to be treated appropriately and effectively.

Exclusion Criteria

These were (1) inability to meet diagnostic criteria of MDR-A BSI in terms of resistance pattern and case definition, (2) coexistence of any other bacteremia (or polymicrobial hemoculture positivity), (3) treatment duration <72 h, (4) Pregnancy, (5) Age <18 years.

Primary MDR-A BSI (adapted from CDC case definitions) - In addition to at least two of the following four criteria:

Fever (38°C) or hypothermia (<36°C)Tachypnea (respiratory rate >24/min)Tachycardia (PR >90/min)Leukocytosis (white blood cell) WBC >12,000/mm 3) or leukopenia (WBC <4000/mm 3) in addition to at least one of the following:

Acinetobacter spp. cultured from two or more blood cultures drawn on separate occasionsAcinetobacter spp. cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy with signs and symptoms and positive laboratory results are not related to an infection at another site.

Secondary MDR-A BSI - If MDR Acinetobacter spp. with identical resistance pattern of the blood isolate is isolated from distant sites (i.e., from endotracheal aspirate, urine or wound culture), it is considered as secondary MDR-A BSI.

Multi-drug Resistance - Acquired non-susceptibility to at least one agent in three or more antimicrobial categories (i.e., ampicillin/sulbactam, aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins + beta-lactamase inhibitors, extended spectrum cephalosporins, trimethoprim-sulfamethoxazole, tetracyclines or, polymyxins). [3]

Extreme-drug Resistance - Resistance to all antibacterials including carbapenems except for tigecycline and COL. [3]

Severity Scores

The severity of bacteremia, acute physiological status and underlying diseases were determined by PBS on the day of bacteremia, APACHE-II score and Charlson comorbidity index (CCI), respectively. [9]

Treatment is considered "early" or "late" if it was initiated within or after the first 24 h, respectively. The combination treatment had to be started at most within 72 h relative to the positive blood culture.

Clinical outcomes were classified into three groups:

(1) Complete response (cure): Recovery of all symptoms, signs and laboratory findings of infection, (2) partial response: Partial recovery of initial symptoms, signs and findings despite obtaining the negative results of blood cultures. (3) Treatment failure: Persistence of infection despite antimicrobial treatment.

Microbiological outcome

Sustained negative results for Acinetobacter spp. during treatment; either in control blood cultures that are obtained every 72 h in case of continued fever or in at least two sets of control blood cultures obtained 72 h after the decrease of fever.

The primary end-point was 14-day mortality while secondary end-points were clinical outcome (cure, improvement, failure or death) and microbiological eradication of MDR-A.

Administration of Colistin

Colistin used in this study was Colimycin Parenteral (Kocak farma, Istanbul, Turkey). It contains 150 mg of 'COL base activity', equivalent to 360 mg (or 4.5 × 10 6 IU) of colistimethate sodium per vial. It was dissolved in 100-mL sterile saline and was given over 30 min. Administration of COL for XDR Gram-negative bacterial infections was based on the results of in vitro antimicrobial susceptibility tests (targeted) or high clinical suspicion of infections due to COL-only susceptible pathogens (empirical), with the approval of infectious diseases consultant, according to the regulations. The dosage of i.v. COL recommended by the manufacturer is 2.5-5.0 mg/kg/day for patients with normal renal function. The total daily dosage was modified for cases of renal impairment according to the manufacturer's instructions. None of the patients received a loading dose of COL within the study period.

Microbiological Tests

Conventional methods and automated systems were used for microbiological identification of Acinetobacter spp. strains isolated from blood cultures. Antimicrobial susceptibilities were determined using disk diffusion, E-test and broth dilution methods at the participating hospitals. Minimum inhibitory concentration (MIC) results were interpreted according to the relevant CLSI criteria.

Statistical Analyses

Statistical Package for the Social Sciences 17.0 Software (Chicago, IL., USA) Program was used for statistical analyses. Categorical variables were compared by $\chi 2$ or Fisher's exact test, continuous variables were tested with Student's t-test or One-way ANOVA test as appropriately. Survival rates were determined by Kaplan-Meier method. In univariate analysis, survival rates of the groups were tested by Log-rank $\chi 2$ test for discrete random variables (i.e. categorical data) and by Cox-regression analysis for continuous random variables (i.e. continuous data). Significant variables were tested by Stepwise multiple Cox-regression in order to determine the independent risk factors for 14-day mortality in MDR-A BSIs. $P < 0.05$ was considered to be statistically significant.

Ethical approval

The study was approved by the Institutional Review Board of Kartal Dr. Lutfi Kirdar Education and Research Hospital (Istanbul). All collected data were conserved confidentially.

Results

A total of 107 consecutive patients, 102 of whom followed in the ICUs within a certain period of time, 36 treated with CM and 71 treated with non-COL based combinations (NCC) were included in the study. The consort diagram of the distribution of patients within the two treatment groups is shown in [Figure 1]. The median duration of follow-up was 40 days (range: 9-297). Rate of treatment success was 77.1% in CM and 77.2% in NCC group ($P = 0.45$).{Figure 1}

Patient characteristics, treatment outcomes and risk factors for mortality are shown in [Table 1], [Table 2], [Table 3]. Because no significant difference was determined between the two treatment groups (CM and NCC) in terms of basic demographic characteristics, disease severity scores, 14-day mortality rates and clinical and microbiological outcomes; all 107 patients were accepted as a whole single group. Univariate and multivariate analyses were

performed to determine the factors effecting 14-day mortality [Table 4]. The proportion of late-onset (>24 h) treatment was higher (P = 0.004) in the CM group, however this difference was not significant in the univariate analysis. CCI, duration of prior ICU stay and PBS were found to be significant risk factors for 14-day mortality in the univariate analysis whereas not verified in the multivariate regression. Older age (P = 0.01, hazard ratio [HR] =1.03 confidence interval [CI = 1.006-1.05]), prolonged prior hospital stay (P = 0.04, HR = 1.03 [1.06-1.1]) and higher APACHE II score (P = 0.05, HR = 1.2 [1.12-1.24]) were determined as independent risk factors for 14-day mortality in the multivariate stepwise Cox regression analysis. Attribution of death was available in 87 patients (37 in CM and 50 in non-COL group) and was investigated in three categories (definitely, probably and not related to bacteremia) based on the clinical and microbiological courses of BSIs. The proportions of the three categories were 21.6 versus 16%, 37.8 versus 52% and 40.5 versus 32% respectively in the two groups. No significant difference (P = 0.17) was determined in terms of attribution to death.{Table 1}{Table 2}{Table 3}{Table 4}

Discussion

Despite a reputation for relatively low virulence, MDR-A infections pose a formidable threat to patients.[10] As being the cause of many hospital outbreaks, this organism is increasingly endemic in the health-care settings. MDR-A BSIs occur most frequently in severely ill patients and have high crude mortality rates. Although the attributable mortality is debatable, as reported between 7.8% and 43% by Blot et al. and Falagas, these infections are clearly associated with hemodynamic instability, longer ICU stay, and longer duration on mechanical ventilation.[2],[11] COL has become the backbone of treatment in recent years owing to its potent bactericidal efficacy against MDR Gram negative bacteria. [12] Until 2010, the year that COL has become country-wide available, most cases of MDR-A BSIs were treated with non-COL based combinations in Turkey. Even at the time period of this study, some delays were being experienced in the supply of the drug due to procurement procedures, which constitutes the main explanation for the relatively higher proportion of late onset treatment in CM group. Still some cases, particularly those not convenient for COL and those well responded to initial empirical therapy are treated with non-COL combinations according to in-vitro susceptibility results.

While MDR and even XDR-Acinetobacter spp. strains are supposed to be COL sensitive by definition, however, in vitro hetero-resistance has been reported during CM. Therefore, as of today, COL-based combinations are widely recommended in the treatment of MDR-A BSIs. [13] COL acts by increasing the permeability of the cell membrane and thus could act synergistically with other antimicrobial agents by facilitating their entrance into the bacterial cell. Current available literature does not conclusively demonstrate better outcomes among the patients treated with COL for MDR-A infections. [14]

One of those several studies investigating the effects of different combinations against MDR-A BSIs, conducted by Lim et al. conclude that 14-day mortality rates were similar (35.5% and 38.5%, P = 0.80) in cases treated with COL and non-COL based treatment arms. [15] This is compatible with our results. In a prospective study, including 200 patients treated with COL and 295 patients treated with comparators (imipenem or meropenem or ampicillin-sulbactam), treatment with COL was found to be associated with increased cumulative mortality. [16] These analyses suggest that CM is less effective when compared to beta lactams probably due to patient factors that give rise to the need for COL treatment, inherently associated with poor survival.

Tigecycline is the second most commonly used antimicrobial for MDR and XDR Acinetobacter spp. infections. The use of tigecycline for BSIs is controversial. Tigecycline monotherapy is related with high (56%) attributable mortality and is not suggested for MDR-A BSIs. [17] Serum concentrations may be suboptimal at the current recommended dosage. Despite this concern, 77.7% of those 27 patients treated with tigecycline based dual combinations were clinically improved in our study. Complete response was obtained in 13 (48.1%) cases, 8 (29.6%) showed partial response and treatment failure was observed in 6 (22.2%) cases with the lowest rate of failure (11.1%) in tigecycline + carbapenem combination group (n = 9). This could be explained by the eradication of the underlying source of infection, or there could be a significant synergy when tigecycline was used in combination with carbapenems, sulbactam and aminoglycosides.

In a study conducted by Gordon and Wareham, tigecycline was used for treatment of nine cases with MDR-A BSI, in combination with a second drug (with amikacin in three cases) in six and alone in three. [18] Over half of the patients were successfully treated, in consistence with our results.

Sulbactam is another drug that is potentially effective against MDR-A BSIs. Monotherapy with sulbactam is not recommended for life-threatening infections; however, various studies reveal evidence favoring its use in combination with other active agents. [19]

Based on the results of previous studies indicating in-vitro synergies with other beta lactams and clinical results showing enhanced activity in combination with rifampin or azitromycin or a quinolone; sulbactam was used in 28 of

the cases combined with other non-COL drugs, mostly aminoglycosides. [20] Until it became available as "sulbactam-only" in 2011, sulbactam was conventionally used as the effective component in cefoperazone-sulbactam combination (in 21 of 28 cases) against MDR Acinetobacter sp. Clinical outcomes were similar with the CM group, including 14 day mortality. These results suggest that sulbactam could be the preferred option for the treatment of MDR-A BSIs, in combinations.

Rifampin is also a treatment of choice, particularly in combination with COL, imipenem or sulbactam. [21] Unfortunately, it was not included in the treatment regimens of any patient in our cohort except one who was successfully treated with imipenem plus oral rifampin, due to lack of its parenteral form in Turkey.

The differences in terms of efficacy within the treatment modalities in the NCC group were not investigated in our study due to the wide diversity of subgroups; however, none of the combinations revealed a significant superiority when compared to each other or COL group.

These results are encouraging because of the potential for high mortality rates in cases of Acinetobacter infections given increasing imipenem resistance and the lack of treatment options.

We suggest that; several host factors including severe co-morbid diseases, multiple organ failure and impaired immunity, may be more important determinants of the outcome than purely the susceptibility to the antimicrobial agent. [11],[22] While the attributable 30-day mortality rate associated with Acinetobacter bacteraemia is reported to be significantly higher (57.5% versus 27.5%) in those due to imipenem resistant isolates when compared to the susceptible ones, discordant antimicrobial therapy has been shown to have a more significant impact on the 30-day mortality than imipenem resistance.[23] ἐmipenem resistance is frequently associated with MDR, and subsequently leads to discordant antimicrobial therapy, and an unfavorable outcome in patients with Acinetobacter spp. bacteraemia. [24] In the study of Esterly et al., patients who received active antimicrobial therapy were less likely to die (93.5% vs. 74.2%; P = 0.02), regardless of carbapenem susceptibility classifications. [25]

The two treatment groups were similar regarding the timing of antimicrobials in addition to their clinical results. Concerning the major confounding factors; we have made risk and severity adjustment as the mean values of CCI, PBS and APACHE II scores were similar within the two groups. Indeed, the results of our multivariate analysis showed that; advanced age, length of prior hospital stay and higher APACHE II scores were independent risk factors for mortality. High APACHE II score (≥21) in patients with MDR-A BSI has been reported to be independent risk factor for 14-day, 30-day and in-hospital mortality in various studies. [26],[27] 30-day mortality was used as the main outcome measure in many other similar studies, however, we adopted 30-day to be a long time period to interpret the causality of mortality for patients with serious co-morbidities. [11],[28],[29] Thus, we decided to use 14-day mortality as the main outcome measure.

Duration of hospital stay before bacteremia onset was found as an independent risk factor leading to increased mortality, in the study of Yang et al. [27] Although the inevitable relation of comorbidities with length of hospital stay and the retrospective design of the study lowering the reliability of this factor, the impact of this issue is undeniable.

Limitations of the study

Retrospective design seems to be the basic limitation of our study. Other limitations were the presence of concomitant foci of infections other than MDR-A BSI, use of other drugs for concomitant infections in some patients and inadequate data about effective source control because of retrospective design. Pharmacokinetic and pharmacodynamic parameters were not available for assessment and COL doses were unstandardized in this respect. It is very difficult to conduct prospective clinical trials on this issue due to ethical concerns.

Conclusion

Colistin monotherapy and non-COL based combinations for MDR-A BSIs revealed no significant differences with respect to 14-day mortality, clinical recovery and microbiological eradication.

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